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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the Therapeutic Goods Act 1989 (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Attachment 1. Product Information ...................................................... 127
I. Introduction to product submission

Submission details

Type of submission: New Chemical Entity

Decision: Approved

Date of Decision: 25 November 2011

Active ingredients: Pitavastatin

Product names: Livalo

Sponsor's name and address: Abbott Australasia Pty Ltd
Locked Bag 5016
Botany NSW 1455

Dose form: Film-coated tablets

Strengths: 1 mg, 2 mg and 4 mg [of free base]

Containers: Polyvinylidene chloride (PVdC) coated polyvinyl chloride (PVC) and aluminium blisters

Pack sizes: 10, 30 and 100 tablets

Approved therapeutic use: Livalo is indicated as an adjunct to diet for the treatment of adult patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia, when response to diet and other non-pharmacological measures is inadequate. Prior to initiating therapy with Livalo, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

Route of administration: Oral (PO)


ARTG Numbers: 176640, 176658 and 176659

Product background

This AusPAR describes the application by Abbott Products (Australia) Pty Ltd to register a new chemical entity, pitavastatin calcium (Livalo), for use as a hypolipidaemic agent. Pitavastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor.
or ‘statin’ and is structurally related to other HMG-CoA reductase inhibitors such as the marketed drugs lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin.

There are two TGA adopted European guidelines relevant to this submission, besides the general guidelines, which are cited throughout this AusPAR:

**CPMP/EWP/3020/03**: Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders. Effective: 20 May 2005

**EMEA/CHMP/EWP/350495/2009**: Concept Paper on the Need to Update the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (CPMP/EWP/3020/03)

**Regulatory status**

Pitavastatin has been approved in Japan (2003), Europe (UK and The Netherlands, August 2010) and USA (August 2009). The approved indications are as follows:

- **Europe**

  *Livazo is indicated for the reduction of elevated total cholesterol (TC) and LDL-C, in adult patients with primary hypercholesterolemia, including heterozygous familial hypercholesterolemia, and combined (mixed) dyslipidaemia, when response to diet and other non-pharmacological measures is inadequate.*

- **USA**

  *Livalo is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.*

**Product Information**

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

**II. Quality findings**

**Drug substance (active ingredient)**

Figure 1a shows the chemical structure of pitavastatin calcium.

Full and adequate details of the synthesis and control were provided in the form of a drug master file (DMF). The synthesis yields an intermediate that is a mixture of four diastereoisomers (precursors for pitavastatin, pitavastatin (-) enantiomer, pitavastatin 3-epimer and pitavastatin 5-epimer). The chemical structures of the diastereoisomers are shown in Figure 1b below.
Figure 1. Chemical structure

a) Pitavastatin calcium

\[
\text{C}_{50}\text{H}_{46}\text{CaF}_2\text{N}_2\text{O}_8 \quad \text{MW} = 880.98 \quad (421.46 \text{ for free pitavastatin})
\]

\[
\text{CAS \#} = [147526-32-7] \quad (147511-69-1 \text{ for free pitavastatin})
\]

b) Diastereoisomers

Drug product

The manufacturing process of the tablets is a simple wet granulation process followed by drying, compression and film coating. Adequate validation of the process was provided and there are appropriate in process controls.

There were no changes to the product on real time storage and the stability data provided supported a shelf life of 3 years when stored below 25°C in Polyvinyl chloride (PVC)/Polyvinylidene chloride (PVDC)/aluminium (Al) blister packs. However, the drug substance is light sensitive and the additional storage condition of ‘protect from light’ will be used.

Bioavailability

The pivotal Phase III clinical efficacy studies (NK-104-301, -302, -304, -305, -306, -307, -308, -309 and -310) were performed using the proposed formulation 1 mg, 2 mg and 4 mg tablets\(^1\). These strengths contain cores in direct scale and given that the pharmacokinetics are linear from 1-8 mg can be considered bioequivalent (that is, 1 x 4 mg, 2 x 2 mg and 4 x 1 mg will all give the same response).

The 1 mg, 2 mg and 4 mg tablets proposed for marketing are identical to those used in the Phase III clinical efficacy studies but they are manufactured at a different site of manufacture using different equipment.

To support registration, four (4) bioavailability studies were provided. These used validated test methods for the determination of pitavastatin and pitavastatin lactone (the main metabolite).

\(^1\) Note that some of the early Phase III clinical studies were performed in Japan, Korea and China using different formulation 1 mg and 2 mg tablets. These had different cores, different film-coats and contained 1 mg and 2 mg of pitavastatin calcium, rather than 1 mg and 2 mg of pitavastatin (as 1.045 mg and 2.09 mg of pitavastatin calcium). Having said that a bioequivalence study performed comparing these two 2 mg tablets (study NK-104-1.35, not evaluated by PCS) indicated bioequivalence.
Study NK-104-1.36 was performed on 4 mg tablets from the SkyePharma (SP) SAS and Pierre Fabre (PF) Medicament Production sites. The results (Table 1) indicated these tablets are bioequivalent and given the linear pharmacokinetics, these results can be extrapolated to the 1 mg and 2 mg tablets.

**Table 1. Pharmacokinetic results**

**Analyte: Pitavastatin**

<table>
<thead>
<tr>
<th></th>
<th>(T_{max}) (h)</th>
<th>(C_{max}) (ng/mL)</th>
<th>(AUC_{0-4}) (ng.h/mL)</th>
<th>(AUC_{0-\infty}) (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Reference (SP)</td>
<td>0.75</td>
<td>58.71</td>
<td>119.40</td>
<td>131.78</td>
</tr>
<tr>
<td>B: Test (PF)</td>
<td>0.75</td>
<td>55.21</td>
<td>117.83</td>
<td>128.24</td>
</tr>
</tbody>
</table>

**Statistical analysis:**

<table>
<thead>
<tr>
<th>B versus A Estimate</th>
<th>median difference</th>
<th>ratio (%)</th>
<th>ratio (%)</th>
<th>ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>0.94</td>
<td>0.987</td>
<td>0.965</td>
</tr>
<tr>
<td></td>
<td>(0.856 – 1.034)</td>
<td>(0.948 – 1.027)</td>
<td>(0.919 – 1.014)</td>
<td></td>
</tr>
</tbody>
</table>

**Analyte: Pitavastatin lactone**

<table>
<thead>
<tr>
<th></th>
<th>(T_{max}) (h)</th>
<th>(C_{max}) (ng/mL)</th>
<th>(AUC_{0-4}) (ng.h/mL)</th>
<th>(AUC_{0-\infty}) (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Reference (SP)</td>
<td>1.50</td>
<td>33.92</td>
<td>318.03</td>
<td>342.12</td>
</tr>
<tr>
<td>B: Test (PF)</td>
<td>1.50</td>
<td>33.62</td>
<td>318.26</td>
<td>351.46</td>
</tr>
</tbody>
</table>

**Statistical analysis:**

<table>
<thead>
<tr>
<th>B versus A Estimate</th>
<th>median difference</th>
<th>ratio (%)</th>
<th>ratio (%)</th>
<th>ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>0.981</td>
<td>1.001</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(0.934 – 1.03)</td>
<td>(0.962 – 1.041)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Study NK-104-1.21US investigated the effect of food on the proposed 4 mg tablet. The results (Table 2) indicate that food increases the time to maximal plasma concentration \(T_{max}\) of pitavastatin from 1 to 2 hours and decreases maximal plasma concentration \(C_{max}\) of pitavastatin by 43%, but does not affect the area under the plasma concentration time curve (AUC) of pitavastatin (Figure 2). Given the linear pharmacokinetics, this result can be extrapolated to the 1 mg and 2 mg tablets.

**Table 2. Pharmacokinetic results**

**Analyte: Pitavastatin**

<table>
<thead>
<tr>
<th></th>
<th>(T_{max}) (h)</th>
<th>(C_{max}) (ng/mL)</th>
<th>(AUC_{0-4}) (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Reference (Fasting)</td>
<td>1.00</td>
<td>58.44</td>
<td>126.76</td>
</tr>
<tr>
<td>B: Test (Fed)</td>
<td>2.00</td>
<td>33.26</td>
<td>112.81</td>
</tr>
</tbody>
</table>

**Statistical analysis:**

<table>
<thead>
<tr>
<th>B versus A Estimate</th>
<th>median difference</th>
<th>ratio (%)</th>
<th>ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>56.9</td>
<td>89.0</td>
</tr>
<tr>
<td></td>
<td>(50.6 – 64.1)</td>
<td>(83.3 – 95.1)</td>
<td></td>
</tr>
</tbody>
</table>
Analyte: Pitavastatin lactone

<table>
<thead>
<tr>
<th></th>
<th>$T_{\text{max}}$ (h)</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>$\text{AUC}_{0-t}$ (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Reference (Fasting)</td>
<td>2.00</td>
<td>43.78</td>
<td>464.45</td>
</tr>
<tr>
<td>B: Test (Fed)</td>
<td>4.00</td>
<td>32.96</td>
<td>382.20</td>
</tr>
</tbody>
</table>

**Statistical analysis:**

<table>
<thead>
<tr>
<th></th>
<th>median difference</th>
<th>ratio (%)</th>
<th>ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B versus A Estimate</td>
<td>-</td>
<td>75.3</td>
<td>82.3</td>
</tr>
</tbody>
</table>

(70.3 – 80.6) (78.5 – 86.3)

Figure 2. Plasma concentrations by treatment 0-24 h (top) and 0 to 36 h (bottom).

Study NK-104IV.1.02EU investigated the bioavailability of a 2 mg dose of an oral solution compared to a 2 mg dose of an IV injection. The absolute bioavailability was estimated to be 51% and it is accepted that similar absolute bioavailability would be observed from the tablets.

Study NKS1014A2115 was also provided which investigated the bioavailability of pitavastatin when released in the jejunum, the ileum and the ascending colon compared to oral administration. This study indicated that the absorption is probably from the jejunum and ileum.

---

2 The company referred to cross study data that indicated that the bioavailability from the 2 mg tablets is the same as from the 2 mg of oral solution.
Details of the current Australian submission were presented to the Pharmaceutical Subcommittee (PSC) of Advisory Committee on Prescription Medicines (ACPM).

**Quality summary and conclusions**

Approval of this submission was recommended with respect to chemistry and manufacturing control.

With respect to bioavailability: Although food did not affect the AUC of pitavastatin, it increased the $T_{\text{max}}$ and decreased the $C_{\text{max}}$ and the Delegate should consider if these affects are clinically relevant before accepting the statement in the PI that food can be taken with or without food.

**III. Nonclinical findings**

**Introduction**

The current Australian nonclinical data package consisted primarily of original study reports along with some literature publications. Studies were well conducted and presented and conformed to relevant Australian and international guidelines. Most pivotal safety studies were conducted according to Good Laboratory practice (GLP), except for two early safety pharmacology studies which were nevertheless carried out in a scientifically valid manner.

In addition to the standard range of nonclinical studies, several additional mechanistic studies were performed as well as studies to qualify various impurities in the drug product. Overall, the data package was extensive and appropriate and allowed suitable assessment of nonclinical safety and efficacy.

**Pharmacology**

**Primary pharmacodynamics**

Pitavastatin is a selective inhibitor of 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase, which is the rate limiting enzyme in the *de novo* synthesis of cholesterol from acetyl CoA that occurs primarily in the mammalian liver.

**Efficacy and mechanism of action**

The mechanism of action of the statins as a class is well established. Pharmacological studies have confirmed pitavastatin's activity at the mechanistic level both in terms of inhibition of HMG-CoA reductase activity and the inhibition of synthesis of cholesterol. In general, there appear to be two separate mechanisms whereby circulating cholesterol levels are reduced in response to inhibition of hepatic cholesterol synthesis by pitavastatin:

1. production of cholesterol containing lipoproteins may be inhibited as a direct result of reduced cholesterol synthesis in the liver and
2. pitavastatin may enhance the uptake and catabolism of low density lipoprotein (LDL) by increasing the number of hepatic LDL receptors on the cell surface which is regulated by the intracellular cholesterol concentration.

Although there was some evidence of hepatic LDL receptor up regulation in hepatic human hepatoma cells (HepG2) cells and guinea-pig liver, the major mechanism
responsible for the hypocholesterolaemic activity appears to be reduced production of very low density lipoprotein (VLDL) and/or LDL.

**In vitro studies**

Pitavastatin competitively inhibited HMG-CoA reductase in rat liver microsomes with an 50% inhibitory concentration (IC$_{50}$) of 6.8 nM (see Table 3 below) and was 2.4 and 6.8 times more potent than simvastatin and pravastatin respectively, in this system.

**Table 3. Inhibition of HMG-CoA Reductase Activity Determined in Rat Liver**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitavastatin</td>
<td>6.8</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>1.2</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>16</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>46</td>
</tr>
<tr>
<td>Lactone</td>
<td>12</td>
</tr>
</tbody>
</table>

**In vitro studies** showed that pitavastatin inhibited cholesterol synthesis in HepG2, skeletal muscle cells and hepatocytes with IC$_{50}$ of 5.8, 3.4 and 24.5nM, respectively.

The IC$_{50}$ ratio of 1/3/6 obtained for pitavastatin, simvastatin and atorvastatin in HepG2 cells is close to the respective clinical dose ratios of 2 mg/5 mg/10 mg. In guinea pig livers, the 50% effective doses (ED$_{50}$) for inhibition of sterol synthesis were 0.33 mg/kg for pitavastatin and 5.1 mg/kg for simvastatin.

Pitavastatin showed a more sustained effect than simvastatin and pravastatin, with significant inhibition of sterol synthesis in the rat liver still observed up to 6 h post dose when the inhibitory effect of the other statins had disappeared (similar findings were seen in guinea pigs).

**In vivo studies**

The *in vitro* findings with pitavastatin were corroborated by *in vivo* measures of effects on lipids and studies were also extended to include animal models of atherosclerosis. Repeated oral dosing of guinea pigs with pitavastatin significantly decreased

- plasma total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels at ≥0.3 mg/kg,
- plasma triglyceride (TG) at ≥1 mg/kg, and
- very low density lipoproteins (VLDL) at 3 mg/kg.

In dogs, twice daily dosing of pitavastatin for 14 days (0.28 mg/kg/day) decreased plasma TC, Phospholipid (PL) and TG concentrations with 0.25 mg/kg/day of the lactone having similar activity. The effect of the lactone was a result of conversion back to pitavastatin *in vivo*. Following daily dosing of animals for 2 weeks, pitavastatin decreased VLDL-TG and Apolipoprotein (ApoB) (as well as VLDL-ApoB) in isolated perfused guinea pig liver.

**Animal models of hyperlipidaemia and atherosclerosis**

Pitavastatin lowered TG in male kwl: Zucker rats and reversed the elevated plasma cholesterol and TG, hepatic lipid content and delayed LDL clearance which characterise guinea pigs with dietary induced hyperlipidaemia. Accelerated LDL clearance was observed in the latter study at 1.0 mg/kg pitavastatin suggesting that like atorvastatin (at 10 mg/kg), the decrease in plasma cholesterol may also involve enhanced expression of
liver LDL receptors. No studies were performed in a mouse model of homozygous familial hypercholesterolaemia (LDL-receptor deficient mice); however, pitavastatin lowered plasma cholesterol, triglyceride and phospholipid in Watanabe heritable hyperlipidaemic (WHHL) rabbits (rabbit model of genetically determined hyperlipidaemia), with 62% and 59% reductions in VLDL-C and intermediate density lipoprotein (IDL)-C observed, respectively, after 26 weeks.

Additional studies (in vitro and in vivo) showed pitavastatin to have anti atherosclerotic effects. It reduced cholesteryl ester in an LDL loaded mouse peritoneal macrophage cell line, suppressed intimal thickening in a balloon endothelisation carotid artery model and suppressed the progression of aortic atherosclerosis and stabilised the atherosclerotic plaque in Watanabe heritable hyperlipidemic (WHHL) rabbits.

Overall, the primary pharmacodynamic findings support the use of pitavastatin for the proposed indication and suggest that its mechanism of action is similar to other HMG-CoA reductase inhibitors currently registered in Australia.

Activity of pitavastatin epimers, enantiomers and metabolites

Pitavastatin has two chiral carbon atoms and consequently four optical isomers: the 3R, 5S(+) enantiomer is the desired active pharmaceutical ingredient. The remaining two epimers and other enantiomer were at least 100 times less potent than pitavastatin at inhibiting HMG-CoA reductase.

The primary metabolite of pitavastatin in humans is pitavastatin lactone, which is also the primary metabolite in dogs and monkeys. Pitavastatin lactone is not pharmacologically active but is rapidly converted to pitavastatin. While the minor 8-hydroxy metabolite of pitavastatin has a similar IC50 for HMG-CoA reductase inhibition to the parent drug (in rat liver microsomes) it should contribute little to the overall pharmacological activity.

Secondary pharmacodynamics

Repeated (14 day) oral pitavastatin treatment in hamsters (which have a comparable lithogenic and biliary profile to humans) showed lowered plasma TC with no effect on biliary lipids, suggesting a low potential to induce gallstones.

One week studies with pitavastatin in rats and guinea-pigs at oral doses considerably higher than the ED50 for sterol synthesis had no effect on plasma adrenocorticotropic hormone (ACTH) or steroid hormone levels (testosterone, oestrone, corticosterone), suggesting that unwanted effects on steroid hormone levels are unlikely at therapeutic doses.

Safety pharmacology

Pitavastatin was administered orally to mice and rats, rabbits and dogs, and intravenously (IV) to anaesthetised dogs in an adequate safety pharmacology program demonstrating sufficient exposure.

While pitavastatin appears to cross the blood brain barrier there was no effect on general behaviour in mice at 3 mg/kg orally (PO), with central nervous system (CNS) effects limited to inhibition of acetic acid induced writhing frequency at 10 mg/kg (corresponding to ≥23 times the clinical plasma Cmax).

Gastrointestinal transit in mice was unaffected but gastric acid secretion tended to increase, and urinary excretion of electrolytes (sodium and chloride) and urine volume were decreased in rats at 30 mg/kg (≥17 times the clinical plasma Cmax).

3 Based on a 12 mg/kg dose in mice, compared to a 4 mg dose, Cmax of 55 ng/mL; Clinical Study PKH/NKN98389N/ NK-104.1.01
Heart rate was slightly but significantly increased at 3 and 6 h postdose in dogs dosed at 10 mg/kg PO (corresponding to an animal: human C\textsubscript{max} of ≥94) but the ambulatory electrocardiogram (ECG) was unremarkable.

Pitavastatin did not affect the hERG current but the lactone metabolite had weak effects on both hERG and action potentials of guinea pig papillary muscle at 3 μM. The lactone suppressed hERG current by about 13% in hERG transfected HEK293 cells at 1 μM (>1000 times the estimated clinical free C\textsubscript{max} of lactone). The No Observable Effect Level (NOEL) of 0.3 μM is equivalent to circa 300 times the estimated clinical free C\textsubscript{max} of lactone.

Pitavastatin lactone significantly increased action potential duration at 60% (APD\textsubscript{60}) and APD at 90% (APD\textsubscript{90}) by 4-5% in isolated guinea pig papillary muscles at 3 µM but had no effect at 1 µM, corresponding to >1000 times the estimated clinical free plasma C\textsubscript{max}.

No significant ECG abnormalities were noted in dogs in the PO and IV cardiovascular safety studies, nor in any of the repeat dose toxicity studies conducted in dogs or monkeys. Neither pitavastatin nor its lactone metabolite caused QT prolongation\textsuperscript{4} at 4 mg or at 16 mg in clinical studies.

Overall, there are no specific concerns raised from the safety pharmacology studies. In particular, pitavastatin is not considered to represent a torsadogenic risk at the recommended therapeutic doses.

**Pharmacokinetics**

Pitavastatin was absorbed relatively rapidly after an oral dose (time to maximal concentration (T\textsubscript{max}) 1-2 h) in rats and humans, but more slowly in dogs, rabbits and monkeys. Kinetics appeared to be tri exponential in rats, rabbits, dogs and monkeys, with terminal elimination half lives (t\textsubscript{1/2}) broadly similar across the laboratory species of about 4-8 h (humans: 4 mg: 8.9 h; 2 mg: 8.2 h; 1 mg: 1.4 h) and half-lives of about 20-40 h for radioactivity after administration of radioactive carbon labelled \textsuperscript{14}C-pitavastatin to laboratory animals or about 68 h in humans. Bioavailability of an oral dose was high in rats, rabbits and dogs (80-100%), lower in monkeys (20-30%) and approximately 50% in humans. In rodents, exposure was generally higher in females, with no accumulation noted in either sex upon repeated dosing. Volume of distribution was low in animal species (0.38-1.53 L/kg) and moderate in humans (226 L, 3.2 L/kg for a 70 kg person).

Pitavastatin was highly bound to plasma proteins in all species and humans (not less than 96%) with limited transfer into blood.

Oral dosing of \textsuperscript{14}C-pitavastatin to rats and monkeys did not show any particular tissue accumulation of radioactivity, with highest levels in the gastrointestinal tract and organs associated with metabolism and excretion. Results in pigmented rats were similar to albino rats, suggesting no special affinity of pitavastatin for melanin in eyes and pigmented skin.

Like rosuvastatin and pravastatin, pitavastatin undergoes little metabolism and its elimination mainly depends upon transporter mediated excretion from the liver into the bile, with subsequent enterohepatic recirculation or faecal excretion. The extensive enterohepatic circulation demonstrated in bile duct cannulated rats and dogs helped to explain pitavastatin’s liver specific distribution and extended duration of action. Faecal excretion dominated after oral dosing in rats, guinea pigs, dogs, monkeys, as it does in humans (78.6% of the dose; 15.1% in urine).

\textsuperscript{4} QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.
Even though the main cytochrome P450 (CYP) enzyme isoform involved in the metabolism of pitavastatin in human liver was CYP2C9 (generating the 8-hydroxy metabolite), the metabolic clearance was smaller than the other HMG-CoA reductase inhibitors. The lactone (formed via an ester type pitavastatin glucuronide conjugate in the liver by UDPGT1A3 and 2B7) was quantitatively the most important metabolite; in humans the lactone circulated at levels approximately two thirds those of pitavastatin, whilst 8-hydroxy pitavastatin was at much lower levels (area under the concentration versus time curve (AUC) values of 3175, 2074 and 16 ng eq. h/mL for pitavastatin, lactone and 8-hydroxy pitavastatin, respectively).

Overall, while there were quantitative differences, the metabolic profile was qualitatively similar in the animal species with no unique human metabolites. Thus, comparisons of the pharmacokinetic profiles in the laboratory animal species used in the pivotal repeat dose toxicity studies (rats, dogs and monkeys) indicated that sufficient similarities existed to allow them to serve as appropriate models for the assessment of pitavastatin toxicity in humans.

**Potential drug interactions**

Pharmacokinetic interaction studies showed that there are unlikely to be interactions as a result of displacement of other highly protein bound compounds (such as warfarin and digoxin) from their protein binding sites or through effects on CYP isoenzymes.

As pitavastatin undergoes only low metabolic clearance by the CYP P450 system, any changes in its metabolism by inhibition or induction of CYP are unlikely. The major CYP isoform in the human liver involved in metabolism of pitavastatin is CYP2C9 (17% at 0.5 μM). However, pitavastatin did not affect the in vitro metabolism (4-hydroxylation) of tolbutamide, a model substrate for CYP2C9, suggesting that concomitant administration of pitavastatin is unlikely to cause a significant interaction via CYP2C9. Pitavastatin may equally impact on the activity of CYP isoenzymes but there was no inhibitory effect on the metabolic activity of various human CYP isoforms with the exception of CYP2C8, where a 2.5μM concentration of pitavastatin decreased activity by 30%.

Pitavastatin is a substrate for human hepatic organic anion transporting polypeptide 1B1 (hOATP1B1), which accounts for 90% of its total hepatic clearance. Hirano et al. suggested that several drugs (especially cyclosporin A, rifampicin, rifamycin SV, clarithromycin and indinavir) have the potential to interact with OATP1B1-mediated uptake of pitavastatin.

Indeed, cyclosporin A (0.5 to 20 μmol/L) concentration dependently inhibited OATP1B1-mediated uptake of 14C-pitavastatin into Xenopus oocytes expressing human liver specific OATP1B1 with an IC50 value 2.91 μmol/L [ATR-149-035]. Enalaprilat and nipradilol had no effect on pitavastatin uptake but atazanavir inhibited uptake, together with rifampicin.

Clinically, from a total of 12 pharmacokinetic drug interaction studies the only interactions resulting in a doubling or more of concentrations were seen with erythromycin and cyclosporin; with the most marked effect on pitavastatin bioavailability observed when it was given concurrently with cyclosporin (sponsor’s Summary of Clinical Pharmacology Studies).

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5 Hirano M et al. (2006) Drug-drug interaction between pitavastatin and various drugs via OATP1B. Drug Metab. Dispos. 34, 1229-1236.
Relative exposure

Exposure ratios were calculated based on AUC0–24h and/or Cmax values obtained in the animal studies. Toxicokinetic analyses were not performed in the rat 1 and 6 month studies but there was sufficient data from the 13 week rat study together with the additional single dose comparative pharmacokinetic evaluations in rats to demonstrate adequate exposure to pitavastatin. The concentration of lactone, the main metabolite of pitavastatin was measured in studies in the dog and monkey and exposure confirmed.

Table 4a. Relative exposure in oral repeat-dose studies.

<table>
<thead>
<tr>
<th>Study Details</th>
<th>NOAEL (mg/kg)</th>
<th>Dose (mg/kg/day)</th>
<th>AUC0–24h (ng.h/mL)/Animal : Human Exposure Ratio (X)</th>
<th>Cmax (ng/mL)/Animal : Human Exposure Ratio (X)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>4 Weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNBL.138.01</td>
<td>NOAEL: not determined i.e. &lt;70</td>
<td>70</td>
<td>5570/36x</td>
<td>5950/39x</td>
</tr>
<tr>
<td>Mouse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB6F1-Tg rasH2</td>
<td></td>
<td>125</td>
<td>8060/53x</td>
<td>12930/85x</td>
</tr>
<tr>
<td>n=18/sex</td>
<td></td>
<td>250</td>
<td>48560/317x</td>
<td>69810/456x</td>
</tr>
<tr>
<td>13 Weeks</td>
<td>NOAEL: not determined i.e. &lt;25</td>
<td>25</td>
<td>528/3x</td>
<td>723/5x</td>
</tr>
<tr>
<td>KOW14/9523</td>
<td></td>
<td>75</td>
<td>2402/16x</td>
<td>5621/37x</td>
</tr>
<tr>
<td>Mouse</td>
<td></td>
<td>225</td>
<td>22486/147x</td>
<td>23274/152x</td>
</tr>
<tr>
<td>Crl: CD-1(ICR)BR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=4/sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 Weeks</td>
<td>NOAEL: not calculated</td>
<td>30</td>
<td>1076/7x</td>
<td>1326/9x</td>
</tr>
<tr>
<td>SNBL.138.03</td>
<td></td>
<td>75</td>
<td>4904/32x</td>
<td>4787/31x</td>
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<tr>
<td>Mouse</td>
<td></td>
<td>150</td>
<td>15840/104x</td>
<td>43480/284x</td>
</tr>
<tr>
<td>CB6F1-Tg rasH2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=18/sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>91 Weeks</td>
<td>NOAEL: not determined i.e. &lt;1**</td>
<td>12</td>
<td>NC</td>
<td>NC</td>
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<tr>
<td>KOW16/982522</td>
<td></td>
<td>30</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Mouse</td>
<td></td>
<td>75</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Crl: CD-1(ICR)BR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=5/sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

i.e.=that is
### Table 4b. Relative exposure in oral repeat-dose studies.

<table>
<thead>
<tr>
<th>Study Details</th>
<th>NOAEL (mg/kg)</th>
<th>Dose (mg/kg/day)</th>
<th>AUC₀⁻²₄ₕ (ng·h/mL) / Animal : Human Exposure Ratio (X)</th>
<th>Cₘₐₓ (ng/mL) / Animal : Human Exposure Ratio (X)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
<td></td>
</tr>
<tr>
<td>13 Weeks KOW</td>
<td>NOAEL: not determined i.e. &lt;10</td>
<td>10</td>
<td>10527/69x</td>
<td>6740/44x</td>
</tr>
<tr>
<td>12/942992 Rat Crl:CD (SD) BR n=4/sex</td>
<td></td>
<td>30</td>
<td>57829/374x</td>
<td>50924/333x</td>
</tr>
<tr>
<td>50</td>
<td>15163/1014x</td>
<td>118297/773x</td>
<td>81252/1477x</td>
<td>65032/1182x</td>
</tr>
<tr>
<td>92 Weeks: F</td>
<td>1</td>
<td>NC</td>
<td>NC</td>
<td>3741/681x</td>
</tr>
<tr>
<td>104 Week: M</td>
<td>1</td>
<td>NC</td>
<td>NC</td>
<td>235/4x</td>
</tr>
<tr>
<td>KOW 13/971903 Crl:CD BR rats n=5/sex</td>
<td>25</td>
<td>NC</td>
<td>NC</td>
<td>3741/681x</td>
</tr>
<tr>
<td>13 Weeks AG25001 Dog (Beagle) n=4-5/sex</td>
<td>1</td>
<td>NC</td>
<td>NC</td>
<td>239/4x</td>
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<td>3</td>
<td>NC</td>
<td>NC</td>
<td>1346/24x</td>
<td>1058/19x</td>
</tr>
<tr>
<td>10</td>
<td>NC</td>
<td>NC</td>
<td>7637/139x</td>
<td>4931/90t times</td>
</tr>
<tr>
<td>52 Weeks AG25004 Dog (Beagle) n=4-6/sex</td>
<td>0.3</td>
<td>384/2x</td>
<td>288/2x</td>
<td>107/2x</td>
</tr>
<tr>
<td>1</td>
<td>1360/9x</td>
<td>1363/9x</td>
<td>382/7x</td>
<td>325/6x</td>
</tr>
<tr>
<td>3</td>
<td>7750/51x</td>
<td>5340/35x</td>
<td>2890/53x</td>
<td>1830/33x</td>
</tr>
<tr>
<td>4 Week RFG2514 Monkey (Cynomolgus) n=2/sex</td>
<td>NOAEL: not determined i.e.&lt;3</td>
<td>3</td>
<td>552/4x</td>
<td>476/3x</td>
</tr>
<tr>
<td>8</td>
<td>1588/10 times</td>
<td>4016/26x</td>
<td>373/7x</td>
<td>248/5x</td>
</tr>
<tr>
<td>15</td>
<td>4434/29x</td>
<td>78828*, 4071*</td>
<td>755/14x</td>
<td>37693*, 302*</td>
</tr>
<tr>
<td>26 Week RFG2515 vehicle: Monkey (Cynomolgus) n=4-6/sex</td>
<td>3</td>
<td>0.5</td>
<td>89/0.6x</td>
<td>51/0.3x</td>
</tr>
<tr>
<td>1</td>
<td>492/3x</td>
<td>382/2x</td>
<td>35/0.6x</td>
<td>43/0.8x</td>
</tr>
<tr>
<td>3</td>
<td>704/5x</td>
<td>459/3x</td>
<td>110/2x</td>
<td>66/1x</td>
</tr>
<tr>
<td>6</td>
<td>1468/10 times</td>
<td>1320/9x</td>
<td>240/4x</td>
<td>217/4x</td>
</tr>
</tbody>
</table>

NC: Not calculated; (*) Where there is a marked difference between the values of the two individual animals, both values are provided; (**) Toxicokinetics not determined at dose level of 1 mg/kg
Table 5. Kinetic parameters for maximum clinical dose of *pitavastatin administered to humans

<table>
<thead>
<tr>
<th>Study details</th>
<th>Subjects</th>
<th>Dose (mg/kg)</th>
<th>AUC_{0-24} (ng·h/mL)</th>
<th>C_{max} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKH/NKN98389N/NK-104.1.01</td>
<td>healthy male Caucasian subjects n = 6</td>
<td>0.08(^*) i.e. 4 mg tablet</td>
<td>153</td>
<td>55</td>
</tr>
</tbody>
</table>

\(^*\) tablet; \(#\): based on recommended maximum clinical dose of 4 mg/day in a 50 kg patient.

Toxicology

General toxicity

Pitavastatin inhibits HMG-CoA reductase in mouse, rat, guinea pig rabbit, dog and cynomolgus monkey and has been shown to lower blood cholesterol after repeated dosing in all species except the rat\(^6\). Therefore these test species were appropriately used in a variety of safety evaluation studies.

Acute toxicity

Pitavastatin showed a moderate level of acute toxicity. The maximum non lethal dose ranged from 200 to 500 mg/kg in rats and 500 to 1000 mg/kg in mice and was associated with necropsy findings in the gastrointestinal tract. Deaths occurred in one dog at 100 mg/kg and another at 1000 mg/kg; hepatic congestion and haemorrhage of the small and large intestine were observed at necropsy, indicating the liver and gastrointestinal tract as target organs. No adverse effects were observed at the maximum dose tested (50 mg/kg) in a limited acute toxicity study in monkeys (n=1/sex).

Repeat-dose toxicity

Studies were conducted of up to 13 weeks duration in mice, 6 months in rats, 12 months in dogs and 6 months in cynomolgus monkeys. All involved oral administration, with the exception of 2 week IV studies in rats and dogs. The duration of pivotal studies, species used (rats, dogs, cynomolgus monkeys), group sizes and the use of both sexes were consistent with relevant TGA adopted European Union (EU) guidelines. The monkey was selected as a species to further investigate the cataract effect on the eye lens seen in the dog.

The toxicology findings for pitavastatin were consistent with those of HMG CoA reductase inhibitors as a class\(^7\) and included forestomach thickening in rodents; kidney toxicity (particularly in rabbits); liver toxicity; thyroid gland effects; gallbladder effects; myopathy in rodents; cataracts in rats and dogs; and testicular degeneration in dogs. However, other known class effects on the gall bladder, lymphatic system, CNS and testes were not noted for pitavastatin. The major targets for pitavastatin toxicity were: forestomach in rats and mice; kidney in monkeys and rabbits; eyes (cataracts), lung and liver in dogs; liver, thyroid and muscle in rodents. Exposure margins at the No Observable Adverse Effect Levels

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\(^6\) Published data from other studies in rats ([Singer et al., 1984 and Endo et al., 1979] both cited by [MacDonald and Halleck, 2004]) indicate that there is a marked induction of HMG-CoA reductase activity in rat liver with repeated dosing of statins, offering an explanation of their lack of effect on circulating cholesterol in this species with repeated dosing.

(NOAELs) in the pivotal animal toxicology studies corresponded to 7.6 times (rat 6 month\textsuperscript{8}) 2 times (dog 12 month\textsuperscript{9}), and 3 times (monkey 6 month\textsuperscript{10}) the anticipated exposure (based on AUC) at the maximum recommended human dose.

**Thyroid**

Increased thyroid weights with follicular cell hypertrophy were seen following dosing of rats for 13 weeks at ≥30 mg/kg/day (relative exposure: AUC, 333) but not at 10 mg/kg (NOEL, relative exposure, 44). Pitavastatin also induced thyroid tumours in the carcinogenicity study in rats.

Mechanistic studies showed that pitavastatin increased thyroid weights, decreased thyroxine (T\textsubscript{4}) and increased thyroid stimulating hormone (TSH) concentrations in rats; these effects correlated with an increase in UDP-GT activity in liver microsomes. The histological changes in the thyroid result from decreased T\textsubscript{4}, which elicits increases in TSH which drive a continual stimulation of the thyroid resulting in hypertrophy and eventual hyperplasia and tumour formation. Similar events have been described for simvastatin\textsuperscript{11} and have been shown to be a rat specific phenomenon that is not clinically relevant.

**Gastrointestinal effects – Forestomach**

Effects of forestomach thickening with hyperkeratosis and hyperplasia were noted in both repeated dose toxicity and lifetime carcinogenicity studies of pitavastatin, leading to neoplastic lesions in the latter. These effects were seen at an exposure ratio of 3 in mice (13 week study) and 8 in rats (6 month study) with an exposure to the NOEL of 0.9 in the rat study. Mechanistic studies showed alleviation of forestomach effects in rodents by co-administration of mevalonate, suggesting a class effect that is a consequence of pharmacological activity (HMG-CoA reductase inhibition). Similar results have been observed in rats with other statins given orally but not after subcutaneous dosing, indicating that the effects are a local effect in the forestomach\textsuperscript{12,13}. There is no human equivalent of the rodent forestomach and therefore these lesions are unlikely to be of relevance to the clinical use of pitavastatin in humans.

**Hepatic toxicity**

The severe hepatotoxicity reported for some other statins (necrosis, cellular atypia, and cholestasis) was not observed with pitavastatin. Reversible increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were observed in rats only at very high doses (relative exposure, AUC, 773) over a 1 month dosing period. These effects were not seen in rats receiving 10 mg/kg/day for 6 months (NOEL at a relative exposure of 44 with respect to AUC). Reversible increases in transaminases were also seen in dogs at 3 mg/kg/day (relative exposure 35) or higher for 3 or 12 months with a 12 month NOEL of 1 mg/kg/day (relative exposure 9). Enzyme increases were generally without histological correlates, except in the 3 month dog study where the 10 mg/kg/day dose level caused centrilobular dilatation of liver sinusoids, resolving over the recovery period. There was also increased centrilobular hepatocyte hypertrophy in a 13 week study in male mice at ≥75 mg/kg or females at 225 mg/kg, as well as with lifetime treatment in the mouse carcinogenicity study, in males receiving 12, 30 or 75 mg/kg/day. Pitavastatin did not induce drug metabolising enzymes in mice. The mouse carcinogenicity study

\textsuperscript{8} 1 mg/kg, AUC of 1170 ng·h/mL from Fujino et al., 1999a;
\textsuperscript{9} 0.3 mg/kg, AUC: 288 ng·h/mL;
\textsuperscript{10} 3 mg/kg, AUC: 459 ng·h/mL
\textsuperscript{11} Smith PF et al. (1991) Studies on the mechanism of simvastatin-induced thyroid hypertrophy and follicular cell adenoma in the rat. Toxicol. Pathol. 19(3), 197-205.
established a NOEL for liver hypertrophy of 1 mg/kg/day (the exposure ratio at the NOEL was not determinable as no TK data was provided; however, in mice, at 12 mg/kg, relative exposure [with respect to C<sub>max</sub>], was 8).

Hepatic adverse effects described for other statins have been shown to be alleviated by co administration of mevalonic acid<sup>13</sup>. This was also shown for pitavastatin in dogs. Overall, the qualitatively mild changes in the liver are unlikely to pose a risk to patients during clinical use: the adverse liver effects observed in mice, rats and dogs are a consequence of HMG-CoA reductase inhibition and are seen only at high relative exposure levels.

**Renal toxicity**

Renal toxicity consisting of necrosis and regeneration of renal tubules and increased kidney weights was observed in monkeys in a 1 month study (at 3 mg/kg; relative exposure 3) as well as in a 6 month study (≥0.5 mg/kg/day; relative exposure 0.3). There was also some very slight swelling of the proximal tubular epithelium at 6 mg/kg/day (relative exposure, 9; not seen in the recovery group).

Given that renal toxicity was not encountered at the highest doses tested in pivotal studies in both mice (13 week study, 225 mg/kg/day; relative exposure 147) and rats (3 and 6 month studies, 50 and 10 mg/kg/day, respectively; relative exposure 1014 and 69, respectively), and that there were minimal findings for dogs (minor kidney weight changes), the renal toxicity would appear to be a species specific effect. In monkeys, both urinary and faecal excretion of unchanged pitavastatin is very much lower than in humans. Pitavastatin is metabolised to a greater extent in the monkey than in humans; approximately twice as much pitavastatin is metabolized in monkey liver microsomes as in human microsomes (Study R99007).

Overall, the mild gross and microscopic pathological findings seen in the kidney in monkeys did not appear to impact or alter kidney function. The findings were reversible and there were no changes in the tissues of distal tubule, glomerulus, interstitium and renal pelvis, with no particular changes in the relevant laboratory parameters. On balance, it can be concluded that renal toxicity was specific to the monkey and thus its clinical relevance is considered to be low.

**Skeletal muscle**

In toxicology studies there were no effects on skeletal muscle in mice (13 week study; the relative exposure was 147 based on AUC), rats (26 week study, the relative was exposure 44 based on AUC), and dogs (12 month study; relative exposure was 35 based on AUC). Increased incidences of skeletal muscle myofibre atrophy observed in the mouse and rat carcinogenicity studies were attributed to a combined effect of pitavastatin and ageing. In the carcinogenicity studies, muscle atrophy was seen in mice (from 12 mg/kg in males and 1 mg/kg in females; relative exposure based on C<sub>max</sub> was 15 for males at 12 mg/kg; no TK data for females at 1 mg/kg) and rats (at 25 mg/kg/day in males; relative exposure based on C<sub>max</sub> was 681).

The well known skeletal muscle effects of statins have been described previously <sup>14</sup> and are known to have clinical correlates particularly in the case of cerivastatin where rhabdomyolysis led to its withdrawal. Detailed investigations to assess tissue levels of relevant molecules such as ubiquinone were not included in the pitavastatin studies. Such investigations may have complemented the nonclinical data package but are not considered critical since there is reasonable evidence (based on reversal by mevalonate) for the involvement (either directly or indirectly) of a pharmacological mechanism in the

myotoxic effect of other HMG-CoA reductase inhibitors. In vitro, IC$_{50}$ values for inhibition of cholesterol synthesis in human skeletal muscle cell lines (Study R101130; Tokyo Research labs., Kowa, Japan) were 3.4 nM for pitavastatin and 0.3 nM for cerivastatin, with values for simvastatin, atorvastatin and fluvastatin similar to pitavastatin (4.1 to 4.8 nM) and pravastatin having a weaker action (IC$_{50}$: 164 nM).

Overall, the weight of evidence suggests that the potential for myotoxicity with pitavastatin is probably lower than that with cerivastatin and possibly similar to that with currently registered HMG-CoA reductase inhibitors such as simvastatin, atorvastatin and fluvastatin. While skeletal muscle findings for pravastatin in toxicology studies were restricted to relatively high exposure margins, rare cases of rhabdomyolysis characterise the statins as a class and therefore appropriate pharmacovigilance should also apply to this drug.

**Lens**

The dog is particularly sensitive to statin effects on the eye; pitavastatin was shown to accumulate in the lens with slow clearance. Consequently, opacities and cataracts were seen in dogs in the repeat dose studies: 13 week study at 3 mg/kg (relative exposure [C$_{max}$]: 19) and 10 mg/kg (relative exposure [C$_{max}$]: 90), and in the 12 month study at 1 mg/kg (relative exposure: 9) and 3 mg/kg (relative exposure: 35). The NOEL established in the 12 month study was 0.3 mg/kg/day (relative exposure: 2). No cataracts were observed in rats (3 and 6 month studies, 50 and 10 mg/kg/day, respectively; relative exposure: 1014 and 69, respectively) or monkeys (1 and 6 month studies, 15 and 6 mg/kg/day, respectively; relative exposure: 29 and 10, respectively). In mice, ocular opacities were seen at 13 weeks at ≥75 mg/kg (relative exposure: 16) but were not seen following lifetime exposure at the same dose in the 92 week carcinogenicity study (NOEL 30 mg/kg, relative exposure [C$_{max}$]: 30). Binding studies of pitavastatin using lens protein of various species (including humans) showed that the dog lens had a higher level of binding than other species with ratios of drug concentration in lens:plasma (PEYE [IN VITRO]) values of 0.59 in dogs, 0.54 in mice, 0.18 in monkeys 0.17 in rats, 0.06 in rabbits; human value of 0.05-0.17. The lens concentration in humans at the 4 mg clinical dose was estimated to be 7 ng/g, considerably below the concentration range of 123 to 616 ng/g measured in dogs.

Overall, lens findings in the dog have been previously reported as a statin class effect without any human clinical correlation$^{14}$ and it is therefore considered unlikely that humans are at risk of developing cataracts.

**Lung**

Lipid pneumonia like pulmonary lesions (composed of foam and inflammatory cells) were seen in the 3 and 12 month oral dose dog studies at 3 mg/kg (relative exposure: 35) with a NOEL of 1 mg/kg/day (12 month study, relative exposure: 9). Co-administration of mevalonate for 3 months suppressed these findings, demonstrating they were related to the pharmacological activity of pitavastatin (inhibition of HMG-CoA reductase). As foam cells were not observed in organs other than the lungs in dogs and there were no lung findings in rats and monkeys, it is unlikely that the lung findings are clinically relevant. Clinical adverse events in the respiratory system with pitavastatin are similar in incidence to other statins (sponsor’s Clinical Overview).

**Genotoxicity**

The potential genotoxicity of pitavastatin was investigated in an appropriately conducted standard battery of tests. A clastogenic effect was observed in Chinese hamster lung (CHL) cells *in vitro*, but only at high concentrations inducing significant cytotoxicity (50%).
Pitavastatin was negative in the Ames test in vitro as well as in several in vivo tests (UDS test in rats, micronucleus tests in mice and rats, Comet assay in mice) where adequate exposure was demonstrated.

Overall, the weight of evidence suggests that pitavastatin does not pose a particular genotoxic risk in clinical use.

**Carcinogenicity**

The carcinogenic potential of pitavastatin by the oral route was investigated in long term studies in mice and rats. Group sizes and dose levels were appropriate as recommended in the TGA adopted EU guideline for Carcinogenic Potential\(^\text{15}\).

Target organs identified in the nonclinical species were the forestomach (papillomas and carcinomas) in mice and rats, and the thyroid (adenocarcinomas) in rats, as previously seen with other statins (McDonald and Halleck, 2004).\(^\text{7}\)

The development of papillomas and carcinomas in the forestomach can be considered a natural progression of the histopathological changes in the forestomach seen in the repeated dose toxicity studies (see discussion above under heading Gastrointestinal effects: forestomach). Preneoplastic lesions of benign squamous cell papillomas occurred in mice at 75 mg/kg/day (relative exposure \([C_{\text{max}}]\): 178) and in rats at 25 mg/kg (relative exposure range, \([C_{\text{max}}]\): 564–681). Forestomach (squamous cell) carcinomas occurred in male rats at 25 mg/kg (relative exposure \([C_{\text{max}}]\): 681). These lesions occurred in an organ not present in humans and are not deemed to be of clinical relevance.

An increase in thyroid follicular cell adenocarcinomas was observed in male rats treated with pitavastatin for 2 years but only at doses causing exposures much higher than the maximum clinical dose (at 25 mg/kg/day; relative exposure \([C_{\text{max}}]\): 681). There was also an increased incidence of thyroid preneoplastic lesions in females, evident at 25 mg/kg/day (relative exposure \([C_{\text{max}}]\): 564). A mechanistic study in rats using a tumour promoter (DHPN) and pitavastatin, with and without T4 supplementation, suggested that pitavastatin increased the clearance and reduced the circulating levels of T4 (as previously discussed under the heading Thyroid), resulting in the production of thyroid tumours in rats. This occurs by way of a feedback increase in TSH levels and consequent long term stimulation of the thyroid tissue, leading to hypertrophy, hyperplasia and neoplasia.

Pitavastatin also was not carcinogenic in a 26 week study using CB6F1-Tg rasH2 transgenic mice. In an additional short term study, it did not induce tumourgenesis nor did it promote tumourigenicity of urethane or influence lung tumour growth in Tg-RasH2 mice. Pitavastatin lactone is not present in rodent plasma. However, rat liver microsomes produce significant amounts of pitavastatin lactone. Therefore, this metabolite has been considered to have been tested in the 92 week rat study.

The relative exposure at the NOEL for tumourigenicity was 564 in rats (based on \(C_{\text{max}}\)) and 178 (based on \(C_{\text{max}}\)) in mice in lifetime studies, and was 104 (based on AUC) in Tg-rasH2 mice after 26 weeks.

Overall, given the large exposure margins to the NOEL and the species specific nature of the observed tumours, pitavastatin is not considered to pose a carcinogenic risk to humans.

\(^{15}\) Note for guidance on carcinogenic potential. 3BS7a CPMP/SWP/2877/00.
Reproductive toxicity

Studies submitted by the sponsor covered all stages (fertility, early embryonic development, embryofetal and pre, peri and postnatal development). Numbers of animals and the timing and duration of treatment were appropriate.

Table 6. Relative exposure

<table>
<thead>
<tr>
<th>Study</th>
<th>Species &amp; strain</th>
<th>Day of sampling: treatment period</th>
<th>Dose (mg/kg/day)</th>
<th>AUC0–24h ng·h/mL</th>
<th>**Exposure ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF9932</td>
<td>Rat (Crj:CD [SD])</td>
<td>Dosing from GD7 to GD17 (last day of dosing; 11 Days)</td>
<td>1</td>
<td>1250</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>3330</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>12620</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>(during periods of fetal organogenesis and late pregnancy)</td>
<td>Dosing GD17 to GD21 (last day of dosing; 5 Days)</td>
<td>1</td>
<td>610</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>4100</td>
<td>27</td>
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<td></td>
<td>10</td>
<td>16690</td>
<td>109</td>
</tr>
<tr>
<td>G2526</td>
<td>Rabbit (Kbl:JW);</td>
<td>GD6 (Day 1 of dosing)</td>
<td>0.1</td>
<td>552</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>n=7-12</td>
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<td>0.3</td>
<td>1544</td>
<td>10</td>
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<td>1</td>
<td>5197</td>
<td>34</td>
</tr>
<tr>
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<td>GD18 (Day 13 of dosing)</td>
<td>0.1</td>
<td>607</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
<td>2045</td>
<td>13</td>
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<td></td>
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<td>1</td>
<td>22538</td>
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(*): Calculated as animal: human AUC0–24h; (#): AUC comparison with the maximum clinical dose of 4 mg in healthy male Caucasian subjects (153 ng.h/mL, clinical study PKH/NKN98389N/NK-104.1.01); Dosing route: PO.

Plasma exposure in pregnant animals was comparable to that observed in non pregnant animals, with high multiples of the proposed clinical systemic exposure obtained. Placental transfer of pitavastatin was demonstrated in rats and found in a number of foetal tissues at ≤36% of maternal plasma levels following a single dose of 1 mg/kg during gestation. Lactating rats were found to readily excrete pitavastatin in milk (milk: plasma ratio of 1.1, 2.9, 7.2, 3.3 at 1, 3, 6, 24 h postdose, respectively). The 5-ketone metabolite was also detected at low levels (36 ng/g at 6 h).

Male and female fertility were unaffected in rats treated with 10 and 30 mg/kg/day, respectively (NOEL relative exposure: 69 and 333, respectively). While testicular changes (decreased testicular weight, disrupted spermatocyte maturation, atrophy/degeneration of seminiferous tubules) have been previously observed with many statins in dogs, both histological and sperm assessments in the pitavastatin repeat dose studies in dogs (up to 12 months) failed to reveal such changes.

There was decreased food consumption, decreased body weight gain and mortality in treated male and female rabbits at ≥1 mg/kg/day during a fertility study (relative exposure: 28). However, there were no effects of pitavastatin on reproductive function in
males and females or on foetal pathology under conditions of significantly lowered plasma TC concentrations. From this study the NOAEL of pitavastatin was estimated to be 0.5 mg/kg/day for general toxicity to male and female parent animals and 2 mg/kg/day for reproductive functions of parent animals and for early embryonic development.

There were no adverse findings at 3 mg/kg/day (NOEL relative exposure: 22) in embryofetal developmental studies in pregnant rats dosed with 3, 10, 30 mg/kg/day pitavastatin during organogenesis. Maternal body weight gain and food consumption were reduced at 30 mg/kg (NOAEL, maternal toxicity 10 mg/kg/day: relative exposure, 109).

No toxicological effects on dams were observed following treatment of pregnant rabbits during organogenesis with pitavastatin at 0.1 mg/kg/day. In the 0.3 and 1 mg/kg/day groups, decreased faeces, abortions and deaths of some dams were observed, with drug induced changes also observed in the liver, kidney, and gallbladder at 0.3 mg/kg/day and above. However, no external, significant visceral or skeletal foetal anomalies were observed in any treatment group. Thus, the NOAEL for general toxicity and reproduction in dams was 0.1 mg/kg/day (relative exposure: 4) and the NOAEL for foetuses was 1 mg/kg/day (relative exposure: 34).

Pregnant rats given pitavastatin at 0.1 to 30 mg/kg/day from organogenesis through to weaning showed maternal toxicity consisting of mortality at ≥1 mg/kg/day, suppression of body weight and decreased food intake at 30 mg/kg/day and impaired lactation at all doses which contributed to a decrease in live newborn, an increase in stillborn and a decrease in viability index on Day 4 after birth in the F1 generation. There was no effect of treatment on behaviour, reproduction performance or development of the F2 generation. A follow up peri postnatal study (RFG2512) established a NOAEL for general toxicity and reproduction in dams and in the F1 generation of 0.3 mg/kg/day pitavastatin (likely exposure ratio of approximately 1 based on extrapolation).

Overall, embryo-foetal development studies with pitavastatin showed no treatment related teratogenicity and the peri/postnatal studies in rats showed higher rates of maternal deaths with increased viability of offspring. Similar findings have been reported for fluvastatin where maternal deaths have been reported which can be overcome by co-administration of mevalonic acid. Similar results with mevalonic acid supplementation were observed for pitavastatin. The effects on dams and consequential effects on offspring are thus likely to be caused by inhibition of HMG-CoA reductase (as for other statins;). It is reasonable to expect that administration of pitavastatin during pregnancy in humans could result in adverse effects on the developing fetus as a result of reduced fetal formation of cholesterol and other essential sterols derived from HMG-CoA reductase substrates. Pitavastatin, like other statins, is appropriately contraindicated during pregnancy, lactation and in women of childbearing potential who are not using effective contraception.

Metabolites

The primary metabolite of pitavastatin in humans is pitavastatin lactone. It is also the primary metabolite in dogs and monkeys but a minor metabolite in rats, rabbits, and undetectable in mice. The lactone is inactive. Studies were carried out with the lactone metabolite and no new toxicological results (in dogs) were found compared with pitavastatin. The lactone was not genotoxic in either the bacterial gene mutation or chromosome aberration studies.

References

Small amounts of the 8-hydroxy derivative, which is an active metabolite, were also detected in various assays such as in metabolism studies of \(^{14}\text{C}\)-pitavastatin in liver microsomes of rat, dog, rabbit, guinea pig, monkey and human\(^\text{17}\). The metabolite 8-Hydroxy pitavastatin was detected in liver microsomes from all species except the dog. The levels of 8-hydroxy pitavastatin formed varied across the species (monkey>>man> rat>guinea pig> rabbit>dog). A 2 week mechanistic study was performed in rats to see if the 8-hydroxy metabolite could induce renal toxicity similar to that noted in the 4 and 26 week monkey repeat dose studies. Treatment with 200 mg/kg twice a day (bd) for 2 weeks and 400 mg/kg bd for 1 week caused moribundity and mortality such that no treated animals survived the scheduled administration period. In the moribund animals, degeneration of proximal renal tubules was observed microscopically and an increase in blood urea nitrogen values was detected in both the 200 and 400 mg/kg bd dose groups. In addition, an increase in creatinine concentrations was also detected in the 400 mg/kg bd dose group. These biochemical changes were evident in the animals showing histopathological changes of the proximal renal tubules. The renal effects were considered to be attributable to the test article. However, since the severity of the effects was slight it was considered that secondary changes due to dystrophy indicated by clinical findings could not be ruled out.

**Impurities**

Single dose and 4 week repeated dose oral toxicity studies were conducted in rats on the known stereoisomers [3-epimer, 5-epimer and the (-) enantiomer] and they showed a lower toxicity in comparison to the parent compound. The known 5-ketone process impurity (it is a metabolite [M-3] and also a degradant) was evaluated in a single dose oral toxicity study in mice, where the toxicity was comparable to that of pitavastatin. The epimers and enantiomer of pitavastatin produced equivocal/positive findings in a chromosomal aberration assay in Chinese hamster lung cells but bacterial reverse mutation assays and mouse micronucleus tests were negative. Overall, the weight of evidence suggested that these impurities were not of genotoxic concern and that the toxicology data submitted were sufficient to qualify the proposed limits of stereoisomers in the final drug product.

**Antigenicity**

Pitavastatin did not show any antigenic potential: no anaphylactic symptoms were observed following antigenicity testing with pitavastatin in guinea pigs.

**Dependence**

CNS activity was largely unaffected. No dependency studies were conducted.

**Phototoxicity**

Pitavastatin absorbs light in the 290 to 700 nm range with a minor peak at 328 nm (and major peak at 245 nm). No specific study to investigate the potential phototoxicity of pitavastatin was conducted. The tissue distribution studies in pigmented and non pigmented rats did not indicate any particular affinity of radioactivity for skin or eyes, in either pigmented or non pigmented animals. The likelihood that pitavastatin will provoke phototoxic reactions is small.

Pregnancy classification

The pregnancy categorisation (D)\(^{18}\) is consistent with other statins as a class.

Use in children

No studies have been conducted in juvenile animals. Pitavastatin should not be used in children aged below 18 years as safety and efficacy have not been established.

Nonclinical summary

- An extensive set of nonclinical data were submitted for pitavastatin. Studies were of adequate design and conduct. Pivotal toxicity, toxicokinetics and safety studies were conducted according to the relevant TGA adopted EU guidelines and GLP.

- Extensive pharmacological studies confirmed that pitavastatin inhibits HMG-CoA reductase and the synthesis of cholesterol. \textit{In vitro} findings were corroborated by \textit{in vivo} measures of effects on lipids and extended to models of atherosclerosis.

- Safety pharmacology studies covered the CNS, cardiovascular, respiratory, renal and gastrointestinal systems. Increases in heart rate were observed in dogs at high doses (≥94-times the clinical \(C_{\text{max}}\)). Pitavastatin lactone had mild inhibitory effects on the hERG K\(^+\) channel and slightly increased action potential duration (APD) in guinea pig papillary muscle but only at more than 1000 times the estimated clinical free plasma concentration of lactone. ECG abnormalities were not observed in pitavastatin-treated animals; Livalo treatment is considered to represent a minimal torsadogenic risk.

- Pharmacokinetic studies indicated rapid absorption of pitavastatin in all species (mice, rats, guinea-pigs, rabbits, dogs, monkeys and humans). The plasma half-life of pitavastatin was generally shorter in the laboratory animal species (typically ≤4-8 h) compared to humans (≈9 h at the maximum clinical dose). Plasma AUC was generally dose proportional in all species examined. PO administration of radiolabelled pitavastatin to rats and monkeys resulted in highest levels in the liver, with significant levels in heart, skeletal muscle, lung and kidney. Penetration of the blood brain barrier was low. Plasma protein binding was high (not less than 96\%) in humans and laboratory animal species. Placental transfer of pitavastatin and excretion into milk was shown in rats.

- Like rosuvastatin and pravastatin, pitavastatin undergoes little metabolism and its elimination mainly depends upon transporter mediated excretion from the liver into the bile, with subsequent enterohepatic recirculation or faecal excretion. The extensive enterohepatic circulation demonstrated in rat and dog underlies pitavastatin’s liver specific distribution and extended duration of action. Faecal excretion dominated after oral dosing in rats, guinea pigs, dogs, monkeys, as it does in humans (78.6\% of the dose; 15.1\% in urine). The main metabolic pathways of pitavastatin include cyclisation into lactone and \(\beta\)-oxidation of the side-chain, hydroxylation of the ring and conjugation with glucuronic acid or taurine. The low metabolic clearance of pitavastatin involves CYP2C9 and CYP2C8 but unchanged pitavastatin was the dominant circulating species.

- Pitavastatin had no effects on warfarin activity and pharmacokinetic drug interaction studies showed there are unlikely to be interactions as a result of displacement of other compounds from their protein binding sites or through effects on CYP

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\(^{18}\) Category D: “Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.”
Isoenzymes. Pitavastatin is actively taken up into liver through OATP1B1: competition for, or inhibition of, this transporter by other drugs (such as cyclosporin A) may lead to interactions with pitavastatin.

- Pivotal repeat dose toxicity studies were conducted with pitavastatin in rats (26 weeks), dogs (52 weeks) and monkeys (26 weeks). Adequate relative exposure was observed at the NOAELs. Target organs were the forestomach (thickening) in rats and mice; the kidney (necrosis, tubule regeneration or pale kidneys) in monkeys and rabbits; eyes (cataracts), lung (lipid lesions) and liver (increase in transaminases) in dogs; and liver (elevated transaminases in rats; centrilobular hepatocyte hypertrophy in mice), thyroid (follicular cell hypertrophy) and muscle (degeneration) in rodents. All of these findings (except for the lung lesions in dogs) are well known class effects of statins that generally occur at high relative exposure margins: many of these effects are reversed by co treatment with mevalonic acid and/or are species specific (see discussions above).

- Pitavastatin was negative in genotoxicity assays for bacterial mutagenicity, deoxyribonucleic acid (DNA) strand breakage or damage, and \textit{in vitro} and \textit{in vivo} clastogenicity. A clastogenic effect was seen in CHL cells in the \textit{in vitro} chromosome aberration test but only at high concentrations inducing significant cytotoxicity. The weight of evidence suggests that pitavastatin does not pose a genotoxic risk.

- Long term studies (92 weeks to 2 years) in rodents and a short term (6 month study) in transgenic CB6F1-Tg rash2 mice revealed no carcinogenic effects, except for rat specific thyroid tumours in males and pre neoplastic thyroid lesions in females. These tumours (also seen with other statins) are not clinically relevant as they are known to be related to a species specific liver enzyme induction and ‘rat specific’ increased metabolism and clearance of thyroid T4. Rodent-specific papillomas and carcinomas in the forestomach (not an organ in humans) were considered a natural progression over time of the pre neoplastic changes in the forestomach seen in the repeat dose toxicity studies.

- Pitavastatin had no effect on male and female fertility in rats and rabbits and did not elicit testicular changes in dogs (usually seen with most other statins). Embryofetal development studies in rats and rabbits showed no treatment related teratogenic effects of pitavastatin even at overtly maternotoxic doses: fetal NOAELs corresponded to relative exposure margins of approximately 20-30.

- Peri/post natal studies in rats showed high rates of maternal mortality, impaired lactation and decreased viability of offspring. The maternal and F1 generation NOAEL of 0.3 mg/kg corresponds to an exposure similar to that anticipated in humans at the maximum clinical dose. Similar findings were previously observed with fluvastatin and can be overcome with co-administration of mevalonic acid. Pitavastatin, like other statins, is contraindicated during pregnancy.

- Additional studies (toxicity or genotoxicity studies) were performed to qualify metabolites (lactone, 8-OH metabolite), impurities and related substances (epimers or enantiomer); some additional studies explored mechanisms underlying the various identified target organ toxicities.

### Conclusions and recommendations

- Pitavastatin, as a HMG-CoA reductase inhibitor, belongs to a well established class of drugs. It has a similar mode of action and safety profile to other statins currently marketed in Australia. The Australian nonclinical data submission was extensive and the studies supported the proposed indication and the relevant statements in the proposed Product Information (PI).
- The in vitro and in vivo primary pharmacology data were consistent with pitavastatin being a potent inhibitor of HMG-CoA reductase. Oral administration in dogs and guinea-pigs produced favourable changes in plasma cholesterol and triglycerides. Moreover, pitavastatin lowered atherogenic lipoproteins (LDL and VLDL) in animal in vivo models.

- High doses of pitavastatin caused cataracts in dogs, thyroid lesions in rats, elevated liver transaminases in dogs and rats, renal toxicity in rabbits (and monkeys) and forestomach thickening with hyperkeratosis and hyperplasia in rats and mice. These effects have all been either addressed adequately by clinical data, are known species specific effects or, by analogy with other statins, are not thought to be clinically relevant.

- Relative to other statins, there was a very high exposure margin at the NOEL for the mild liver changes and skeletal muscle degeneration, suggesting a low potential for these adverse effects.

- There are no indications from the nonclinical data to suggest any particular genotoxic or carcinogenic risk with pitavastatin.

- There are no nonclinical objections to the registration of pitavastatin calcium (Livalo) as monotherapy for the proposed indications.

IV. Clinical findings

Introduction

The development program for Livalo was commenced in Japan in 1992 and a few years later in the EU and the US (1998). It consisted of 77 studies (40 healthy volunteer and 37 patient studies) of which 26 healthy volunteer and 18 patient studies were conducted for the EU and USA registration.

Twenty five studies examined the pharmacokinetics of pitavastatin. These studies examined 698 healthy subjects (149 female), 6 male subjects with fatty liver, 6 male subjects with hepatic impairment and 21 subjects (7 female) with renal impairment. No studies examined the pharmacokinetics of pitavastatin in the target population. Three in vivo studies (NK-104-1.25US, NK104-1.34US and NK104-1.23US) examined the pharmacodynamics (PD) of pitavastatin in 234 healthy subjects (109 females). No studies examined the PD of pitavastatin in the target patient population.

With respect to efficacy, the clinical development program included 5 dose ranging studies (NK-104.2.02, NK-104.2.03, NK-109-209, NKS104A2204, NK-104-210). These were 12 to 16 weeks duration and assessed doses from 1 to 64 mg against placebo and atorvastatin. There were two pivotal Phase III studies NK-104-301 and NK-104-302 in primary hypercholesterolaemia and mixed dyslipidaemia which were non inferiority studies against atorvastatin 10 and 20 mg and simvastatin 20 and 40 mg, respectively. In addition, there were 3 specific population studies: in the elderly (NK-104-306), in those with additional cardiovascular risk factors (NK-104-304), and in Type 2 diabetics (NK-104-305). There were 4 open label extension studies NK-104-307, 308, 309, 310 of 44 to 60 weeks duration which enrolled patients from the Phase III studies. There were also 2 extension periods of the 2 Phase II studies (NK-104-211 and NKS104A2204E1). An integrated efficacy analysis was also conducted using data from the Phase II and III studies.

There was also a clinical development program conducted for Asian registration which included studies in Japan, Korea and China. Synopses of these studies were included in the
current Australian submission. The full, translated study report for a small study in heterozygous familial hypercholesterolaemia was provided as well as an interim report from a large postmarketing surveillance study in Japan.

Pharmacokinetics

Introduction

Different formulations of pitavastatin were used during its development and the formulation marketed in Japan is different to the "European" formulation that is the subject of this application. The European formulation, a 2 mg tablet, contains 2.09 mg pitavastatin calcium, equivalent to 2.00 mg pitavastatin, whereas the Japanese 2 mg tablet contains 2 mg pitavastatin calcium, equivalent to 1.9090 mg of pitavastatin.

Methods

Analytical methods

The levels of pitavastatin and its lactone metabolite were determined using validated methodology. The earlier assay used was based on high pressure liquid chromatography (HPLC) with ultraviolet (UV) detection; this was superseded by a liquid chromatography with mass spectrometry (LC/MS/MS) method.

Pharmacokinetic data analysis

The pharmacokinetic parameters determined in the pharmacokinetic (PK) studies included the area under the plasma concentration time curve from time zero to the last quantifiable concentration (AUC0-t), area under the plasma concentration time curve from time zero to infinity (AUC0-inf), maximal plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), half life (t1/2), apparent volume of distribution (Vd/F), Vd/Fm (fraction of drug metabolised), oral clearance (CL/F), bioavailability (F), renal clearance of the drug from plasma (CLr) cumulative amount of unchanged drug excreted into the urine (Ae(ur)) and cumulative amount of unchanged drug excreted into the urine from time 0 to the last time point (Ae(ur, 0-last)). In most cases analyses were performed using SAS, Release 8.2 (SAS Institute, Cary, North Carolina) according to the Study Analysis Plan (SAP). Non compartmental PK parameters were calculated using WinNonlin, Version 4.1 (Pharsight Corporation). Analysis of variance (ANOVA) was performed using sequence, subject within sequence, period, and treatment as factors. Natural log transformed Cmax and AUC were the dependent variables.

Statistical analysis

All statistical summaries and analyses were performed using SAS® Version 8.2 or higher (STATISTICAL ANALYSIS SYSTEM, SAS-Institute, Cary NC, USA) and WinNonlin® Professional version 4.0.1 or a later version (Pharsight Corporation, USA).

Absorption

An open label, single centre study (SNY419/01392682) examined the absorption, distribution and excretion of a single oral dose of 32 mg 14C-pitavastatin in 6 healthy male subjects, aged 40 to 65 years. Blood, urine and faecal samples were collected predose and up to 168 hours postdose. The mean oral apparent plasma clearance, CL/F, was 183 mL/minute and the apparent volume of distribution, Vz/F, was 226 L, which was high compared to total body water (approx 42 L), suggesting that tissue binding was greater than plasma protein binding. The main radioactive components identified in plasma up to
24 hours postdose were unchanged pitavastatin (H9), pitavastatin lactone as well as two unidentified minor metabolites, which accounted for more than 5% of the radioactivity.

**Bioavailability**

A single centre, open label, single dose, randomised two way crossover study [NK-104IV.1.02.EU] assessed the single dose pharmacokinetics of 2 mg pitavastatin following IV administration compared to oral administration of 2 mg pitavastatin in 21 fasted Caucasian males, aged 21 to 55 years. There was a wash out period of 7 days between dosing. Plasma and urine samples were taken predose and up to 48 hours post dosing for the determination of the PK parameters of pitavastatin (NK-104) and its major metabolite NK-104 lactone. In plasma, the T_max for NK-104 PO and IV formulations were 0.68 and 0.99 hours, respectively, C_max was 21.4 and 60.9 ng/mL (approximately 3 fold difference), respectively, AUC_{inf} was 47.4 and 86.9 ng.h/mL (approximately 2 fold difference), respectively, clearance (CL/F) was 838 and 410 mL/min, respectively, and t_{1/2} was 5.2 and 4.6 hours, respectively. The variability of PK data at these time points was low in the IV treatment period (CV%: 16%) but moderate after oral dosing (CV%: 54%). In terms of AUC_{0-inf}, the oral bioavailability (F) of NK-104 was 51% (geometric mean). In urine, the NK-104 concentrations were highest in samples taken during the 0 to 12 hour collection interval for both treatment periods. The mean NK-104 Ae_{ur,0-last} for the PO and IV formulations were 6299 and 16051 ng, respectively. Mean renal clearance was low amounting to less than 1% of the calculated plasma clearance following either formulation.

An unbalanced (with respect to sequence) open label, randomised, five treatment five period crossover study. Study NKS104A2115 assessed the relative bioavailability of an 8 mg dose of NKS-104 when released at targeted regions of the jejunum, ileum and ascending colon compared to oral administration in 6 healthy subjects (1 female), aged 18-65 years. There was a wash out period of at least 5 days between treatments, which were administered under fasted conditions. Plasma samples were collected up to 48 hours postdose for the determination of the PKs of NKS-104 and NKS-104 lactone. The mean C_{max} of NKS-104 was 116, 160, 118, 59, 7 ng/ml following oral drug administration and drug administration at the proximal jejunum, distal jejunum, distal ileum and ascending colon, respectively. For mean AUC_{0-t} the values were 286, 279, 294, 170 and 16 ng.h/mL, respectively.

For NKS-104, the relative bioavailability estimated as the geometric mean ratios of AUC_{0-t} to the immediate release (IR) tablet were 0.89 (90% CI 0.37, 2.16) when the Enterion tablet was administered directly to the proximal jejunum (first metre of the small bowel), 0.92 (90% CI 0.38, 2.23) when the Enterion tablet was administered directly to the distal jejunum/proximal ileum (third to fourth metre of the small bowel), 0.28 (90% CI 0.11, 0.71) when the Enterion tablet was administered directly to terminal ileum (last metre of the small bowel) and 0.03 (90% CI 0.01, 0.08) when the Enterion tablet was administered directly to ascending colon. The width of the confidence intervals (CI) shows the high variability of the individual ratios. These results indicate that the drug should be formulated in such a way that it is released in the first 4 metres of the small intestine.

**Bioequivalence**

The European Phase III studies were conducted with a product manufactured by SkyePharma, France, whereas, the formulation that is the subject of this application is made by Pierre Fabre, France. The two formulations are identical except that the SkyePharma tablets are plain round white biconvex film coated tablets, whereas, the Pierre Fabre tablets are embossed on one side with ‘KC’ and ‘1’, ‘2’ or ‘4’ on the reverse containing pitavastatin calcium equivalent to 1 mg, 2 mg or 4 mg pitavastatin, respectively.

A randomised, open label, balanced, two way crossover, two period, single oral dose administration study (NK-104-1.36) compared the pharmacokinetics of pitavastatin after
single doses of 2 tablet formulations (manufactured by Pierre Fabre and the SkyePharma, respectively) conducted in 32 healthy subjects (8 females), aged 18 to 41 years. Subjects received a single dose of pitavastatin 4 mg (SkyePharma or Pierre Fabre product) following an overnight fast, with a wash out period of at least 7 days between dosing. Blood samples for the determination of the PKs of pitavastatin and its lactone metabolite were taken predose and up to 48 hours postdose. The Cmax for the SkyePharma and Pierre Fabre formulations were 66.0 and 61.4 ng/mL, respectively, whereas, the AUC0-inf was 159.7 and 158.1 ng.h/mL, respectively. The 90% confidence intervals for Cmax and AUC were within the accepted range of 80 to 125%, therefore the SkyePharma and Pierre Fabre manufactured tablets are bioequivalent.

The impact of the different manufacturing sites on tablet dissolution was investigated in Study NK-104-1.38. This report reviewed and compared the in vivo results of two studies (NK-104-1.35 and NK-104-1.36) and the in vitro pharmaceutical data, including the dissolution profiles of the batches utilised in these studies.

The f2 values for the 2 mg and 4 mg batches were greater than 50% (52 and 55.2% respectively), indicating dissolution within ±10% and similarity between the two dissolution profiles. The comparable dissolution profiles were reflected in the bioequivalence of the two 2 mg tablets and of the two 4 mg tablets in human subjects.

### Influence of food

A randomised, open label, cross over study (NK-104-1.21US) compared the pharmacokinetics of a single oral 4 mg dose of NK-104 under fed versus fasted conditions in 34 healthy males, aged 18 to 45 years. In the first period, one group of 17 subjects received NK-104 within 30 minutes of ingesting a high-fat meal\(^\text{19}\) and the other group of 17 subjects received NK-104 after a 10 hour fast. There was a 7 day wash out prior to the cross over treatment period. Blood samples for pharmacokinetic analyses were collected predose and up to 72 hours post dose. The Cmax, AUC0-inf and T1/2 were 33.3 ng/mL, 112.8 ng.hr/mL and 7.1 hours, respectively in the fed group and 58.4 ng/mL, 145.5 ng.hr/mL and 8.4 hours, respectively, in the fasted group. The mean NK-104 Cmax fed to fasted ratio (90% confidence interval) was 57 (51-64%), indicating that a high fat meal reduced the peak concentration of NK-104 by 43%. The median Tmax increased from 1 to 2 hours under fasted compared to fed conditions. No significant decrease in average bioavailability was observed when NK-104 was administered with food; the 90% confidence intervals for AUC0-t, AUC0-72, and AUC0-inf were 83-95, 83-95 and 83-96%, respectively, all within the 80-125% no significant effect limits.

### Distribution

The sponsor refers to a published study\(^\text{20}\) regarding the in vitro protein binding of pitavastatin and summarises the result as follows:

Pitavastatin is highly bound to plasma protein with an unbound fraction (fp) of 0.4 to 0.5% in human plasma. Among isolated human plasma proteins, the major pitavastatin binding protein is human serum albumin (concentration 4%) with an unbound fraction of 0.4% to 0.5%. Pitavastatin binding to α1-AGP (α1-acid glycoprotein, concentration 0.06%) is also strong (fp 5.1 to 5.7%). The fp was similar in both animal and human samples.

\(^{19}\)The high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800-1000 calories) meal derived approximately 150, 250, and 500-600 calories from protein, carbohydrates, and fat, respectively in accordance with FDA guidance.

Protein binding was also evaluated in Study NK-104-1.24, which examined the PK of pitavastatin in subjects requiring haemodialysis, with moderate renal impairment and healthy subjects. In this study, subjects with moderate renal impairment displayed a similar pitavastatin protein binding percentage to that of the healthy subjects, whereas, subjects requiring haemodialysis had a greater free fraction of pitavastatin (mean 0.55%) compared to that of subjects with moderate renal impairment subjects (mean 0.41%) or healthy subjects (0.41%).

Elimination

Excretion

Study SNY419/013926 examined the excretion of a single oral dose of 32 mg \(^{14}\)C-pitavastatin in urine and faecal samples. Radioactivity was primarily excreted in the faeces and accounted for 78.6% of the dose, with 89% of the total faecal radioactivity being recovered by 96 hours. By contrast, only 15.1% of the radioactivity was recovered in the urine. Excretion of radioactivity in urine was initially rapid with 80% of the total radioactivity recovered by 24 hours postdose, increasing to 97% by 72 hours. In the faeces, unchanged pitavastatin accounted for 58.2% of radioactivity and four metabolites represented less than 15%. Three of these metabolites corresponded to the lactone, 8-hydroxy and arylidihydriodiol metabolites. Five major radioactive components were identified in urine (H4, H6, H8, H9, and H13) which accounted for 91% of total urinary radioactivity. These components were identified as unchanged pitavastatin (3% of administered dose), pitavastatin lactone, glucuronic acid conjugate of pitavastatin, 8-hydroxy pitavastatin and arylidihydriodiol pitavastatin. Several minor metabolites were also present in urine, none of which accounted for more than 5% of sample radioactivity (<1% of the dose).

Metabolism

The \textit{in vitro} metabolism of pitavastatin was examined using \(^{14}\)C-pitavastatin in human and animal liver microsomes by Fujino \textit{et al}\textsuperscript{21}. Metabolism of \(^{14}\)C-pitavastatin by human liver microsomes was minimal and following 2 hours of incubation at 37°C the composition of functional radioactivity in human microsomes consisted mainly of parent compound with the ratio of unchanged pitavastatin as 78.8%. The ratio of minor metabolite 8-hydroxy pitavastatin (M-13) was 16.3%, levels of other metabolites, dehydrogenated pitavastatin and propenoic acid derivative were low or not detected. The apparent Km (Michaelis constant) value of 8-hydroxy pitavastatin was 45 \(\mu\)mol/L and the maximum rate (Vmax) was 77 pmol/min/mg protein with a metabolic clearance (Vmax/Km) of 18 \(\mu\)L/min/mg protein. In addition, the pitavastatin metabolic patterns were unchanged in the human S-9 fraction compared to microsomes. Hydroxylation is generally a major biotransformation pathway for statins including fluvastatin, simvastatin, cerivastatin and atorvastatin. However, in human microsomal metabolism, the Vmax/Km of hydroxylation was 100 times, 50 times, 8 times and 30 times higher forlovastatin, simvastatin, atorvastatin and fluvastatin, respectively, compared with that of pitavastatin suggesting that compared to other statins, pitavastatin undergoes little hydroxylation.

Study ATR-148-100 examined the uptake of \(^{14}\)C-pitavastatin into \textit{Xenopus laevis} transgenic oocytes that express human liver specific sodium (Na\(^+\)) independent organic anion transporter, OATP1B1 (also known as LST-1, OATP-C or OATP2). Uptake of pitavastatin by the transgenic oocytes was saturable with a Km value of 5.53 \(\mu\)mol/L. In addition, the uptake of \(^{14}\)C-pitavastatin into human hepatocytes was evaluated and, as in the oocytes, pitavastatin uptake was saturable with a Km of 2.99 \(\mu\)mol/L. The Km value of radioactive

hydrogen labelled [3H]-oestradiol-17 β-D-glucuronide, a specific substrate of OATP1B1, was 23.72 μmol/L in this system suggesting that pitavastatin uptake into human liver is possibly mediated by OATP1B1.

Hirano et al.\(^{22}\) examined the involvement of the transporters OATP1B1 and OATP1B3 in pitavastatin uptake in the liver using stably transfected HEK293 cells expressing human OATP1B1 and OATP1B3 and in human hepatocytes. Uptake in the OATP1B1 and OATP1B3 expressing cells was saturable with Km values of 3.0 and 3.3 μmol/L for OATP1B1 and OATP1B3, respectively. In human hepatocytes, the observed uptake clearance for pitavastatin was almost completely accounted for by OATP1B1 and OATP1B3 and about 90% of the total hepatic clearance was accounted for by OATP1B1.

Study AE-2544 examined the human cytochrome P450 enzyme (CYP) isoforms involved in the metabolism of pitavastatin and lactone in microsomes from lymphoblastoid cell lines expressing a range of human CYPs (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP 2C9-Arg, CYP2C9-Cys, CYP2C19, CYP2D6-Val, CYP2D6-Met, CYP2E1 and CYP3A4). The results suggested that pitavastatin and lactone were only slightly metabolised by the human CYP isoforms examined. The inhibitory effect of pitavastatin on the enzyme activity of various CYPs was also investigated. These studies identified that pitavastatin, at concentrations of either 500 nmol/L or 2.5 mol/L, had no effect on the metabolic activity of human CYP isoforms except for CYP2C8, which was slightly inhibited.

Study R101029 investigated the mechanism of lactonisation, the major metabolic reaction of pitavastatin using human small intestinal, renal or liver microsomes. UDP-glucuronosyl transferase (UGT)-mediated lactone formation was observed in human small intestinal and renal microsomes as well as in hepatic microsomes. The lactonisation reaction in both human hepatic and renal microsomes had a Vmax/Km value 1.4 times higher than that of a CYP mediated reaction. The UGT molecular species involved in the lactonisation reaction were identified as UGT1A3 and UGT2B7; however, other UGT molecular species were also shown to be involved in the reaction at higher pitavastatin concentrations.

**Pharmacokinetics of metabolites**

Study NK-104IV.1.02.EU examined the pharmacokinetics of NK-104 lactone (the primary and inactive metabolite) of NK-104 following single 2 mg doses of IV and PO pitavastatin. In plasma, the Cmax (19.0 and 21.2 ng/mL) and AUCt-inf (168.7 and 172.5 ng.h/mL) of NK-104 lactone were similar following oral and IV dosing, respectively. The lactone metabolite was eliminated from plasma with a terminal t1/2 of approximately 12 hours for both formulations. In urine, the Ae(ur, 0-last) was 25.4 and 40.8 μg/mL for the PO and IV forms, respectively. The renal clearance of the parent compound and the metabolite only played a minor role, with a fraction of CLR relative to plasma clearance of less than 2% on average.

Study NKS104A2115 assessed the relative bioavailability of an 8 mg dose of NKS104 (pitavastatin calcium) when released at targeted regions of the jejunum, ileum and ascending colon compared to oral administration in 6 healthy subjects. Following oral drug administration and administration at the proximal jejunum, distal jejunum, distal ileum and ascending colon the mean Cmax of NK-104 lactone was 83, 79, 61, 28, 6 ng/mL, respectively. For mean AUC0-t the values were 820, 693, 581, 310 and 77 ng.h/mL, respectively.

Study NK-104-1.21US compared the pharmacokinetics of NK-104 lactone following a single oral 4 mg dose of NK-104 under fed versus fasted conditions. Similar to its effect on the PK of NK-104, food reduced the Cmax and AUC0-inf for the lactone metabolite from 43.8 to 33.0 ng/mL and 496.2 to 414.8 ng.h/mL. The mean Cmax fed-to-fasted ratio (90% confidence interval) was 75.3 (70-81%) for NK-104 lactone. The median Tmax increased

\(^{22}\) Masaru Hirano, Kazuya Maeda, Yoshihisa Shitara, and Yuichi Sugiyama Contribution of OATP2 (OATP1B1) and OATP8 (OATP1B3) to the Hepatic Uptake of Pitavastatin in Humans, *JPET* 311:139–146, 2004
from 2 hour to 4 hours under fasted and fed conditions, respectively. The drop in $\text{AUC}_{0\text{-inf}}$ was not significant as the 90% confidence interval was 80-87% and therefore within the 80-125% no significant effect limits.

Study NK-104-1.36 compared the pharmacokinetics of pitavastatin after single 4 mg doses of 2 tablet formulations manufactured by two different manufacturing sites. The mean $C_{\text{max}}$ of the lactone metabolite from SkyePharma and Pierre Fabre were similar (37.5 and 37.3 ng/mL, respectively) as was the $\text{AUC}_{0\text{-inf}}$ (388.6 and 395.7, respectively).

Single and multiple dose and food effects
Study PKH/NKN98389N/NK-104.1.01 examined the pharmacokinetics of pitavastatin lactone following single and repeated oral doses of 1, 2, 4, 8, 16 and 24 mg. The $C_{\text{max}}$ of the NK-104 lactone significantly increased with food at doses greater than 1 mg and following repeated dosing at doses of 2, 4 and 16 mg. The $\text{AUC}_{0\text{-24}}$ of the lactone metabolite also increased with food at doses of 8 and 24 mg and at doses $\geq$2 mg following repeated dosing. For instance, the $\text{AUC}_{0\text{-24}}$ of the lactone metabolite following repeat dosing of 4 mg increased from 194 to 282 ng.h/mL ($P = 0.015$) compared to a single dose. Urinary excretion of the lactone metabolite was low (<2.6% of administered dose) and independent of the dose and administration conditions.

Study HPC/NKN00435N/NK-104.1.19 examined the pharmacokinetics of NK-104 lactone following single and repeated oral administration of NK-104 (24 mg to 64 mg). For the lactone metabolite, $C_{\text{max}}$ and $\text{AUC}_{0\text{-24}}$ were lower and the $T_{\text{max}}$ prolonged when pitavastatin was administered under fed conditions compared to fasted, suggesting that delayed absorption of the parent drug influenced the rate of metabolite formation. By contrast, there was no significant difference for $C_{\text{max}}$/dose, $T_{\text{max}}$ and $\text{AUC}$/dose following repeat administration. The dose normalised $C_{\text{max}}$, $\text{AUC}_{0\text{-24}}$ and $\text{AUC}_{0\text{-}\infty}$ were significantly higher after the 32 mg dose than for all other doses. High values were also observed after the 48 mg dose for $\text{AUC}_{0\text{-}\infty}$ at Day 1 and $\text{AUC}_{0\text{-24}}$ at Day 21. Urinary excretion of lactone was low (<3%) under each administration condition and steady state was achieved at Day 10 (after 2 days of repeat dosing).

Age, gender and race
Study NK-104-1.22US examined the effects of age, gender and race (Black/Caucasian) on the PK of pitavastatin lactone. The geometric mean $\text{AUC}_{0\text{-inf}}$ was higher in elderly than in non elderly subjects (660.79 and 470.53 ng.hr/mL, respectively), whereas for $C_{\text{max}}$ the geometric mean was similar in both groups (44.65 and 41.69 ng/mL, respectively), as were the elimination $t_{1/2}$ (15.94 and 13.80 hours, respectively). In male and female subjects the geometric mean $\text{AUC}_{0\text{-inf}}$ was higher in female subjects than in male subjects (625 versus 455 ng.hr/mL, respectively), as was the $C_{\text{max}}$ (49.15 and 37.19 ng/mL, respectively). By contrast, the $t_{1/2}$ was similar in female and male subjects (15.3 hours and 13.9 hours, respectively). In Black and Caucasian subjects the geometric mean $\text{AUC}_{0\text{-inf}}$ for NK-104 lactone was higher in Caucasians (582 and 459 ng.hr/mL), whereas the $C_{\text{max}}$ was (45 ng/mL and 39 ng/mL, respectively) and the $t_{1/2}$ (14.82 versus 14.11 hours, respectively) were similar.

Race
Study NK-104-1.35 examined the pharmacokinetics of NK-104 lactone following the administration of 2 tablet formulations of pitavastatin in 30 European and Japanese men. In these studies, the pitavastatin lactone, median $T_{\text{max}}$ was 1.5 hours (range: 1–3 hours) and lactone concentrations were detected up to 48 h following dosing. In addition, the $t_{1/2}$ of pitavastatin lactone was prolonged compared to that of pitavastatin with a median $t_{1/2}$ of about 8 to 10 hours compared to 4 to 6 hours, respectively. As seen in the studies which examined the parent compound, the two formulations of pitavastatin were bioequivalent.
in the European subjects in regard to lactone metabolite pharmacokinetics and there were no racial differences identified for the lactone PKs between the Japanese and European men.

**Hepatic impairment**

Study NK-104-HK compared the PK of NK-104 lactone following a single oral 2 mg dose of NK-104 in subjects with Child-Pugh\(^\text{23}\) Grade A or B impaired hepatic function and subjects with normal hepatic function. The C\(_{\text{max}}\) and AUC of NK-104 lactone were 0.90 and 0.84 fold lower in Child-Pugh Grade A subjects and 0.48 and 0.67 times lower in Child-Pugh Grade B subjects, respectively, compared to healthy subjects. By contrast, the T\(_{\text{max}}\) of the lactone metabolite was similar in all three groups.

**Dose proportionality**

A double blind, randomised, placebo controlled, ascending dose, parallel group study (PKH/NKN98389N/NK-104.1.01) examined the pharmacokinetics of pitavastatin following single and repeated oral doses in 48 healthy male Caucasians, aged 18 to 22 years. Doses of 1 mg, 2 mg, 4 mg, 8 mg, 16 mg and 24 mg of NK-104 were assessed successively with each dose examined in 8 subjects, 6 on active drug and 2 on placebo. Study drug was taken on Day 1 in the fasted state and daily from Day 8 to Day 21 following a standard breakfast\(^\text{24}\). Plasma and urine samples for the determination of the PKs of NK-104 and its lactone metabolite were taken predose and up to 72 hours postdose on Days 1 to 4 and Days 21 to 24. In addition, samples were taken on Days 8 to 10 predose and up to 48 hours postdose and on Day 12 up to 20 hours.

Overall the pharmacokinetics of pitavastatin were similar following single oral doses taken fasted on Day 1 and with a concomitant intake of food on Day 8. In general, although pitavastatin absorption was slightly delayed following a meal (longer T\(_{\text{max}}\) lower C\(_{\text{max}}\) for pitavastatin), the extent of absorption for all dose levels other than 1 mg was not altered (no change in AUC for pitavastatin). In addition, other than the AUC\(_{0-24}\) for the 4, 16 and 24 mg doses, the pharmacokinetics of pitavastatin following repeated dosing for 14 days with a standard breakfast (steady state on Day 21) were similar to PKs following a single dose (Day 8). For the 4 mg dose AUC\(_{0-24}\) increased from 102 to 153 ng.h/mL (P = 0.001) from Days 8 to 21, for the 16 mg dose it increased from 396 to 508 ng.h/mL (P <0.001) and for the 24 mg dose it increased from 567 to 732 ng.h/mL (P = 0.002). Comparison of the Day 9 to Day 21 time zero results (predose) indicated that steady state was reached at Day 14 (after 6 days of multiple dosing). The absorption rate of parent drug remained constant as the T\(_{\text{max}}\) of both parent drug and metabolite did not vary with increasing dose. The C\(_{\text{max}}\) and AUC of pitavastatin increased linearly with the dose and the linear relationship was confirmed by the constancy of normalised values of the parameters (C\(_{\text{max}}\)/dose) and (AUC/dose) versus dose. On average, there was more than a doubling of pitavastatin AUC for a doubling of dose over the range from 1 to 8 mg (increase in AUC of 2.5 to 2.8 times with a doubling of dose).

A double blind, placebo controlled, ascending doses (24, 32, 48 and 64 mg), parallel group, single and repeated oral dose study (HPC/NKN00435N/NK-104.1.19) examined the pharmacokinetics of single and repeated oral administration of NK-104 (24 mg to 64 mg) in 32 healthy male Caucasians, aged 19 to 40 years. At each dose level 6 subjects were administered active drug and 2 were given placebo, only 24 subjects were included in the PK analysis. Blood and urine samples were taken on Day 1 (predose and up to 72 hours postdose).

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\(^{23}\) The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

\(^{24}\) Standard breakfast consisted of: 300 ml milk with chocolate, 5 pieces of toast, 10g butter, 30 g marmalade, 1 sugar.
following dosing), on Day 8 (predose and up to 24 hours postdose) and on Day 21 (predose and up to 96 hours postdose). Under fed conditions the C\text{max} after a single dose of 24, 32, 48 and 64 mg pitavastatin was 178, 414, 515 and 734 ng/mL, respectively, and the AUC\text{0-24} was 535, 1184, 1441 and 2030 ng.h/mL, respectively.

The T\text{max} increased and C\text{max}/dose decreased significantly for pitavastatin following single doses under fed (Day 8) compared to fasted (Day 1) conditions whereas food had no effect on AUC. For example the C\text{max}/dose for a 24 mg dose was 304 and 178 ng/mL under fasted and fed conditions respectively. By contrast, repeated dosing did not affect the C\text{max}/D, T\text{max} or AUC/D of pitavastatin. Steady state was achieved at Day 12 (after 4 days of repeat dosing) for pitavastatin. For pitavastatin, C\text{max} and AUC increased linearly with dose from 24 to 64 mg. The absorption rate of NK-104 was reproducible irrespective of the dose since T\text{max} of the parent drug did not vary with increasing doses. As in the preceding study, urinary excretion of pitavastatin was low (<3%) under each administration condition and the percentage of excretion was not affected by either the dose or repeated administration.

Study NK-104-1.34US examined the pharmacokinetics of pitavastatin at steady state at two dose levels (therapeutic [4 mg] and supratherapeutic [16 mg]) in 174 healthy subjects. Blood samples for the pharmacokinetic analysis of pitavastatin were obtained up to 24 hours following dosing on Day 4. Total and peak exposures of pitavastatin and pitavastatin lactone increased proportionally with increasing dose for the pitavastatin 4 mg and 16 mg groups. For instance, pitavastatin AUC\text{0-t} increased approximately 4 times (from 205 to 840 ng.h/mL) in the 16 mg dose group compared to the 4 mg dose group. The median T\text{max} for pitavastatin was 0.580 hours for both the 4 mg and 16 mg groups. The t\text{1/2} was also similar in the 2 treatment groups, approximately 22.5 hours and 17.5 hours for the pitavastatin 4 mg and 16 mg groups, respectively.

**Time dependency**

Jones and Schoeller\textsuperscript{25} first identified that the production of cholesterol occurs predominately in the early morning (AM) and therefore the majority of statins (fluvastatin, pravastatin, simvastatin) currently available recommend administering the medication at night (PM) due to their short half-lives\textsuperscript{26}.

A multiple dose, randomised, open label, two sequence, two way, two period crossover study (NK-104-1.23US) compared the PK following 14 days AM and PM treatment with 4 mg pitavastatin. Thirty-six subjects (15 female), aged 21 to 43, were randomly assigned to treatment sequence AB or sequence BA, 27 subjects completed the study. Blood samples for PK assessment were taken predose on Days 12 and 13 of Period 1 and on Days 54 and 55 of Period 2 and on Days 14 and 56 predose and up to 24 hours following dosing. There was a 28 day washout between dosing periods. The pharmacokinetic parameters for pitavastatin were similar for both dosing regimens and the ratio (90% CI) of the geometric means for AUC\text{0-24} and C\text{max} were 0.89 (0.83-0.95) and 0.94 (0.82-1.08), respectively, which were both within the 0.8 to 1.25 limits, indicating that the time of dosing did not affect the PK of pitavastatin.

**Intra- and inter-individual variability**

Following IV and oral dosing in Study NK-104IV.1.02.EU the coefficients of variation were 16% and 54%, respectively.


**Pharmacokinetics in target population**

No studies specifically targeted this group.

**Special populations**

**Children**

No studies specifically targeted this group.

**Elderly**

An open label, parallel study (NK-104-1.22US) examined the effect of age, gender and race (the results of which will be discussed separately) on the PK of NK-104 in 48 healthy subjects, aged 19 to 80 years. Subjects were enrolled in the following 4 treatment cohorts: 12 elderly male subjects ≥65 years of age, 12 elderly female subjects ≥65 years of age, 12 non elderly male subjects 18-45 years of age and 12 non elderly female subjects 18-45 years of age. Each cohort was to include 6 Caucasian and 6 Black or African American subjects to prevent an imbalance in race. A single dose of NK-104 was administered on Day 1 after a 10 hour fast. Blood samples for pharmacokinetic analyses were collected predose and up to 72 hours postdose.

The C\textsubscript{max} of NK-104 was higher in the elderly compared to the non elderly subjects (77 ng/mL verses 65 ng/mL, respectively), as was the median T\textsubscript{max} (1.00 and 0.50 hours, respectively), t\textsubscript{1/2} (12.6 and 10.3 hours, respectively) and AUC\textsubscript{0-inf} (196 and 152 ng.h/mL, respectively), whereas clearance (CL/F) was lower (20.4 and 26.4 L/hr, respectively).

Statistical analysis comparing the C\textsubscript{max} and AUC of the two groups indicated that elderly subjects have higher systemic exposure by about 10% in C\textsubscript{max} and 30% in AUC.

**Gender**

Study NK-104-1.22US also examined the effect of gender on the PK of pitavastatin. The C\textsubscript{max}, t\textsubscript{1/2} and AUC were all higher in females compared to male subjects whereas the median T\textsubscript{max} was higher in males than females (1.0 and 0.5 hours, respectively). Statistical analysis comparing the C\textsubscript{max} and AUC of the genders indicates that female subjects have higher systemic exposure by about 60% with respect to C\textsubscript{max} and by 54% with respect to AUC.

**Weight**

No studies specifically examined the effect of weight.

**Race**

Study NK-104-1.22US also examined the effect of race (Black/Caucasian) on the PK of pitavastatin. Although the C\textsubscript{max} was lower in Black subjects compared to Caucasians (58 and 76 ng/mL, respectively), the AUC\textsubscript{0-inf} was similar between the two groups (159 and 172 ng.h/mL).

An open, randomised, two way, balanced crossover study (NK-104-1.35) examined the pharmacokinetics of 2 tablet formulations of pitavastatin in 30 European and Japanese men, aged 18 to 45 years. Each subject took a single 2 mg dose of pitavastatin JP (marketed Japanese formulation, Livalo®) and a single dose of pitavastatin EU (European Clinical Investigation formulation). Subjects were randomised to the treatment sequences, blood samples were taken predose, up to 48 hours following dosing and there was a wash out of at least 7 days between doses. The PK of the Japanese and European pitavastatin formulations were similar in the European and also in the Japanese subjects. In the European subjects the C\textsubscript{max} was 24.6 and 23.9 ng/mL for the EU and JP formulations respectively, median T\textsubscript{max} was 1.0 hour for both formulations and AUC\textsubscript{0-inf} was 55.6 and 59.3 ng.h/mL, respectively. Pitavastatin concentrations for both formulations declined
rapidly and by 6 to 24 hours following dosing were below the limit of quantification. In the Japanese subjects, the C\text{max} for the EU and JP formulations were 26.1 and 26.0 ng/mL respectively, median T\text{max} was 0.5 and 1.0 hours, respectively and AUC\text{0-inf} was 71.5 and 69.5 ng.h/mL, respectively. The primary bioequivalence analysis in European subjects indicated that the pitavastatin C\text{max}, AUC\text{0-t} and AUC\text{0-inf} for the EU and JP formulations were bioequivalent. The secondary analysis compared the combined PKs of both formulations of pitavastatin between the European and Japanese subjects and also compared the pitavastatin PK of the EU formulation in Europeans to the PK of JP formulation in the Japanese subjects. Both analyses indicated that neither race nor formulation affected the PKs of pitavastatin.

**Hepatic impairment**

The pharmacokinetics of pitavastatin in subjects with hepatic impairment were investigated in two studies in Asian subjects and have not been repeated in a European population.

Study NK-104-106 was an open label, parallel fixed dose study (2 mg NK-104) which compared the pharmacokinetics in 6 male Japanese subjects with impaired hepatic function and 6 Japanese subjects with normal hepatic function, aged 22 to 30 years. Impaired hepatic function was defined as raised transaminases due to fatty liver (ALT concentrations 57-225 IU/L approximately 1.25 to 5 times the upper limit of normal [ULN]). Blood and urine samples were taken on Days 1 and 7 predose and up to 12 hours following administration. Mean AUC\text{0-24} of the unchanged compound on Day 7 was slightly lower in subjects with impaired hepatic function (98.1 ng.hr/mL) compared to subjects with normal hepatic function (119.8 ng.hr/mL). The difference in logarithmically transformed mean AUC\text{0-24} between the two groups was 0.84 and the 90% confidence interval ranged from 0.59 to 1.20. Mean C\text{max} of the unchanged compound on Day 7 was 40.63 ng/mL in the subjects with impaired hepatic compared to 47.67 ng/mL in the normal subjects. The difference in logarithmically transformed mean C\text{max} between the groups was 0.88 and the 90% confidence interval ranged from 0.54 to log 1.41. Large between group differences were not observed in mean AUC\text{0-24} or mean C\text{max} for the lactone metabolite. The investigators noted that the body weight of the subjects in the fatty liver group was greater than the control group (91 versus 66 kg, respectively), therefore the results were adjusted for the differences in body weight. Between group difference of AUC\text{0-24} of the unchanged compound on Day 7 was 1.17 following adjustment for differences in the mean body weights between the subjects with impaired hepatic function and the normal subjects and the 90% confidence interval ranged from 0.81 to 1.69. The corresponding weight adjusted C\text{max} 1.20 and the 90% CI ranged from 0.79 to 1.83. No significant difference was found at any of the time points examined in urinary excretion rates between the impaired hepatic function group and the normal hepatic function group, with their total excretion rates in 24 hours on Day 1 being approximately 5%.

The second study examining hepatic impairment was a single site, open label, parallel group study (NK-104-HK) comparing the PK of NK-104, administered as a single oral 2 mg dose in subjects with Child-Pugh Grade A (6 males) or B (6 males) impaired hepatic function and 6 males with normal hepatic function who acted as age and weight matched controls. The subjects enrolled were aged 26 to 61 years and blood and urine samples for the determination of NK-104 PKs were taken predose and up to 72 hours following dosing. The mean C\text{max} in the Child-Pugh Grade A, Child-Pugh Grade B and normal subjects were 81, 163 and 60 ng/mL, respectively, and the AUC\text{0-t} values were 202, 495 and 126 ng.h/mL, respectively. The mean C\text{max} and AUC\text{0-t} of pitavastatin were 1.34 and 1.60 times greater in the Child-Pugh Grade A group and 2.69 and 3.93 fold greater in the Child-Pugh Grade B group, respectively, compared to healthy subjects. The mean apparent clearance (CL/F) of pitavastatin decreased in relation to the severity of the hepatic impairment from 15.2 to 4.7 L/h in the normal and Child-Pugh Grade B, respectively. By contrast, the
absorption rate of NK-104 remained constant as the $T_{\text{max}}$ was similar regardless of the level of impairment. These results suggest that there is an increase in pitavastatin $C_{\text{max}}$ and $\text{AUC}_{0-t}$ in relation to the severity of the hepatic impairment.

**Renal impairment**

An open label, parallel single dose study (NK-104-1.24) investigated the pharmacokinetics of 4 mg pitavastatin in 30 subjects (11 female) who had varying degrees of renal failure, aged 26 to 81 years. There were 10 subjects in each of the 3 groups which were: (A) chronic renal failure requiring haemodialysis; (B) moderate renal impairment (glomerular filtration rate (GFR) of 30 to <50 mL/min); and (C) healthy subjects age and sex matched to Groups A and B (GFR >80 mL/min). Plasma and urine samples for PK analysis were obtained predose and up to 48 hours post dosing.

The pitavastatin pharmacokinetic parameters $C_{\text{max}}$ (1.4 and 1.6 times in Groups A and B, respectively), $\text{AUC}_{0-t}$ (1.7 and 1.8 times, respectively), $\text{AUC}_{0-\text{inf}}$ (1.9 and 1.8 times, respectively) and $t_{1/2}$ were significantly higher and CL/F (0.5 and 0.6 times, respectively) was lower in both the haemodialysis group and the group with moderate renal impairment compared to the healthy subjects. The $V_d/F$ was lower in the haemodialysis group than the other two groups. There were no discernible differences between the subject groups for the other pharmacokinetic parameters.

**Evaluator’s overall comments on pharmacokinetics in special populations.**

- There were small but significant increases in the $C_{\text{max}}$ (1.1 fold) and AUC (1.3 fold) of NK-104 in elderly compared to non elderly subjects.
- Females had significantly higher $C_{\text{max}}$ (1.6-fold) and AUC (1.5-fold) values than males.
- When comparing Black and Caucasians subjects there was a small but significant decrease in $C_{\text{max}}$ (0.8-fold) but no difference in AUC between the two groups.
- There was no difference in the PK of NK-104 in Japanese and Caucasian subjects.
- Child-Pugh Grade A and B hepatic impairment increased the $\text{AUC}_{0-t}$ by 1.6 and 3.9 fold, respectively.
- Renal impairment affected the PK of NK-104 in a similar fashion in both subjects requiring haemodialysis and subjects with moderate renal impairment and $C_{\text{max}}$ and AUC were increased by up to 1.6 and 1.8 fold, respectively.

**Interactions**

**In vitro pharmacokinetic interactions**

The potential interactions between pitavastatin and several fibrate drugs (gemfibrozil, bezafibrate, clofibrate and ciprofibrate) were evaluated in vitro by examining plasma protein binding and metabolic inhibition in human liver microsomes.

The binding of pitavastatin to plasma proteins was not affected by gemfibrozil, bezafibrate, clofibrate and ciprofibrate, whereas the metabolic clearance of pitavastatin was decreased in a dose dependent manner by the four fibrates (Study R101113). The metabolic clearance of pitavastatin in the absence of fibrates ranged from 3.1 to 4.3 μL/min/mg protein. By contrast, the metabolic clearance of cerivastatin was 30.9 μL/min/mg protein and was completely inhibited by gemfibrozil. Metabolism of gemfibrozil by human hepatic microsomes was inhibited by fluvastatin but not by pitavastatin or cerivastatin. Gemfibrozil induced inhibition of CYP2C8 and CYP2C9, two iso enzymes not implicated in the metabolism of pitavastatin, had little to no effect on metabolism of pitavastatin.
The effects of pitavastatin on the metabolism of tolbutamide, a substrate for CYP2C9, were compared with those of fluvastatin in Study R99035. The formation of pitavastatin 8-hydroxide (M-13) was inhibited to a small extent by tolbutamide and pitavastatin did not inhibit the hydroxylation of tolbutamide over a wide concentration range (0.5 to 25 μmol/L). By contrast, fluvastatin, which is metabolised by CYP2C9, competitively inhibited the hydroxylation of tolbutamide in a concentration dependent manner with a Ki value of 1 μmol/L.

The inhibitory effect of atazanavir (0.05, 0.15, 0.5, 1.5, 5 μmol/L), enalaprilat (1, 3, 10, 30, 100 μmol/L) and nipradilol (1, 3, 10, 30, 100 μmol/L) on OATP1B1 mediated 14C-pitavastatin (3 μmol/L) uptake was examined in HEK293 cells expressing OATP1B (Study FBM 06-T350). 14C-Pitavastatin was absorbed into HEK293 cells expressing OATP1B1 and, in the presence of pitavastatin, uptake of radiolabelled drug was reduced. By contrast, enalaprilat and nipradilol did not affect OATP1B1-mediated uptake (IC50 values >100 μmol/L), whereas, atazanavir (IC50 value of 2.10 μmol/L) and rifampicin (IC50 values of 3.14 and 1.95 μmol/L) demonstrated an inhibitory effect.

The clinical significance of in vitro inhibition was evaluated by Hirano et al.27. The R values of the maximum unbound concentration of inhibitor at the inlet to the liver and the inhibition constant Ki for OATP1B1 indicate that several drugs (especially cyclosporin A, rifampicin, rifamycin SV, clarithromycin and indinavir) may potentially interact with OATP1B1 mediated uptake of pitavastatin.

Study ATR-149-035 examined the effect of cyclosporin A on the uptake of pitavastatin and pravastatin in Xenopus laevis oocytes that expressed human liver specific OATP1B1. Cyclosporin A (0.5 to 20 μmol/L) concentration dependently inhibited OATP1B1 mediated uptake of 14C-pitavastatin and 14C-pravastatin with IC50 values of 2.91 ± 0.78 μmol/L and 1.21 ± 0.16 μmol/L, respectively.

The binding of pitavastatin (final concentration 0.3 μg/mL) to plasma proteins was unaffected by warfarin (3 and 15 μg/mL), diazepam (15 and 75 μg/mL), digitoxin (0.1 and 0.5 μg/mL), phenylbutazone (100 and 500 μg/mL), phenytoin (20 and 100 μg/mL), furosemide (0.5 and 2.5 μg/mL), ibuprofen (50 and 250 μg/mL), nitrendipine (0.1 and 0.5 μg/mL) and glibenclamide (100 and 500 μg/mL). Pitavastatin (final concentrations 0.3 and 1 μg/mL) had no effect on the binding of 14C-warfarin (3 μg/mL), 14C-diazepam (15 μg/mL), 3H-digitoxin (0.1 μg/mL), 3H-propanolol (1.0 μg/mL), 14C-nitrendipine (0.1 μg/mL) and 3H-glibenclamide (100 μg/mL). Although the unbound fraction of 3H-digitoxin was slightly affected at high concentrations of pitavastatin (1 μg/mL), no significant interactions between digitoxin and pitavastatin were identified at therapeutic concentrations of pitavastatin (0.03 to 0.1 μg/mL).

In vivo pharmacokinetic interactions

The steady state pharmacokinetics of pitavastatin administered alone were compared to the steady state pharmacokinetics of pitavastatin when co administered with bezafibrate in an open label, randomised, sequential design study (477-01) in 34 healthy males, aged 18 to 45 years. The study treatments administered were:

- Treatment A1, 4 mg pitavastatin;
- Treatment A2, 4 mg pitavastatin + 400 mg bezafibrate;
- Treatment B1, 10 mg atorvastatin;

• Treatment B2: 1 x 10 mg atorvastatin + 400 mg bezafibrate;
• Treatment C1, 20 mg pravastatin;
• Treatment C2, 20 mg pravastatin + 400 mg bezafibrate.

All treatments were administered orally 30 minutes after breakfast for 6 consecutive days. Blood samples for pharmacokinetic analysis were taken predose on Days 5 and 6 and up to 48 hours postdose on Day 6. When administered alone the mean C\text{max} for pitavastatin was 38.5 ng/mL and AUC_{0-24} was 146 ng.h/mL. Following co administration with bezafibrate, the C\text{max} was unchanged but the AUC_{0-24} increased to 162 ng.h/mL. The mean clearance (CL/F) of pitavastatin decreased slightly with co administration of bezafibrate from 32200 to 29300 mL/h. Mean trough values on Days 5, 6 and 7 were 1.442, 1.453 and 1.458 ng/mL, respectively for Period 1 (mono-administration) and 1.769, 1.677 and 1.824 ng/mL for Period 2 (concomitant administration), therefore, attainment of steady state was not affected by co administration of bezafibrate. The C\text{max} of the lactone metabolite was 32.75 ng/mL when pitavastatin was administered alone and the AUC_{0-24} was 422 ng.h/mL. The values for both parameters were unaffected when bezafibrate was co administered.

Statistical analysis of the PK parameters suggests that co administration of bezafibrate had no affect on the PKs of pitavastatin or its lactone metabolite. By contrast, co administration of bezafibrate with either atorvastatin or pravastatin increased the C\text{max} of both statins.

A single centre, open label, one sequence, crossover study (NK-104-109) compared the steady state pharmacokinetics of pitavastatin with the steady state pharmacokinetics of pitavastatin after co administration of either fenofibrate or gemfibrozil over a treatment period of 7 days in 24 healthy subjects (3 females), aged 21 to 44 years. Pitavastatin 4 mg was administered orally for 6 days as monotherapy (Days 1 to 6) followed by co administration with either fenofibrate (12 subjects; 160 mg orally with food, once a day (qd)) or gemfibrozil (12 subjects; 600 mg orally before food, bd) for 7 days (Days 8 to 14). Blood samples for pharmacokinetic analysis were obtained predose and up to 48 hours following dosing on Days 6 and 14 and predose on Days 5 and 13. The C\text{max} of pitavastatin increased from 67.7 to 84.3 ng/mL and AUC_{0-24} increased from 152 to 198 ng.h/mL following co administration with fenofibrate. Although C\text{max} remained unchanged, the difference in AUC_{0-24} represented a significant increase of 18%. The C\text{max} of pitavastatin increased from 67.7 to 75 ng/mL and AUC_{0-24} increased from 152 to 193 ng.h/mL following co administration with gemfibrozil. These changes represent a significant increase in C\text{max} and AUC_{0-24} of 31% and 45%, respectively. Fenofibrate co administration had no significant affect on the C\text{max} or AUC of pitavastatin lactone. By contrast, gemfibrozil 600 mg bd co administration with pitavastatin 4 mg qd decreased the steady state C\text{max} and AUC_{0-24} of pitavastatin lactone by 28% and 15%, respectively.

An open label, fixed dose study (NK-104-20) compared the pharmacokinetics of pitavastatin following administration of pitavastatin alone with those following co administration with cyclosporin in 6 healthy males, aged 21 to 27 years. The subjects were administered 2 mg of pitavastatin under fasted conditions once daily for 6 days. On Day 6 they received a single dose of cyclosporin 2 mg/kg 1 hour prior to pitavastatin dosing. Blood samples for PK analysis were taken on: Day 1 at predose; Day 4 at predose and up to 24 hours postdose; and Day 6 at predose and up to 48 hours postdose. The mean C\text{max} (from 27.6 to 179.3 ng/mL) and AUC_{0-24} (from 76.9 to 347 ng.h/mL) of pitavastatin markedly increased when co administered with cyclosporin. The ratio of the geometric mean values after co administration with cyclosporin versus those following administration of pitavastatin alone was 6.6 (90% CI: 5.0 to 8.6) for C\text{max} and 4.6 (90% CI: 4.0 to 5.1) for AUC_{0-24}, indicative of an interaction between pitavastatin and cyclosporin. By contrast, the C\text{max} and AUC_{0-24} of the lactone metabolite were not affected by co
administration and the ratio for $C_{\text{max}}$ was 1.1 (90% CI 0.9 to 1.2) and the ratio for $\text{AUC}_{0-24}$ was 1.1 (90% CI 1.0 to 1.2).

An open label, single dose, randomised, two period, crossover study (NK-104-GJ) evaluated the effect of grapefruit juice (GJ) on the pharmacokinetics of a single 2 mg dose of pitavastatin in 12 healthy Asian males, aged 21 to 25 years. Subjects drank 200 mL double strength GJ or water three times a day for 2 days. On Day 3, pitavastatin 2 mg was administered to each subject in the fasted state with either 200 mL double strength GJ or water in the morning. In addition, the subjects received either 200 mL double strength GJ or water 0.5 and 1.5 hours after the single administration of pitavastatin. There was a 3 week wash out between study periods. The AUC for pitavastatin was slightly increased (from 84.9 to 95.6 ng.h/mL for $\text{AUC}_{0-24}$) when single doses of pitavastatin were taken with GJ compared to when it was taken with water; however, all 90% confidence intervals were within the 0.80 to 1.25 limits allowing for bioequivalence to be concluded. For the lactone metabolite, AUC also increased slightly when pitavastatin was taken with GJ; however, bioequivalence could only be concluded for $\text{AUC}_{0-24}$, not for $\text{AUC}_{0-t}$ or $\text{AUC}_{0-\infty}$ for which the upper limits of the 90% CIs were just outside the cut off of 1.25 (1.26 and 1.28, respectively). Time to reach maximum concentration for pitavastatin and lactone was also increased when pitavastatin was taken with GJ. The $C_{\text{max}}$ achieved for both pitavastatin and pitavastatin lactone was slightly lower when pitavastatin was taken with GJ; the limits of the 90% confidence interval were within the specified limits for the lactone indicating bioequivalence but the lower limit for pitavastatin was marginally below the 0.80 cut off. This study suggests that any changes seen in the PK of pitavastatin when co administered with grapefruit juice are small and are unlikely to be clinically significant.

A randomised, open label, single centre, three period, six sequence crossover study (JPC-04-335-18) evaluated the pharmacokinetic interaction between ezetimibe (SCH 58235) and pitavastatin when administered in combination in 18 healthy males, aged 20 to 25 years. Subjects were assigned to groups A, B, C, D, E or F (three per group). Ezetimibe 10 mg alone, pitavastatin 2 mg alone or ezetimibe 10 mg plus pitavastatin 2 mg were administered for 7 days each in one of the periods and there was a wash out period of 7 days between treatments. Blood samples for pharmacokinetic analysis were taken prior to drug administration in Period 1 and predose and up to 24 hours postdose on Day 7. The point estimates and 90% CIs for $C_{\text{max}}$ and $\text{AUC}_{0-24}$ were 102% (90% CI: 84.5% - 122%) and 109% (90% CI: 92.1% - 128%), respectively, for plasma ezetimibe concentration, 106% (90% CI: 90.1% - 124%) and 106% (90% CI: 93.0% - 120%), respectively, for the plasma SCH 60663 (phenolic glucuronide of ezetimibe) concentration, and 99.8% (90% CI: 88.3%-113%) and 97.5% (90% CI: 90.5% - 105%), respectively, for plasma pitavastatin concentration. Therefore, there appears to be little PK interaction when ezetimibe is co administered with pitavastatin.

An open label, fixed sequence, two treatment, crossover study (NK-104-1.25US) examined the effect of multiple dose administration of pitavastatin 4 mg on the steady state pharmacokinetics of warfarin (R- and S- isomers) in 24 healthy males, aged 19 to 44 years. The subjects received warfarin 5 mg once daily on Days 1 to Day 3. On Days 4 to Day 9, the warfarin dose was titrated to achieve an international normalised ratio (INR) measurement between 1.2 and 2.2. The subjects continued to receive the maintenance dose of warfarin on Days 10 through to Day 21. In addition, the subjects received pitavastatin 4 mg once daily in the morning on Day 14 through to Day 22. The drugs were administered fasted and blood samples for PK analysis were obtained: predose on Days 9 to 12; predose and up to 24 hours after dosing on Day 13; before dosing on Days 18 to 20; and predose and up to 48 hours after dosing on Day 21. Co administration of single daily doses of 4 mg pitavastatin with warfarin affected neither the $C_{\text{max}}$ nor $\text{AUC}$ of R- and S-warfarin and the median $T_{\text{max}}$ and geometric mean $\text{CL/F}$ of warfarin were comparable between treatments.
A single centre, open label, three sequence dosing period crossover study (NK-104-1.26) assessed the effect of multiple administrations of 4 mg pitavastatin on the steady state pharmacokinetics of digoxin and vice versa in 19 healthy males, aged 23 to 50 years. One subject was withdrawn due to a prolonged PR interval. Each subject was involved in three sequential dosing periods:

- Period 1, Days 1 to 10, digoxin 0.25 mg 12 hourly on Day 1 and once daily on Days 2 to 10;
- Period 2, Days 11 to 17, co-administration of digoxin 0.25 mg and pitavastatin 4 mg once daily; and
- Period 3, Days 18 to 27, pitavastatin 4 mg once daily.

All treatments were administered to fasted subjects and blood and urine samples for the pharmacokinetic analysis of digoxin were obtained on Days 10 and 17 and for pitavastatin analysis on Days 17 and 27 predose and up to 24 hours postdosing. The estimated pharmacokinetic variables were similar for pitavastatin and its lactone metabolite when pitavastatin was administered alone or co-administered with digoxin. The 90% CI of the ratio for the geometric means of AUC₀−τ for pitavastatin when administered alone and co-administered with digoxin were within the range of 0.80 to 1.25. By contrast, for Cmax the lower limit of the 90% CI of the ratio was slightly outside this range (0.91: 0.78 to 1.05); however, this change is unlikely to be clinically significant. For the lactone metabolite, the 90% CI of the ratio for both parameters Cmax and AUC₀−τ were within the range of 0.80 to 1.25. This study indicates that there is little or no pharmacokinetic interaction between pitavastatin and digoxin. The pharmacokinetic variables for digoxin when administered alone or co-administered with pitavastatin were also similar. Due to the short measurement period (24 hours) and relatively long half-life of digoxin, the t½ and elimination rate constant for digoxin could not be estimated. The 90% CI of the ratios for the geometric means of Cmax and AUC₀−τ for digoxin when administered alone and co-administered with pitavastatin were within the range of 0.80 to 1.25.

A single centre, open label, randomised study (NK-104-1.27) examined the interaction of rifampicin at steady state on the pharmacokinetics of pitavastatin and vice versa in 18 healthy males, aged 18 to 48 years. Each subject was involved in two treatment periods (A followed by B), which were separated by at least 7 days, as follows:

- Treatment A, Days 1 to 5, pitavastatin 4 mg once daily; and
- Treatment B, Days 1 to 10, rifampicin 600 mg once daily; Days 11 to 15 co-administration of rifampicin 600 mg once daily and pitavastatin 4 mg once daily.

All treatments were administered to fasted subjects and blood samples for the pharmacokinetic assessment of pitavastatin were taken predose on Days 4 and 14, predose and up to 24 hours postdose on Days 5 and 15 and for rifampicin, predose on Days 9 and 14 and predose and up to 24 hours postdose on Days 10 and 15. The Cmax of pitavastatin approximately doubled (from 65 to 138.5 ng/mL) when pitavastatin was co-administered with rifampicin compared to when pitavastatin was given alone. In addition, AUC₀−τ increased by approximately 30% (from 158.8 to 215.1 ng.h/mL) when pitavastatin was co-administered with rifampicin, whereas the t½ and mean residence time shortened by approximately 13 hours and 3 hours, respectively. A reduction of approximately 11 times in the volume of distribution was also seen. For the lactone metabolite, there was a reduction of approximately 20% in Cmax and 60% in AUC₀−τ when pitavastatin was co-administered with rifampicin compared to pitavastatin alone and the half-life and mean residence time shortened by approximately 6 hours and 3 hours, respectively. The point estimates for the ratio of geometric means and 90% CIs of pitavastatin Cmax and AUC₀−τ were 2.00 (1.57 to 2.56) and 1.29 (1.10 to 1.51), respectively, indicating that there was a PK interaction between the two drugs. For the lactone metabolite, the point estimates for...
C\textsubscript{max}\ were similar whereas the lower limit of the 90% CI for lactone C\textsubscript{max} was slightly outside the 0.80 to 1.25 range (0.83; 0.75 to 0.90). For the AUC\textsubscript{0–\tau} of the lactone, both point estimates were below 0.80 (0.42; 0.40 to 0.45), indicating an interaction between pitavastatin and rifampicin leading to a 60% reduction in lactone AUC\textsubscript{0–\tau}. The C\textsubscript{max} and AUC of rifampicin were reduced by approximately 15% when it was co administered with pitavastatin. Similar changes were obtained for all other pharmacokinetic parameters of rifampicin when the two drugs were co administered. The geometric mean ratios for rifampicin C\textsubscript{max} and AUC\textsubscript{0–\tau} were 0.82 to 0.85, with the lower limits of the 90% CIs being slightly below the 0.80 limit.

A randomised, single centre, open label, two way crossover study (NK-104-1.28) assessed the effect of multiple dose administrations of enalapril (an OATP1B1 substrate) on the steady state pharmacokinetics of pitavastatin and its lactone metabolite in 18 healthy males, aged 20 to 45 years. Each subject was involved in two randomly determined treatment periods under fasted conditions with a minimum 7 day wash out between treatments, which consisted of:

- Treatment A, Days 1 to 5, pitavastatin 4 mg once daily; and
- Treatment B, Days 1 to 11, enalapril 20 mg once daily; Days 7 to 11, pitavastatin 4 mg once daily.

Blood samples for pharmacokinetic analysis of pitavastatin and its lactone metabolite were obtained predose and up to 24 hours postdose on Days 5 (Treatment A) and 11 (Treatment B). Blood samples for pharmacokinetic analysis of enalapril and enalaprilat were taken predose and up to 24 hours postdose on Days 6 and 11 (Treatment B). The mean pharmacokinetic parameters for pitavastatin and lactone were similar when pitavastatin was co administered with enalapril compared to when it was administration alone. For pitavastatin the point estimates of the ratio of the geometric means of AUC\textsubscript{0–\tau} and C\textsubscript{max} when administered alone and co administered with enalapril were 0.93 and 1.06, respectively, and although the 90%CI for AUC\textsubscript{0–\tau} was within the range 0.80 to 1.25, the lower 90%CI for C\textsubscript{max} was marginally outside this range 0.80 to 1.25 (0.93; 0.76 to 1.13). For the lactone metabolite the point estimates were 1.02 and 0.99, respectively, and the 90% CIs were within the range 0.80 to 1.25. The pharmacokinetic parameters of enalapril and enalaprilat were similar when enalapril was co administered with pitavastatin compared to administration alone and the 90% CIs of the ratio of the geometric means for these parameters were within the range of 0.80 to 1.25.

A randomised, single centre, open label, two way crossover study (NK-104-1.29) assessed the effect of multiple dose administrations of atazanavir (an inhibitor of UDP-glucuronosyl transferase, which primarily acts upon UGT1A1, 1A3 and 1A4 and has less of an effect on UGT 1A6, 1A9 and 2B7) on the pharmacokinetics of pitavastatin in 18 healthy males, aged 23 to 51 years. Subjects were involved in two treatment periods (Treatment A or B) in a random order, which were separated by a 5 to 7 day wash out, as follows:

- Treatment A, Days 1 to 5, pitavastatin 4 mg once daily; and
- Treatment B, Days 1 to 9, atazanavir 300 mg once daily; Days 5 to 9: pitavastatin 4 mg once daily.

All doses were administered within 5 minutes of completion of a light breakfast. Blood samples for the determination of pitavastatin and lactone PKs were taken predose and up to 24 hours postdose on Days 5 and 9 and for atazanavir PKs predose and up to 24 hours postdose on Days 4 and 9. The mean pharmacokinetic parameters for pitavastatin and its lactone metabolite were similar when pitavastatin was co administered with atazanavir compared to when it was administered alone. The ratio of the geometric means for pitavastatin C\textsubscript{max} when pitavastatin was administered alone or with atazanavir was 1.60 (90% CI: 1.39 to 1.85). By contrast, the point estimate for AUC\textsubscript{0–\tau} was 1.31 (90% CI: 1.23 to
1.39) suggesting that an interaction between pitavastatin and atazanavir exists, which results in an increase in pitavastatin exposure. For the lactone metabolite, the point estimates and the 90% CI of the ratios of the geometric means for $C_{\text{max}}$ and $AUC_{0-t}$ when pitavastatin was administered alone or with atazanavir were within the range 0.80 to 1.25. The $C_{\text{max}}$ and $AUC_{0-t}$ of atazanavir increased slightly ($C_{\text{max}}$ from 3948 to 4445 ng/mL and $AUC$ from 20474 to 21799 ng.h/mL) when atazanavir was co administered with pitavastatin compared to administration alone, whereas the other pharmacokinetic parameters were similar under both conditions. The point estimates for the $C_{\text{max}}$ and $AUC_{0-t}$ of atazanavir when administered alone or co administered with pitavastatin were 1.13 and 1.06 and the upper bounds of the 90% CIs were 1.32 and 1.26, respectively, suggesting, that the atazanavir concentrations are slightly increased when it is co-administered with pitavastatin; however, these increases are relatively small and are unlikely to be clinically relevant.

A single centre, open label, crossover study (NK-104-1.30) examined the pharmacokinetic interaction between itraconazole (a CYP3A4 inhibitor) 200 mg once daily and a single oral 4 mg dose of pitavastatin in 18 healthy males, aged 21 to 49 years. The dosing schedule consisted of the following:

- Day 1, oral dose of pitavastatin 4 mg once daily;
- Days 5 to 7 and 9, oral dose of itraconazole 200 mg once daily only; and
- Day 8, co administration of an oral dose of itraconazole 200 mg and pitavastatin 4 mg once daily, with all treatments being administered under fasting conditions.

Blood samples for pharmacokinetic analysis of pitavastatin and pitavastatin lactone were obtained predose and up to 72 hours following dosing on Days 1 and 8. The NK-104 $C_{\text{max}}$ (64 to 50 ng/mL, administered alone and with, respectively), $AUC_{0-t}$ (138 to 106 ng.h/mL, respectively) and $AUC_{0-\text{inf}}$ (156 to 123 ng.h/mL) were lower for pitavastatin and pitavastatin lactone following co administration with itraconazole, whereas the other pharmacokinetic parameters were similar following co administration. The ratio of the geometric means for pitavastatin $C_{\text{max}}$ was 0.78 (90%CI: 0.69 to 0.88) and for $AUC_{0-t}$ was 0.77 (90% CI: 0.71 to 0.84). For the lactone metabolite, although the 90% CI of the ratio of the geometric mean for $AUC_{0-t}$ was within the range 0.80 to 1.25 the value for $C_{\text{max}}$ was outside this range (0.81; 0.76 to 0.86). These results indicate that the pitavastatin exposure is decreased by 23% when co administered with itraconazole, whereas co administration had less of an effect on the lactone metabolite. The effects of pitavastatin on itraconazole pharmacokinetics were not investigated in this study.

A randomised, single centre, open label, crossover study (NK-104-1.31) assessed the effect of multiple dose administrations of erythromycin, a CYP3A4 and OATP1B1 inhibitor, on the pharmacokinetics of pitavastatin in 18 healthy males, aged 20 to 45 years. Each subject was involved in two treatment periods (Treatment A or B) in a random order, with a minimum 2 day wash out between treatments, as follows:

- Treatment A, Days 1 to 6, erythromycin 500 mg four times daily, Day 4, pitavastatin, 4 mg once daily;
- Treatment B, Day 1, pitavastatin 4 mg once daily.

Treatments were administered approximately 3 hours following breakfast. Blood samples for pharmacokinetic analysis of pitavastatin and pitavastatin lactone were obtained predose and up to 72 hours following dosing on Day 4 of Treatment A and Day 1 of Treatment B. The $C_{\text{max}}$ of pitavastatin increased from 50 to 181 ng/mL and the $AUC_{0-t}$ increased from 110 to 311 ng.h/mL when it was co administered with erythromycin compared to when it was administered alone and. The apparent volume of distribution decreased approximately 3 fold when pitavastatin was co administered with erythromycin compared to administration alone. There was a small decrease in the mean AUC of
pitavastatin lactone when pitavastatin was administered with erythromycin compared to when it was administered alone, whereas the other pharmacokinetic parameters were similar for both treatments. The ratio of the geometric means for pitavastatin C\text{max} was 3.62 (90%CI: 2.96 to 4.42) and for AUC\text{0-t} it was 2.82 (90% CI: 2.47 to 3.21). By contrast, for the C\text{max} of the lactone metabolite the 90% CIs of the ratio of the geometric means were within the range 0.80 to 1.25, although the upper 90% CI for AUC\text{0-t} for lactone was within this range, the lower 90% CI was outside this range (0.87; 0.79 to 0.95). These results indicate that there was a significant pharmacokinetic interaction between erythromycin and pitavastatin resulting in an increase in pitavastatin AUC\text{0-t} and C\text{max}. The effects of co administration of pitavastatin on erythromycin pharmacokinetics were not examined in this study.

**Evaluator's overall comments on pharmacokinetic interactions.**

- Co administration of bezafibrate, grape fruit juice, ezetimibe, digoxin and enalapril with pitavastatin had little to no effect on pitavastatin PK.
- Fenofibrate increased the AUC\text{0-24} of pitavastatin by 18%.
- Gemfibrozil induced significant increases in pitavastatin C\text{max} and AUC\text{0-24} of 31% and 45%, respectively.
- Cyclosporin increased the C\text{max} and AUC\text{0-24} of pitavastatin (by 6.6 and 4.6 fold, respectively) and it is recommended that co administration of these two drugs is contraindicated.
- Erythromycin co administration produced an approximate 3 fold increase in systemic exposure to pitavastatin and co administration should be contraindicated.
- Co administration of itraconazole (a CYP3A4 inhibitor) induced a 23% decrease in the AUC of pitavastatin.
- The pharmacokinetic parameters of enalapril and enalaprilat were similar when enalapril was co administered with pitavastatin compared to administration alone and co administration of a single daily doses of 4 mg pitavastatin with warfarin did not affect the C\text{max} nor AUC of R- and S-warfarin.

**Exposure relevant for safety evaluation**

The exposure to pitavastatin increased linearly with dose and on average there was more than a doubling of pitavastatin AUC for a doubling of dose over the range of 1 to 8mg (AUC increased 2.5 to 2.8 fold with doubling of dose). Repeat dosing significantly increased the exposure to pitavastatin by 1.28 to 1.5 fold at doses of 4, 16 and 24 mg.

**Evaluator's overall conclusions on pharmacokinetics**

No studies examined the pharmacokinetics of pitavastatin in the target population, in breast feeding mothers or in women during pregnancy.

The oral bioavailability of NK-104 is 51%.

The mean oral apparent plasma clearance of pitavastatin was 183 mL/minute and apparent volume of distribution, Vz/F, was 226 L, which compared to total body water (approx 42 L) was high, suggesting that tissue binding was greater than plasma protein binding.

Pitavastatin is highly bound to plasma protein with an unbound fraction (fp) of 0.4% to 0.5% in human plasma. Among isolated human plasma proteins, the major pitavastatin binding protein is human serum albumin (concentration 4%) with an unbound fraction of
0.4% to 0.5%. Pitavastatin binding to α1-AGP (α1-acid glycoprotein, concentration 0.06%) is also strong (fp 5.1 to 5.7%).

In plasma, the $T_{\text{max}}$ for 2 mg NK-104 PO and IV formulations was 0.68 and 0.99 hours, respectively, $C_{\text{max}}$ was 21.4 and 60.9 ng/mL (approximately a 3 fold difference), respectively, $\text{AUC}_{\text{inf}}$ was 47.4 and 86.9 ng.h/mL (approximately a 2 fold difference), respectively, clearance (CL/F) was 838 and 410 mL/min, respectively, and $t_{1/2}$ was 5.2 and 4.6 hours, respectively.

Following administration of 2 mg NK-104 PO and IV formulations, the $C_{\text{max}}$ of the primary and inactive metabolite of pitavastatin, was, 19.0 and 21.2 ng/mL, respectively, and $\text{AUC}_{\text{inf}}$ was 168.7 and 172.5 ng.h/mL, respectively. The $t_{1/2}$ of the lactone metabolite was approximately 12 hours for both formulations.

The mean NK-104 $\text{Ae}(\text{ur, 0 – last})$ values for the PO and IV formulations were 6299 and 16051 ng, respectively, indicating that mean renal clearance was low and amounted to less than 1% of the calculated plasma clearance following either formulation.

Following doses of $^{14}$C-pitavastatin the main radioactive components identified in plasma up to 24 hours postdose was unchanged pitavastatin and pitavastatin lactone. In addition, two unidentified minor metabolites which accounted for more than 5% of the radioactivity were also identified. Radioactivity was primarily excreted in the faeces and accounted for 78.6% of the dose, with 89% of the total faecal radioactivity being recovered by 96 hours. By contrast, only 15.1% of the radioactivity was recovered in the urine. Excretion of radioactivity in urine was initially rapid with 80% of the total radioactivity recovered during 24 hours postdose, increasing to 97% by 72 hours. In the faeces, unchanged pitavastatin accounted for 58.2% of radioactivity and four metabolites represented less than 15%.

In comparison to lovastatin, simvastatin, atorvastatin and fluvastatin, metabolism of $^{14}$C-pitavastatin by human liver microsomes was minimal suggesting that compared to other statins, pitavastatin undergoes little hydroxylation.

Pitavastatin uptake into human liver is in part mediated by OATP1B1, whereas pitavastatin and its lactone metabolite were only slightly metabolised by the human CYP isoforms. The UGT molecular species involved in the lactonisation reaction were identified as UGT1A3 and UGT2B7.

The registered Japanese formulation and that manufactured by SkyePharma and the formulation, which is the subject of this application (Pierre Fabre), were bioequivalent.

A high fat meal reduced the peak concentration of NK-104 by 43% and increased the median $T_{\text{max}}$ from 1 hour to 2 hours. By contrast, no significant decrease in average bioavailability was observed when NK-104 was administered with food and the 90% confidence intervals for $\text{AUC}_{0-72}$ and $\text{AUC}_{0-\text{inf}}$ were all within the 80-125% limits.

The mean $C_{\text{max}}$ for the lactone metabolite decreased by approximately 25% following a high fat meal, whereas the median $T_{\text{max}}$ increased from 2 hour to 4 hours. By contrast, there was no significant change in the $\text{AUC}_{0-\text{inf}}$ of the lactone metabolite.

Steady state of pitavastatin was reached following 4 to 6 days of repeat dosing. The $C_{\text{max}}$ and AUC of pitavastatin increased linearly with dose over the dosage range of 1 to 64 mg, whereas, the absorption rate of parent drug remained constant as the $T_{\text{max}}$ of both parent drug and metabolite did not vary with increasing dose. Time of dosing (AM or PM) did not affect the PK of pitavastatin.

Elderly subjects have higher systemic exposure to pitavastatin (by about 10% in $C_{\text{max}}$ and 30% in AUC) compared to non elderly subjects. Females had significantly higher $C_{\text{max}}$ (1.6 fold) and AUC (1.5 fold) values than males. The PKs of pitavastatin are similar in Black, Asian and Caucasian subjects.
Mean AUC\textsubscript{0-24} of the unchanged compound on Day 7 was slightly lower in subjects with impaired hepatic function (98.1 ng.hr/mL) compared to subjects with normal hepatic function (119.8 ng.hr/mL). There was a 16% decrease in AUC\textsubscript{0-24} and 12% decrease in C\textsubscript{max} in subjects with fatty liver, a form of hepatic impairment, compared to healthy subjects. The mean C\textsubscript{max} and AUC\textsubscript{0-4} of pitavastatin were 1.34 and 1.60 times greater in subjects with Child-Pugh Grade A, and 2.69 and 3.93 fold greater in subjects with Child-Pugh Grade B, respectively, compared to healthy subjects.

Pitavastatin C\textsubscript{max} was 1.4 and 1.6 fold higher in patients requiring haemodialysis and patients with moderate renal impairment, respectively, compared to healthy subjects. In addition, AUC\textsubscript{0-t} was increased 1.7 and 1.8 times, respectively, whereas CL/F was 0.5 and 0.6 fold lower, respectively.

Bezafibrate, grape fruit juice, ezetimibe, digoxin and enalapril when co administered with pitavastatin had little to no effect on pitavastatin PKs. Fenofibrate increased the AUC\textsubscript{0-24} of pitavastatin by 18%. Gemfibrozil induced significant increases in pitavastatin C\textsubscript{max} and AUC\textsubscript{0-24} of 31% and 45%, respectively. Cyclosporin increased the C\textsubscript{max} of pitavastatin 6.6 times and AUC\textsubscript{0-24} 4.6 times and it is recommended that co administration of these two drugs is undertaken with caution. Erythromycin co administration produced an approximate 3 fold increase in systemic exposure to pitavastatin. Co administration of itraconazole (a CYP3A4 inhibitor) induced a 23% decrease in the AUC of pitavastatin. The pharmacokinetic parameters of enalapril and enalaprilat were similar when enalapril was co administered with pitavastatin compared to administration alone and co administration of a single daily doses of 4 mg pitavastatin with warfarin did not affect the C\textsubscript{max} nor AUC of R- and S-warfarin.

The evaluator believes that all of the questions regarding PKs identified in the study materials are appropriately addressed in the proposed PI.

Pharmacodynamics

Mechanism of action

The results of studies relating to the \textit{in vitro} mechanism of action of pitavastatin indicate that pitavastatin inhibits cholesterol synthesis from acetic acid but not mevalonolactone. In addition, it enhanced binding of LDL to the LDL receptor and increased LDL receptor mRNA expression, as well as expression of HMG-CoA reductase mRNA. Therefore, the results are consistent with pitavastatin being a hydroxymethylglutaryl coenzyme A reductase inhibitor.

Primary pharmacology

Study NK-104-1.23US compared the cholesterol lowering effects of pitavastatin following 14 days AM and PM treatment with 4 mg pitavastatin. The reduction in LDL-C was slightly greater following evening dosing (Treatment A) than after morning dosing (Treatment B) (-39.96\% versus -37.23\%, respectively), but the difference in LDL-C reduction between the two dose regimens (2.73\%) was considered clinically marginal. There were no statistically significant differences between morning and evening dosing for the other lipid parameters.

Secondary pharmacology

\textit{In vitro}

Study KOW002HG examined the effects of pitavastatin and its lactone metabolite on the hERG current in hERG transfected HEK293 cells using whole cell patch clamp techniques.
The results indicated that pitavastatin and its lactone metabolite did not affect the hERG current at concentrations up to $1 \times 10^{-5}$ and $3 \times 10^{-7}$ mol/L, respectively. These concentrations were approximately 80 and 4 times greater than the maximum exposures at the clinical dose of 4 mg/day, respectively. Safety margins based upon the free fraction of pitavastatin and lactone were 10000 and 300 times (assuming 0.5% and 1.38% free fraction values) greater than the maximum exposures at the clinical dose of 4 mg/day, respectively.

**In vivo**

A double blind, double dummy placebo controlled, randomised, single centre, four arm, parallel group study (NK-104-1.34US) examined the effect of pitavastatin on electrocardiogram (ECG) parameters with a focus on cardiac repolarisation (QTc duration) at steady state at two dose levels (therapeutic [4 mg] and supratherapeutic [16 mg]) compared with placebo in 174 healthy subjects (94 female), aged 18 to 45 years. Subjects were randomly assigned to one of four treatment groups as follows:

- Placebo Group, no active ingredient;
- Pitavastatin 4 mg Group, one 4 mg dose of pitavastatin daily for 4 days;
- Pitavastatin 16 mg Group, one 16 mg dose of pitavastatin daily for 4 days; and
- Moxifloxacin 400 mg Group, one 400 mg dose of moxifloxacin for 1 day.

All medication was taken in the fasting state and 171 subjects were included in the pharmacodynamic population. The pharmacodynamic 12 lead ECGs for all four parallel dose groups were collected at intervals of approximately 1 minute, providing five ECGs for each time point at 13 selected time points at Baseline on Day -1 and on Day 4. Assessment of ECG on Day 4 were at baseline and at 15 and 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing. In the positive control group (moxifloxacin), the one sided lower limit of the 95% CI of the mean difference from the placebo group in the QTcI was greater than 5 ms at 1.5 to 4 hours after dosing. The null hypothesis for moxifloxacin was rejected and it was concluded that the study had sufficient sensitivity.

Similar results were found for the mean difference from the placebo group in the QTcF and QTcB, in which the one sided lower limit of the 95% CI was greater than 5 ms at 1.5 to 6 hours after dosing. The largest mean difference in QTcI following administration of placebo in the group designated to receive 4 mg pitavastatin was 2.57 ms at 16 hours after dosing, and the largest upper limit of the CI was 5.52 ms (16 hours after dosing). Similarly, the largest mean difference in QTcI following placebo in the 16 mg pitavastatin group was 2.93 ms (16 hours after dosing) and the largest upper limit of the CI was 5.87 ms (16 hours after dosing). The one sided upper limits of the 95% CI of mean difference from the placebo group were well below 10 ms and it was concluded that the mean increase from the placebo group in the QTcI was less than 10 ms. The largest upper limit of the CI in the QTcF was 6.03 ms (16 mg pitavastatin group at 16 hours after dosing) and the largest upper limit of the CI in the QTcB was 8.11 ms (pitavastatin 16 mg group at 3 hours after dosing).

Analysis of variance without baseline adjustment also indicated that there was no increase of 10 ms or greater in the difference from baseline in either the pitavastatin 4 mg or 16 mg groups. The mean change in heart rate (HR) in the 4 and 16 mg pitavastatin groups were similar to those observed in the placebo group suggesting that pitavastatin had little effect.

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29 The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval QTc is often calculated.
on HR. The mean differences from the placebo group in the QTcI for the pitavastatin 4 mg and 16 mg groups were comparable between males and females. There was no evidence of morphological change from baseline on Day 4 in the groups receiving 4 mg pitavastatin, 16 mg pitavastatin or placebo. By contrast, one subject in the moxifloxacin 400 mg group had a new morphological change: a negative T wave abnormality, detected on Day 4 that was not present at baseline. No subject had an increase in the time matched difference from baseline in the QTcI or QTcF of greater than 30 ms. Two subjects each in the pitavastatin 4 mg and 16 mg groups had a single increase in the difference from baseline in the QTcB of greater than 30 ms but less than 60 ms. Individual changes in the difference from time matched baseline in the QTc intervals in subjects receiving pitavastatin were similar to those observed in the group receiving placebo. One subject in the pitavastatin 4 mg group and two subjects in the pitavastatin 16 mg group had a QTcI of greater than 450 ms but less than 480 ms, whereas two subjects in the placebo group had a QTcI greater than 450 ms but less than 480 ms.

**Relationship between plasma concentration and effect**

In Study PKH/NKN98389N/NK-104.1.01, which was conducted in healthy volunteers, lipid parameters were assessed alongside the pharmacokinetic parameters and identified a dose response relationship for LDL-C reduction after seven days of treatment at doses up to 8 mg. With the highest dose of pitavastatin, LDL-C was reduced by 56.4% after 7 days of treatment and by 53.3% three days after the last dose, following 14 days of medication. Similar analyses were conducted in Study HPC/NKN00435N/NK-104.1.19 where doses ranged from 24 mg to 64 mg, however, no dose effect relationship was seen.

**Pharmacodynamic interactions with other medicinal products or substances**

Study NK-104-1.25US examined the effect of multiple dose administration of pitavastatin 4 mg on the steady state pharmacodynamics of warfarin by measuring any effect on the International Normalised Ratio (INR) and prothrombin time (PT) in healthy subjects. The mean PT and INR values achieved steady state visually during the maintenance dose period (Day 10 through Day 13). When warfarin was administered with single daily doses of pitavastatin 4 mg there were no drug interaction effects on the steady state pharmacodynamics of warfarin as assessed by PT and INR.

**Evaluator’s overall conclusions on pharmacodynamics**

- No studies examined the pharmacodynamics of pitavastatin in the target population.
- Although pitavastatin induced a slightly greater reduction in LDL-C levels following dosing compared to morning dose the difference was deemed to be clinically insignificant.
- There is little evidence that supra therapeutic doses of pitavastatin (16 mg) affect QT interval.
- The data relating to a dose and PD response relationship existing for pitavastatin is equivocal.
- Pitavastatin did not affect the steady state PD of warfarin.
Efficacy

Dose-response studies

There were three Phase II, placebo controlled, dose ranging studies in patients with primary hypercholesterolaemia (NK-104-209 and NK-104.2.02) and combined dyslipidaemia (NK-104.2.03). There were also 2 placebo controlled dose ranging Phase IIb studies (NKS104A2204 and NK-104-210).

Studies NK-104.2.02 and NK-104.2.03

Design

Both NK-104.2.02 and NK-104.2.03 were multinational, multicentre, randomised, double blind, parallel group, dose ranging studies which evaluated the efficacy and safety of NK-104 1 mg, 2 mg, 4 mg, and 8 mg compared to placebo. After a wash out period (if required), patients entered a 4 week single blind, placebo run in period followed by a 12 week double blind, active treatment period. During the run in hypolipidaemic drugs were ceased, a low fat and cholesterol diet established and compliance monitored. All laboratory assessments were conducted by a central laboratory.

Study participants

Inclusion criteria were:

- 18-75 years;
- females of child bearing potential to be on oral contraception of at least 3 months; and
- willingness to adhere to the National Cholesterol Education Program (NCEP) Step-1 or equivalent diet.

In NK-104.2.02 subjects had primary hypercholesterolaemia with LDL-cholesterol ≥160 mg/dL (4.13 mmol/L) but ≤250 mg/dL (6.46 mmol/L), and triglyceride (TG) level ≤300 mg/dL (3.43 mmol/L) at Visit 3. In NK-104.2.03 subjects had primary mixed or combined hyperlipidaemia with LDL-C level ≥135 and ≤300 mg/dL (≥3.5 and <7.8 mmol/L) and TG ≥175 and ≤500 mg/dL (≥2.0 and ≤5.7 mmol/L).

Exclusion criteria were:

- pregnancy, or not taking oral contraception;
- BMI > 30 kg/m2 (>33 in NK-104.2.03);
- alcohol abuse;
- hypersensitivity to HMG-CoA reductase inhibitors;
- use of prohibited concomitant medications;
- compliance <80% during run in period;
- diabetes or fasting serum glucose ≥7 mmol/L at Visit 2;
- renal impairment or serum creatinine > 1.8 mg/dL or nephrotic syndrome;
- uncontrolled hypertension or diastolic blood pressure (DBP) ≥110 mmHg or systolic blood pressure (SBP) ≥180 mmHg;
- history of myocardial infarction, unstable angina, stroke, transient ischaemic attack (TIA), percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG);
- NYHA class 3 or 4 congestive cardiac failure\(^{30}\);
- active liver disease or AST or alanine aminotransferase (ALT) > 2 times ULN;
- muscular or neuromuscular disease or creatinine kinase (CK) > 3 times ULN without explanation;
- malignancy within past 10 years;
- known cataracts;
- human immunodeficiency virus (HIV) infection;
- severe depression or suicidal tendencies;
- Type I, IIb, III, IV or V hyperlipidaemia\(^{31}\);
- familial hypercholesterolaemia or LDL-C > 250 mg/dL at Visit 3; and
- hypercholesterolaemia secondary to hypothyroidism.

**Objectives**

The primary objective was assessment of efficacy of the 4 doses of pitavastatin in terms of reduction in serum LDL-C, with other lipid parameters (total cholesterol, HDL-C, triglycerides, apolipoprotein A1 and B) and safety as secondary objectives.

**Study treatment**

Patients took 2 tablets once daily at bedtime during the single and double blind treatment periods. Two placebo tablets were taken during the 4 week run in and NK-104 at doses of 1 mg, 2 mg, 4 mg (2 x 2 mg tablets) and 8 mg or matching placebo were taken during the 12 week treatment period. Subjects in the 1, 2 and 8 mg dose groups also took one placebo tablet. Prohibited concomitant medications included: immunosuppressives, antifungals, warfarin, mibebradil, niacin, erythromycin or like antibiotics, corticosteroids and androgens.

**Randomisation and blinding**

A centralised randomising system was used. Study medication was blinded and investigators did not receive lipid values during the treatment period until after study completion.

**Statistical methods**

The primary endpoint was the percentage change from baseline in the LDL-C as calculated using the Friedewald formula\(^ {32}\). The baseline value was the mean of values at Visit 3 and 4. The intent-to-treat (ITT) population was defined as all randomised patients who received

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\(^{30}\) In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient’s quality of life. Class 1 (mild) to Class IV (severe).

\(^{31}\) Type I is a rare disorder characterized by severe elevations in chylomicrons and extremely elevated triglycerides, always reaching well above 1000 mg/dL and not infrequently rising as high as 10,000 mg/dL or more. Type IIb is the classic mixed hyperlipidemia (high cholesterol and triglyceride levels), caused by elevations in LDL and VLDL. Type III is known as dysbetalipoproteinemia, remnant removal disease, or broad-beta disease. Patients with type III hyperlipidemia have elevations in intermediate-density lipoprotein (IDL), a VLDL remnant, and a significant risk for developing coronary artery disease. Type IV is characterized by abnormal elevations of VLDL and triglyceride levels are almost always less than 1000 mg/dL. Serum cholesterol levels are normal. Type V is characterized by elevations of chylomicrons and VLDL. Triglyceride levels are invariably greater than 1000 mg/dL, and total cholesterol levels are always elevated. The LDL cholesterol level is usually low. Given the rarity of Type I disease when triglyceride levels above 1000 mg/dL are noted, the most likely cause is Type V hyperlipidemia.

\(^{32}\) Friedewald formula: LDL-C (mg/dL) = TC - (HDL-C + Triglycerides/5) or LDL-C (mmol/L) = TC - (HDL-C + Triglycerides/2.2)
double blind medication and had at least one baseline and one post randomisation LDL-C value. Analysis was carried out on the ITT population with last observation carried forward (LOCF). Comparison between the 5 treatment groups was by analysis of variance (ANOVA) with centre as a random variable and baseline LDL-C as a fixed variable. A linear regression analysis was used to assess the dose response relationship.

Sample size

To detect a difference of 7% in the change in LDL-C between 2 doses, with a standard deviation of 10%, 43 patients per group (225 in total) gave the studies an 80% power at a 5% error risk. To allow for variability between countries and centres, non evaluable data and non eligibility the sample was increased by 30% to 325 patients in NK-104.2.02 and by 50% to 375 in NK-104.2.03.

Study conduct

The studies were sponsored by Laboratoires Negma and conducted in 1999-2000 at 25 (NK-104.2.02) and 44 (NK-104.2.03) centres in Canada and Europe. There was one major amendment in both studies which excluded PTCA and CABG patients.

Participant flow

In NK-104.2.02 there were 370 patients enrolled, 261 were randomised and 248 subjects completed the study. In NK-104.2.03, 395 subjects were enrolled, 252 were randomised and 246 patients completed the study. There were 251 and 249 patients in the ITT populations in the two studies, respectively.

Baseline characteristics

The patients were predominantly male (67-71%) and Caucasian (97-99%) with a mean age of 51.7 to 53 years. About half were smokers and most (74-87%) had 1 or 2 risk factors for CHD. Baseline lipid profiles were similar between treatment groups. Compliance was <80% in 2.8% and 1.6% of subjects in the two studies, respectively.

Primary outcome

In NK-104.2.02, the adjusted mean percentage decrease in LDL-C was -33.3%, -38.2%, -46.5%, and -54.5%, in the 1 mg, 2 mg, 4 mg, and 8 mg groups, respectively, compared to -4.0% in the placebo group (Table 7). Each dose was statistically significant compared with placebo, as was the between group comparison (p≤0.027).

Table 7. Study NK-104.2.02. Percentage decrease between baseline and last valid value for LDL-C (ITT population N=251).

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Placebo</th>
<th>Pitavastatin (QD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12, LOCF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>Adjusted mean</td>
<td>-4.0</td>
<td>-3.3</td>
</tr>
<tr>
<td>SD</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>p-value diff vs placebo</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*the relative variation of the parameter during treatment was estimated by a model adjusted on baseline value and centre, with centre as fixed effect.

In NK-104.2.03, the adjusted mean percentage change from baseline in LDL-C was -27.0%, -31.4%, -41.5%, and -46.2% in the NK-104 1 mg, 2 mg, 4 mg, and 8 mg groups, respectively, compared with -1.6% in the placebo. All groups were significantly different compared to placebo (p<0.001) and compared to each other were also significantly different apart from the 4 mg and 8 mg groups (p=0.093) and 1 mg and 2 mg groups (p=0.112).
Secondary outcomes

In NK-104.2.02, decreases in total cholesterol (TC) and triglycerides (TG) were dose related and significant compared to placebo (p<0.001) (Table 8). The increase in HDL-C (7.6% to 9.4%) had an inverse relationship with dose and there was no significance difference between the pitavastatin doses. Apo-B decreased significantly with increasing dose while with Apo-A1 the increase was less with higher doses but was not statistically significant over 1 mg.

Table 8. Study NK-104.2.02. Percentage change between baseline and last valid value for total cholesterol, HDL-C, triglyceride, Apo A1 and Apo B (II population, N=251).

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Placebo</th>
<th>Pitavastatin (QID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12, LOCF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>Baseline mean (SD)</td>
<td>7.4 (0.7)</td>
<td>7.3 (0.8)</td>
</tr>
<tr>
<td>Mean % change</td>
<td>-1.3</td>
<td>-22.8</td>
</tr>
<tr>
<td>p-value for diff vs placebo</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>Baseline mean (SD)</td>
<td>1.6 (0.6)</td>
<td>1.8 (0.7)</td>
</tr>
<tr>
<td>Adjusted mean % change</td>
<td>-2.1</td>
<td>-14.8</td>
</tr>
<tr>
<td>p-value for diff vs placebo</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>Baseline mean (SD)</td>
<td>1.5 (0.4)</td>
<td>1.4 (0.3)</td>
</tr>
<tr>
<td>Adjusted mean % change</td>
<td>2.5</td>
<td>9.4</td>
</tr>
<tr>
<td>p-value for diff vs placebo</td>
<td>0.001</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Adjusted means were not calculated for TC as the model assumptions were not met

In NK-104.2.03, all doses lowered TC and TG though there was no significant difference between 1 mg and 2 mg, and 4 mg and 8 mg, on reduction in TC. In addition the 4 mg dose produced a greater reduction in TG than the 8 mg dose (-24.8% versus -22.5%). Mean HDL-C increased but without any significant difference between dose groups. There was a significant increase in mean Apo-A1 in the 4 mg and 8 mg groups only. The reduction in Apo B was greater with increasing dose though not significantly different between the 1 and 2 mg, and 4 and 8 mg, groups.

Summary

Pitavastatin at doses of 1 mg, 2 mg, 4 mg and 8 mg resulted in a dose related reduction in plasma LDL-C with reductions also seen in TC, TG and ApoB. There was an increase in HDL-C which was not related to the dose. One of the two studies did not find significant differences between the 1 mg and 2 mg doses or between the 4 mg and 8 mg doses in LDL-C reduction.

Study NK-104-209

This was a randomised, multicentre, parallel group, dose ranging study assessing the efficacy of 8 mg, 16 mg, 32 mg, and 64 mg of pitavastatin in patients with primary hypercholesterolaemia.

After a 6 to 8 week dietary run in phase there were two 8 week double blind treatment periods. In the second treatment period placebo subjects were to be switched to 64 mg pitavastatin. The treatment was placebo, 8 mg, 16 mg, 32 mg and 64 mg of pitavastatin or 80 mg of atorvastatin which was randomised in a 1:2:2:2:2:2 ratio. Atorvastatin treatment was open label whereas pitavastatin and placebo were blinded.
Study participants
The study included subjects 18 to 80 years with plasma mean LDL-C levels at two consecutive qualifying visits ≥130 mg/dL and ≤220 mg/dL, and triglycerides ≤400 mg/dL. Exclusion criteria were similar to the previous studies.

Statistical methods
The primary endpoint was change from baseline in LDL-C at Week 8 analysed by analysis of covariance (ANCOVA) in the ITT population with LOCF. LDL-C was determined by ultracentrifugation. A sample size of 350 was selected for safety analysis.

Study conduct
Study NK-104-209 was sponsored by Sankyo Pharma and conducted in 2001 at 49 sites in the USA. After 3 months it was noted that there were 6 serious adverse events (SAEs) of rhabdomyolysis which on unblinding were in the 32 mg and 64 mg dose groups. These dose groups were ceased and the protocol amended to allow continuation of the 8 mg and 16 mg dose groups. The second treatment period was dropped and the study continued with 4 groups. One month later a number of subjects with elevated CK (>10 times ULN) and myalgia were noted and the study was prematurely terminated.

Outcomes
There were 442 patients randomised. At Week 8, both the 8 mg and 16 mg doses resulted in a significant reduction in LDL-C (-38.1% and -46.5%) which was similar to 80 mg atorvastatin (-47.3%) and significantly different than placebo (8.0%) (p<0.001).

Summary
This study was prematurely terminated due to safety reasons (elevated CK, myalgia and rhabdomyolysis) in the 16 mg, 32 mg and 64 mg dose groups. There was evidence of significant reduction in LDL-C after 8 weeks with the 8 and 16 mg doses.

Studies NKS104A2204 and NK-104-210
Study NKS104A2204 was a 12 week multicentre, randomised, double blind placebo controlled, parallel group Phase IIb study to evaluate the efficacy and safety of pitavastatin (4 and 8 mg) in lowering LDL-C, compared to placebo and to open label atorvastatin (forced titration of 10 to 20 mg then to 40 mg). Patients had primary hypercholesterolaemia or mixed dyslipidaemia.

In this study, the 8 mg treatment arm was prematurely terminated due to cases of myalgia, CK elevation (> 10 x ULN) and suggestion of rhabdomyolysis in 2 cases. All study recruitment was also ceased at this point. Overall, 357 of the planned 588 subjects were randomised and most of the 8 mg dose group (78%) did not complete the study. For this reason no inferential analysis was undertaken on the 8 mg group. The study did find that the 4 mg dose group resulted in a least squares mean (LSM) reduction from baseline in LDL-C of 39.7% (95% CI: -45.2, -34.3, p<0.001).

Study NK-104-210 was a 12 week multicentre, randomised, double blind placebo controlled, parallel group Phase IIb study to evaluate the efficacy and safety of pitavastatin (4 and 8 mg) compared to placebo and open label atorvastatin. The design was essentially the same study as Study NKS104A2204. The study was sponsored by Sankyo Pharma rather than Novartis and conducted at 23 sites in the USA. Due to the safety concerns in NKS104A2204, the 8 mg dose group was prematurely terminated 6 months after commencement and randomisation ceased. Overall 134 of the 225 planned subjects were randomised. Only an abbreviated clinical study report was provided. Most subjects in the 8 mg group did not complete 12 weeks of treatment. In the small 4 mg dose group (n=28) the mean percentage change from baseline in LDL-C was -36.9%. There was one case of elevated CK in the 8 mg group.
Summary

The 8 mg pitavastatin had evident safety concerns. Due to the premature cessation of the 8 mg dose groups and the failure to complete randomisation, no meaningful efficacy conclusions can be drawn from these trials.

Main (pivotal) studies

NK-104-301 (atorvastatin non-inferiority study)

Design

NK-104-301 was an 18 to 20 week, randomised, multicentre, double blind, double dummy, active controlled, non inferiority Phase III study in patients with primary hypercholesterolemia or combined dyslipidemia. After a 6 to 8 week wash out/dietary lead in period there was a 12 week treatment period in which subjects were randomised to one of 4 groups. Subjects received dietary counselling on the European Atherosclerosis Society (EAS) dietary guidelines.

Objectives

The primary objective was to demonstrate the non inferiority of pitavastatin 2 mg qd versus atorvastatin 10 mg qd, and pitavastatin 4 mg qd versus atorvastatin 20 mg qd, with respect to the reduction of LDL-C after 12 weeks of treatment following up titration for the higher doses. Secondary objectives included comparison of the effects on TC, HDL-C, non-HDL-C, TG, TC:HDL-C ratio, non-HDL-C:HDL-C ratio, Apo-B, Apo-A1, Apo-B:Apo-A1 ratio, high sensitivity C reactive protein (hsCRP), oxidised LDL and LDL-C target attainment, safety and tolerability.

Study participants

- For inclusion subjects were:
  - Male or female,
  - 18 to 75 years,
  - Primary hypercholesterolaemia or combined (mixed) dyslipidaemia,
  - LDL-C ≥160 and ≤220 mg/dL (≥4.2 and ≤5.7 mmol/L) and TG ≤400 mg/dL (≤4.6 mmol/L),
  - Subjects also needed to comply with a fat and cholesterol restrictive diet.

Exclusion criteria were:

- homozygous familial hypercholesterolaemia,
- secondary dyslipidaemia,
- uncontrolled diabetes with HbA1c >8%,
- conditions affecting absorption, metabolism or excretion of a drug,
- pancreatic disease history,
- liver injury with ALT or AST >1.5 times ULN,
- impaired renal function with creatinine >1.5 times ULN,
- urinary obstruction or difficulty voiding,
- serum CK >5 times ULN,
- uncontrolled hypothyroidism,
• recent severe illness or trauma,
• major surgery within 3 months,
• significant cardiovascular disease within 3 months (myocardial infarction (MI), PTCA, CABG or unstable angina),
• symptomatic heart failure,
• significant cardiac arrhythmias,
• left ventricular (LV) ejection fraction <0.25,
• history of cerebrovascular disease,
• HIV infection,
• poorly controlled hypertension,
• active malignancy or history of in past 10 years,
• drug or alcohol abuse, and
• body mass index (BMI) >35 kg/m².

Treatments
Pitavastatin 2 mg was a small tablet and 4 mg a larger tablet, atorvastatin (Pfizer) was supplied in an over capsule of the 10 mg and 20 mg tablets. This was due to unavailability of placebo atorvastatin tablets. Matching small and large placebo tablets for pitavastatin and placebo capsules for atorvastatin were used in a double dummy design. Subjects took 1 small tablet, 1 large tablet and 1 capsule once daily at bedtime.

Prohibited medications included: any agent affecting lipid levels, systemic steroid hormones including contraceptives (except implants or IM injections), anticoagulants and antiplatelet (except aspirin or ticlopidine), HIV protease inhibitors, cyclosporine, azole antifungals, nefazodone, continuous macrolide antibiotics, danazol, glitazones/thiazolidinediones and grapefruit juice.

Outcomes/endpoints
The primary efficacy variable was the percent change from baseline to study endpoint (LOCF) in LDL-C in the FAS. Analysis of the Per Protocol (PP) population to Week 12 was also undertaken. Baseline LDL-C was the mean of measurements at Week -2, -1 and 0. LDL-C was calculated using the Friedewald formula or ultracentrifugation if the TG was >400 mg/dL. Blood samples were taken after 12 hours of fasting and analysed by a central laboratory.

Sample size
A sample of 800 randomised patients (300 per pitavastatin group and 100 per atorvastatin group) allowed the study to have 99% power to reject the null hypothesis that the mean percent decrease from baseline was at least 6% greater in the atorvastatin groups assuming a 6% non inferiority limit, a 2.5% one sided significance level and a standard deviation (SD) of 12% (reduction from baseline LDL-C).

Randomisation
Subjects were randomised to 1 of 4 treatment groups:
• pitavastatin 2 mg,
• pitavastatin 4 mg (2 mg, titrated to 4 mg),
• atorvastatin 10 mg and
• atorvastatin 20 mg (10 mg, titrated to 20 mg)

in a 3:3:1:1 ratio stratified by centre using an interactive voice response (IVRS).

**Blinding**

Blinding was maintained by using matching placebo medication. In addition, study staff was not informed of lipid results during the treatment period until after database lock. No local testing of lipids was allowed.

**Statistical methods**

The primary endpoint was analysed by ANCOVA with treatment and country as factors and baseline LDL-C as a covariate using the full analysis set (FAS) and PP populations. The FAS was defined as all randomised patients who received at least one dose of study medication and who had at least one post baseline lipid assessment. The completer (COM) population was also analysed which was all patients, irrespective of violations, with a week 12 measurement.

Two sided 95% CIs were calculated on the adjusted mean difference between treatment groups. A non inferiority margin of 6% was chosen following agreement from the European Medicines Agency (EMA) and pitavastatin considered non inferior to atorvastatin if the lower bound of the 95% CI was greater than -6% for all doses tested. Secondary variables were analysed using ANCOVA.

**Participant flow**

There were 830 subjects randomised with 821 receiving study medication (616 pitavastatin and 205 atorvastatin) and 817 in the FAS population. The premature discontinuation rate due to adverse events or abnormal laboratory values was 1.9% and 2.0 in the pitavastatin 2 mg and 4 mg groups, respectively, with none in the atorvastatin groups. The rate of major protocol deviations was moderate with 180 patients (22%) excluded from the PP population with the most common reasons being poor compliance, taking prohibited medications and Week 12 visit outside the 14 day window.

**Conduct of study**

The study was conducted at 42 sites in India, Denmark, Russia and Spain between October 2005 and November 2006 and sponsored by Kowa Research Europe Ltd. There were 2 protocol amendments. The first changed the inclusion criteria for LDL-C from ≥3.4 mmol/L to ≥4.2 mmol/L (160 mg/dL), this was implemented prior to patient enrolment. The second clarified use of glitazones and added proteinuria evaluation.

**Baseline data**

The 4 groups were well balanced with respect to baseline demographics and disease characteristics. The mean age was 58 years, 46% of subjects were male, 76% of subjects were Caucasian and 23% of the subjects Indian. Approximately 79% of patients had primary hypercholesterolaemia with the baseline mean LDL-C ranging from 179.8 to 183.5 mg/dL. Overall, 63% to 66% of patients had hypertension, 13% were smokers and the mean BMI was similar across group at approximately 27 kg/m². A statistically significant difference between groups was noted in the prevalence of diabetes (higher in the atorvastatin groups, p=0.013) and in the three NCEP risk categories (more in the high risk category in the pitavastatin 2 mg and atorvastatin 20 mg groups, p=0.018). Between 39% and 46% of patients were taking lipid lowering medications prior to the study with the most common ones being simvastatin and atorvastatin.

**Compliance**

Compliance was checked at each visit, calculated from the number of tablets/capsules dispensed and returned. Non compliance was defined as any patient who had taken <80% or >120% of prescribed medication at two consecutive visits. The mean compliance rate
was approximately 98% across groups. However, 8% of patients were excluded from the PP population due to poor compliance. Dietary compliance was assessed by patient report at each visit and no patients were noted to be noncompliant with the diet.

**Primary outcome**

In the FAS, the mean percentage change in LDL-C from baseline to study endpoint was -37.9%, -37.8%, -44.6%, and -43.5% in the pitavastatin 2 mg, atorvastatin 10 mg, pitavastatin 4 mg and atorvastatin 20 mg groups, respectively. The adjusted mean difference for pitavastatin 2 mg versus atorvastatin 10 mg was -0.15 (95% CI: -3.42, 3.11, p=0.926) and for pitavastatin 4 mg versus atorvastatin 20 mg was 0.96 (95% CI: -2.32, 4.24, p=0.565). These results met the noninferiority criteria (-6%) for both the low and high dose comparisons. Results were comparable for the COM population and the smaller PP population. The reduction in LDL-C was apparent by Week 2 and maximal at Week 8 and maintained to Week 12 (Figures 3 and 4).

**Figure 3. NK-104-301 Mean percent change from baseline in LDL-C (mg/dL) FAS**

![Figure 3](image)

**Figure 4. NK-104-301 Mean percent change from baseline in LDL-C (mg/dL) FAS**

![Figure 4](image)
Secondary outcomes

The proportion of patients reaching target LDL-C by NCEP criteria\(^{33}\) was 56.8%, 65.7%, 77.9% and 70.6% of the pitavastatin 2 mg, atorvastatin 10 mg, pitavastatin 4 mg and atorvastatin 20 mg groups, respectively. There was no significant difference in the adjusted mean difference which were 7.4% (p=0.159) and -3.0% (p=0.556) for the low and high dose comparisons, respectively. Similarly, there was no significant difference in the proportions reaching target LDL-C when using the EAS criteria\(^{34}\) (LDL-C <115 mg/dL).

The elderly (≥65 years) showed greater response on LDL-C reduction than those aged <65 years at both doses (-41.0% versus -36.5% for 2 mg and -48.4% versus -42.9% for 4 mg). Females had greater reduction than males with the 4 mg dose (-47.5% versus -41.1%). Reduction in LDL-C in subgroups of BMI category, LDL-C category, hypertension and diabetes are presented in Table 9. Efficacy was seen across these subgroups, though there was a greater reduction in LDL-C in those with higher LDL-C at baseline, particularly with the 4 mg dose. Efficacy was also demonstrated across NCEP CHD risk categories and primary diagnosis, though the LDL-C reduction was greater in those with primary hypercholesterolaemia than combined dyslipidaemia (-45.4% versus -41.9%) in the 4 mg dose group.

There were no significant differences in the reduction of other lipid variables in the pitavastatin compared to atorvastatin groups. Total cholesterol (TC) decreased by 27.7% and 32.4%, HDL-C increased by 4.3% and 5.0% and TG decreased by 14.1% and 19.1% in the pitavastatin 2 mg and 4 mg groups, respectively. The TC: HDL-C ratio reduced by 1.71 in the 2 mg group and 1.96 in the 4 mg group, with no significant difference to atorvastatin. There was also a decrease in Apo-B and small increase in Apo-A1 levels.

Summary

This study demonstrated non inferiority of pitavastatin to atorvastatin on LDL-C reduction at the low dose (2 mg versus 10 mg) and high dose (4 mg versus 20 mg) after 12 weeks of treatment. Results were confirmed on the PP population analysis. Target LDL-C (NCEP and European Atherosclerosis Society (EAS) criteria) was greater for the 4 mg dose than 2 mg. Results were not significantly different to atorvastin on target LDL-attainment or on other secondary lipid variables. Efficacy was seen across subgroups.

\(^{33}\) National Cholesterol Education Program (NACEP) Adult Treatment Panel (ATP) III Guidelines uses the presence of clinical atherosclerotic disease, the presence of other major risk factors and the 10 year risk to categorise patients. The goal LDL-C is then determined based on high, moderate or low risk category, as per the table below.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>High: CHD [A] or 10-Year Risk [C] &gt; 20%</td>
<td>&lt; 100 mg/dL (≤ 2.6 mmol/L)</td>
</tr>
<tr>
<td>Moderate: 2+ Risk Factors [B] and 10-Year Risk ≤ 20%</td>
<td>130 mg/dL (≤ 3.4 mmol/L)</td>
</tr>
<tr>
<td>Low: 0 or 1 Risk Factors</td>
<td>&lt; 160 mg/dL (≤ 4.2 mmol/L)</td>
</tr>
</tbody>
</table>

\(^{34}\) EAS target criteria. European Atherosclerosis Society Guidelines were simplified and a target of LDL-C <115 mg/dL used as this criteria.
Table 9. Study NK-104-301

<table>
<thead>
<tr>
<th>Study NK-104-302 (simvastatin non-inferiority study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study NK-104-302 was a Phase III non-inferiority study in patients with primary hypercholesterolaemia or mixed dyslipidaemia in which pitavastatin 2 mg or 4 mg was compared to simvastatin 20 mg or 40 mg. The design, objectives, inclusion/exclusion criteria, efficacy variables, statistical methods, sample size and blinding were the same as NK-104-301. A central laboratory was used and study staff not informed of lipid results during the study. Subjects were again randomised to one of 4 treatment groups in a 3:3:1:1 ratio. For those subjects randomised to the higher dose group, the study medication was up titrated from 2 mg to 4 mg pitavastatin and 20 mg to 40 mg simvastatin at 4 weeks.</td>
</tr>
</tbody>
</table>
Participant flow

There were 857 subjects randomised and 848 received study medication (631 pitavastatin and 217 simvastatin) with 843 in the FAS. Premature discontinuations ranged from 3.6% to 8.3% in the four groups with discontinuation due to adverse events (AEs) higher in the pitavastatin groups (4.1% and 2.5%) compared to the simvastatin groups (1.9% and 0.9%). The rate of major protocol deviations was less than in Study NK-104-301, with 127 patients (15%) excluded from the PP population. The most common reason was not having the Week 12 lipid assessment followed by poor compliance, taking prohibited medications and the Week 12 visit outside the 14 day window.

Conduct of study

This study was conducted in 2005-2006 at 45 centres in Russia, Norway, UK, Finland and Italy. There was one protocol amendment which clarified use of glitazones and added proteinuria evaluation.

Baseline data

The 4 groups were well balanced with respect to baseline demographics and disease characteristics. Compared to NK-104-301, the mean age was similar at 58 years, there were more females (61%) and all but 4 patients were Caucasian. Approximately 80% of patients had primary hypercholesterolaemia and the baseline mean LDL-C ranged from 183.6 to 184.1 mg/dL. Overall 59% to 66% of patients had hypertension, 6% to 8% diabetes, 13% to 18% were smokers and the mean BMI was similar across groups at approximately 28 kg/m². There was noted to be a statistically significant difference between groups in NCEP risk category (p=0.025) with more simvastatin 40 mg (45%) in the moderate category compared to the other dose groups (29% to 34%). Between 18% and 36% of patients were taking lipid lowering medications prior to the study with the most common ones being simvastatin and atorvastatin.

Compliance

The mean compliance rate was approximately 97% to 98% across groups. The exclusion of patients from the PP population due to poor compliance was approximately 4% which was lower than the 8% reported in NK-104-301. There were 6 (<1%) patients noted to be non compliant with dietary counselling.

Primary outcome

In the FAS population, the mean percentage change in LDL-C from baseline to study endpoint was -39.0%, -35.0%, -44.0% and -42.8% in the pitavastatin 2 mg, simvastatin 20 mg, pitavastatin 4 mg and simvastatin 40 mg groups, respectively. The adjusted mean difference for pitavastatin 2 mg versus simvastatin 20 mg was 4.08 (95% CI: -0.82, 7.34, p=0.014) and for pitavastatin 4 mg versus simvastatin 40 mg was 1.08 (95% CI: -2.13, 4.29, p=0.509). These results met the non inferiority criteria (-6%) for both the low and high dose comparisons and were comparable for the COM population and the smaller PP population. As with NK-104-302 the reduction in LDL-C was apparent by Week 2 and maximal at Week 8 and maintained to Week 12 for both doses.

Secondary outcomes

The proportion of patients reaching target LDL-C by NCEP criteria was 70.0%, 64.5%, 79.6% and 78.2% of the pitavastatin 2 mg, simvastatin 20 mg, pitavastatin 4 mg and simvastatin 40 mg groups, respectively. There was no significant difference in the adjusted mean difference: -4.0% (p=0.461) and -1.0% (p=0.836) for the low and high dose comparison, respectively. The proportion reaching target LDL-C by EAS criteria was 59.6%, 48.6%, 75.2% and 75.5% in the 4 groups respectively. The adjusted mean difference was not significantly different for the high dose, though it was for the low dose (difference -11.0% p=0.47). The PP analysis had similar results and the low dose
comparison was no longer significant. As some patients were found to have additional cardiovascular risk factors after database lock, a post hoc analysis was conducted. This did not alter the findings.

As with NK-104-301, the elderly and females had a greater LDL-C reduction than the younger or male patients. LDL-C reduction was seen across subgroups or BMI category, baseline LDL-C category, hypertension and diabetes with no significant interactions. NCEP CHD risk category and primary diagnosis (primary hypercholesterolaemia or combined dyslipidaemia) did not influence response, though there were only 8 patients with heterozygous familial hypercholesterolaemia and this resulted in a significant treatment by primary diagnosis interaction (p=0.047) (Table 10).

Table 10. Study NK-104-302. Mean percent change (SD) from baseline to endpoint in LDL-C (mg/dL) by baseline characteristics (FAS).

Other lipid variables

Pitavastatin 2 mg resulted in a significantly greater decrease in TC than simvastatin (-27.9% versus -25.2%, adjusted mean difference 2.59, p=0.041). The high dose reduction (-31.5% versus -30.5%) was not significantly different. HDL-C increased similarly in all groups (5.5% to 6.8%). Non-HDL-C decreased in all groups with a significant difference in the low dose group (3.6%, p=0.021). The decrease in TG was similar, as were the ratios of TC: HDL-C, non-HDL-C:HDL-C. Apo-B decreased, Apo-A1 increased and the Apo-B:Apo-A1 ratio decreased in all groups with no significant differences. There was a significantly greater decrease in hsCRP in the pitavastatin 2 mg compared to the simvastatin 20 mg group (-0.94 versus 0.09, adjusted mean difference 1.06, p=0.022). In the pitavastatin 4 mg group, the hsCRP increased (0.23) and the difference with simvastatin 40 mg was not significant.

Summary

This study found that pitavastatin was non-inferior to simvastatin for both doses and that the 2 mg dose resulted in statistically superior effect on LDL-C reduction compared to simvastatin 20 mg. Results were confirmed in the PP analysis. The proportion of patients reaching target LDL-C by NCEP criteria was not significantly different while on EAS.
criteria it was significantly greater for pitavastatin 2 mg than simvastatin 20 mg (60% versus 49%). Pitavastatin 2 mg also resulted in a greater reduction in TC and non-HDL-C. Decreases in the lipid ratios were comparable between groups.

Clinical studies in special populations

NK-104-304 (High CHD Risk simvastatin, non-inferiority study)

Design

Study NK-104-304 was Phase III, randomised, multicentre, double blind, double dummy, parallel group, active controlled, 18 to 20 week study of pitavastatin 4 mg compared to simvastatin 40 mg in patients with primary hypercholesterolaemia or mixed dyslipidaemia and 2 or more risk factors for coronary heart disease (CHD). After a 6 to 8 week washout and dietary run in period subjects entered a 12 week treatment period. Patients could then enter a 44 week extension study (NK-104-309). Lipid analysis was conducted at a central laboratory and LDL-C estimated from fasting samples using the Friedewald formula (unless TG >400 mg/dL when ultracentrifugation as used).

Objectives

The primary objective was demonstration of non inferiority of pitavastatin 4 mg compared to simvastatin 40 mg on LDL-C reduction using an up-titration regimen after 12 weeks treatment. Secondary objectives were changes in other lipid variables, as per previous trials.

Study participants

The study included males and females, 18 to 75 years, with primary hypercholesterolemia or combined dyslipidemia as defined by elevated plasma LDL-C ≥3.4 mmol/L (130 mg/dL) and ≤5.7 mmol/L (220 mg/dL) despite dietary therapy and elevated TG levels of ≤4.6 mmol/L (400 mg/dL) at 2 visits during the lead in period, with 2 or more risk factors for CHD disease. Risk factors were smoking, hypertension, low HDL-C (<1.0 mmol/L, 40 mg/dL), family history of premature CHD, or age ≥45 years for men and ≥55 for women. Exclusion criteria were the same as NK-104-301 and 302.

Treatment, randomisation and blinding

Patients were randomised in a 2:1 ratio by IVRS to pitavastatin or simvastatin and commenced treatment at 2 mg and 20 mg, respectively, which was force titrated to 4 mg and 40 mg at Week 4. To maintain the blind a double dummy design was used with patients taking one small tablet, one large tablet and one capsule each day. Prohibited medications were the same as in previous trials. Study staff were blinded to lipid results.

Endpoints, sample size and statistical methods

The primary and secondary endpoints and statistical methods were the same as previous trials. The non inferiority margin remained -6%. A sample size of 300 (200 pitavastatin and 100 simvastatin) gave the study a 99% power as in NK-104-301 and 302 (α=0.25, SD=12 and 6% non inferiority limit).

Participant flow

Overall 355 patients were randomised (236 pitavastatin and 119 simvastatin) with 99% in the FAS and 266 (74.9%) in the PP population. There were 5.5% and 10.1% of the pitavastatin and simvastatin groups, respectively, who prematurely discontinued with the most frequent reason being adverse events (3.8% and 5.0%, respectively). Major protocol deviations occurred in 22.9% and 29.4% of the pitavastatin and simvastatin groups respectively. These were moderately balanced between groups with the most frequent deviations being “no Week 12 lipid assessment” and “use of prohibited medication”. It was also noted that 5.5% and 5.0% of the 2 groups had less than 2 cardiovascular risk factors.
Conduct of study

The study was conducted at 43 sites in Europe in 2005-2006. There were 2 protocol amendments, the first clarified the results sent to sites to ensure blinding and the second amendment clarified the use of glitazones, poorly controlled hypertension and added proteinuria assessment.

Baseline data

The groups were well balanced on baseline characteristics. There were more males (68%), the mean age was approximately 60 years and all but one patient was Caucasian. Most patients had primary hypercholesterolaemia (83% and 86%), followed by mixed dyslipidaemia (15% and 12%) and only 7 patients had heterozygous familial hypercholesterolaemia. There were 6.4% and 6.7% with diabetes and 53% and 59% with hypertension in the pitavastatin and simvastatin groups, respectively. The mean BMI was 27.6 kg/m² and most patients (71% and 66%) were in the moderate NCEP risk category. Risk factors for CHD are outlined in Table 11. Prior lipid modifying medication was noted in 34.8% and 39.5% with the most common being simvastatin. Baseline lipid were comparable with the LDL-C approximately 166 mg/dL.

Compliance

Poor treatment compliance (<80% or > 120%) was noted in 3.8% of the pitavastatin and 4.2% of the simvastatin groups. No patients were excluded from the PP population due to dietary non-compliance.

Primary outcome

In the FAS, the mean change from baseline in LDL-C was -43.9% and -43.8% in the pitavastatin and simvastatin groups, respectively with an adjusted mean difference of 0.31 (95% CI: -2.47, 3.09, p=0.820). This met the non inferiority criteria of -6%. This result was confirmed in the PP population with an adjusted mean difference of -0.61 (p=0.637), as well as in the completer population (Table 12). A reduction of about 35% in LDL-C was seen at 2 weeks and continued to decline to Week 12 (Figure 5).
Table 11. NK-104-304. Risk factors for coronary heart disease (Safety Population).

<table>
<thead>
<tr>
<th>CHD Risk Factor</th>
<th>Pitavastatin 4 mg QD N=22</th>
<th>Simvastatin 40 mg QD N=119</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalents at screening; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical CHD</td>
<td>16 (6.9%)</td>
<td>11 (9.2%)</td>
</tr>
<tr>
<td>Symptomatic coronary artery disease</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>5 (2.1%)</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>0 (0.0%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15 (6.4%)</td>
<td>8 (6.7%)</td>
</tr>
<tr>
<td>Major cardiovascular risk factors at Week 0; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension – treated</td>
<td>108 (46.4%)</td>
<td>64 (53.8%)</td>
</tr>
<tr>
<td>Hypertension – untreated</td>
<td>12 (6.4%)</td>
<td>6 (5.0%)</td>
</tr>
<tr>
<td>Family history of premature CHD</td>
<td>104 (44.6%)</td>
<td>52 (43.7%)</td>
</tr>
<tr>
<td>Age (see Table 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>106 (45.5%)</td>
<td>52 (43.7%)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>127 (54.5%)</td>
<td>67 (56.3%)</td>
</tr>
<tr>
<td>TC at baseline; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥160 mg/dL</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>160 – &lt; 200 mg/dL</td>
<td>5 (2.1%)</td>
<td>4 (3.4%)</td>
</tr>
<tr>
<td>200 – &lt; 240 mg/dL</td>
<td>95 (40.8%)</td>
<td>53 (44.5%)</td>
</tr>
<tr>
<td>240 – &lt; 280 mg/dL</td>
<td>110 (47.2%)</td>
<td>43 (36.1%)</td>
</tr>
<tr>
<td>2280 mg/dL</td>
<td>23 (9.9%)</td>
<td>19 (16.0%)</td>
</tr>
<tr>
<td>HDL-C at baseline; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 mg/dL</td>
<td>29 (12.4%)</td>
<td>6 (5.0%)</td>
</tr>
<tr>
<td>50 – &lt; 60 mg/dL</td>
<td>54 (23.2%)</td>
<td>29 (24.4%)</td>
</tr>
<tr>
<td>40 – &lt; 50 mg/dL</td>
<td>87 (37.3%)</td>
<td>53 (44.3%)</td>
</tr>
<tr>
<td>&lt;40 mg/dL</td>
<td>63 (27.0%)</td>
<td>31 (26.1%)</td>
</tr>
<tr>
<td>LDL-C at baseline; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥160 mg/dL</td>
<td>97 (41.6%)</td>
<td>50 (42.0%)</td>
</tr>
<tr>
<td>160 – &lt; 190 mg/dL</td>
<td>102 (43.8%)</td>
<td>48 (40.3%)</td>
</tr>
<tr>
<td>≥190 mg/dL</td>
<td>24 (14.6%)</td>
<td>21 (17.6%)</td>
</tr>
<tr>
<td>Systolic blood pressure at Week 0; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥120 mmHg</td>
<td>53 (22.7%)</td>
<td>22 (18.5%)</td>
</tr>
<tr>
<td>120 – 129 mmHg</td>
<td>63 (27.0%)</td>
<td>27 (22.7%)</td>
</tr>
<tr>
<td>130 – 139 mmHg</td>
<td>80 (34.3%)</td>
<td>51 (42.9%)</td>
</tr>
<tr>
<td>140 – 159 mmHg</td>
<td>57 (15.9%)</td>
<td>19 (16.0%)</td>
</tr>
<tr>
<td>≥160 mmHg</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

CHD=coronary heart disease; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; QD=once daily; TC=total cholesterol. Baseline was defined as the mean of results at Week -2, Week -1 and Week 0 or the mean of results at Week -1, Week -2, Week -3 and Week 0. For patients who had their Visit 4 (Week 0) blood sample taken after the date of first dose of study treatment, baseline values were calculated as the mean of Week -2 and Week -1 or Week -1 and Week -2, as applicable.
Table 12. NK-104-304. Change from baseline to endpoint or Week 12 in LDL-C (mg/dL) (FAS, COM and PP populations).

<table>
<thead>
<tr>
<th></th>
<th>FAS</th>
<th>COM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitavastatin 4 mg QD</td>
<td>166.1 (20.11)</td>
<td>166.0 (21.56)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>166.9 (23.47)</td>
<td>166.0 (21.56)</td>
</tr>
<tr>
<td>Endpoint LDL-C</td>
<td>92.9 (23.51)</td>
<td>87.5 (22.66)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>93.3 (24.67)</td>
<td>93.3 (24.67)</td>
</tr>
<tr>
<td>% change from baseline to endpoint</td>
<td>-43.77 (12.779)</td>
<td>-43.13 (12.454)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-42.64 (9.913)</td>
<td>-47.13 (12.454)</td>
</tr>
<tr>
<td>% change from baseline to Week 12</td>
<td>-43.59 (13.905)</td>
<td>-43.59 (13.905)</td>
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<tr>
<td>Mean (SD)</td>
<td>-43.59 (13.905)</td>
<td>-43.59 (13.905)</td>
</tr>
<tr>
<td>Adjusted Mean Difference</td>
<td>0.31 (1.57; 1.94)</td>
<td>0.87 (1.57; 1.94)</td>
</tr>
<tr>
<td>P-value (test for difference)</td>
<td>0.829</td>
<td>0.857</td>
</tr>
</tbody>
</table>

Figure 5. NK-104-304. Mean percent change from baseline in LDL-C (mg/dL) FAS

Secondary outcomes

The proportion of patients that reached LDL-C targets were similar between groups according to NCEP criteria (87.1% versus 85.6%) and EAS criteria (87.1% versus 81.4%) in the pitavastatin and simvastatin groups, respectively. Neither difference was statistically significant. Subgroup analysis found consistent effect by country, gender, BMI category, baseline LDL-C category, risk category and hypertensive status. There was no
analysis by race as study subjects were Caucasian. While it appeared there was a greater response to pitavastatin in non diabetics compared to diabetics (-44.4% versus -37.5%), there were only 15 diabetic patients in this group. Likewise, a lesser reduction in LDL-C in those with combined dyslipidaemia compared to primary hypercholesterolaemia (-39.1% versus -45.4%) may have been due to small numbers with dyslipidaemia (n=35). Simvastatin treatment resulted in a greater LDL-C reduction in the elderly (≥65 years) compared to younger patients (-47.9% versus -42.3%), though such an effect was not seen with pitavastatin (-42.9 versus -44.2%). This resulted in a significant (p=0.024) treatment by age group interaction.

There were no significant differences in any of the other lipid parameters except for TG where there was a significantly greater reduction with pitavastatin (-19.8% versus -14.8%, adjusted mean difference 5.23%, p=0.044).

Summary

In a population of patients with high coronary heart disease risk (2 or more risk factors), pitavastatin 4 mg was found to be non inferior to simvastatin 40 mg in the reduction of LDL-C. The effect in the FAS was supported by the PP analysis. LDL-C target attainment was 87.1% by NCEP and EAS criteria and results were consistent across subgroups. There were no significant differences in the change from baseline of the secondary lipid parameters except for a greater reduction in TG with pitavastatin (-19.8% versus -14.8%).

**NK-104-305 (Type II Diabetes Mellitus atorvastatin non-inferiority study)**

**Design and objectives**

NK-104-305 was Phase III, randomised, multicentre, double blind, double dummy, parallel group, active controlled, non inferiority, 18 to 20 week study of pitavastatin 4 mg compared to atorvastatin 20 mg in patients with Type II diabetes mellitus and combined dyslipidaemia. Patients who completed the study could enter a 44 week extension Study NK-104-310. The study was conducted at 47 sites in Germany, Poland, the Netherlands, Denmark, the UK and India in 2005-2007.

The primary objective was the demonstration of non inferiority of pitavastatin 4 mg qd versus atorvastatin 20 mg qd in reducing LDL-C when administered for 12 weeks using an up-titration method in patient with diabetes mellitus (DM) and combined dyslipidaemia. The study was the same as NK-104-304 in terms of design, dietary advice, efficacy variables, statistical methods (including a -6% non inferiority margin), randomisation, blinding and prohibited medications. Patients were randomised in a 2:1 ratio. Study treatment was pitavastatin 2 mg and atorvastatin 10 mg which was force-titrated at week 4 to 4 mg and 40 mg, respectively.

**Study participants**

Inclusion criteria were: males and females 18 to 75 years; Type II DM on oral hypoglycaemics or insulin but not glitazones; HbA1c ≤7.5%; absence of diabetic retinopathy, cataracts or diabetic nephropathy; BMI ≤35 kg/m²; not pregnant or lactating and using approved contraception; compliant with EAS recommended diet during lead in period (6-8 weeks); and LDL-C ≥2.6 mmol/L (100 mg/dL) and ≤5.7 mmol/L (220 mg/dL) and TG ≥1.7 mmol/L (≥150 mg/dL) at 2 consecutive visits during dietary lead in period. Exclusion criteria were the same as previous studies.

**Sample size**

The sample size chosen was 400 randomised patients (266 pitavastatin and 133 atorvastatin). As with previous studies this resulted in a 99% power to reject the null hypothesis that the decrease in LDL-C was at least 6% greater in the atorvastatin group compared to pitavastatin with the assumed SD of 12% at 2.5% significance level.
Participant flow

Overall 418 patients were randomised (279 pitavastatin and 139 atorvastatin), with 274 (98.6%) and 136 (97.8%) respectively in the FAS. Of these 248 (88.9%) and 124 (89.2%) were in the completer (COM) population. There was a moderate rate of major protocol deviations (23.3% versus 23.0%) with the main being failed hyperlipidaemia criteria, no Week 12 assessment and prohibited medications. This resulted in the PP population consisting of 76.7% and 77.0% of patients in the 2 groups, respectively. The rate of premature discontinuation was similar (6.1% versus 6.5%) with the main reason being adverse events (2.5% versus 4.3%).

Conduct of study

The protocol was amended twice after the study commenced. The main changes in Amendment 1 were the exclusion of glitazones and inclusion of insulin, addition of proteinuria assessment. Amendment 2 increased the sample size to 400 to allow sufficient numbers to enter the extension Study NI-104-310.

Baseline data

Study subjects were mainly male (57%), with a mean age of 60 years, 88% were Caucasian and 12% Indian and the mean BMI was 29 kg/m². These factors were balanced between groups. The mean duration of DM was similar (6.24 versus 6.12 years) as was the mean baseline HbA1c (6.49% versus 6.47%). Most patients had hypertension (78.2% versus 75.9%). About half the patient were taking lipid modifying medications with the most common being simvastatin (20.7% versus 25.5%) and atorvastatin (16.7% versus 16.1%). Baseline lipid values were similar between groups and the mean baseline LDL-C was 143.0 and 145.9 in the pitavastatin and atorvastatin groups, respectively. Risk factors for CHD were well balanced.

Compliance

The mean compliance rate was 98% in both groups. There were 4.3% and 3.6% of subjects in the 2 groups who were excluded from the PP set due to poor compliance.

Primary outcome

The mean change from baseline in LDL-C was -40.78% in the pitavastatin and -43.25% in the atorvastatin group with an adjusted mean difference of -2.33 (95% CI: -6.18, 1.52) (Table 13). As the lower bound of the CI was beyond the preset limit of -6%, the reduction of LDL-C in diabetics was not non-inferior. This was confirmed in the PP population where the difference was -3.72 (95% CI: -7.77, 0.32). The change in LDL-C was maximal at Week 8 and maintained to Week 12 (Figure 6).
Table 13. NK-104-305. Change from baseline to endpoint or Week 12 in LDL-C (mg/dL) (FAS, COM and PP populations).

<table>
<thead>
<tr>
<th></th>
<th>Pitavastatin 4 mg QD</th>
<th>Atorvastatin 20 mg QD</th>
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<tr>
<td>Baseline LDL-C</td>
<td>412.8 (27.41)</td>
<td>146.0 (26.98)</td>
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<td>Mean (SD)</td>
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<td>% change from baseline to endpoint</td>
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<td>Mean (SD)</td>
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<td>-.4335 (16.378)</td>
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<td>Adjusted Mean Difference (95% CI)</td>
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<td>107</td>
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<td>Baseline LDL-C</td>
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<td>144.3 (25.70)</td>
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<td>78.4 (21.32)</td>
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<td></td>
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<td>Mean (SD)</td>
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<td>-45.91 (13.981)</td>
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<td>Adjusted Mean Difference (95% CI)</td>
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<td>P-value (test for difference)</td>
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<td>124</td>
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<tr>
<td>Baseline LDL-C</td>
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<td>144.3 (25.66)</td>
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<tr>
<td>Mean (SD)</td>
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<td>79.5 (23.80)</td>
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<td>% change from baseline to Week 12</td>
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<tr>
<td>Mean (SD)</td>
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<td>P-value (test for difference)</td>
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</table>

CI=confidence interval; COM=complete; FAS=full analysis set; LDL-C=low-density lipoprotein cholesterol; N=number of patients; PP=per protocol; QD=once daily; SD=standard deviation.

Figure 6. NK-104-305. Mean percent change from baseline in LDL-C (mg/dL) (FAS)

Secondary outcomes

There were no statistically significant differences in the proportions reaching LDL-C targets, though the rates were higher with atorvastatin (77.4% versus 80.2% for NCEP criteria, 90.4% versus 84.3% for EAS).
There was a greater LDL-C reduction in patients ≥65 years and this was more marked with atorvastatin, although there was no significant interaction between treatment and age (p=0.477). Pitavastatin had a greater effect in female diabetics compared to males (-43.89% versus -38.93% reduction in LDL-C) while atorvastatin response was less in females (-41.05% versus -44.85%) and this resulted in a statistically significant treatment by gender interaction (p=0.017). There were some small differences across other subgroups (race, BMI category, baseline LDL-C category, hypertension, HbA1c ≤6.5% or >6.5%, and baseline HDL-C and TG categories) though in general there was a consistent response to pitavastatin.

At Week 12 the change from baseline in TC was -28.21% and -31.56% in the pitavastatin and atorvastatin groups, respectively, with a significant adjusted mean difference of -3.14 (p=0.02). The increase in HDL-C (7.34% versus 8.20%) was similar between treatment groups though there was less improvement in HDL-C in diabetics with baseline HbA1c ≤6.5% treated with pitavastatin compared to with atorvastatin (5.92% versus 8.33%). The response to atorvastatin was significantly better than pitavastatin for TG (-20.11 versus -27.16%), non-HDL-C (-35.73 versus -39.72%), oxidised LDL, small density LDL and adiponectin. There were no significant differences for Apo-B, Apo-A1, ratios of Apo-B:Apo-A1, non-HDL-C: HDL-C, TC:HDL-C, hsCRP and remnant like partial cholesterol (RLP-C).

Summary

Pitavastatin 4 mg treatment in Type II diabetics with combined dyslipidaemia resulted in a 40.7% decrease in LDL-C after 12 weeks of treatment, however the response was greater with atorvastatin 20 mg (43.3% reduction) and non inferiority was not achieved. Furthermore, a smaller proportion of pitavastatin patients reached LDL-C targets (77% versus 82% on NCEP criteria and 84 versus 90% on EAS criteria), though the differences were not statistically significant. The response to pitavastatin was greater in female than male diabetics (-43.89% versus -38.39%). There was a greater effect with atorvastatin on TC, TG, non-HDL-C, oxidised LDL, small density LDL and adiponectin with other variables having no significant differences. Of note in this study, the LDL-C response had higher variability than expected. The SD was estimated to be 12% however the actual SD was 19.6% in the pitavastatin and 16.4% in the atorvastatin groups.

NK-104-306 (Elderly pravastatin non inferiority study)

Design

NK-104-306 was Phase III, randomised, multicentre, double blind, double dummy, parallel group, active controlled, non inferiority, 8 to 20 week study of pitavastatin in elderly (≥65 years) patients with primary hypercholesterolaemia or combined dyslipidaemia. Patients who completed the study could enter a 60 week extension study NK-104-308. The study was conducted at 60 sites in Germany, the Netherlands, Denmark, Israel and the UK in 2005-2006. The study was the same as NK-104-304 and NK-104-305 in terms of design, dietary advice, efficacy variables, statistical methods (including a -6% non inferiority margin) and prohibited medications.

Objectives

The primary objective was the demonstration of non inferiority of pitavastatin versus pravastatin (1 mg qd versus 10 mg qd, 2 mg qd versus 20 mg qd, and 4 mg qd versus 40 mg qd) in reducing LDL-C when administered for 12 weeks (using an up-titration method for patients in the higher dose group). The secondary objectives were the same as for Studies NK-104-304 and NK-104-305.

Study participants

Inclusion criteria were: elderly male and female patients (≥65 years), with primary hypercholesterolemia or combined dyslipidemia with LDL-C ≥3.4 mmol/L (130 mg/dL) and ≤5.7 mmol/L (220 mg/dL) despite dietary therapy, and elevated TG of ≤4.6 mmol/L
(400 mg/dL) at 2 consecutive visits despite dietary therapy; and CK ≤1.5 times ULN. Exclusion criteria were essentially the same as NK-104-301.

Treatments, randomisation and blinding

Patients were randomised to one of 6 treatment groups: pitavastatin 1 mg qd, pitavastatin 2 mg qd, pitavastatin 4 mg qd (2 mg, titrated to 4 mg qd), pravastatin 10 mg qd, pravastatin 20 mg qd or pravastatin 40 mg qd (20 mg, titrated to 40 mg qd) in a 2:2:2:1:1:1 by an IVRS. As pravastatin placebo tablets were not available pravastatin was over-encapsulated to maintain the blind. Pitavastatin tablets were 3 sizes for the different doses. Patients took 3 tablets and one capsule each night in a double dummy design. As with previous studies, study staff was not informed of lipid results during the active treatment phase of the trial.

Sample size

A sample size of 900 allowed 200 patients in each of the 3 pitavastatin groups and 100 in each of the 3 pravastatin groups. As with previous studies this provided a 99% power, assuming the same SD of 12% (reduction in LDL-C), non inferiority limit of -6% and α=0.25.

Participant flow

Overall 962 patients were randomised, 651 to pitavastatin and 311 to pravastatin. Of these, 942 were in the FAS, 862 in the completer (COM) population and 760 in the PP population. Premature discontinuation rates were 9.1% and 12.6% in the pitavastatin and pravastatin groups, respectively, with discontinuation due to AEs the main reason (4.7% versus 5.0%). Exclusion from the PP population occurred in 21.0% of subjects with the main reasons begin lack of “Week 12 lipid assessment” (8.6% versus 10.3%), “Week 2 visit outside the window” (5.1% versus 6.4%), or “prohibited medications” (4.6% versus 3.5%).

Conduct of study

There were 2 protocol amendments. The first tightened subject discontinuation criteria if creatinine kinase (CK) was elevated and added potassium measurements at all visits. The second specified TG criteria for randomisation.

Baseline data

The groups were comparable on baseline and disease characteristics. In the study, 55.7% were female, the mean age was 70 years and all, except 7, patients were Caucasian. About 90% had primary hypercholesterolaemia, disease duration ranged from 3.0 to 4.0 years, 15.2% to 16.1% were in the high NCEP risk category (except for 11.8% in the pravastatin 40 mg group), 8.7% to 12.5% were smokers and around half had hypertension. Diabetes prevalence ranged from 2.9% to 8.1%. Baseline LDL-C was similar (162.8 to 166.6 mg/dL) and other lipid parameters were comparable across groups. Prior lipid lowering medications were taken by 10.7% to 20.8% with the most common being simvastatin.

Compliance

Compliance with study medication was high (mean 98.2% to 99.1%) and 2.1% of patients were excluded from the PP population due to poor compliance. There were 2 pitavastatin and 5 pravastatin (0.7% overall) patients who did not comply with dietary counselling on the fat and cholesterol restrictive diet.

Primary outcome

Across the 3 dose groups, there was greater reduction in LDL-C with pitavastatin that was both non inferior and statistically superior to pravastatin. In the FAS the adjusted mean difference was 8.79 (95% CI: 5.28, 10.96), 10.23 (95% CI: 7.02, 12.62) and 10.46 (95% CI: 7.28, 12.81) for the low, medium and high dose comparisons, respectively (p<0.001 for all comparisons) (Table 14). There was an evident dose response with a -31.43% reduction in
the 1 mg, -38.99% in the 2 mg, and -44.31% in the 4 mg pitavastatin group. There was also a dose response seen in the pravastatin groups. Results remained statistically superior in the PP and COM populations. The decrease in LDL-C was seen at 2 weeks and maintained to 12 weeks.

Table 14. NK-104-306. Change from baseline to endpoint or Week 12 in LDL-C (mg/dL) (FAS, COM and PP populations).

Secondary outcomes

The proportion of elderly subjects reaching LDL-C targets according to EAS criteria was 59.9%, 79.5% and 88.1% in the 1 mg, 2 mg and 4 mg pitavastatin groups, respectively, and was significantly higher than in all pravastatin groups (37.9%, 51.0%, 65.7%) (p<0.001 for all comparisons). Target attainment according to NCEP criteria was only significantly higher in the 1 mg group (83.1% versus 65.0%, adjusted mean difference -18.0 p=0.001).

There were no treatment by subgroup interactions. Response was consistent across age subgroup (65-69, 70-74 and ≥75 years), gender, BMI category, NCEP CHD risk category, baseline LDL-C category, hypertension, diabetes (though the numbers were small), primary diagnosis (though too few with heterozygous familial hypercholesterolaemia).

On other lipid variables there was a significantly greater reduction with pitavastatin in all 3 dose groups in TC, non-HCL-C and Apo-B (p<0.001). HDL-C increased by only a small amount in the 3 dose groups (0.63%, 2.14% and 4.13%) and the adjusted mean difference of -3.37 and -3.07% for the medium and high dose groups was statistically significant. TG reduction was also greater with pitavastatin, though only significantly so in the 1 mg and 4
mg dose groups. The ratios of TC:HDLC-C and non-HDL-C:HDLC-C were also significantly lower in the three dose groups. There were no significant differences in the change on Apo-A1 though the small increase in the Apo-B: Apo-A1 was significantly different for the 3 comparison groups. There was no significant difference on the change on hsCRP.

Summary

In elderly patients (≥65 years) with primary hypercholesterolaemia or mixed dyslipidaemia, pitavastatin at doses of 1 mg, 2 mg and 4 mg was found to be non-inferior and statistically superior to pravastatin (10 mg, 20 mg and 40 mg, respectively). Results were confirmed in the PP population. There was also evidence of a dose response with greater reductions with the higher dose. Target attainment was significantly higher with pitavastatin and by EAS criteria was 59.9%, 79.5% and 88.1% in the 1 mg, 2 mg and 4 mg pitavastatin groups, respectively. Target attainment by NCEP criteria was only significantly greater for the 1 mg dose. Results were consistent across subgroups and there were also significantly better changes with pitavastatin across a number of lipid variables.

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

The sponsor’s Summary of Clinical Efficacy included data from a pooled analysis from 4 Phase II studies (NK-104.2.02, NK-104.2.03, NKS104A2204 and NK-104-210) and 5 Phase III studies (NK-104-301, NK-104-302, NK-104-304, NK-104-305 and NK-104-306) conducted for the European development program. Study NK-104-209 was not included due to the high doses as only studies with 1, 2 and 4 mg doses were pooled.

Demographics from the pooled analysis showed a mean age of 59.8 to 64.4 years, about half of the subjects were females and at least 91% were Caucasian in the 3 pitavastatin dose groups. Between 63% and 79% of patients had primary hypercholesterolaemia and 21 to 36% combined dyslipidaemia with <1% heterozygous familial hypercholesterolemia (HeFH). There was a high NCEP risk category at baseline in 10.4%, 32.0% and 38.5% of the 1 mg, 2 mg and 4 mg groups respectively. Overall the prevalence of hypertension was between 49.2% and 59.8%. The prevalence of diabetes was higher in the 4 mg group (22.8%) than the 1 mg and 2 mg groups (3.6% and 6.3%) due to the diabetic study. Previous use of lipid lowering medications occurred in 31% to 39% of pitavastatin patients.

A comparison across active controlled studies in percentage change from baseline in LDL-C is summarised in Table 15. In the pooled analysis the mean percentage change at study endpoint (Week 12 LOCF) in LDL-C was -30.8%, -38.0% and -43.2% for those treated with 1 mg, 2 mg and 4 mg, respectively (Table 16). It is noted that due to differences in study enrolment there were more elderly patients in the 1 mg group and more diabetics in the 4 mg group. For other lipid parameters at study endpoint, the mean percentage change in TC was -21.6%, -27.1% and -30.8%; for TG was -13.4%, -15.3% and -19.4%; for HDL-C was 3.4%, 4.7% and 6.4%; for non-HDL-C was -28.5%, -34.9% and -39.6%; for Apo-A1 was 3.6%, 5.7% and 6.0%; for Apo-B was -24.7%, -29.6% and -34.2% for the 1 mg, 2 mg and 4 mg doses, respectively. LDL-C target attainment by NCEP criteria at week 12 was 83.1%, 70.1% and 81.8% in the 3 doses groups; it was 59.9%, 63.8% and 80.6% by EAS criteria.
Table 15. Change from baseline to endpoint or Week 12 in LDL-C Across active-controlled Efficacy studies.

<table>
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<th>N</th>
<th>LDL-C (mg/dL)</th>
<th>Percent change</th>
<th>p-value</th>
<th>vs</th>
<th>Adjusted Mean difference (95% CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Week 12 LOCF</td>
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<td>23.5</td>
<td>-4.38</td>
<td>14.4</td>
<td>0.029</td>
</tr>
<tr>
<td>NK-104-305</td>
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<tr>
<td>Pita 4 mg</td>
<td>274</td>
<td>142.8</td>
<td>27.4</td>
<td>-4.08</td>
<td>19.6</td>
<td>0.035</td>
</tr>
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<td></td>
</tr>
<tr>
<td>Ater 20 mg</td>
<td>136</td>
<td>146.0</td>
<td>27.0</td>
<td>-4.33</td>
<td>16.4</td>
<td>0.035</td>
</tr>
<tr>
<td>NK-104-306</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pita 1 mg</td>
<td>207</td>
<td>164.4</td>
<td>22.9</td>
<td>-3.11</td>
<td>11.8</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pita 2 mg</td>
<td>224</td>
<td>162.8</td>
<td>20.5</td>
<td>-3.90</td>
<td>13.1</td>
<td>0.001</td>
</tr>
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<td></td>
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<tr>
<td>Simv 20 mg</td>
<td>210</td>
<td>163.5</td>
<td>21.9</td>
<td>-4.43</td>
<td>13.7</td>
<td>0.001</td>
</tr>
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<td></td>
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<tr>
<td>Simv 40 mg</td>
<td>103</td>
<td>163.6</td>
<td>22.3</td>
<td>-2.24</td>
<td>14.1</td>
<td>0.001</td>
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<td>NK-104-307</td>
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<td>Pita 1 mg</td>
<td>207</td>
<td>164.4</td>
<td>22.9</td>
<td>-3.11</td>
<td>11.8</td>
<td>0.001</td>
</tr>
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<td></td>
<td></td>
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<tr>
<td>Pita 2 mg</td>
<td>224</td>
<td>162.8</td>
<td>20.5</td>
<td>-3.90</td>
<td>13.1</td>
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<tr>
<td>Simv 20 mg</td>
<td>210</td>
<td>163.5</td>
<td>21.9</td>
<td>-4.43</td>
<td>13.7</td>
<td>0.001</td>
</tr>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Simv 40 mg</td>
<td>103</td>
<td>163.6</td>
<td>22.3</td>
<td>-2.24</td>
<td>14.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 16. Change from baseline to Week 12 endpoint in LDL-C in the pooled analysis.

<table>
<thead>
<tr>
<th>Treatment (FAS)</th>
<th>LDL-C (mg/dL)</th>
<th>Percent change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 12 Endpoint</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>Pita 1 mg</td>
<td>349</td>
<td>173.4</td>
</tr>
<tr>
<td>Pita 2 mg</td>
<td>945</td>
<td>179.3</td>
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<tr>
<td>Pita 4 mg</td>
<td>153</td>
<td>171.5</td>
</tr>
<tr>
<td>Ater 10 mg</td>
<td>118</td>
<td>180.8</td>
</tr>
<tr>
<td>Ater 20 mg</td>
<td>238</td>
<td>161.4</td>
</tr>
<tr>
<td>Simv 20 mg</td>
<td>107</td>
<td>184.1</td>
</tr>
<tr>
<td>Simv 40 mg</td>
<td>128</td>
<td>175.4</td>
</tr>
<tr>
<td>Prav 10 mg</td>
<td>103</td>
<td>163.6</td>
</tr>
<tr>
<td>Prav 20 mg</td>
<td>96</td>
<td>137.3</td>
</tr>
<tr>
<td>Prav 40 mg</td>
<td>102</td>
<td>166.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>154</td>
<td>184.9</td>
</tr>
</tbody>
</table>

There was a slightly greater reduction in LDL-C in the elderly ≥65 years compared to those <65 years with a noticeable dose response for both age groups. There were also greater decreases in TC, TG, non-HDL-C and Apo-B in the elderly age group. Likewise, the LDL-C reduction was greater (7% to 11%) in females compared to males. There were too few numbers of subjects with BMI <19 kg/m² to draw conclusions and in higher BMI groups there was no evident difference in effect on the change in LDL-C. A dose response in change in LDL-C was seen across NCEP risk categories of low, moderate and high as well as baseline LDL-C groups (<160, 160 to <190, 190 to <220 and ≥220 mg/dL) and HDL-C groups (<40, 40 to <60 and ≥60 mg/dL) as well in hypertension and diabetes. Dose response was seen in both primary hypercholesterolaemia and combined/mixed dyslipidaemia though response was slightly greater in primary hypercholesterolaemia.

Supportive studies

Long term controlled studies

NK-104-309 was a 44 week, multicentre, double blind, double dummy, parallel group, active controlled, extension study in 178 patients with primary hypercholesterolemia or combined dyslipidaemia and two or more risk factors for coronary heart disease (CHD). It
was an extension study of NK-104-304 and was conducted in 2006-2008 at 35 sites in Europe and India.

**NK-104-310** was a 44 week, multicentre, double blind, double dummy, parallel group, active controlled, extension study in 214 diabetic patients with combined dyslipidemia. It was an extension study of NK-104-305 and was conducted in 2006-2007 at 28 sites in Europe.

**Objectives**

In NK-104-309, the primary objectives were to assess long term safety and tolerability and to assess the efficacy of pitavastatin 4 mg compared to simvastatin 40 mg and 80 mg on LDL-C target attainment by EAS and NCEP criteria after a total treatment time of 24 and 52 weeks. Secondary objectives were assessment of efficacy on other lipid parameters. In NK-104-310 the objectives were the same but the comparator was atorvastatin 20 mg and 40 mg.

**Methods**

Patients were eligible if they completed the primary study and continued directly into the long term study on the same randomised medication. Patients on simvastatin or atorvastatin who had not achieved LDL-C target by NCEP criteria at Week 8 of the primary study were up titrated to simvastatin 80 mg or atorvastatin 40 mg at visit one, the others who had reached target were maintained on simvastatin 40 mg or atorvastatin 20 mg. In both study pitavastatin was continued at 4 mg qd. The studies were double blind to week 16 then single blind for the remainder. Unblinding occurred at Week 16 in order to report data from the primary study. Double dummy treatment was maintained for the entire study with patients taking one tablet (pitavastatin or placebo) and 2 capsules (simvastatin/atorvastatin or placebo) each evening. Study staff remained blinded to actual lipid results though results were flagged by the central laboratory if LDL-C exceeded the NCEP target. Fat and cholesterol low diet was maintained throughout the study duration. Prohibited medications remained the same as the primary study.

**Statistical methods**

Data were summarised but there was no statistical analyses performed. The primary efficacy variable was the proportion of patients reaching the LDL-C target (NCEP and EAS) at Week 16 and Week 44, as well as the proportion reaching the NCEP LDL-C/Non-HDL-C target (Step 9) at Weeks 16 and 44. Results were analysed on the LOCF. The efficacy population was defined as all eligible patients who received at least one dose of study medication and had at least one lipid assessment after visit 1 during the extension study. There were no sample size calculations.

**Study conduct**

In NK-104-309 there was one site inspection by the Danish Medicines Agency and 3 protocol amendments. The first added alerts to investigators when a patient’s target LDL-C was exceeded by ≥10 mg/dL. The second tightened CK monitoring and the third cancelled a planned interim analysis of the study due to delay in regulatory submission. In NK-104-310 there were also 3 amendments, the first was the same as in NK-104-309, the

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35 For NCEP ATP III LDL-C target (step 7), as diabetics are considered high risk of CHD the target LDL-C of <100 mg/dL was used.

36 In NK-104-310 all diabetic patients are high risk the EAS target LDL-C is also <100 mg/dL.

37 Patients who achieved their LDL-C target at each visit and had TG level >200 mg/dL, were assigned a Non-HDL-C target which was 30 mg/dL higher than their LDL-C target. These patients had to meet both their LDL-C target and their Non-HDL-C target to have achieved their Step 9 “target”. Step 9 attainment for the remaining patients (i.e., patients who did not achieve their LDL-C target or did not have TG >200 mg/dL) was the same as their LDL-C target attainment. Step 9 of the ATP III Guidelines At-A-Glance Quick Desk Reference of the NCEP on High Blood Cholesterol (National Institutes of Health Publication No. 01-3305)
Participant flow and baseline characteristics

In NK-104-309 there were 121 pitavastatin and 57 simvastatin patients entered with all except 1 pitavastatin patient included in the efficacy population. There were 5 (8.8%) of the simvastatin patients who were titrated to the 80 mg dose. Premature discontinuation was higher with simvastatin (9.9% versus 17.5%) with most due to adverse events (5.8% versus 12.3%). The groups remained comparable in terms of demographic and baseline characteristics (68% were male, all Caucasian and the mean age was 60.4 years). CHD disease risk factors were similar except for a higher proportion of simvastatin patients had a high TC ≥280 mg/dL (6.6% versus 17.5%). There were only 2 patients with poor compliance.

In NK-104-310, there were 143 pitavastatin and 71 atorvastatin (20/40 mg) patients with all, except 2 pitavastatin included in the efficacy population. Premature discontinuation was higher with pitavastatin (10.5% versus 4.2%) with most due to adverse events (3.5% versus 2.8%). There were 7 (9.9%) atorvastatin patients who were up titrated to 40 mg. Participant characteristics were similar between groups. About half the patients were male and the majority Caucasian (approximately 90%). Baseline lipids were comparable except for a slightly high HDL-C in the pitavastatin group with 4.9% versus 0% having HDL-C ≥60 mg/dL. Mean compliance was 99% in both groups and no patients had poor compliance of <80% or >120%.

Outcomes

NK-104-310. Target attainment was generally higher with pitavastatin than the combined simvastatin groups: 81.7% versus 75.4% at week 44 by NCEP criteria and 84.2% versus 73.7% by EAS criteria (Table 17). There was a trend for decreasing target attainment with time (NCEP target of 91.5%, 85.8% and 81.7% at weeks 0, 16 and 44, respectively, in the pitavastatin group). The same was seen for the simvastatin group and also when examined by EAS criteria. The NCEP Step 9 target was also achieved by more pitavastatin than simvastatin treated patients (79.2% versus 70.2% at week 44).

Table 17. NK-104-309. LDL-C and LDL-C:non-HDL-C Target Attainment

In NK-104-309, the mean percentage change from primary study baseline to Week 52 in LDL-C was similar between groups (-41.81 versus -41.37). The reduction in LDL-C at Week 52 was slightly less than that seen at week 12 in the primary study (around 45%). The mean change in LDL-C over time is presented in Figure 7. After 52 weeks of treatment, the mean TC reduction was 27.4% in both groups and there was a small increase in mean TC during the extension study (9.3 mg/dL vs15.0 mg/dL). Similarly the mean percentage reduction in non-HDL-C after 52 weeks (37% versus 36.8%) was not as great as that seen at Week 12 of the primary study (-43.1% versus -44.8%). HDL-C showed ongoing increase
in both groups with each having a 14% increase after 52 weeks. TG reduction was not maintained in either treatment group and rose from a -24.4% mean reduction at Week 12 to -11.5% at Week 52 in the pitavastatin group. Changes in ratios of TC:HDL-C, non-HDLc:HDL-C and Apo-B:Apo-A1 were maintained through the extension study. There was high variability in hsCRP data and greater mean reduction with simvastatin at week 52 (-0.42 versus -1.81 mg/mL). Oxidised LDL remained reduced during the extension study.

**Figure 7. NK-104-309. Mean percent change in LDL-C from Core study baseline (Efficacy population).**

**NK-104-310.** At Week 0 of this extension study the target attainment was lower with pitavastatin than atorvastatin: 77.7% versus 88.6% by NCEP and 86.3% versus 94.3% by EAS criteria. However, by week 44 (52 weeks of treatment in total) target attainment was similar (78.0% versus 77.5% by NCEP and 87.9% and 88.7% by EAS criteria) (Table 18). Target attainment with atorvastatin was noted to decline despite the up-titration in 7 patients. Similarly, the NCEP step 9 LDL-C/non-HDL-C target was lower with pitavastatin at week 0 (66.2% versus 81.4%) but comparable after 52 weeks of treatment (66.7% versus 63.4%).

**Table 18. NK-104-310. LDL-C and LDL-C: non-HDL-C target attainment**

<table>
<thead>
<tr>
<th>Efficacy population</th>
<th>Pitavastatin 4 mg (QD)</th>
<th>Atorvastatin 20/40 mg (QD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n (%)</td>
</tr>
<tr>
<td>LDL-C target attained</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCEP End of core/Week 0</td>
<td>139</td>
<td>108 (77.7)</td>
</tr>
<tr>
<td>Week 16</td>
<td>141</td>
<td>112 (79.4)</td>
</tr>
<tr>
<td>Week 44</td>
<td>141</td>
<td>110 (78.0)</td>
</tr>
<tr>
<td>EAS End of core/Week 0</td>
<td>130</td>
<td>120 (86.3)</td>
</tr>
<tr>
<td>Week 16</td>
<td>141</td>
<td>125 (88.7)</td>
</tr>
<tr>
<td>Week 44</td>
<td>141</td>
<td>124 (87.9)</td>
</tr>
<tr>
<td>LDL-C/non-HDL-C target attained (NCEP Step 9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of core/Week 0</td>
<td>139</td>
<td>92 (66.2)</td>
</tr>
<tr>
<td>Week 16</td>
<td>141</td>
<td>95 (67.4)</td>
</tr>
<tr>
<td>Week 44</td>
<td>141</td>
<td>94 (66.7)</td>
</tr>
</tbody>
</table>

In **NK-104-310** the mean percentage reduction in LDL-C after 52 weeks of treatment was similar between groups (-41.0% versus -41.4%) as was TC (-27.6% versus -29.2%), non-HDL-C (-36.6% versus -38.5%), TG (-22.4% versus -25.8%) and Apo-B (-34.0% versus -36.7%). The increase in Apo A1 at the end of the primary study (4.9% versus 3.8%) was lost by Week 52 (-2.6% versus -3.7%). HDL-C increase continued through the extension study to 12.7% and 16.5% in the 2 groups, respectively. After a year of treatment with
pitavastatin the reduction in LDL-C was still greater in those with better glycaemic control (HbA1c ≤ 6.5%) than those with poor control (HbA1c > 6.5%) (-44.5% versus -39.6%). The same was seen for atorvastatin. The decreases in the TC: HDL-C, non-HDL-C: HDL-C and Apo-B:Apo-A1 ratios were maintained. Oxidised LDL reduction was maintained (-23.3 versus -26.8%). Adiponectin levels had increased slightly in both groups at the end of the extension study.

Summary

NK-104-309. Following 52 weeks of treatment with pitavastatin 4 mg and simvastatin 40 or 80 mg, a greater proportion of high CHD risk patients reached LDL-C targets with pitavastatin by NCEP criteria (81.7% versus 75.4%) and by EAS criteria (84.2% versus 73.7%). LDL-C:non HDL-C target attainment was reached by 79.2% and 70.2% of the pitavastatin and simvastatin groups. With time there was a small but noticeable decline in response on target attainment and individual lipid parameters (LDL-C, TC, TG, non-HDL-C, Apo-B) at Week 52 compared to Week 12. This was seen in both treatment arms. Despite this, LDL-C was reduced by 40% after 52 weeks of treatment and HDL-C increase (14%) was maintained.

In NK-104-310 after 1 year of treatment in diabetic patients LDL-C target attainment by both criteria was similar with pitavastatin and atorvastatin (78.0% versus 77.5% by NCEP and 87.9% and 88.7% by EAS criteria) despite a higher target seen with atorvastatin after 12 weeks. Mean LDL-C reduction was -41% in both groups at 52 weeks and the changes on lipid parameters were similar between treatments and maintained with longer term treatment.

Long term open label studies

There were 4 long term, open label, uncontrolled studies included with the current submission: NKS104A2204E1, NK-104-307, NK-104-308, NK-104-09

NKS104A2204E1 was a 52 week extension of NKS104A2204E1. Both studies were prematurely discontinued due to reports of elevated CK and myalgia in the 8 mg pitavastatin group in the primary study. There were 53 patients enrolled with a maximum treatment duration of 55 days. No data were available for evaluation.

NK-104-307

Methods

NK-104-307 was a 52 week open label extension study of pitavastatin 4 mg in 1353 subjects with primary hypercholesterolaemia and combined dyslipidaemia who had completed one of the two pivotal trial NK-104-301 and NK-104-302. All patients received pitavastatin 4 mg qd irrespective of treatment received in the feeder study. Due to delay in approval of the study, 86.8% of patients had a gap in treatment between studies and 33.4% of all patients had commenced other lipid modifying treatment during this time. This had to be ceased 1 week prior to entering the extension study.

The primary objective was safety with efficacy on lipid levels as secondary objectives. Dietary advice was continued. Inclusion and exclusion criteria and prohibited medications remained the same as the primary studies. The efficacy population was all patients who received at least one dose of study medication and had at least one lipid assessment in the extension period. There were only descriptive statistics and no sample size calculations.

Study conduct

The study was conducted in Europe, Russia and India at 72 centres in 2006-2007. The protocol was amended twice. The first allowed for a treatment gap between primary and extension studies and clarified study withdrawal for change in liver function of CK values. The second was administrative.
Participant flow

There were 1353 patients enrolled with 1346 in the efficacy population; 155 (11.4%) of these prematurely discontinued with 4.1% of them due to adverse events. Treatment compliance was high at 97.9%.

Baseline characteristics

There were more females (57.5%), mean age was 58.6 years, the majority were Caucasian (88.2%) followed by Indian (11.5%) and the mean BMI 27.6 kg/m². Most had primary hypercholesterolaemia (78.8%) or hypertension (67.9%) and 6.9% had diabetes. At entry into the primary studies the proportions in the high, moderate and low NCEP risk categories were: 41.6%, 28.0% and 30.4%, respectively.

Outcomes

LDL-C was noted to rise after the treatment gap and then reduce after 2 weeks treatment in the extension study back to levels seen after 12 weeks of treatment in the primary study. This reduction was the maintained to Week 52 and at this time the mean percentage reduction was -42.9%. Similar findings were seen with TC, non-HDL-C, TG, Apo-B, oxidised LDL and the ratios of TC:HDL-C, non-HCL:C:HDL-C, Apo-B:Apo-A1. HDL-C was found to continue to increase by 5.6% at the end of the primary study and by 14.3% at the end of 52 weeks in the extension study. The increase in Apo-A1 of 6.7% at the end of the primary study was not maintained and reduced to 2.4% after 52 weeks. LDL-C target attainment was maintained (74.0% and 73.5% by NCEP and EAS criteria, respectively) (Table 19).

Table 19. NK-104-307. Patients with LDL-C target attainment (Efficacy population).

<table>
<thead>
<tr>
<th>All Patient: N=1346</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% of patients with target attained according to NCEP criteria)</td>
</tr>
<tr>
<td>Proportion achieving target levels, End of Core Study</td>
</tr>
<tr>
<td>Proportion achieving target levels, Visit 1 (Week 6)</td>
</tr>
<tr>
<td>Proportion achieving target levels, Visit 9 (Week 52)</td>
</tr>
<tr>
<td>Number (% of patients with target attained according to EAS criteria)</td>
</tr>
<tr>
<td>Proportion achieving target levels, End of Core Study</td>
</tr>
<tr>
<td>Proportion achieving target levels, Visit 1 (Week 6)</td>
</tr>
<tr>
<td>Proportion achieving target levels, Visit 9 (Week 52)</td>
</tr>
</tbody>
</table>

Summary

In this group of 1353 patients with primary hypercholesterolaemia or mixed dyslipidaemia, after one year of treatment with pitavastatin 4 mg qd the reduction in LDL-C was maintained, with a mean reduction of 42.9% from the primary study baseline. LDL-C target attainment was 74% (either criteria) and HDL-C showed some ongoing improvement (mean increase of 14.3% from primary study baseline). Other lipid parameters remained similar to that seen at the end of 12 weeks treatment.

NK-104-308 (Elderly)

This was a 60 week, open label, extension study of NK-104-306 in 545 elderly subjects with primary hypercholesterolaemia or mixed dyslipidaemia. All subjects commenced on pitavastatin 2 mg qd and could be titrated up to 4 mg qd after 8 weeks if the target LDL-C (by NCEP criteria) was not reached. As with NK-104-307, a number of patients (25.4%) had a gap in treatment between the primary and the extension studies. Objectives were the same as NK-104-307 with the exception of evaluation of the 2 mg qd dose as well as
the 4 mg. Other aspects of the study methodology were the same as NK-104-307. The study was conducted in 2006-2007 at 47 sites in Europe and Israel. There were two protocol amendments, the first clarified eligibility given the treatment gap and the second amendment was administrative in nature.

Participant flow and characteristics

Of the 545 patients enrolled, 537 (98.5%) subjects were in the efficacy analysis, 447 (83%) patients received pitavastatin 2 mg and 90 (17%) subjects were given pitavastatin 4 mg. Overall, 85.5% completely completed the extension study and 15.5% prematurely discontinued with 7.0% due to AEs (6.9% versus 7.8% in the 2 mg and 4 mg groups, respectively). Dispensing errors were noted in 12 patients (receipt of 4 mg pitavastatin during the first 8 weeks instead of 2 mg). Mean compliance was 97.5% and 4 patients were noted to have poor compliance. The mean age of patients was 70.3 years and 54.5% were female. The baseline LDL-C was 164.1 mg/dL.

Outcomes

At the end of the primary study the mean percentage reduction in LDL-C was -37.0% and after 60 weeks of treatment it was slightly greater and similar between the 2 mg and 4 mg groups (-43.2% versus -44.3%). The mean change in LDL-C was slightly greater with 4 mg than 2 mg at the end of the extension study (96.6 versus 91.8 mg/dL). At Week 60 the proportion of patients achieving NCEP LDL-C target was 98.7% and 70.1% for the 2 mg and 4 mg groups, respectively (93.8% overall). This compares to a target attainment rate of 85.8% at the end of the primary study. Using EAS criteria the proportions were 91.0% and 79.2%, respectively (89% overall). The mean reduction in TC at 60 weeks was 28.3% and 30.5% for those receiving 2 mg and 4 mg, respectively. HDL-C increased during the extension study and it was similar for both doses at Week 60 (9.6%). There was little change in Apo-A1. Non HDL-C decreased by -40%, TG by -20%, Apo-B by -37% and oxidised LDL by -31%. There was little change in Apo-A1. The TC: HDL-C, Apo-B: Apo-A1 and non-HDL-C: HDL-C ratios all showed continued small reductions on top of that seen at the end of the primary study.

Summary

Sixty weeks of treatment with pitavastatin in elderly patients resulted in a 40% mean reduction of LDL-C with similar results for the 2 mg and 4 mg doses. LDL-C target attainment at Week 60 in those receiving 2 mg pitavastatin was 98.7% and 91.0% using NCEP and EAS criteria, respectively. In the 17% of patients who had not met LDL-C target at Week 8 and were up titrated to 4 mg, the target attainment at the end of the study was 70.1% and 79.2% by the 2 criteria. Changes in other lipids and ratios were slightly improved from the primary study and HDL-C showed some ongoing increase (9.6% at Week 60).

NK-104-09 (HeFH)

NK-104-09 was a multicentre, open label, long term safety and efficacy study of pitavastatin 2 mg and 4 mg in 36 patients with heterozygotic familial hypercholesterolaemia (HeFH). The study, sponsored by Kowa Company Ltd, was conducted in Japan between 1996 and 1999 and a translated clinical study report was provided.

The primary efficacy objective was change in TC, with TG, HDL-C and LDL-C as secondary endpoints. After a 4 week washout and dietary run in period, patients commenced on 2 mg and were up titrated at Week 8 to 4 mg if there were no safety concerns. Treatment duration was 52 to 104 weeks.
Study participants
Adults, 20 to 75 years of age with confirmed HeFH were included (TC ≥230 mg/dL [≥6.0 mmol/L] with tendinous xanthoma, or a first degree relative with hypercholesterolaemia with TC ≥230 mg/dL with tendinous xanthoma.

Exclusion criteria were:
- homozygotic FH,
- apheresis therapy,
- previous serious adverse drug reaction,
- poorly controlled diabetes or hypertension,
- renal or liver dysfunction,
- history of myocardial infarction (MI) or stroke within 3 months,
- cardiac failure, and
- pregnancy, lactating or planning pregnancy.

There were 36 patients treated with 33 (91.7%) of them treated for 6 months, 32 (88.9%) treated for 12 months and 6 (16.7%) patients treated for 104 weeks. The mean age as 51.5 years and 52.8% of participants were female. The mean BMI was 24.5 kg/m². The mean baseline TC was 343.8 mg/dL and LDL-C was 260.0 mg/dL.

Outcomes
The mean change from baseline to Week 52 was -34.4% and -45.2% for TC and LDL-C, respectively. The reduction in TC was seen by 4 weeks, maximal by 12 weeks and maintained over the study duration. At Week 52, TG had reduced by -34.0%, Apo-B by -32.4% whereas HDL-C had increased by 5.4%.

Summary
The study provides some supportive evidence for pitavastatin 4 mg in lowering TC and LDL-C over 52 weeks of treatment in patients with HeFH.

Other studies including Japanese, Korean and Chinese studies
There were 8 efficacy studies conducted for the clinical development program in Japan. The translated synopses for these studies were included the current Australian submission. The only clinical study report (CSR) provided was for NK-104-09 in HeFH. The studies were:

NK-104-04: an open label, uncontrolled, 8 week Phase II study of 4 mg pitavastatin in 30 patients with hyperlipidaemia.

NK-104-05: a Phase II, double blind, randomised, controlled, parallel group, 12 week, dose response study of 1 mg, 2 mg and 4 mg pitavastatin in 258 patients with hyperlipidaemia.

NK-104-06: an early Phase II double blind, placebo controlled, randomised, crossover, study of pitavastatin 2 mg versus placebo in 44 subjects with hyperlipidaemia.

NK-104-08: a Phase III open label, long-term (52 week) flexible dose (1 mg to 4 mg) study in 313 patients with hyperlipidaemia.

NK-104-11: a Phase III, double blind, randomised, parallel group, active controlled, pravastatin 10 mg, 12 week study of pitavastatin 2 mg in 238 patients with hyperlipidaemia.
**NK-104-12**: a Phase III, open label, 12 week study of pitavastatin 1 mg, 2 mg and 4 mg in 35 elderly subjects.

**NK-104-14**: a Phase III open label, 8 week study of pitavastatin 2 mg in 34 non insulin dependent diabetes mellitus patients with hyperlipidaemia.

There were also synopses for one Korean study (CWP-PTV-001, a Phase III, multi centre, randomised, open label, parallel group study of pitavastatin 2 mg versus simvastatin 20 mg over 8 weeks in 103 Koreans with hypercholesterolaemia) and one Chinese study (NK-104 2.01 CH, a Phase II/III multicentre, randomised, blinded, parallel group study pitavastatin 2 mg and 4 mg versus atorvastatin 10 mg in 340 Chinese subjects with hypercholesterolaemia).

In addition, there were synopses of 3 Japanese post marketing studies: LIVS-02 (a prospective postmarketing surveillance study of pitavastatin in 50 subjects with chronic liver disease); LIVS-03 (a PK study in renal impairment) and LIVS-01.

**LIVS-01**

This was a postmarketing surveillance study of pitavastatin with prospective central registration. A translated interim 52 week clinical study report was also provided in the current Australian submission. This provided data from the first 52 weeks of surveillance. The main safety results from this study are discussed below under Safety. The patients were followed for 2 years. A sample of 15,000 was targeted in order to detect adverse events with an incidence of 0.05% of higher. Over a 15 month registration period (2003-2005) there were 20,279 subjects surveyed with 19,925 subjects were evaluated for safety and 17,755 subjects for efficacy. Two thirds of the subjects were female with a mean age of 63 years and 16% aged ≥75 years. Most (98%) had hypercholesterolaemia. Half had hypertension, 25% diabetes, 14.5% heart disease and 7.8% liver disease with 18.9% who had received previous statin therapy.

Over the first 12 month of treatment, 29.0% discontinued surveillance with 15.0% ceasing visits and 5.7% reported to have adverse events. There was a reported significant reduction in LDL-C of -29.7% at the last evaluation with a reduction of -32.8% and -19.5% in those without and with a history of previous hyperlipidaemia medication. A similar level of reduction in LDL-C was seen in patient with liver disease (-28.7%), diabetes (-28.0%) and renal disease (-28.6%). There was a small increase in HDL-C in the total population of 2.6% and reduction of 6.4% in TG. The rate of target attainment on LDL-C by patient category of low, medium and high risk is presented in Figure 8. This shows a 90% attainment (for target of LDL-C <160 mg/dL) of those in the low risk prevention group which reduced to 67% (target of LDL-C <120 mg/dL) for those at high risk.
Summary

This study provides supplementary efficacy data in a “real world” setting for Japanese patients. While the methodology was only briefly described in the CSR and the data interim, the efficacy data was in line with that seen in the formal clinical development program. The data is further discussed from a safety perspective below under Safety.

Evaluators overall conclusions on clinical efficacy

The clinical development program for pitavastatin was comprehensive and included studies for Japanese and European/US registration.

The clinical development program included 5 dose ranging studies (NK-104.2.02, NK-104.2.03, NK-109-209, NKS104A2204, and NK-104-210). These were of 12 to 16 weeks duration and assessed doses from 1 to 64 mg against placebo and atorvastatin. There were two pivotal Phase III studies, NK-104-301 and NK-104-302, in primary hypercholesterolaemia and mixed dyslipidaemia which were non inferiority studies against atorvastatin 10 and 20 mg and simvastatin 20 and 40 mg, respectively. In addition, there were 3 specific population studies: the elderly NK-104-306, those with additional cardiovascular risk factors NK-104-304, and in Type 2 diabetics in NK-104-305. There were also 4 open label extension studies, two controlled (NK-104-309 and NK-104-310) and two uncontrolled (NK-104-307 and NK-104-308) studies of 44 to 60 weeks duration which enrolled patients from the Phase III studies. A translated CSR from a long term uncontrolled Japanese study in HeFH was also included. An integrated efficacy analysis was also conducted using data from the Phase II and III studies.

The design and conduct of the European studies was conducted in accordance with the relevant TGA adopted EU guidelines for medications to treat lipid disorders38 and for Good Clinical Practice. A non inferiority margin of 6% in the active comparator studies was

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38CPMP/EWP/3020/03: Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders. Effective: 20 May 2005  
EMEA/CHMP/EWP/350495/2009: Concept Paper on the Need to Update the Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (CPMP/EWP/3020/03)
deemed appropriate (a doubling of statin dose has often been associated with a decrease in LDL of approximately 6% and this margin has been used in other statin trials). In all studies pitavastatin was taken once daily in the evening.

LDL-C was the primary efficacy endpoint throughout the program with LDL-C target attainment by NCEP and EAS criteria as well as other lipid parameters being secondary endpoints. Change in lipid levels was assessed after a 12 week treatment period (8 weeks in NK-104-209). The studies had appropriate wash out of other lipid lower medications, a 4 to 8 week dietary lead in period and dietary counselling during the trials. Lipid parameters were measured centrally and study staff blinded to results. LDL-C was evaluated on fasting samples using the Friedewald formula (unless TG >400 mg/dL when ultracentrifugation as used). The efficacy population was the FAS with LOCF with the PP population and completer population used for confirmation.

The program included adult patients with primary hypercholesterolaemia or combined/mixed dyslipidaemia with a small number of patients with HeFH.

NK-104.2.02 and NK-104.2.03 were both multinational, multicentre, randomised, double blind, parallel group, dose ranging studies which evaluated the efficacy and safety of NK-104 1 mg, 2 mg, 4 mg, and 8 mg compared to placebo. The first study was in primary hypercholesterolaemia the second in mixed dyslipidaemia. In NK-104.2.02, the mean percentage reduction in LDL-C was -33.3%, -38.2%, -46.5%, and -54.5%, in the 1 mg, 2 mg, 4 mg, and 8 mg groups, respectively, compared to -4.0% in the placebo group. A dose related reduction in plasma LDL-C was also seen NK-104.2.03. Both studies also had dose related reductions in TC, TG and Apo-B. There was an increase in HDL-C which was not dose related. One of the 2 studies did not find significant differences between the 1 mg and 2 mg doses or between the 4 mg and 8 mg doses with respect to LDL-C reduction.

NK-104-209 was a randomised, multicentre, parallel group, dose ranging study assessing the efficacy of 8 mg, 16 mg, 32 mg, and 64 mg of pitavastatin in patients with primary hypercholesterolaemia. This study was prematurely terminated due to safety reasons (elevated CK, myalgia and rhabdomyolysis) in the 16 mg, 32 mg and 64 mg dose groups. There was evidence of significant reduction in LDL-C after 8 weeks with the 8 and 16 mg doses.

The two other dose ranging studies, NKS104A2204 and NK-104-210, were 12 week multicentre, randomised, double blind placebo controlled, parallel group studies evaluating the efficacy and safety of pitavastatin (4 and 8mg) in lowering LDL-C, as compared to placebo and to open label atorvastatin. These were also prematurely terminated due to safety concerns with the 8 mg dose.

The first 2 dose ranging studies provide the main efficacy data because of the premature termination of the other 3 trials due to myopathy at the 8 mg dose. From these studies it was determined that the maximum tolerated dose was 8 mg with efficacy seen at the lowest, 1 mg dose.

In the 5 Phase III program trials the subjects were approximately 60 years old (except for the studies in the elderly), predominantly Caucasian and about half of them were female. Overall trial completion was high (90 to 95%) and compliance was good.

The two pivotal trials NK-104-301 and NK-104-302 were 18 to 20 week, randomised, multicentre, double blind, double dummy, active controlled, non inferiority Phase III study in patients (817 and 843) with primary hypercholesterolemia or combined dyslipidemia. Pitavastatin 2 mg and 4 mg were compared to atorvastatin 10 mg and 20 mg (Study 301) and simvastatin 20 mg and 40 mg (Study 302).

NK-104-301 demonstrated non inferiority of pitavastatin to atorvastatin at the low dose (2 mg versus 10 mg) and high dose (4 mg versus 20 mg) after 12 weeks of treatment. Results were confirmed in the PP population analysis. Target LDL-C (NCEP and EAS criteria) was
greater for the 4 mg dose than the 2 mg (77.9% versus 56.8%) dose. Results were not significantly different to atorvastin with respect to target LDL-attainment or other secondary lipid variables. Efficacy was seen across subgroups.

**NK-104-302** found that pitavastatin was non inferior to simvastatin for both doses and that the 2 mg dose resulted in statistically superior effect on LDL-C reduction compared to simvastatin 20 mg. Results were confirmed on the PP analysis. The proportion of patients reaching target LDL-C by NCEP criteria was not significantly different. However, on EAS criteria it was significantly greater for pitavastatin 2 mg than simvastatin 20 mg (60% versus 49%, respectively). Pitavastatin 2 mg also resulted in a greater reduction in TC and non-HDL-C. Decreases in the lipid ratios were comparable between the groups.

There were three 12 week non inferiority studies of pitavastatin in special populations. **NK-104-304** enrolled 355 patients at high CHD risk (2 or more risk factors). Pitavastatin 4 mg was found to be non inferior to simvastatin 40 mg in the reduction of LDL-C. The effect in the FAS was supported by the PP analysis. LDL-C target attainment was 87.1% by NCEP and EAS criteria. Results were consistent across subgroups and there were no significant differences in the secondary lipid parameters except for a greater reduction in TG with pitavastatin (-19.8% versus -14.8%).

**NK-104-305** assessed 418 patients with Type II diabetes mellitus with combined dyslipidaemia. Pitavastatin 4 mg treatment resulted in a 40.7% decrease in LDL-C. This response was however greater with atorvastatin 20 mg (43.3% reduction) and non inferiority was not achieved. There was also a smaller proportion of patients reaching LDL-C targets (77% versus 82% on NCEP criteria and 84 versus 90% on EAS criteria), though the differences were not statistically significant. The response to pitavastatin was greater in female than male diabetics (-43.8% versus -38.39%). With respect to other lipid variables, there was a greater effect with atorvastatin on TC, TG, non-HDL-C, oxidised LDL, small density LDL and adiponectin with other variables having no significant differences. Of note in this study was that the LDL-C response had higher variability than expected. The SD was estimated to be 12% but the actual SD was 19.6% in the pitavastatin and 16.4% in the atorvastatin groups. This may explain some to the variability in responses seen.

**NK-104-306** evaluated 962 elderly (≥65 years) patients and compared the 3 dose levels of pitavastatin with pravastatin (10, 20 and 40 mg qd). The three dose level comparisons were non inferior and statistically superior to pravastatin. This was confirmed in the PP analysis. There was also evidence of a dose response with greater reductions noted with the higher dose. Target attainment was significantly higher with pitavastatin and by EAS criteria it was 59.9%, 79.5% and 88.1% in the 1 mg, 2 mg and 4 mg pitavastatin groups, respectively. Target attainment by NCEP criteria was only significantly greater for the 1 mg dose. Results were consistent across subgroups and there were also significantly better changes across a number of lipid variables.

Results from the pooled efficacy analysis on mean reduction in LDL-C across the Phase III trials are summarised in Table 20 below.
Table 20. Change from baseline to Week 12 endpoint in LDL-C across active controlled Efficacy studies.

<table>
<thead>
<tr>
<th>Study FAS/ITT</th>
<th>N</th>
<th>LDL-C (mg/dL)</th>
<th>Percent change</th>
<th>p-value</th>
<th>vs</th>
<th>Adjusted Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Week 12 LOCF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>NK-104-301</td>
<td>315</td>
<td>183.6</td>
<td>16.8</td>
<td>-37.9</td>
<td>14.0</td>
<td>0.926</td>
</tr>
<tr>
<td>Pta 2 mg</td>
<td>298</td>
<td>182.0</td>
<td>16.7</td>
<td>-44.6</td>
<td>15.0</td>
<td>0.555</td>
</tr>
<tr>
<td>Pta 4 mg</td>
<td>102</td>
<td>179.8</td>
<td>16.9</td>
<td>-37.8</td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td>Aitor 10 mg</td>
<td>102</td>
<td>181.9</td>
<td>16.7</td>
<td>-42.5</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td>NK-104-302</td>
<td>319</td>
<td>184.1</td>
<td>16.5</td>
<td>-44.0</td>
<td>14.5</td>
<td>0.509</td>
</tr>
<tr>
<td>NK-104-304</td>
<td>310</td>
<td>184.6</td>
<td>17.2</td>
<td>-35.0</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td>NK-104-305</td>
<td>310</td>
<td>184.0</td>
<td>15.7</td>
<td>-42.8</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>NK-104-306</td>
<td>233</td>
<td>165.1</td>
<td>20.3</td>
<td>-44.0</td>
<td>12.8</td>
<td>0.829</td>
</tr>
<tr>
<td>NK-104-307</td>
<td>118</td>
<td>165.9</td>
<td>23.5</td>
<td>-43.8</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>NK-104-308</td>
<td>274</td>
<td>142.8</td>
<td>27.4</td>
<td>-40.8</td>
<td>19.6</td>
<td>0.235</td>
</tr>
<tr>
<td>NK-104-309</td>
<td>136</td>
<td>146.0</td>
<td>27.0</td>
<td>-43.3</td>
<td>16.4</td>
<td></td>
</tr>
</tbody>
</table>

In the pooled analysis the mean percentage reduction at Week 12 in LDL-C was 31%, 38% and 43% for those treated with 1 mg, 2 mg and 4 mg, respectively. A slightly greater response was seen in the elderly compared to younger patients and in females compared to males. Response was seen across BMI groups, NCEP risk categories, baseline LDL levels, hypertension, diabetes and primary diagnosis variables.

The two long term controlled studies were 44 week, multicentre, double blind, double dummy, parallel group, active controlled, extension studies with NK-104-309 being in 178 patients two or more risk factors for CHD and NK-104-310 in 214 diabetic patients. If LDL-C targets were not met in the primary study, the comparator could be up titrated: simvastatin 40 to 80 mg and atorvastin 20 to 40 mg. Pitavastatin remained at 4 mg.

In NK-104-309, after 52 weeks of treatment a greater proportion of high CHD risk patients reached LDL-C targets with pitavastatin (81.7% versus 75.4% by NCEP criteria and 84.2% versus 73.7% by EAS criteria). With time there was a small but noticeable decline in response on target attainment and individual lipid parameters (LDL-C, TC, TG, non-HDL-C, Apo-B) at Week 52 compared to Week 12. This was seen in both treatment arms. Despite this, LDL-C was reduced by 40% after 52 weeks of treatment and the HDL-C increase (14%) was maintained.

In NK-104-310 after 1 year of treatment in diabetic patients, LDL-C target attainment by both criteria was similar with pitavastatin and atorvastatin (78.0% versus 77.5% by NCEP criteria, respectively, and 87.9% and 88.7% by EAS criteria, respectively) despite a higher target seen with atorvastatin after 12 weeks. Mean LDL-C reduction was -41% in both groups at 52 weeks and the changes in lipid parameters were similar between treatments and maintained with longer term treatment.
There were 3 open label long term studies of pitavastatin 4 mg (irrespective of the dose in the primary study). NK-104-307 was a 52 week open label extension study of pitavastatin 4 mg in 1353 subjects who had completed one of the two pivotal trials; NK-104-301 or NK-104-302. LDL-C reduction was maintained at 42.9% and LDL-C target attainment was 74% by either NCEP or EAS criteria. Other lipid parameter changes were maintained.

NK-104-308 was a 60 week extension study in 545 elderly patients (from NK-104-306). Treatment commenced on 2 mg and 17% of patients up titrated to 4 mg during the study. LDL-C target attainment at Week 60 was high for the 2 mg group, 98.7% and 91.0% using NCEP and EAS criteria, respectively. For those on 4 mg it was 70.1% and 79.2%, respectively.

A small, open label, uncontrolled, long term Japanese study (NK-104-09) in 36 patients with HeFH found some supportive evidence for LDL-C and TG reduction after 52 weeks of treatment with pitavastatin 4 mg.

The efficacy data presented was mainly in Caucasian subjects with smaller numbers of Indians. Efficacy in Asian patients was demonstrated for the Japanese authorisation. There were few Black subjects in the efficacy studies and there have been no studies in children or adolescents or in homozygous FH.

There were no long term morbidity and mortality data with pitavastatin submitted.

Safety

Introduction

There are 77 studies in the pitavastatin development program (40 healthy volunteer and 37 patients with hyperlipidaemia) of which 26 healthy volunteer and 18 patient studies contributed to the EU/US program. The pooled safety analysis included the 5 Phase II randomised, controlled trials and 5 Phase III randomised, active controlled studies and 4 of the 6 long term extension studies. Two studies, NKS104A2204E1 and NK-104-211, were extensions of the Phase II trials which were prematurely terminated and these have been discussed separately. There were also 2 studies of an extended release formulation (Phase II NKS104A2205 and its extension CNKS104A220E1) which are only briefly discussed as this formulation is not being developed further.

Collection of safety data during the clinical trials included standard monitoring of adverse events (AEs) and serious adverse events (SAEs) as well as haematology, chemistry (including liver function and creatinine kinase (CK)), physical examination, vital signs, urinalysis, pregnancy screens and 12 lead electrocardiograms (ECGs). Protein excretion was also assessed in 4 of the Phase III studies. CK was closely monitored and elevated results (>5 times the upper limit of normal (ULN) or >1.5 times ULN for elderly) were repeated. Subjects were withdrawn if the CK was > 10 times ULN, or > 5 times ULN for the elderly. Laboratory assessments were performed at a central laboratory and were the same site for all Phase II and III trials except for NK-104.2.02 and NK-104.2.03.

For the integrated safety analysis, data were analysed in 4 groups. Group 1 included the short term 12 to 16 week Phase II and III core studies. Groups 2, 3 and 4 included extension study data. Group 2 assessed data by the longest period of exposure until a gap in treatment. Therefore this Group does not include NK-104-308 due to all subjects having a gap after NK-104-306. Group 3 includes all Phase II and III core and extension studies at target doses and the treatment gap was ignored in calculating duration of exposure. Group 3 was the most complete group. Group 4 included all Phase II and III core and extension studies but only includes data during the longest period of continuous exposure. Data in
Groups 2 and 3 were presented by the dose taken at the time of the event while in Group 4 it was presented by drug. Subgroup analyses were performed on Group 3.

The safety population consisted of all patients who took at least one dose of study medication. Treatment emergent AEs (TEAEs) were coded by body System Organ Classes (SOC) and Preferred Terms (PTs) using Medical Dictionary for Regulatory Activities (MedDRA) classification. AEs were collected from first dose of study medication to 30 days post the last dose.

**Patient exposure**

In the Phase II and III studies there were a total of 3448 patients, with 309 exposed to pitavastatin 1 mg, 951 to pitavastatin 2 mg and 1540 to pitavastatin 4 mg. In the 4 extension studies there were 2284 patients, with 1617 (70.8%) on pitavastatin 4 mg and 539 patients on pitavastatin 2 mg.

In the Group 1 short term studies, there were 3448 pitavastatin patients (1 to 64 mg); 208 placebo subjects, 505 patients given atorvastatin (10 to 80 mg), 336 subjects given simvastatin (20 mg and 40 mg) and 301 patients given pravastatin (10 mg, 20 mg and 40 mg). In this group, 1540 received pitavastatin 4 mg and 951 received pitavastatin 2 mg. The mean exposure was approximately 12 weeks for doses 1 mg, 2 mg and 4 mg. For the 8 mg dose the exposure was 7.4 weeks due to the premature discontinuation of studies with this dose. In Group 3 the mean exposure to pitavastatin 1 mg, 2 mg and 4 mg was 11.6, 16.7 and 37.4 weeks, respectively, with total patient years exposures of 68.7, 823.5 and 1728.6 years, respectively.

In the Japanese HeFH study there were 36 patients; 2 patients received treatment for <52 weeks, 25 patients for 52 to <104 weeks and 7 patients for ≥104 weeks.

As pitavastatin 1 mg was used in only two dose ranging studies and the elderly study, the mean age (64.4 years) was higher in this dose group than for the other dose groups. Likewise pravastatin was only used in the elderly study and so the mean age was 70.2 years. In Group 1 pitavastatin subjects were aged from 18 to 89 years, 50.6% were females, 92.7% Caucasian, 25.1% had a BMI of ≥30 kg/m², 13% had diabetes, 55% were hypertensive, 70% had primary hypercholesterolaemia, 29.5% combined dyslipidaemia and 0.5% HeFH. At least 80% of trial subjects in Group 3 received at least one concomitant medication, typically beta blockers, antithrombotics, ACE inhibitors, diuretics, calcium channel blockers, anti inflammatories and analgesics.

**Adverse events**

In Group 1 short term studies, the TEAE rate in the 3448 pitavastatin treated subjects was 41.5% compared to 54.3% in placebo, 37.2% in atorvastatin, 38.1% in simvastatin and 52.8% in pravastatin treated patients. The rate of TEAEs did not appear dose dependent at the lower doses (50.5%, 35.3% and 39.4% in the 1 mg, 2 mg and 4 mg pitavastatin groups, respectively) but rose to 47.8% to 75.8% in the 8 mg to 64 mg groups, respectively. The rates of mild, moderate and severe TEAEs were 23.6%, 15.6% and 1.9%, respectively. In the Group 3 short and long term studies, the TEAE rate was 50.0%, 37.0% and 51.7% in the 1 mg, 2 mg and 4 mg groups, respectively.

In Group 1, the most common TEAEs reported in the 2 mg and 4 mg pitavastatin dose groups were nasopharyngitis (3.8% and 4.3%, respectively), myalgia (2.8% and 3.1%), headache (2.8% and 2.9%), constipation (1.5% and 2.2%), nausea (1.4% for both), diarrhoea (1.5% and 1.9%), back pain (1.8% and 1.4%), influenza (1.6% and 1.3%), arthralgia (1.5% and 1.2%), fatigue (0.7% and 1.0%) (Table 21). The rate of increased blood CK was 1.7% overall and 0.8% and 0.7% in the 2 mg and 4 mg groups, respectively.
The incidence of myalgia was dose dependent, occurring in 1.9%, 2.8%, 3.1%, 5.2% and 9.8% of the 1, 2, 4, 8, and 16 mg groups, respectively, compared to a rate of 1.4% in the placebo group. Other events that appeared dose related were muscle spasms, blood CK increased, events reported by the investigators as rhabdomyolysis, ALT increased, AST increased, pain in extremity, myopathy, blood in urine, rash, headache, nausea, fatigue and pruritus (Table 21).39

Table 21. TEAEs reported by ≥1% of subjects (and >1 subject in any group) by Number (%) of subjects and by randomised doses of pitavastatin in Phase II/III placebo and active controlled core studies (Group 1).

39 Sponsor comment: “None of the cases reported as rhabdomyolysis, at doses less than 32 mg, required hospitalisation or fulfilled criteria for clinically important rhabdomyolysis.”
Comparison with other statins

A comparison of the TEAEs by MedDRA SOC between pitavastatin and the 3 other statins (dose groups combined) is shown in Table 22. In general, the AE profiles were comparable. The TEAE rate was higher with pitavastatin 2 mg and 4 mg (35.3% and 39.4%) than with atorvastatin 10 mg and 20 mg (22.9% and 32.5%) though less than atorvastatin 40 mg and 80 mg (52.9% and 58.3%). Diarrhoea occurred less frequently with pitavastatin 2 mg and 4 mg (1.5% and 1.9% versus 0% to 10.4% for the atorvastatin groups) and was noted to increase with increasing atorvastatin dose. Constipation was more frequent with pitavastatin 4 mg (2.2%) than the atorvastatin groups (0.1-3%). Myalgia rates were more frequent with pitavastatin than the lower atorvastatin groups (2.8% and 3.1% versus 0.8% for both 10 mg and 20 mg and 2.0% for 40 mg), while the rate was higher with atorvastatin 80 mg (8.3%).

40 Sponsor comment: “This table includes all pitavastatin doses up to 64 mg against clinical doses of comparators, yet the AE rates overall and muscle events are comparable and less than with placebo and splitting the doses out is problematic because there are only small numbers of patients in the comparator dose groups because of the unbalanced randomisation. The sponsor added that there are few patients taking atorvastatin 10 mg in particular and most of these patients are from the 301 study which had low AE rates in all groups. The sponsor considered it misleading to conclude that pitavastatin 2 mg has a higher AE rate than ator 10 mg.”
Table 22. No (%) of subjects reporting TEAEs by System Organ Class (≥1% in any group) with pitavastatin, atorvastatin, simvastatin, pravastatin in placebo and active controlled studies (12 week duration). Group 1.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Placebo (N=200)</th>
<th>Pita Overall* (N=348)</th>
<th>Ater Overall† (N=509)</th>
<th>Simv Overall‡ (N=326)</th>
<th>Prava Overall§ (N=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td>4 (1.9)</td>
<td>50 (1.5)</td>
<td>8 (1.6)</td>
<td>5 (1.6)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Ear &amp; Labyrinth Disorders</td>
<td>5 (2.6)</td>
<td>26 (0.8)</td>
<td>6 (1.2)</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>3 (1.5)</td>
<td>25 (0.7)</td>
<td>5 (1.0)</td>
<td>3 (1.0)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>31 (14.9)</td>
<td>84 (14.1)</td>
<td>69 (13.7)</td>
<td>34 (10.4)</td>
<td>42 (14.6)</td>
</tr>
<tr>
<td>Gen. Disorders &amp; Admin. Site Cond</td>
<td>11 (5.3)</td>
<td>30 (10.9)</td>
<td>25 (5.2)</td>
<td>7 (2.1)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>3 (1.5)</td>
<td>12 (0.3)</td>
<td>3 (0.6)</td>
<td>4 (1.2)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Infections &amp; Infections</td>
<td>47 (22.6)</td>
<td>457 (13.7)</td>
<td>54 (10.7)</td>
<td>50 (15.6)</td>
<td>92 (30.6)</td>
</tr>
<tr>
<td>Injury, Poisoning &amp; Proc. Comp.</td>
<td>4 (1.5)</td>
<td>46 (1.9)</td>
<td>12 (2.4)</td>
<td>4 (1.2)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Investigations</td>
<td>10 (4.8)</td>
<td>147 (4.5)</td>
<td>19 (3.8)</td>
<td>7 (2.1)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Metabolism &amp; Nutrition Disorders</td>
<td>0</td>
<td>32 (0.9)</td>
<td>9 (1.8)</td>
<td>6 (1.2)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Musculoskeletal &amp; Connective Tissue Disorders</td>
<td>78 (38.8)</td>
<td>364 (10.6)</td>
<td>45 (9.1)</td>
<td>59 (11.6)</td>
<td>32 (10.6)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>2 (1.0)</td>
<td>2 (0.1)</td>
<td>1 (0.2)</td>
<td>3 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>26 (12.9)</td>
<td>219 (6.4)</td>
<td>76 (5.0)</td>
<td>23 (6.8)</td>
<td>35 (8.2)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>9 (4.3)</td>
<td>60 (1.7)</td>
<td>6 (1.2)</td>
<td>1 (0.3)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Renal &amp; Urinary Disorders</td>
<td>3 (1.5)</td>
<td>44 (1.3)</td>
<td>13 (2.6)</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Reproductive System &amp; Breast Disorders</td>
<td>1 (0.5)</td>
<td>6 (0.2)</td>
<td>1 (0.2)</td>
<td>5 (0.2)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Respiratory, Thoracic &amp; Mediastinal Disorders</td>
<td>9 (4.2)</td>
<td>32 (1.0)</td>
<td>18 (0.6)</td>
<td>10 (2.0)</td>
<td>15 (0.5)</td>
</tr>
<tr>
<td>Skin &amp; Subcut. Tissue Disorders</td>
<td>4 (1.9)</td>
<td>98 (2.9)</td>
<td>10 (2.0)</td>
<td>2 (0.6)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Surgical &amp; Medical Procedures</td>
<td>3 (1.0)</td>
<td>5 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>1 (0.5)</td>
<td>14 (0.4)</td>
<td>5 (1.0)</td>
<td>1 (0.3)</td>
<td>3 (1.0)</td>
</tr>
</tbody>
</table>
| Source: [Module 5.3.5.11S, Table 1.4] - TEAEs reported in all Phase II and Phase III clinical studies in Europe and US. NCI-104-202, NCI-104-203, NCI-104-A2204, NCI-104-209, NCI-104-210, NCI-104-301, NCI-104-302, NCI-104-304, NCI-104-305 and NCI-104-306. Includes pitavastatin dose groups 1 mg, 2 mg, 4 mg, 8 mg, 16 mg, 32 mg and 64 mg; includes atorvastatin dose groups 10 mg, 20 mg, 40 mg and 80 mg; includes pravastatin dose groups 10 mg, 20 mg and 40 mg; includes simvastatin dose groups 20 mg and 40 mg; includes placebo dose groups 10 mg, 20 mg and 40 mg.

The TEAE rate with pitavastatin 2 mg and 4 mg was similar to simvastatin 20 mg and 40 mg (35.3% and 39.4% versus 34.6% and 39.7%, respectively). The AE profile was comparable between the 2 treatments. A comparison with pravastatin from Group 1 data was not meaningful due to pravastatin only being used in the elderly study (NK-104-306). Data from this study found that the AE rates were 54.6%, 51.3% and 52.4% with 1 mg, 2 mg and 4 mg pitavastatin, respectively, compared to 55.3%, 49.0% and 52.9% with 10 mg, 20 mg and 40 mg pravastatin, respectively. The AE profiles were similar between treatments.

**Long term exposure**

The long term data relates to the 2 mg and 4 mg pitavastatin doses as the 1 mg dose was not used in the extension studies. In Group 3, the mean exposure to 2 mg pitavastatin was 16.7 weeks (compared to 12.0 weeks in Group 1) and the TEAE rate was 37.0%. The mean exposure to pitavastatin 4 mg was 37.4 weeks (compared to 11.9 in Group 1) and the TEAE rate was 51.7%. As expected, with longer exposure there was a general increase in the rates of specific AEs.

**Causality**

In Group 1, the most common treatment related TEAEs when all doses of pitavastatin were combined were myalgia, constipation, blood CK increased, headache, fatigue, nausea and increased ALT. The most common treatment related TEAEs for the 2 mg and 4 mg pitavastatin doses were myalgia, constipation, headache and nausea.

**Severity**

In Group 3, the rates of severe TEAEs were 2.6%, 2.3%, and 2.7% in the 1 mg, 2 mg and 4 mg pitavastatin groups, respectively. A summary of mild, moderate and severe TEAEs by dose is shown in Table 23.
**Table 23. TEAEs reported by ≥1% of subjects by number (%) of subjects and by dose at onset of pitavastatin (target doses) by Severity in Phase II/III core and extension studies (Group 3).**

<table>
<thead>
<tr>
<th>MedDRA SOC/Preferred Term</th>
<th>Pita 1 mg (N=309)</th>
<th>Pita 2 mg (N=2562)</th>
<th>Pita 4 mg (N=2400)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%) of Subjects</strong></td>
<td>Mild</td>
<td>Mod</td>
<td>Severe</td>
</tr>
<tr>
<td>Cardiovascular Disorders</td>
<td>15 (27.5)</td>
<td>6 (20.4)</td>
<td>8 (26.6)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>4 (7.0)</td>
<td>10 (3.9)</td>
<td>9 (3.1)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>2 (0.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (1.6)</td>
<td>9 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (1.3)</td>
<td>3 (1.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>3 (0.8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluoride</td>
<td>4 (1.3)</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (1.3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**AEs of special interest**

Due to differing exposure to the 4 statins, TEAEs of special interest were calculated by patient year exposure (Table 24).
Table 24. Selected TEAEs of interest by SMQ and Preferred Term (≥1% of subjects and >1 Subject) by Number (incidence per patient-year exposure) of subjects and by Dose at Onset of pitavastatin (target doses) in Phase II/III core and extension studies (Group 3).

Rhabdomyolysis41, Myopathy and Elevated CK42:

In the Phase II studies NKS104A2204 and NK-104-209 there were 9 cases of rhabdomyolysis reported by investigators. These were all with doses of pitavastatin of 8 mg or above. There were 19/648 (3.0%) patient with CK elevations > 10 times ULN with rates of 0.4%, 6.9%, 20.6% and 9.0% with doses of 8 mg, 16 mg, 32 mg and 64 mg, respectively. Of the 9 cases, 7 had CK > 50 times ULN, 8 were SAEs and 6 required hospitalisation. The number of rhabdomyolysis cases varied depending on the definition used and this is presented in Table 25.

41 There are a number of definitions of rhabdomyolysis with varying levels of CK increase, whether there is muscle symptoms, myoglobinuria, myoglobinaemia. All definitions include renal impairment with increased creatinine. However in the 2 Phase II trials in which rhabdomyolysis was reported no evidence of organ impairment was necessary.

42 The ULN for CK at the central laboratory was 120 IU/L so 10 times was 1,200 IU/L and 50 times was 6,000 IU/L or greater.
In Group 1, musculoskeletal and connective tissue disorders had a rate of 8.5% and 8.0% in the 2 mg and 4 mg dose groups, respectively. The most frequent TEAEs in this SOC was myalgia with a dose dependent rate of 1.9%, 2.8% and 3.1% in the 1 mg, 2 mg and 4 mg pitavastatin dose groups, respectively. This can be compared to 1.4% in the placebo group and 0.8-2.0% in the atorvastatin 10 mg-40 mg groups, 8.3% in the atorvastatin 80 mg group, 2.8% and 3.9% in the simvastatin 20 mg and 40 mg groups, and 2.1% to 2.9% in the pravastatin 10 mg to 40 mg groups (Tables 26 and 27). In Group 3, the rate of musculoskeletal and connective tissue disorders was 11.0% and 13.3% and for myalgia was 3.3% and 4.1% in those receiving 2 mg and 4 mg, respectively.

Table 25. Analysis and summary of reported rhabdomyolysis cases and reports of elevated CK in Phase II clinical studies NKS104/A2204 and NK-104-209.

Table 26. TEAEs reported in >1% subject in Musculoskeletal and Connective Tissue Disorders and CK TEAEs reported in Investigations by Number (%) of Subjects and by Randomised doses of pitavastatin and placebo in Phase II/III placebo and active controlled core studies (Group 1).
In Group 1, symptomatic myopathy (muscle pain, spasm or weakness) occurred in 8.6% of pitavastatin patients with 5.5% with normal CK, 2.7% with mildly elevated CK and 0.2% with each with moderately or markedly elevated CK. The incidence of symptomatic myopathy in the 2 mg and 4 mg pitavastatin was less than in the placebo group (6.8% and 6.0% versus 10.1%) and in line with the active comparators. There were no cases of symptomatic myopathy with CK ≥10 times ULN in patients treated with 4 mg or less of pitavastatin.

Some 27.8% of patients had elevated CK and no myopathy symptoms (asymptomatic myopathy), with mild elevations in 27.5%, moderate in 0.3% and marked elevation in 0.03%. For subjects treated with 2 mg or 4 mg pitavastatin, the rate of elevated CK with no symptoms was lower than in the placebo group (28.0% and 28.4% versus 34.1%). This was similar to atorvastatin (25.0% to 26.7%) and simvastatin (26.2% to 30.8%) but higher than pravastatin (12.6% to 19.6%). The rate of asymptomatic myopathy with CK ≥10 times ULN was 0.1% with both the 2 mg and 4 mg doses.

In Group 1, the incidence of rhabdomyolysis/myopathy with 2 and 4 mg pitavastatin was 0.136 and 0.122 per patient year compared to 0.061, 0.102 and 0.130 for atorvastatin 10 mg, 20 mg and 40 mg, respectively, and 0.259 and 0.148 for simvastatin 20 mg and 40 mg, respectively. Most other muscular events had a similar incidence between treatments except for a higher rate with pravastatin which was likely due confounding by age in this group.

The incidence of rhabdomyolysis/myopathy was higher in the first 4 weeks of pitavastatin treatment (0.43% of patients per week) than after longer exposure; between 24 and 52 weeks the incidence was still 0.16% of patients per week. A similar trend was found with CK > 1x ULN, symptomatic myopathy and myalgia. This was also the case with simvastatin.

**Renal and urinary disorders**

In Group 1, the rate of renal and urinary disorders was 1.3% and 1.0% in the 2 mg and 4 mg pitavastatin groups, respectively, compared to 1.4% in the placebo group, 0%-2.1% in
the atorvastatin group, 1.7%-1.9% in the simvastatin group and 0%-1.0% in the pravastatin group. The most frequent TEAEs were pollakiuria (abnormally frequent urination) (0.3% versus 0% placebo) and blood in urine (0.2% versus 0%). The frequency of blood in the urine rose with increasing dose to 5.9% and 6.1% with the 32 mg and 64 mg doses, respectively. There were 5 SAEs: urinary incontinence (2 mg dose group), increased creatinine (4 mg dose group), myoglobinuria (32 mg dose group), proteinuria and haematuria (64 mg dose group) and one renal failure (64 mg dose group). There were no renal/urinary SAEs in the placebo group.

In Group 3, the rate of renal/urinary disorders was 2.2% and 1.8% in the 2 mg and 4 mg dose groups, respectively. These included haematuria (0.6% and 0.5%), nocturia (0.3% and 0.2%), leukocyturia (0.2% for both), chronic renal failure (0.1% and 0.2%) and urinary calculus (0% and 0.2%). The additional SAEs were bladder prolabse and urethral stricture. In Group 3, the incidence of acute renal failure TEAEs (Standardized MedDRA Queries (SMQ)) was 0.005 and 0.002 per patient year for the 2 mg and 4 mg doses, respectively, which was less than with simvastatin (0.024 at 20 mg and 0.013 at 40 mg).

Hepatobiliary disorders

In Group 1, the rate of Hepatobiliary SOC TEAEs was 0.1% which can be compared to 0.5% in the placebo group. There was one case of cholestatic jaundice (1 mg), 2 of acute cholecystitis (2 mg and 4 mg) and 1 hepatic steatosis (4 mg). In the Investigations SOC, for all pitavastatin doses, the rate of ALT increased was 1.1% and the rate of AST increased was 0.7%, with lower rates in the 2 mg (1.1% and 0.3%) and 4 mg (0.3% and 0.2%) dose groups.

There were no serious Hepatobiliary TEAEs with pitavastatin in Group 1, though there were 4 subjects with SAEs in the Investigation SOC: 2 with AST increased and 2 with ALT increased, all of whom were on high pitavastatin doses (32-64 mg). With the comparators, there were 2 cases cholelithiasis (one with simvastatin and one with pravastatin).

In Group 3, the rate of Hepatobiliary SOC TEAEs in the 4 mg group increased to 0.7%, and there was also a rise in increased AST (1.1%) and increased AST (0.7%). Rates with 2 mg pitavastatin were steady. The rate of possible drug related hepatic disorders (SMQ) in Group 3 was 0.087, 0.024 and 0.25 per patient year exposure in the 1 mg, 2 mg and 4 mg pitavastatin groups, respectively. For the 2 and 4 mg dose group these rates were comparable to simvastatin (0.024 and 0.040 for 20 mg and 40 mg, respectively) and atorvastatin 20 mg (0.051). In contrast to rhabdomyolysis/myopathy which tended to occur earlier during treatment, drug related hepatic disorders had onsets which occurred throughout the 52 treatment period.

Eye disorders

Due to a finding of cataracts in dogs in the nonclinical studies, the Eye disorder SOC was analysed. The rate of Eye disorder TEAEs in Group 1 was 0.7% compared to 1.4% in the placebo group. There were 8 cases of conjunctivitis, 2 of reduced visual acuity, 2 of blurred vision and 2 of vitreous floaters. There were no other disorders occurring in >1 patient. There were no reports of cataracts in pitavastatin treated patients. In Group 3, the rate of Eye disorders was 1.6% and 1.5% in the 2 mg and 4 mg groups, respectively. The rate of conjunctivitis was 0.4% and the rate for cataracts was 0.2%.

Japanese program

A summary of the integrated safety analysis of 886 patients from the 2 Phase II and III studies in the Japanese program reported that the AE rate was 65.0% with treatment related AEs in 22.2% of patients. The most frequent AEs were cold syndrome (8.5%),

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44 Note: this Japanese data could not be verified as only summary data included in the current Australian submission.
abdominal pain (4.4%), pharyngitis (4.0%), cough (4.0%), headache (2.8%) and back pain (2.8%). The most frequent laboratory AEs were increases in gamma-glutamyl transferase (GGT) (12.2%), CK (10.2%), ALT (9.1%), AST (7.2%) and lactate dehydrogenase (LDH) (5.4%), hyperglycaemia (4.3%), leukocytosis (3.3%), proteinuria (3.3%), haematuria (3.2%) and decreased testosterone (3.0%).

**Healthy volunteers**

In healthy volunteers treated with pitavastatin doses of ≥24 mg there were notable increases in AST, ALT and CK. A Thorough QT study found no QTcI prolongation at therapeutic and supratherapeutic doses (16 mg).

**Serious adverse events and deaths**

**Deaths**

There were no deaths in the Phase II studies, 2 in the short term Phase III studies (1 on pitavastatin 4 mg and 1 on simvastatin 20 mg) and 5 in the long term studies (2 patients on 2 mg and 3 patients on 4 mg pitavastatin). The causes of death in the pitavastatin patients were non-Hodgkin’s lymphoma, bronchopneumonia and cerebrovascular accident, myocardial infarction, hypoxic encephalopathy, cardiac death, and myocardial ischaemia. The death while on simvastatin was a sudden cardiac death. None of the deaths were considered treatment related. There was also one death due to a subarachnoid haemorrhage in a patient treated with pitavastatin 16 mg. There were no deaths in the Japanese, Chinese or Korean studies or in the healthy volunteer studies.

**SAEs**

In Group 1, there were a total of 68 serious TEAEs with 45 in the pitavastatin group. The SAE rate was 1.3% with pitavastatin compared to 1.6% for atorvastatin, 3.0% for simvastatin, 1.3% for pravastatin and 0.5% for placebo. The rate of SAEs was not obviously dose dependent at lower doses (0.3%, 1.1%, and 1.4% for 1, 2 and 4 mg) but increased noticeably with doses of 32 mg (8.8%) and 64 mg (9.1%). The most common SAEs were rhabdomyolysis (0.2%), myocardial infarction (0.2%), ALT increased (0.1%), AST increased (0.1%), blood CK increased (0.1%), myalgia (0.1%) and burning sensation (0.1%). The SAEs which occurred at the 2 mg and 4 mg dose level were myocardial infarction (0.1% and 0.3%) and burning sensation (0.2% and 0%). The MI rate in the placebo group was 0.5%. The rate of treatment related SAEs as assessed by the investigator was 0.3% (8 cases of rhabdomyolysis, 1 case of burning sensation with generalised pruritus and one case of acute pancreatitis).

In Group 3, the SAE rate was 2.6% and 3.0% in the pitavastatin 2 mg and 4 mg groups, respectively, compared to 0.8% and 3.8% with 20 mg and 40 mg atorvastatin respectively, and 1.5% and 5.0% with 20 mg and 40 mg simvastatin, respectively. In elderly subjects in the extension study (NK-104-308), SAEs reported by more than one subject were prostate cancer (6 subjects, 1.1%), osteoarthritis (four subjects: 0.7%), angina pectoris, myocardial infarction, breast cancer and cerebrovascular accident (two subjects each; all 0.4%).

There were 21 patients with SAEs in the Japanese program with none considered treatment related and none in the Chinese or Korean studies. In the healthy volunteers treated with pitavastatin, there were 2 spontaneous abortions in the EU/US studies and one subject with tonsillitis in a Japanese study.

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45 Since 2005 the FDA and European regulators have required that nearly all new molecular entities are evaluated in a Thorough QT (TQT) study to determine a drug's effect on the QT interval. [http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf]

46 Sponsor comment: “At doses up to 64 mg.”

47 Sponsor comment: “At all pitavastatin doses.”

48 Sponsor comment: “At any dose.”
Laboratory, ECG and vital sign findings

Creatine kinase

In Group 1, a shift from normal CK at baseline to high CK at study endpoint occurred in 6.1%, 7.0%, 7.1% and 9.8% of the 1 mg, 2 mg, 4 mg and 8 mg pitavastatin groups, respectively, compared to 9.6% in the placebo group. These rates were comparable to simvastatin (7.9% to 8.4%) and atorvastatin (4.2% to 6.7%) but higher than pravastatin (1.0% to 5.2%). Higher rates of CK elevation were seen with pitavastatin 16 mg to 64 mg (19.6% to 38.2%). Elevation of CK >1 x ULN was reported in 21.4 to 21.8% of patients in the pitavastatin 1 mg to 4 mg groups, respectively, and this was lower than placebo (30.3%), similar to simvastatin and atorvastatin and higher than pravastatin. In Group 3, the rate of CK >1 x ULN was 17.2% and 28.3% in the 2 mg and 4 mg groups, respectively.

ALT

In Group 1, a shift from normal ALT at baseline to high ALT at study endpoint was slightly higher for the 1 mg to 4 mg doses than placebo (5.2% to 7.7% versus 4.3%). There was a notable dose dependent increase, with rates of 19.6% to 42.4% in the 16 mg to 64 mg dose groups. At the proposed doses of pitavastatin, the rates were lower than simvastatin (11.8% to 12.1%) and atorvastatin (6.8% to 13.7%) but higher than pravastatin (1.0% to 4.9%). Elevation of ALT >1 x ULN was reported in 19.4% to 26.0% of pitavastatin 1 mg to 4 mg groups which was higher than placebo (16.3%) and pravastatin and similar to atorvastatin and simvastatin. The rate of ALT >3 x ULN was 0.3%, 0.5% and 0.1% in the 1 mg, 2 mg and 4 mg dose groups, respectively, which was higher than those of atorvastatin and pravastatin (no cases for either) and similar to simvastatin 40 mg (0.4%) treatment. In Group 3, the rate of ALT >1 x ULN was 18.5% and 35.5% in the 2 mg and 4 mg groups, respectively.

AST

In Group 1, a shift in AST from normal at baseline to high at study endpoint was greater with pitavastatin 1 mg to 4 mg than placebo (4.2% to 7.0% versus 0.5%) with a dose dependent increase as seen with ALT. The increase was in line with the other statins. In Group 3, the rate of ALT >1 x ULN was 15.8% and 32.4% in the 2 mg and 4 mg groups, respectively.

Haematology and other biochemistry

There were no notable findings on haematology in terms of shifts from baseline to high or low values. There were no other notable biochemistry findings.

Proteinuria

Urine dipsticks were conducted during the study and positive results sent for laboratory analysis. These results were not pooled. In response to an FDA request, 24 hour urine collection was conducted to assess protein excretion in 4 Phase III studies (NK-104-301, 302, 304 and 305). This commenced after study start so the subject numbers were limited. A protein: creatinine ratio lower limit of 0.26 mg/mg (30 mg/mmol) was taken as the clinical threshold for new proteinuria. Integrated data from the 4 studies included 334 subjects, 5.8% and 11.4% of the pitavastatin 2 mg and 4 mg groups, respectively. Data was available for the atorvastatin and simvastatin groups but not for any of the placebo or pravastatin groups. There was a small mean change from baseline in the urine protein:creatinine ratio in the pitavastatin 2 mg and 4 mg groups which was slightly higher than with simvastatin or. There were 5.5% and 1.1% of the pitavastatin 2 mg and 4 mg groups, respectively, who shifted from a ratio of <0.26 to ≥0.5 mg/mg.

ECG

In the Thorough QT study (NK-104-1.34US) there was no evidence of an effect of pitavastatin (4 mg and 16 mg) on the QT interval. In Group 1, a shift from normal to
abnormal and clinically significant ECG was low (0-1% for pitavastatin 1 mg to 8 mg). In Group 3, the rate was 1.3%, 0.7% and 2.6% of the pitavastatin 1 mg, 2 mg and 4 mg groups, respectively. Overall, there were no changes of note in mean cardiac cycle measurements in the clinical studies. There was one patient in extension study NK-104-307 who had a prolonged QT interval and arrhythmia and who was treated with pitavastatin 4 mg. In the elderly study (NK-104-306) there were 5 pitavastatin patients who had clinically significant ECG changes reported as AEs. These were T wave depression, first degree AV block, atrial fibrillation, myocardial infarction and QRST changes on anterolateral leads. There was one patient on pravastatin with sinus bradycardia. In the extension of this study there was one atrial fibrillation and one tachycardia.

**Safety in special populations**

Subgroup analyses on the integrated safety database were conducted on Group 3.

**Gender**

There were no differences in TEAE rates between females and males, apart from a higher rate in females than males treated with 1 mg pitavastatin (55.9% versus 45.2%). The nature of AEs was similar between the sexes.

**Age**

TEAE rates were higher in the elderly (≥65 years) than younger patients across the 1 mg, 2 mg and 4 mg doses. There was also a higher rate of serious TEAEs in the elderly. There were more AEs of rhabdomyolysis/myopathy (6.6% versus 2.3% with 2 mg) and additional muscular events in the elderly, particularly with the 2 mg dose which did not appear dose dependent. There was also a small increase in acute renal failure in the elderly (1 mg: 0.5% versus 0%; 2 mg: 0.3% versus 0%; 4 mg: 0.2% versus 0.1%).

**Race**

Most patients were Caucasian with the second largest ethnic group being South Asian (Asian and Indian). TEAE rates were lower in the South Asians than Caucasians at 2 mg (12.7% versus 38.7%) but similar at 4 mg (46.8% versus 52.1%). Selected AEs of interest had generally lower rates in the South Asian patients when treated with the 2 mg dose, however when treated with the 4 mg dose the rate of myalgia was higher in South Asians (8.3% versus 3.7%). There were too few subjects from other ethnic groups to draw any conclusions.

**Baseline LDL-C**

Baseline LDL-C category (<160, 160-190, 190-220, and ≥220 mg/dL) did not appear to influence AE rates or nature.

**NCEP risk category**

There were no notable findings by NCEP risk category (low, moderate and high).

**Primary diagnosis**

There were no notable safety findings by primary diagnosis (primary hypercholesterolaemia or combined dyslipidaemia) though the number of patients with HeFH was low.

**Diabetes and hypertension**

The rate of TEAEs or Serious TEAEs was not higher in diabetic patients. There were no notable findings relating to the nature of AEs in diabetics. The rate of AEs in hypertensive patients was unremarkable compared to those without hypertension although there were more cases of acute renal failure in the hypertensive group.
BMI

AE rates and nature did not appear to be affected by BMI (19 to <30 or ≥30 kg/m²).

Renal or hepatic impairment

There is evidence that renal impairment and hepatic impairment both affect the PK of pitavastatin. In the small group of subjects with renal impairment (10 with moderate impairment and 10 patients on haemodialysis) in Study NK-104-1.24 there were no notable safety findings. The integrated database was not analysed by baseline renal or hepatic function.

Immunological events

Not applicable.

Safety related to drug-drug interactions and other interactions

There were 12 pharmacokinetic drug interaction studies with no safety issues raised. Increased exposure to pitavastatin was noted in particular with gemfibrozil49, erythromycin and cyclosporine. A list of the excluded medications and those permitted with limitations in the Phase III program was submitted. Drug interactions were not examined in the Phase III program.

Discontinuation due to adverse events

In the Group 1 short term studies, the trial discontinuation rate was 7.1%, 5.9% and 5.7% in the 1 mg, 2 mg and 4 mg pitavastatin groups, respectively. Higher rates occurred in the higher dose groups due to the premature study termination and a higher rate of AEs. TEAEs leading to discontinuation occurred in 3.9%, 3.3% and 3.1% of the 1 mg, 2 mg and 4 mg pitavastatin groups, respectively, compared to 1.9% in the placebo groups, 4.0% in combined atorvastatin groups, 3.0% in the simvastatin groups and 5.3% in the pravastatin groups. The rates for pitavastatin 1-4 mg doses were greater than those for atorvastatin 10 mg (0%), similar to atorvastatin 20 mg and 40 mg (2.1% and 3.9%) and less than that of atorvastatin 80 mg (11.5%). Discontinuation rates were also similar to the 2 simvastatin doses (3.7% with 20 mg and 3.9% with 40 mg). With higher pitavastatin doses the TEAE discontinuation rate increased from 4.6% at 8 mg to 36.4% at 64 mg. The most common TEAEs leading to discontinuation of pitavastatin (all doses) were myalgia (1.0%), blood CK increased (0.6%), ALT increased (0.4%), AST increased (0.3%), fatigue (0.3%), and pain in extremity (0.3%).

In the Group 3 short term and extension studies, the discontinuation rate was 7.8%, 7.0% and 9.4% and the rate due to TEAEs was 3.9%, 3.3% and 3.7% in the pitavastatin 1 mg, 2 mg and 4 mg groups, respectively. The shorter exposure time with the comparator statins made the interpretation of the lower discontinuation rates difficult.

The discontinuation rate due to “adverse drug reactions” was reported as 2.8% in a summary of the Japanese studies. The rate due to TEAEs was not stated.

Postmarketing experience

Periodic Safety Update Reports (PSURs)

The international birth date of pitavastatin was 17 July 2003 in Japan. Since then there have been 12 PSURs (Product Safety Update Reports) from number 1 dated 16 March

49 Sponsor comment: “The concern with gemfibrozil is of a pharmacodynamic interaction, that is, of two drugs known to cause myopathy administered together.”
2004 to number 12 dated 11 September 2009. The serious unlisted ADRs over this time are listed in Table 28. There were 2 deaths: one due to rhabdomyolysis and one due to interstitial pneumonia. The case of interstitial pneumonia was thought to be drug related and the patient was on valsartan as well as pitavastatin. The patient with rhabdomyolysis had received pitavastatin 2 mg for just under 1 year when symptoms began.


<table>
<thead>
<tr>
<th>SOC</th>
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<tr>
<td></td>
<td>Cataract operation</td>
<td>3</td>
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</tbody>
</table>

*fatal case.

**LIVS-01**

This was a postmarketing surveillance study in Japan in which 20,279 patients were surveyed and 19,925 enrolled between 2003 and 2005, with follow up to 2007. The main areas of focus in the study were rhabdomyolysis, muscle symptoms, elevated CK, elevated AST or ALT, cataracts and use of concomitant medication. The study report included in the Australian submission only related to the first year of surveillance but details from the 2 years were included in the sponsor’s Summary of Clinical Safety.

There were an estimated 28,969 patient years of exposure in the study with 11,454 at 1 mg, 17,336 at 2 mg and 119 patient years at 4 mg. During the 2 years, 42.5% of patients discontinued and 7.4% reported as discontinued due to adverse events. ADRs were reported in 10.4% of patients and 0.13% (n=27) had a serious ADR. There were no deaths in the study. The most frequent ADRs were increased (levels of) CK (2.7%), increased AST (1.8%), increased ALT (1.5%), myalgia (1.1%) and increased GGT (1.0). The most frequent
serious ADRs were hepatobiliary events (0.04%). There were 36 cataract associated AEs, 6 reported as ADRs and of these 3 required surgery, there were also 3 cataract operations. There were 2 cases of rhabdomyolysis (0.01%) with one being serious.

**Rhabdomyolysis/myopathy**

There have been 56 postmarketing reports of serious rhabdomyolysis/myopathy according to the Standard MedDRA Query (SMQ) to July 2009. Of these, 52 were spontaneous and 4 were from LIVS-01. In this study, the rate of rhabdomyolysis/myopathy (serious and non serious) was 4.4%, 3.8% and 4.5% in patients treated with 1 mg, 2 mg and 4 mg pitavastatin, respectively. Over the 2 years, the incidence of serious rhabdomyolysis/myopathy was noted to increase with increasing dose from 0.01% with 1 mg to 0.03% with 2 mg. There were no cases with 4 mg pitavastatin although the numbers were too small (n=247) to be able to draw any definite conclusions.

**Hepatobiliary disorders**

From 2003 to 2009 there were 39 hepatobiliary disorder serious ADRs from post marketing surveillance in the Japan region, including results from Study LIVS-01. These were associated with increased transaminases of 10 to >20 times ULN. In Study LIVS-01 the incidence of hepatobiliary disorders (serious and non serious ADRs) was 0.06%. Of the 8 serious hepatobiliary ADRs in LIVS-01 none had liver failure but 2 patients had increased bilirubin (≥3 mg/dL) suggesting impaired hepatic function.

**Renal and urinary disorders**

From post marketing surveillance most renal and urinary disorders were non serious and were mainly urinary discolouration and pollakiuria. There were 5 renal ADRs (3 serious): renal impairment, nephrotic syndrome, interstitial nephritis, non-serious renal failure, and non-serious renal disorder. The rate of renal and urinary disorders in LIVS-01 was 0.09%.

**Other post marketing studies**

LIVS-02 was a postmarketing surveillance study of 50 Japanese patients with chronic liver disease who were followed for 6 months. A brief translated CSR was included. LIVT-03 was a Japanese open label, parallel group, pharmacokinetic study of pitavastatin 2 mg in 6 patients with renal impairment and 6 subjects with normal renal function.

There were also 5 translated Korean study synopses included in the postmarketing section of the Australian submission and these have been listed below for reference. Due to the small numbers, frequently uncontrolled design and differing methodology, no further assessment was undertaken.

CWP-PTV-201 was an 8 week open label, single group study of pitavastatin 2 mg (and optional titration to 4 mg) in 131 Korean patients with dyslipidaemia and high risk of CHD. CWP-PTV-301 was an 8 week randomised, open label, parallel group study of 87 Korean patients with hypercholesterolaemia in which patients were randomised to pitavastatin or their usual statin therapy. CWP-PTV-501 was a single group, uncontrolled, open label study of pitavastatin 2 mg in 24 Korean patients with dyslipidaemia. CWP-PTV-601 was a single group, open label, dose titration study of pitavastatin 2 mg (with titration to 4 mg if required) in 51 patients with dyslipidaemia. CWP-PTV-S01 was an 8 week randomised, open label, parallel group study of pitavastatin (2 mg to 4 mg) compared to atorvastatin (10 mg to 20 mg) in 289 patients with hypercholesterolaemia.

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50 The sponsor comment that cataract was an item of special interest in LIVS-01: “Thirty-six patients had cataract surgery and 24 patients had a diagnosis of cataract in this study”. The sponsor confirmed that six were reported as ADRs.
Evaluator's overall conclusions on clinical safety

Pitavastatin has been evaluated in 77 studies of which 26 healthy volunteer and 18 patient studies contributed to the EU/US program. The pooled safety analysis of pitavastatin included 5 Phase II and 5 Phase II randomised controlled studies and 4 long term extension studies. The main groupings in the integrated safety analysis were Group 1 (short term 12 to 16 week Phase II and III studies) and Group 3 (all Phase II and III core and extension studies, ignoring treatment gaps). In the Phase II and III studies there were 309 patients exposed to pitavastatin 1 mg, 951 patients exposed to pitavastatin 2 mg and 1540 patients exposed to pitavastatin 4 mg. In the 4 extension studies there were a total of 2284 patients, with 1617 (70.8%) subjects on pitavastatin 4 mg and 539 subjects on pitavastatin 2 mg. The mean exposure in Group 1 was 12 weeks for doses of 1 to 4 mg. The mean exposure in Group 3 was 37.4 weeks for the 4 mg dose. A post marketing surveillance study (LIVS-01) conducted in Japan enrolled approximately 20 000 patients, with nearly all the patients treated with 1 mg or 2 mg pitavastatin. There were an estimated 28,969 patient years of exposure in the study; 11,454 patient years at 1 mg, 17,336 patient years at 2 mg and 119 patient years at 4 mg.

In the short term studies (Group 1), the TEAE rate was 50.5%, 35.3% and 39.4% in the 1 mg, 2 mg and 4 mg pitavastatin groups, respectively. There was a dose dependent increase in TEAEs at the higher doses of 8 mg to 64 mg. The AE nature was as would be expected with this class of drug; the most common TEAEs were nasopharyngitis, myalgia, headache, constipation, nausea, diarrhoea, back pain, influenza, arthralgia and fatigue. Myalgia, muscle spasms, nausea, headache, fatigue, increased CK, increased AST, increased ALT, pruritus, blood in the urine and myopathy all demonstrated dose dependent increases. TEAEs were in line with the comparator statins (simvastatin, atorvastatin, pravastatin).

There were 6 deaths in the clinical program in pitavastatin patients: non-Hodgkin’s lymphoma, bronchopneumonia and cerebrovascular accident, myocardial infarction, hypoxic encephalopathy, cardiac death and myocardial ischaemia. There was also one death from a subarachnoid haemorrhage with 16 mg XL dose. There have been 2 deaths reported from post marketing surveillance; one from rhabdomyolysis and one from interstitial pneumonia.

There were 45 SAEs in pitavastatin treated patients in the short term core studies. The SAE rate was 1.3% with pitavastatin (all doses up to 64 mg) which can be compared to 1.6% for atorvastatin, 3.0% for simvastatin, 1.3% for pravastatin and 0.5% for placebo. The rate of SAEs was higher with pitavastatin doses of 8 mg and above. Most SAEs were cardiovascular disease related and at the 1 to 4 mg doses there were no SAEs related to elevated ALT, AST, CK or rhabdomyolysis. In Group 3 the SAE rate was 2.6% and 3.0% in the 2 mg and 4 mg groups, respectively, which was in line with the other statins.

Overall, the discontinuation rate in Group 3 was 12.3% at pitavastatin doses of 1 to 4 mg. Discontinuations due to AEs were reported in 3.6%, 3.4% and 4.3% of the 1 mg, 2 mg and 4 mg groups, respectively. The most common reason was myalgia. Discontinuation of pitavastatin (at doses of 1 to 4 mg) due to AEs was similar to that which occurred at the lower doses of the comparators and less than with higher comparator doses.

The adverse events of interest with statins are rhabdomyolysis/myopathy, liver disorders/transaminase changes and renal disorders. The data from the Japanese postmarketing surveillance added to the information on these adverse events.

The risk of rhabdomyolysis was present at doses of 8 mg and above; there were 9 cases in the Phase II program while no cases were reported in patients given the 1 to 4 mg doses.

In the long term analysis (Group 3), musculoskeletal and connective tissue disorders had a rate of 11.0% and 13.3% in the 2 mg and 4 mg dose groups, respectively. This was slightly higher than in the short term studies (Group 1); 8.5% and 8.0% for the 2 mg and 4 mg
groups, respectively. Except for a higher rate seen with atorvastatin 80 mg (19.8%), these rates were in line with the other statins. In Group 1, symptomatic myopathy (muscle pain, spasm or weakness) occurred in 8.6% of patients and elevated CK without myopathy symptoms was frequent with mild elevations (1 to <10 times) in 27.5% of patients, moderate (≥10 times to <50 times) in 0.3% of patients and marked elevation (≥50 times) in 0.03% of patients. The rate of CK elevation between 1 to <10 times ULN was no greater than placebo. The rate of patients reporting higher CK levels was not higher than with the comparators. In Group 1, the incidence of rhabdomyolysis/myopathy at the 2 and 4 mg pitavastatin doses was 0.136 and 0.122 per patient year, respectively, compared to 0.061, 0.102 and 0.130 for atorvastatin 10 mg, 20 mg and 40 mg, respectively, and 0.259 and 0.148 for simvastatin 20 mg and 40 mg, respectively.

Overall, the 1 to 4 mg pitavastatin doses did not appear to have a greater risk of myopathy than the comparators.

The rate of renal and urinary disorders was comparable to the other statins and not higher than in the placebo group. With high doses (34 and 64 mg) of pitavastatin there was a risk of haematuria. The most frequent TEAEs were abnormally frequent urination (0.3%) and blood in the urine (0.2%) which appeared related to the high pitavastatin doses. The incidence of acute renal failure TEAEs (SMQ) was 0.005 and 0.002 patients per patient year for the 2 mg and 4 mg doses, respectively, compared to 0.024 and 0.013 for simvastatin 20 mg and 40 mg, respectively. Proteinuria was assessed on a subgroup and a small mean change in the urine protein: creatinine ratio was not remarkable.

Hepatobiliary disorders were not elevated compared to placebo in Group 1 (0.1% versus 0.5%) while in Group 3 the rate of hepatobiliary System Organ Class (SOC) TEAEs increased to 0.7%. In Group 3, the rate of increased ALT >3 times ULN was 0.3% and 0.7% in the 2 mg and 4 mg dose groups, respectively. Liver enzyme (AST and ALT) elevations were dose dependent and the rate of ALT >3 times ULN was higher with pitavastatin (0.1% to 0.5%) than with pravastatin (0%) and atorvastatin (0%). As these are rare events this finding could be due to the lower exposure in the comparator groups.

There were no other notable haematology or biochemistry findings. ECG findings were unremarkable and there was no evidence of QT prolongation in the thorough QT trial.

There was an increased frequency of AEs and SAEs in the elderly and this included an increased risk of rhabdomyolysis/myopathy which did not appear to be dose dependent. The ethnicity was predominantly Caucasian. South Asians in general had a lower rate of TEAEs although myopathy in those treated with 4 mg was higher. There were too few participants from other racial groups to draw any definite conclusions with respect to effects of race. Assessment of safety in other subgroups did not reveal any signals. There was a higher rate of AEs in women treated with the 1 mg dose but not with the other doses.

**List of questions**

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a “list of questions” to the sponsor is generated.

**Efficacy**

Are there any clinical trial data in patients with homozygous familial hypercholesterolaemia? This information or lack thereof needs to be included in the product information.
Safety

Are there any data relating to the effect of pitavastatin on endocrine function? This information or lack thereof needs to be included in the product information.

Clinical summary and conclusions

Pharmacokinetics

No studies examined the pharmacokinetics of pitavastatin in the target population or in breastfeeding mothers or in women during pregnancy.

The oral bioavailability, mean oral apparent plasma clearance and apparent volume of distribution of NK-104 were 51%, 183 mL/minute and 226 L, respectively.

Pitavastatin is highly bound to plasma protein with an unbound fraction (fp) of 0.4% to 0.5% in human plasma. The major pitavastatin binding protein is human serum albumin (concentration 4%) with an unbound fraction of 0.4% to 0.5%. Pitavastatin binding to α1-AGP (α1-acid glycoprotein, concentration 0.06%) is also strong (fp 5.1 to 5.7%).

In plasma, the T\text{max}, C\text{max}, AUC_{\text{inf}}, CL/F and t\text{1/2} of NK-104 following a 2 mg PO dose were 0.68 hours, 21.4 ng/mL, 47.4 ng.h/mL, 838 mL/min and 5.2 hours, respectively. The C\text{max}, AUC_{\text{inf}} and t\text{1/2} of the primary and inactive metabolite of oral pitavastatin, pitavastatin lactone, were 19.0 ng/mL, 168.7 ng.h/mL and approximately 12 hours, respectively. The mean NK-104 A\text{e}_{\text{ur, 0 – last}} was 6299 ng indicating that mean renal clearance was low and amounted to less than 1% of the calculated plasma clearance.

Following doses of 14C-pitavastatin, the main radioactive components identified in plasma up to 24 hours postdose was unchanged pitavastatin and pitavastatin lactone. In addition, two unidentified minor metabolites, which accounted for more than 5% of the radioactivity, were also identified.

Radioactivity was primarily excreted in the faeces and accounted for 78.6% of the dose, with 89% of the total faecal radioactivity recovered by 96 hours. By contrast, only 15.1% of the radioactivity was recovered in the urine. Excretion in urine was initially rapid with 80% of the total radioactivity recovered during 24 hours postdose which had increased to 97% by 72 hours.

In the faeces, unchanged pitavastatin accounted for 58.2% of radioactivity and four metabolites represented less than 15% of the radioactivity.

In comparison to lovastatin, simvastatin, atorvastatin and fluvastatin, the metabolism of 14C-pitavastatin by human liver microsomes was minimal. This suggests that pitavastatin undergoes little hydroxylation compared to other statins.

Pitavastatin uptake into human liver is in part mediated by OATP1B1, whereas pitavastatin and its lactone metabolite were only slightly metabolised by the human CYP isoforms (including CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4).

The UGT molecular species involved in the lactonisation reaction were identified as UGT1A3 and UGT2B7.

The formulation used for the Phase 3 studies manufactured by SkyePharma, the formulation which is the subject of this application (Pierre Fabre) and Japanese commercial formulation are bioequivalent.

A high fat meal reduced the peak concentration of NK-104 by 43% and increased the median T\text{max} from 1 hour to 2 hours. By contrast, no significant decrease in average bioavailability was observed when NK-104 was administered with food and the 90%
confidence intervals for AUC<sub>0-t</sub>, AUC<sub>0-72</sub> and AUC<sub>0-inf</sub> were all within the 80-125% no significant effect limits.

For the lactone metabolite, the mean C<sub>max</sub> decreased by approximately 25% following a high fat meal and the median T<sub>max</sub> increased from 2 to 4 hours. The AUC<sub>0-inf</sub> was unchanged.

Steady state plasma levels of pitavastatin were reached following 4 to 6 days of repeat dosing.

The C<sub>max</sub> and AUC of pitavastatin increased linearly with the dose over the dosage range of 1 to 64 mg whereas the absorption rate of parent drug remained constant; the T<sub>max</sub> of both parent drug and metabolite did not vary with increasing dose.

Time of dosing (AM or PM) did not affect the PK of pitavastatin.

Elderly subjects had higher systemic exposure compared to non-elderly subjects (by about 10% in C<sub>max</sub> and by about 30% in AUC).

Females had significantly higher C<sub>max</sub> (1.6 fold) and AUC (1.5 fold) values than males.

PKs of pitavastatin were similar in Black, Asian and Caucasian subjects.

Mean AUC<sub>0-24</sub> of the unchanged compound on Day 7 was slightly lower in subjects with impaired hepatic function (98.1 ng.hr/mL) compared to subjects with normal hepatic function (119.8 ng.hr/mL).

There was a 16% decrease in AUC<sub>0-24</sub> and 12% decrease in C<sub>max</sub> in subjects with fatty liver, a form of hepatic impairment, compared to healthy subjects.

The mean C<sub>max</sub> and AUC<sub>0-t</sub> of pitavastatin were 1.34 and 1.60 times greater in subjects with Child-Pugh Grade A, respectively, and 2.69 and 3.93 times greater in subjects with Child-Pugh Grade B, respectively, compared to healthy subjects.

The pitavastatin C<sub>max</sub> was 1.4 and 1.6 times higher in patients requiring haemodialysis and patients with moderate renal impairment, respectively, compared to healthy subjects. In addition, AUC<sub>0-t</sub> was 1.7 and 1.8 times higher, respectively, and CL/F was 0.5 and 0.6 times lower in these two patient groups, respectively.

Bezafibrate, grape fruit juice, ezetimibe, digoxin and enalapril when co administered with pitavastatin had little to no effect on pitavastatin PKs, however, fenofibrate increased the AUC<sub>0-24</sub> of pitavastatin by 18% and gemfibrozil significantly increased both pitavastatin C<sub>max</sub> and AUC<sub>0-24</sub> by 31% and 45%, respectively.

Cyclosporin increased the C<sub>max</sub> and AUC<sub>0-24</sub> of pitavastatin 6.6 and 4.6 times, respectively, and it is therefore recommended that co administration of these two drugs is contraindicated.

Erythromycin co administration produced an approximate 3 fold increase in systemic exposure to pitavastatin and co administration should be contraindicated.

Co administration of itraconazole (a CYP3A4 inhibitor) induced a 23% decrease in the AUC of pitavastatin.

The pharmacokinetic parameters of enalapril and enalaprilat were similar when enalapril was co administered with pitavastatin compared to administration alone. Co administration of single daily doses of 4 mg pitavastatin with warfarin did not affect the C<sub>max</sub> or the AUC of R- and S-warfarin.

**Pharmacodynamics**

No studies examined the pharmacodynamics of pitavastatin in the target population.
Although pitavastatin induced a slightly greater reduction in LDL-C levels following night time dosing compared to a morning dose the difference was deemed to be clinically insignificant.

There is little evidence that supra therapeutic doses of pitavastatin (16 mg) affect QT interval.

The data relating to a dose and PD response relationship existing for pitavastatin is equivocal.

Pitavastatin did not affect the steady state PD of warfarin.

**Clinical efficacy**

The clinical development of pitavastatin has been comprehensive with studies for both Japanese and EU/US registration. The studies were conducted in accordance with guideline for GCP and for assessment of medications for lipid disorders. The primary efficacy endpoint throughout the development program was reduction LDL-C with LDL-C target attainment (by NCEP and EAS criteria) and other lipid parameters as secondary endpoints. Change in lipid levels were assessed after appropriate washout of other lipid lowering medication, implementation of appropriate diet and after 12 weeks of treatment. LDL-C was evaluated using the Friedewald equation at a central laboratory and the study staff were blinded to the results. Statistical analyses used the LOCF and ANCOVA. Adults with primary hypercholesterolaemia or combined dyslipidaemia were included with a small number of patients with HeFH. Patients with secondary dyslipidaemia were excluded from the program.

There were 5 dose ranging studies assessing doses of 1 mg to 64 mg once daily. Three studies assessed the higher doses of pitavastatin (8 mg to 64 mg in NK-104-209 and 4 mg to 8 mg in NKS104A2204 and NK-104-210) and these all found muscle toxicity at doses of 8 mg and above and were prematurely terminated. The other 2 studies (NK-104.2.02 and NK-104.2.03) assessed doses of 1 mg to 8 mg and found efficacy at all doses and a 33.3% mean reduction in LDL-C with the 1 mg dose. The minimum effective dose was 1 mg and the 4 mg chosen was set as the maximal dose due to the risks seen with the 8 mg dose.

There were 5 Phase III trials, with 2 pivotal trials (NK-104-301 and NK-104-302) and 3 trials in specific populations (elderly, diabetics and those with CVD risk factors). Except the elderly study which also included the 1 mg dose, these trials assessed the 2 mg and 4 mg pitavastatin doses. All 5 trials were non inferiority studies with a non inferiority margin on mean percentage reduction in LDL-C of 6%.

From pooled analysis after 12 weeks of treatment, pitavastatin 1 mg, 2 mg and 4 mg reduced LDL-C by approximately 31%, 38% and 43%, respectively. LDL-C target attainment by NCEP criteria at Week 12 was 83%, 70% and 82% for the three doses, respectively. By EAS criteria the LDL-C target attainments were 60%, 64% and 81% for the 3 doses, respectively. Efficacy was seen with reductions in TC, TG, non-HDL-C and Apo-B. There was also a small mean increase in Apo-A1 and HDL (of 3.4%, 4.7% and 6.4% for the latter, respectively).

In comparison to the other statins:

- Pitavastatin 1 mg was superior to pravastatin 10 mg in the elderly.
- Pitavastatin 2 mg was non inferior to atorvastatin 10 mg in non diabetics and superior to simvastatin 20 mg and pravastatin 20 mg (elderly).
- Pitavastatin 4 mg was superior to pravastatin 40 mg in the elderly, non inferior to atorvastatin 20 mg in non diabetics, non inferior to simvastatin 40 mg in those with high CHD risk.
- Pitavastatin 4 mg was not inferior to atorvastatin 20 mg in the Type II diabetics. While pitavastatin 4 mg did not meet the non-inferiority criteria compared to atorvastatin 20 mg in diabetic patients, there was still a mean LDL-C reduction of 40.7% (compared to 43.3% with atorvastatin) which is clinically relevant.

The efficacy on secondary lipid parameters was comparable to the currently marketed statins. It should be noted that maximal doses of comparators were not used in these studies (atorvastatin 40 mg and 80 mg, simvastatin 80 mg and pravastatin 80 mg).

Efficacy of pitavastatin (2 mg titrated to 4 mg at 8 weeks) in heterozygous familial hypercholesterolaemia was assessed in a small Japanese study and after 12 weeks treatment it found statistically significant reductions in TC, LDL-C and Apo-B. Pooled analysis found slightly greater LDL-C reductions in the elderly and in females. Efficacy was seen across subgroups of BMI, NCEP risk categories, baseline LDL levels, hypertension, diabetes and primary diagnosis.

Long-term efficacy of the 4 mg dose was assessed in 2 controlled 44-week extension studies of the diabetic and CHD risk factor core studies. After 52 weeks of treatment, LDL-C reduction was maintained at approximately 41% from baseline. The target attainment for diabetics was 78% by NCEP and 88% by EAS criteria. For those with CHD risk factors, target attainment at 52 weeks was 82% by NCEP criteria and 84% by EAS criteria.

There were also 3 open label uncontrolled extension studies which demonstrated maintained reduction in LDL-C and percentage of patients reaching LDL-C targets. In the elderly after 60 weeks of treatment LDL-C target attainment by EAS criteria was 91% for those on 2 mg and 79% for those (17%) requiring up titration to 4 mg.

**Clinical safety**

In the Phase II and III studies there were 309 patients exposed to pitavastatin 1 mg, 951 patients exposed to pitavastatin 2 mg and 1540 patients exposed to pitavastatin 4 mg. In the 4 extension studies there were 2284 patients; 70.8% on pitavastatin 4 mg and 23.6% on pitavastatin 2 mg. The mean exposure in the short-term studies at doses of 1 to 4 mg was 12 weeks. With the extension studies included, the mean exposure was 37.4 weeks for the 4 mg dose. Livalo has been on the market in Japan since 2003 and together with routine monitoring a large post-marketing surveillance study (LIVS-01) was conducted and it has provided supportive safety data. This study enrolled approximately 20,000 patients, with nearly all patients being treated with 1 mg or 2 mg pitavastatin and an estimated 28,969 patient years of exposure.

At the proposed doses for marketing (1 mg to 4 mg), the common AEs were nasopharyngitis, myalgia, headache, constipation, nausea, diarrhoea, back pain, influenza, arthralgia and fatigue.

Deaths were uncommon (n=7) in the clinical program, with cardiac disorders being the most common reason. There have also been 2 deaths reported from postmarketing surveillance (one from rhabdomyolysis and one from interstitial pneumonia).

The rate of SAEs in the short-term studies was 1.3% for all pitavastatin doses which can be compared to 1.6% for atorvastatin, 3.0% for simvastatin, 1.3% for pravastatin and 0.5% for placebo. Most SAEs were cardiovascular disease related and at the 1 to 4 mg doses there were no SAEs related to elevated ALT, AST, CK or rhabdomyolysis. With the long-term studies included, the SAE rate was 2.6% and 3.0% in the 2 mg and 4 mg groups, respectively, which was in line with the other statins.

Discontinuation rate in short and long-term studies was 12.3% for pitavastatin 1 to 4 mg doses. Discontinuation due to AEs occurred in 3.5% of subjects and the most common
reason was myalgia. This rate was similar to the lower doses of the comparator drugs and less than the higher doses.

There were 9 reported cases of rhabdomyolysis, all which occurred at doses of 8 mg or higher. Symptomatic myopathy occurred in 8.6% of patients and asymptomatic myopathy (elevated CK without symptoms) with mild elevations (1 to <10 times) in 27.5% of patients, moderate (≥10 times to <50 times) in 0.3% of patients and marked elevation (≥50 times) in 0.03% of patients. The rate of mildly elevated CK was no greater than in the placebo group and the higher CK levels were in line with those reported for the comparator drugs. In the short term studies, the incidence of rhabdomyolysis/myopathy at the 2 and 4 mg pitavastatin doses was 0.136 and 0.122 per patient year, respectively, which can be compared to 0.061, 0.102 and 0.130 for atorvastatin 10 mg, 20 mg and 40 mg, respectively, and 0.259 and 0.148 for simvastatin 20 mg and 40 mg, respectively.

As with other statins, pitavastatin treatment resulted in uncommon but evident increases in AST and ALT. In the long and short term studies combined, the rate of patients with ALT levels >3 times ULN was 0.3% and 0.7% for the 2 mg and 4 mg doses, respectively. There was also 3 patients (one on 2 mg and two on 4 mg) who had ALT >10 times ULN. There were no cases of liver failure reported. The rates of increased transaminases were higher than in the comparator groups though this may be the result of lower patient numbers in these groups. From postmarketing surveillance, including the LIVS-01 study, there have been 39 serious hepatobiliary adverse drug reactions (ADRs) with transaminase increases of 10 to 20 times ULN and 2 cases with increased bilirubin suggestive of impaired hepatic function.

The rate of renal and urinary disorders and the incidence of acute renal failure were not higher than the placebo group or than other statins. A subset with proteinuria assessment did not have remarkable findings. From postmarketing surveillance there have been 3 serious renal cases linked to pitavastatin (renal impairment, nephritic syndrome and interstitial nephritis).

There were no safety signals on other haematology, biochemistry parameters or on ECGs. There was no evidence of QT prolongation in the Thorough QT trial.

The elderly had a higher risk of AEs and in particular of musculoskeletal disorders but this was not dose dependent. South Asians had a lower risk of AEs but a higher risk of myopathy when treated with 4 mg pitavastatin. There were too few participants from other racial groups to draw any definite conclusions. There were no other notable safety signals in the other subgroups examined.

Pitavastatin doses of 8 mg and above were not tolerable. These were associated with an increased rate of SAEs, of treatment discontinuations, of CK, AST and ALT elevations and of haematuria.

Overall, the adverse event profile of pitavastatin (1 to 4 mg) was comparable to the other statins studied particularly with respect to the known risks of liver and muscle effects. However, data comparing safety to other statins was predominantly available from the short term studies and there were no placebo controlled long term data. There were no new safety signals evident.

51 Sponsor comment: "The rates of increased ALT >3 times upper limit of normal (ULN) was 0.3% in the pitavastatin 1 mg group, 0.5% in the pitavastatin 2 mg group and 0.1% in the pitavastatin 4 mg group. The rates of increased AST >3 times ULN was 0.3% in the pitavastatin 1 mg group, 0.3% in the pitavastatin 2 mg group and 0.3% in the pitavastatin 4 mg group). The sponsor considered that these were higher than in the comparator groups but this may be the result of lower patient numbers in these groups, particularly less number of patients with long term exposure."

52 Sponsor comment: "In the elderly population study (Study 306 which compared pitavastatin 1 to 4 mg to pravastatin 10 to 40 mg) the adverse event rates were comparable between the pitavastatin groups and the corresponding pravastatin groups."
Benefit risk assessment

Benefits

The clinical development program followed the TGA adopted EU guideline recommendations including patient selection, reference therapy, treatment duration, lipid measurement and endpoint selection.

Pitavastatin efficacy in terms of LDL-C reduction was non inferior to the comparator statins (simvastatin, atorvastatin and pravastatin), with the exception of atorvastatin in Type II diabetics. It is noted that the highest marketed doses of the comparators were not assessed.

After 12 weeks of treatment, LDL-C target attainment by NCEP criteria and EAS criteria were 70%-83% and 60%-81%, respectively, for the 3 pitavastatin doses.

Pitavastatin treatment reduced TC, TG, non HDL-C and Apo-B levels. It increased HDL-C at a similar level to the comparator statins.

Efficacy was seen across the diagnoses of primary hypercholesterolaemia, combined dyslipidaemia and HeFH, as well as in the subgroups.

There was persistence of efficacy over 1 year of treatment as measured by LDL-C reduction and LDL-C target attainment, with no evidence of tolerance.

Metabolism is not via CYP3A4 so pitavastatin may have less drug-drug interactions than some of the other statins.

Once daily dosing was efficacious and pitavastatin can be taken with or without food.

The safety profile was in line with the comparator statins and a large post marketing surveillance study of >20,000 patients in Japan found no new safety signals of concern. In addition the product has been on the market in Japan since 2003.

Risks

The major risk with pitavastatin treatment, as with other statins, is myopathy and rhabdomyolysis. Rhabdomyolysis was only seen at doses of 8 mg and above in the clinical trials although 2 cases have been reported from post marketing surveillance.

Other main risk of statins is transaminitis and this was present with pitavastatin though there was no evidence of hepatotoxicity in the clinical trials. These safety risks were in line with the other statins used as comparators (simvastatin, atorvastatin and pravastatin).

Proteinuria has been observed with statins and this risk was seen in the subgroup who had renal protein: creatinine ratios assessed. The risk of acute renal failure in the clinical trials was not greater than with comparators though there have been serious renal disorders reported from post marketing surveillance.

There was a higher risk of AEs in the elderly population.53

There are prominent drug interactions with cyclosporine and erythromycin which contraindicate concomitant use.

There is increased exposure in patients with moderate renal impairment and no data on those with severe renal impairment that are not on haemodialysis.

As no long term outcome studies have been completed, the beneficial effect on mortality and morbidity from cardiovascular disease is unknown.

53 The sponsor comment: “The rates were comparable to other statins.”
Exclusion criteria from the pivotal trials have resulted in a lack of data in patients with poorly controlled diabetes, poorly controlled hypertension and those with a history of cerebrovascular disease.

**Balance**

The benefit of LDL-C reduction in reducing coronary heart disease mortality and morbidity is well established and intensive lipid lowering is one focus in the overall prevention strategy. Following this, the TGA adopted EU guidelines state that a relative reduction in the LDL cholesterol in patients with primary hypercholesterolaemia is an acceptable surrogate endpoint for prevention of cardiovascular morbidity and mortality\(^{38}\) and marketed statins have been approved based on reduction in LDL-C. A reduction in TG and an increase in HDL-cholesterol are also relevant in CHD prevention. Since 1987, 8 statins have been marketed and the muscle and liver risks of statins have been well documented with one, cerivastatin, being withdrawn due to myotoxicity.

Pitavastatin represents another in the statin class of drugs and its safety profile was as might be expected. The major risk of rhabdomyolysis was present, particularly with doses of 8 mg and above. It is therefore important to limit prescribing to 4 mg. The other major risk was transaminitis with a concern for possible hepatotoxicity, although this was not evident in the clinical trial data presented.

These risks with pitavastatin, while present, were not more prominent than with the comparator statins used in the development program and the overall safety was comparable. It is evident that there is a need to ensure a patient’s risk is minimised by prudent prescribing, active monitoring and treatment cessation if there is elevation of CK or persistent elevation of liver enzymes.

As the postmarketing surveillance has included little data on the 4 mg dose, the EU review resulted in a request for an observational study with careful monitoring of this dose and a focus on the risks of myopathy, rhabdomyolysis, acute liver injury, acute renal failure, and interstitial lung disease. This data will be very useful and should be made available for TGA review.

Given increased pitavastatin exposure in patients with moderate renal impairment and the limited clinical data with the 4 mg dose in this population, the clinical evaluator believed it would be prudent for dosage in moderate renal impairment (glomerular filtration rate (GFR) of 30-60 mL/min/1.73 m\(^2\)) to commence at 1 mg once daily with careful titration. The PK data in severe renal impairment should be evaluated when available with consideration to how this may impact on product labelling.

Efficacy of pitavastatin on LDL-C reduction and target attainment was similar to the 3 comparator statins (simvastatin, atorvastatin and pravastatin), although it was not assessed against higher doses of these products. The lack of long term morbidity and mortality data with pitavastatin remains a drawback of this product and it needs to be adequately outlined in the product information. Such a study would also have provided more information on groups for which there were limited data in the clinical program, such as poorly controlled diabetics and hypertensive patients or those with cerebrovascular disease. Given this, care will be needed to ensure the risk-benefit remains positive in these groups.

Pitavastatin has been on the market in Japan since 2003 and has been more recently approved for use in Europe and the US. Data from the Japanese post marketing surveillance and the LIVS-01 study adds to the knowledge of the product and, while the doses used were predominantly 1 mg and 2 mg, there were no major concerns raised from the surveillance study. In addition, in 2009 the FDA had correspondence with the PMDA in Japan asking if there were any concerns regarding pitavastatin’s safety, in particular the
muscle and hepatic safety profile, relative to other statins marketed in Japan. The PMDA stated there were no such concerns.

Given this information, and the demonstrated efficacy, the clinical evaluator concluded that at present the risk-benefit balance for pitavastatin is in line with other statins. The evident risks of pitavastatin need careful management which includes the availability of the low dose, clear product labelling particularly regarding the ‘at risk’ and ‘contraindicated’ populations, active clinical monitoring and vigilant post marketing surveillance.

Clinical conclusions

It is concluded that the overall benefit risk balance of pitavastatin is positive for the indication of:

*Livalo is indicated for the reduction of elevated total cholesterol (TC) and LDL-C, in adult patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia, and combined (mixed) dyslipidaemia, when response to diet and other non-pharmacological measures is inadequate.

The data from the two trials requested by the FDA (severe renal impairment and drug interaction study with lopinavir/ritonavir) and the EU observational study relating to statin risks should be submitted to the TGA for evaluation in a timely fashion. The risk management system must include intensive active monitoring of the known risks and expedited reporting of major muscle and hepatic events.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA’s Office of Product Review (OPR). Table 29 outlines the Ongoing Safety Concerns as proposed by the sponsor.

Table 29. Ongoing Safety Concerns

<table>
<thead>
<tr>
<th>Important Identified risks:</th>
<th>1. Rhabdomyolysis (including myalgia, muscle disorders and myopathy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Liver Disorder</td>
</tr>
<tr>
<td></td>
<td>3. Acute Pancreatitis</td>
</tr>
<tr>
<td>Important Identified class effects</td>
<td>1. Interstitial lung disease</td>
</tr>
<tr>
<td>Important Potential risks:</td>
<td>1. Renal disorders</td>
</tr>
<tr>
<td></td>
<td>2. Thrombocytopenia/Platelet count decreased</td>
</tr>
<tr>
<td>Important Missing information:</td>
<td>1. Rare adverse reactions, particularly at 4 mg</td>
</tr>
<tr>
<td></td>
<td>2. Drug interactions particularly with antibiotics</td>
</tr>
<tr>
<td></td>
<td>3. Patients with cardiovascular and respiratory diseases, immuno-compromised patients</td>
</tr>
<tr>
<td></td>
<td>4. Patients over the age of 75 years</td>
</tr>
<tr>
<td></td>
<td>5. Effect of <em>SLC01B1</em> genetic polymorphism</td>
</tr>
</tbody>
</table>

Routine and additional pharmacovigilance activities (ongoing epidemiology studies) are proposed by the sponsor to monitor ongoing safety concerns associated with pitavastatin.

The ongoing epidemiology studies will monitor and further elucidate rhabdomyolysis (including myalgia, muscle disorders and myopathy), liver disorders (*Identified risks*), interstitial lung disease, renal disorders (*Potential risks*), rare adverse reactions (particularly at the 4 mg dose) and drug-drug interactions (*Important missing information*).
The sponsor’s conclusion in regards to routine risk minimisation activities to mitigate the ongoing safety concerns associated with pitavastatin was considered acceptable, pending the clinical and nonclinical evaluation reports. That is, pitavastatin is already well established in the Japanese market, the results of the clinical study program and postmarketing experience indicate that the risks are consistent with other statins, which are already known to prescribers of this class. Additional risk minimisation activities are proposed for the safety concern; rhabdomyolysis.54

The OPR provides the following recommendations in the context that the submitted RMP was supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted European Union (EU) RMP is applicable without modification in Australia unless so qualified. It was recommended to the Delegate that the sponsor:

1. **Update the RMPs language to provide consistency in the Australian context (replace EU Summary of Product Characteristics (SmPC) with PI), or provide an Australian specific annex which identifies this issue and any Australian relevant changes. It was recommended this annex include but not be limited to the following identified issues:**

   - The application letter includes Australian specific RMP issues such as the pharmacoepidemiology program not being implemented in Australia due to various reasons.
   - The sponsor confirms if the report assessing the effectiveness of the additional risk minimisation activities will be submitted with PSURs to the TGA.
   - The sponsor confirms which specific market research techniques will be used to assess the additional risk minimisation activities.

**Sponsor response:**

The sponsor submitted an Australian Specific Annex to the Pitavastatin RMP v 4.0.

**Please note:**

- The specific RMP issues addressed in the application letter have been included, and updated where necessary, in the Australian Specific Annex.
- Abbott Australasia confirms that the report assessing the effectiveness of the additional risk minimization activities will be submitted as part of the PSURs to the TGA.
- The Australian Specific Annex addresses this issue regarding the assessment of the additional risk minimization activities.
- The recommended starting dose is 2 mg/day and has been amended within the Australian Specific Annex and the proposed PI. The CMI will be revised once the final PI has been confirmed with the TGA.

54Four additional risk minimisation activities are planned to mitigate the risk of rhabdomyolysis; Additional training of company representatives who will discuss pitavastatin with health professionals; Standardised risk minimising information within promotional brochures; Active dissemination of PI at all promotional contact between the company and health professionals; and Standardised medical information communications.
2. **Submit any educational materials for review that will be used with Healthcare Professionals.**

*Sponsor response:*

No educational materials for use with healthcare professionals have been developed at this stage. Please see the Australian Specific Annex with reference to the use of such materials.

3. **The dates for the initiation or completion of the two studies (drug utilisation and retrospective cohort) in the pharmacoepidemiology program were not provided in the RMP. It is recommended that the sponsor provide these dates.**

*Sponsor response:*

In reference to the Pharmacoepidemiology Program (Annex 5 Pat B of RMP version 4.0) an update is provided below:

The late draft post approval safety study (PASS) protocol included Annex 5B has now been supplemented with the draft of the drug utilisation study (DUS) protocol (Attachment 1 to the Australian Specific Annex of Pitavastatin RMP 4.0). These protocols are modular in design with a core protocol to be supplemented with database specific sections adapted to the particular data source. For the DUS there are suitable databases in France and Italy, and for the PASS there is a suitable network of databases in Italy. The studies will be triggered when there is judged to be sufficient data in the target databases to produce meaningful analysis, and at present these trigger points are 2000 patients taking pitavastatin for the DUS, and 15000 patients taking pitavastatin (preferably with substantial numbers taking Pitavastatin 4 mg) for the PASS. The protocols are intentionally not yet finalised so that they can be modified to include any additional safety concerns that may be identified in the PSURs and included in the RMP. Finalised protocols will be reviewed by the RMS in the EU before the studies are performed.

The precise timing of the studies is dependent on the usage of pitavastatin in the territories covered by the target databases after launch and therefore inherently uncertain. It is not anticipated that pitavastatin will be launched in France or Italy before the last quarter of 2011.

Key study notes and projected timelines are described below.

- Database owners will be contacted by the pharmacoepidemiology CRO (RTi Health Solutions) 6 monthly to obtain updates on the quantity of pitavastatin data available. The updates could be more frequent if warranted by sales volume.
- Updates will be planned to coincide with PSURs.
- Plan to be reviewed by the end of 2013 if there is very slow accrual of pitavastatin data in the databases.
- When accrual rates allow the timing of the study to be determined (because the target patient numbers can be predicted), a joint meeting with the database owners will take place to finalise the study protocol (the DUS will be conducted first as a preparation for the PASS) projected for last quarter of 2012.
- By the end of the DUS it is hoped that data accrual in the databases in Italy will enable timelines for the PASS to be drawn up.

**VI. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate’s overview and recommendations:
Quality
The pharmaceutical chemistry evaluator has recommended approval with respect to chemistry and quality control. In relation to bioavailability, the evaluator has commented that 4 studies were submitted which indicated absolute bioavailability was about 51%, absorption is in the jejunum and ileum, bioequivalence has been seen between 1x4 mg, 2x2 mg and 4x1 mg tablets and food has no effect on AUC but reduces C<sub>max</sub> by 43% and delays T<sub>max</sub> from 1 to 2 hours. The advice of PSC was requested.

Nonclinical
The nonclinical evaluator has no objections to the registration of pitavastatin for the proposed indication and notes that it has a similar safety profiles to other registered statins in Australia. The data package was extensive with studies of adequate design and conduct in accordance with relevant EU guidelines and GLP. Acceptable safety pharmacology studies were provided and pharmacokinetic studies indicated that pitavastatin undergoes little metabolism and its elimination depends upon excretion from the liver into bile (like rosuvastatin and pravastatin) with subsequent enterohepatic recirculation or faecal excretion (79% of the dose, 15% urine). The low metabolic clearance involves CYP2C9 and 2C8. Repeat dose toxicity studies had adequate exposure margins and showed typical statin like effects except for some lung lipid lesions in dogs which were thought to not be clinically relevant (NOEL corresponding to a relative exposure margin of 9). High doses caused cataracts in dogs. Pitavastatin did not appear to be genotoxic, carcinogenic or teratogenic. No effects on fertility were seen. High rates of maternal mortality, impaired lactation and decreased offspring viability were seen from the peri/post-natal studies and pitavastatin is therefore contraindicated in pregnancy, like other statins. The RMP includes interstitial lung disease as an important class effect and renal disorders.

Clinical
The clinical evaluator has reviewed the submitted data, which included 28 pharmacology studies, 10 Phase II and III clinical studies, 6 open label extension studies, a study in heterozygous familial hypercholesterolemia and a number of smaller studies in synopsis form along with postmarket data and a post-market surveillance study.
The clinical evaluator recommended approval in the evaluation report. The concerns noted by the evaluator in this submission included:

- General statin risks of myopathy, rhabdomyolysis, liver effects, renal effects including proteinuria.
- Higher risk of adverse events in the elderly.
- Significant interactions with cyclosporine and erythromycin.
- Lack of data on cardiovascular morbidity and mortality and in patients with poorly controlled diabetes, poorly controlled hypertension and a history of cerebrovascular disease.
- Increased exposure in moderate renal impairment and no data in severe renal impairment patients not on haemodialysis.
PD and PK

Twenty five studies examined the pharmacokinetics of pitavastatin and three studies examined the pharmacodynamics. No studies examined the pharmacokinetics or pharmacodynamics of pitavastatin in the target population.

The following findings for pitavastatin were noted by the evaluator:

- The difference in LDL-C lowering between morning and evening doses was clinically insignificant.
- There is little evidence that supra therapeutic doses of pitavastatin (16 mg) affect QT interval.
- The data relating to a dose and PD response relationship existing for pitavastatin is equivocal.
- Oral bioavailability is 51%, $T_{\text{max}}$ for 2 mg was 0.68, $C_{\text{max}}$ was 21.4, $AUC_{\text{inf}}$ was 47.4, clearance (CL/F) was 838 mL/min and $t_{1/2}$ was 5.2h. The $t_{1/2}$ of the lactone metabolite was approximately 12 h.
- The plasma clearance of pitavastatin was a mean 183 mL/minute and apparent volume of distribution was 226 L, suggesting that tissue binding was greater than plasma protein binding.
- Pitavastatin is highly bound to plasma protein with an unbound fraction of 0.4% to 0.5% in human plasma. The major binding proteins were human serum albumin and α1-acid glycoprotein.
- Renal clearance was less than 1%.
- The main components in plasma up to 24 hours postdose were unchanged pitavastatin and pitavastatin lactone along with two minor metabolites. Excretion was primarily faecal (78.6%: 58.2% unchanged pitavastatin and 15% included four metabolites) with lower amounts in urine (15%).
- Compared to other statins, pitavastatin undergoes little hydroxylation. Its uptake into human liver is in part mediated by OATP1B1, whereas pitavastatin was only slightly metabolised by CYP isoforms.
- Steady state was reached in 4 to 6 days of dosing. The $C_{\text{max}}$ and $AUC$ of pitavastatin increased linearly with dose from 1 to 64 mg, whereas, the absorption rate of parent drug remained constant and $T_{\text{max}}$ did not vary with increasing dose. Time of dosing (AM or PM) did not affect the PK.
- Elderly subjects have 10% higher $C_{\text{max}}$ and 30% higher $AUC$ compared to non elderly subjects.
- Females had significantly higher $C_{\text{max}}$ (1.6 fold) and $AUC$ (1.5 fold) values than males. The PKs of pitavastatin are similar in Black, Asian and Caucasian subjects.
- Hepatic: $C_{\text{max}}$ and $AUC_{0-t}$ were 1.34 and 1.60 fold greater in subjects with Child-Pugh Grade A, and 2.69 and 3.93 fold greater in subjects with Child-Pugh Grade B, compared to healthy subjects.
- Renal: $C_{\text{max}}$ was 1.4 and 1.6 times higher in patients requiring haemodialysis and patients with moderate renal impairment compared to healthy subjects. $AUC_{0-t}$ was increased 1.7 and 1.8 fold.

Drug interactions:

- Bezafibrate, grape fruit juice, ezetimibe, digoxin and enalapril when co administered with pitavastatin had little to no effect on pitavastatin PKs.
• Fenofibrate increased the AUC$_{0-24}$ of pitavastatin by 18%.
• Gemfibrozil increased pitavastatin C$_{max}$ and AUC$_{0-24}$ by 31% and 45%, respectively.
• Rifampicin increased pitavastatin C$_{max}$ and AUC by double and 30%, respectively, whereas the C$_{max}$ and AUC of rifampicin decreased by 30%.
• Atazanavir increased pitavastatin C$_{max}$ and AUC of by 1.6 and 1.3 fold, respectively.
• Cyclosporine increased pitavastatin C$_{max}$ by 6.6 fold and AUC$_{0-24}$ by 4.6 fold and its use has been contraindicated in the PI.
• Erythromycin co administration produced an approximate 3 fold increase in systemic exposure to pitavastatin and its use has been contraindicated in the PI.
• Itraconazole (a CYP3A4 inhibitor) induced a 23% decrease in pitavastatin AUC.
• The pharmacokinetic parameters of enalapril and enalaprilat were similar when enalapril was co administered with pitavastatin compared to administration alone.
• 4 mg pitavastatin with warfarin did not affect the C$_{max}$ or AUC of R- and S-warfarin and pitavastatin did not affect the steady state pharmacodynamics of warfarin.

**Efficacy**

The efficacy data submitted were comprehensive and comprised 5 dose ranging studies, 2 pivotal Phase III non inferiority studies against simvastatin and atorvastatin in primary hypercholesterolemia and mixed dyslipidaemia, 3 controlled studies in the elderly, those with cardiovascular risk factors and Type 2 diabetes, 6 open label extension studies and a study in heterozygous familial hypercholesterolemia. Summaries of the studies are shown Tables 30-32 below.

**Table 30. Active controlled Phase III studies**
Table 31. Placebo controlled Phase II studies

<table>
<thead>
<tr>
<th>Study number</th>
<th>Objectives</th>
<th>Design</th>
<th>Treatment</th>
<th>Duration</th>
<th>Population</th>
<th>Total planned</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEC-NK98402N/ NK-104.2.02</td>
<td>Efficacy and safety Dose-response</td>
<td>Double-blind, randomised, placebo-controlled, parallel group, fixed dose, dose-ranging</td>
<td>Pitavastatin 1, 2, 4 or 8 mg QD or placebo QD</td>
<td>12 weeks</td>
<td>Primary hypercholesterolaemia</td>
<td>321 (61 per group)</td>
</tr>
<tr>
<td>HEC-NK98403N/ NK-104.2.03</td>
<td>Efficacy and safety Dose-response</td>
<td>Double-blind, randomised, placebo-controlled, parallel group, fixed dose, dose-ranging</td>
<td>Pitavastatin 1, 2, 4 or 8 mg QD or placebo QD</td>
<td>12 weeks</td>
<td>Combined (mixed) dyslipidaemia</td>
<td>375 (75 per group)</td>
</tr>
<tr>
<td>NK-104-209</td>
<td>Efficacy, safety and tolerability</td>
<td>Double-blind randomised placebo, and open active (atorvastatin) controlled, parallel group, fixed dose</td>
<td>Pitavastatin 8, 16, 32 or 64 mg QD, or placebo QD or ezetimibe 10 mg QD</td>
<td>16 weeks (primary assessment at 8 weeks)</td>
<td>Primary hypercholesterolaemia or combined (mixed) dyslipidaemia</td>
<td>550 (100 per active group and 50 placebo)</td>
</tr>
<tr>
<td>NKS104A2205F</td>
<td>Efficacy (vs placebo) Safety and tolerability (vs placebo and active)</td>
<td>Double-blind randomised placebo, and open active (atorvastatin) controlled, parallel group</td>
<td>Pitavastatin 4 or 8 mg QD or placebo QD or ezetimibe 4 weeks each of 10 to 20 to 40 mg QD</td>
<td>12 weeks</td>
<td>Primary hypercholesterolaemia or combined (mixed) dyslipidaemia</td>
<td>500 (100 pts 4 mg, 300 pts 8 mg, 50 each one and placebo)</td>
</tr>
<tr>
<td>NK-104-210</td>
<td>Efficacy and safety Dose-response</td>
<td>Double-blind randomised placebo, and open active (ezetimibe) controlled, parallel group, fixed dose</td>
<td>Pitavastatin 4 or 8 mg QD or placebo QD or ezetimibe 10 or 40 mg QD</td>
<td>12 weeks</td>
<td>Primary hypercholesterolaemia or combined (mixed) dyslipidaemia</td>
<td>225 (50 pts 4 mg, 100 pts 8 mg, 25 each one group and placebo)</td>
</tr>
</tbody>
</table>

Phase II studies: NK-104.2.02 and NK-104.2.03 were both multinational, multicentre, randomised, double blind, parallel group, dose ranging studies of the efficacy and safety of pitavastatin 1, 2, 4 and 8 mg compared to placebo. The first study was in primary hypercholesterolaemia and the second in mixed dyslipidaemia. In NK-104.2.02 the mean percentage reduction in LDL-C was statistically significant at -33.3%, -38.2%, -46.5%, and -54.5%, in the 1, 2, 4 and 8 mg groups compared to -4.0% for placebo. A statistically significant dose reduction in plasma LDL-C was also seen in NK-104.2.03. Both studies had significant dose reductions in TC, TG, Apo-B. There was an increase in HDL-C which was not dose related. The second study did not find significant differences between the 1 and 2 mg or between the 4 and 8 mg in LDL-C reduction but the other did. NK-104-209 was a randomised, multicentre, parallel group, dose ranging placebo controlled study of the efficacy of 8, 16, 32 and 64 mg of pitavastatin and open label atorvastatin in primary hypercholesterolemia. This study was prematurely terminated due to elevated CK, myalgia and rhabdomyolysis in the 16, 32 and 64 mg groups. A significant reduction in LDL-C was seen after 8 weeks with 8 and 16 mg doses. The two other dose ranging studies, NKS104A2204 and NK-104-210 were 12 week multicentre, randomised, double blind placebo controlled, parallel-group studies of the efficacy and safety of pitavastatin (4 and 8 mg) in lowering LDL-C versus placebo and open label atorvastatin. These were also prematurely terminated due to safety concerns with the 8 mg dose. The maximum tolerated dose was 8 mg with efficacy seen at 1 mg.

Phase III studies: In the 5 Phase III trials, the study designs are summarised above but were essentially non inferiority studies of pitavastatin versus atorvastatin or simvastatin.
or pravastatin for 12 weeks. Study numbers ranged from 300 to 900 patients per study with primary hypercholesterolemia or mixed dyslipidaemia. The subjects were approximately 60 years old (except for the studies in the elderly), predominantly Caucasian and about half female. Overall trial completion was high and compliance good. LDL-C was the primary efficacy endpoint throughout the program with LDL-C target attainment by NCEP and EAS criteria as well as other standard lipid parameters being secondary endpoints (TC, HDL-C, TG, Apo-B, Apo-A1, etc). A non inferiority margin for the primary endpoint of 6% in the active comparator studies was deemed appropriate (a doubling of statin dose has often been associated with a decrease in LDL of approximately 6% and this margin has been used in other statin trials). Change in lipid levels was assessed after a 12 week treatment period (except 8 weeks in NK-104-209). Studies had appropriate wash out of other lipid lowering medications, a 4 to 8 week dietary lead in period and dietary counselling during the trials. LDL-C was mainly evaluated using the Friedewald formula. The efficacy population was the FAS with LOCF.

**NK-104.301:** This was a 12 week randomised, multicentre, double blind, double dummy, active controlled, non inferiority Phase III study in 817 patients with primary hypercholesterolemia or combined dyslipidaemia (LDL 4.2-5.7mmol/L, TG<4.6mmol/L). Pitavastatin 2 and 4 mg compared to atorvastatin 10 and 20 mg demonstrated non inferiority of pitavastatin for the primary endpoint at the low dose (2 mg versus 10 mg) and high dose (4 mg versus 20 mg), (results below). Target LDL-C (NCEP and EAS criteria) was greater for the 4 mg than 2 mg (77.9% versus 56.8%). Results were not significantly different to atorvastatin on target LDL-attainment or on other secondary lipid variables. Efficacy was seen across subgroups and obtained from week 2 and maximal at week 8. The elderly and females had better responses.

**NK-104.302:** This was a 12 week randomised, multicentre, double blind, double dummy, active controlled, non inferiority Phase III study in 843 patients with 80% primary hypercholesterolemia or combined dyslipidaemia (baseline LDL 4.8mmol/L). Pitavastatin 2 and 4 mg compared to simvastatin 20 and 40 mg demonstrated non inferiority of pitavastatin at both doses for the primary endpoint, with 2 mg being statistically superior to simvastatin 20 mg (results below). Target LDL-C (NCEP criteria) was between 65-80% across groups while on EAS criteria it was significantly greater for pitavastatin 2 mg than simvastatin 20 mg (60% versus 49%). Pitavastatin 2 mg also resulted in a greater reduction in TC and non-HDL-C. Efficacy was seen across subgroups and obtained from Week 2 and maximal at Week 8. The elderly and females had better responses.

**NK-104-304:** This was a 12 week randomised, multicentre, double blind, double dummy, active controlled, non inferiority Phase III study in 355 patients with 80% primary hypercholesterolemia or combined dyslipidaemia and high CHD risk (2 or more risk factors), (baseline LDL 4.3mmol/L). Pitavastatin 4 mg was non inferior to simvastatin 40 mg in the reduction of LDL-C (results below). LDL-C target attainment was 87.1% by NCEP and EAS criteria. Results were consistent across subgroups and there were no significant differences in the change of secondary lipid parameters except for a greater reduction in TG with pitavastatin (-19.8% versus-14.8%). Simvastatin resulted in a slightly greater reduction in LDL-C in the elderly than pitavastatin.

**NK-104-305:** This was a 12 week randomised, multicentre, double blind, double dummy, active controlled, non inferiority Phase III study in 418 patients with Type II diabetes mellitus (6+ years) with combined dyslipidaemia (baseline LDL 3.8mmol/L). Pitavastatin 4 mg treatment resulted in a 40.8% decrease in LDL-C however the response was greater with atorvastatin 20 mg (43.8% reduction) and non inferiority was not achieved (lower bound of 95% CI was -6.18%, that is, >6%), (results below in Table 33). Less patients reached LDL-C targets (77% versus 82% on NCEP criteria and 84 versus 90% on EAS criteria), though the differences were not significant. The response to pitavastatin was greater in female than male diabetics (-43.89% versus -38.39%). There was a greater
effect with atorvastatin on TC, TG, non-HDL-C, oxidised LDL, small density LDL and adiponectin with other variables having no significant differences. The LDL-C response in this study had higher variability than expected (standard deviation estimated to be 12% however actual SD was 19.6% in the pitavastatin and 16.4% in the atorvastatin groups).

**NK-104-306:** This was a 12 week randomised, multicentre, double blind, double dummy, active controlled, non-inferiority Phase III study in 962 elderly (mean 70 years) patients with 90% primary hypercholesterolemia or combined dyslipidaemia which compared the 3 dose levels of pitavastatin with pravastatin (10, 20 and 40 mg daily). The three dose level comparisons were non-inferior and statistically superior to pravastatin (results below in Table 33). There was also evidence of a dose response with greater reductions with the higher dose. Target attainment was significantly higher with pitavastatin by EAS criteria (59.9%, 79.5% and 88.1% in the 1, 2 and 4 mg pitavastatin groups, respectively, versus 37.9%, 51% and 65.7%, respectively, for the pravastatin groups). Target attainment by NCEP criteria was only significantly greater for the 1 mg. Results were consistent across subgroups and significantly better for TC, non-HDL-C and Apo-B.

### Table 33. Results from the 5 pivotal Phase III studies

<table>
<thead>
<tr>
<th>Study EAS/TIT</th>
<th>N</th>
<th>LDL-C (mg/dL)</th>
<th>Percent change</th>
<th>p-value</th>
<th>vs</th>
<th>Adjusted Mean difference (95% CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Week 12 LOCF</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<tr>
<td><strong>NK-104-301</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pita 2 mg</td>
<td>315</td>
<td>183.6</td>
<td>16.8</td>
<td>-37.9</td>
<td>14.0</td>
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<tr>
<td>Pita 4 mg</td>
<td>208</td>
<td>182.0</td>
<td>16.7</td>
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<td>102</td>
<td>179.8</td>
<td>16.9</td>
<td>-37.8</td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td>Ator 20 mg</td>
<td>102</td>
<td>181.9</td>
<td>16.7</td>
<td>-43.5</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td><strong>NK-104-302</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pita 2 mg</td>
<td>307</td>
<td>183.6</td>
<td>17.0</td>
<td>-39.0</td>
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<td>0.014</td>
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<td>-44.0</td>
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<td>0.059</td>
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<td>Simv 20 mg</td>
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<td>17.2</td>
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<td>15.5</td>
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<tr>
<td>Simv 40 mg</td>
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<td>184.0</td>
<td>15.7</td>
<td>-42.8</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td><strong>NK-104-304</strong></td>
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<tr>
<td>Simv 40 mg</td>
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<td>23.5</td>
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<td>14.4</td>
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<tr>
<td><strong>NK-104-305</strong></td>
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<td></td>
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<td>Pita 4 mg</td>
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<td>-40.8</td>
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<td>0.235</td>
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<td>146.0</td>
<td>27.0</td>
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<td>16.4</td>
<td></td>
</tr>
<tr>
<td><strong>NK-104-306</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pita 1 mg</td>
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<td>164.4</td>
<td>22.9</td>
<td>-31.4</td>
<td>11.8</td>
<td>&lt;0.001</td>
</tr>
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<td>162.8</td>
<td>20.5</td>
<td>-39.0</td>
<td>13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pita 4 mg</td>
<td>210</td>
<td>163.5</td>
<td>21.9</td>
<td>-44.3</td>
<td>13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prav 10 mg</td>
<td>103</td>
<td>163.6</td>
<td>22.3</td>
<td>-22.4</td>
<td>14.1</td>
<td></td>
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<tr>
<td>Prav 20 mg</td>
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<td>163.7</td>
<td>19.3</td>
<td>-28.8</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Prav 40 mg</td>
<td>102</td>
<td>166.6</td>
<td>21.9</td>
<td>-34.0</td>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>

**Pooled analysis:** In the pooled analysis, the mean percentage reduction at Week 12 in LDL-C was 31%, 38% and 43% for those treated with 1 mg, 2 mg and 4 mg. A slightly greater response was seen in the elderly compared to younger patients and in females compared to males. Responses were seen across BMI groups, NCEP risk categories, baseline LDL levels, hypertension, diabetes and primary diagnosis.

**Long term studies:** There were 7 long term studies (see above) of 44-104 weeks duration. Studies NKS104A2204E1 and NK-104-211 had no evaluable data as they were extensions of the earlier terminated studies. A number of Japanese, Korean and Chinese studies were also conducted however these only included translated synopses and are discussed in the CER.
**NK-104-309:** This was a 44 week, multicentre, double blind, double dummy, parallel group, active controlled, extension study of study NK-104-304 in 178 patients with primary hypercholesterolemia or combined dyslipidaemia and two or more risk factors for coronary heart disease. The study compared pitavastatin 4 mg with simvastatin 40 mg (these patients were maintained on this dose from the previous study) or 80 mg (8.8% of patients were up titrated) on LDL-C target achievement by EAS or NCEP criteria and standard secondary lipid parameters. At 44 weeks, a greater proportion reached LDL-C targets with pitavastatin (81.7% versus 75.4% by NCEP criteria and 84.2% versus 73.7% by EAS criteria) compared to simvastatin 40/80 mg. With time there was a small decline in response on target attainment and individual lipid parameters (LDL-C, TC, TG, non-HDL-C, Apo-B) for both drugs. LDL-C was reduced by about 41% after 44 weeks of treatment compared to 45% at Week 12. HDL-C increased by 14%.

**NK-104-310:** This was a 44 week, multicentre, double blind, double dummy, parallel group, active controlled, extension study of NK-104-305 in 214 diabetic patients with combined dyslipidaemia. The study compared pitavastatin 4 mg with atorvastatin 20 mg (these patients were maintained on this dose from the previous study) or 40 mg (9.9% of patients were up titrated) on LDL-C target achievement by EAS or NCEP criteria and standard secondary lipid parameters. At 44 weeks, LDL-C target attainment by both criteria was similar between pitavastatin and atorvastatin (78.0% versus 77.5% by NCEP and 87.9% and 88.7% by EAS criteria). Mean LDL-C reduction was -41% in both groups at 52 weeks and the changes in lipid parameters were similar between treatments and maintained with longer term treatment.

**NK-104-307:** This was a 52 week open label extension study in 1353 patients who had completed one of the two pivotal trial NK-104-301 and NK-104-302 studies and were all up titrated to pitavastatin 4 mg. The study had a design flaw with 87% of patients having a treatment gap due to a delay in obtaining study approval with 33% of these patients starting alternative lipid therapy. Once recommenced on pitavastatin they reached LDL reductions in 2 weeks which was similar to the primary trials at 12 weeks. LDL-C reduction was maintained to Week 52 at 42.9% and LDL-C target attainment was 74% by either NCEP or EAS criteria. Other lipid parameter changes were maintained.

**NK-104-308:** This was a 60 week extension study of NK-104-306 in 545 elderly patients (mean 70 years) with primary hypercholesterolemia or mixed dyslipidaemia. Treatment commenced on 2 mg and 17% up titrated to 4 mg during the study. This study also had a design flaw with 25.4% having a gap in treatment. LDL-C target attainment at Week 60 was high for the 2 mg group, 98.7% and 91.0% using NCEP and EAS criteria. For those who needed to be up titrated to 4 mg the target attainment was 70.1% and 79.2%, respectively. HDL-C increased by 9.6%.

**NK-104-09:** This was a small, open label, uncontrolled, long term Japanese study in 36 patients with heterozygous familial hypercholesterolemia (HeFH). At Week 52 LDL-C decreased by 34.4%, TC by 45.2%, TG by 34.0%, Apo-B by 32.4% and HDL-C increased by 5.4%.

**LIVS-01:** This was a postmarketing surveillance study in 17,755 Japanese for efficacy showing the reduction in LDL was similar in patients with liver disease, diabetes and renal disease (~29%).

**Safety**

There are 77 studies in the pitavastatin development program (40 healthy volunteer and 37 in hyperlipidaemia) of which 26 healthy volunteer and 18 patient studies contributed to the EU/US program. The pooled safety analysis included the 5 Phase II randomised controlled trials and 5 Phase III randomised active controlled studies and 4 of the 6 long term extension studies. A total of 3448 patients were exposed to pitavastatin in the Phase
II and III studies with 1540 given pitavastatin 4 mg. Safety data was assessed according to different groups, with Group 3 being the most complete (all Phase II and III studies, core and extension, regardless of treatment gaps). Exposure in Group 3 was for a mean of 37 weeks on pitavastatin 4 mg. Overall discontinuation rate in group 3 was 12.3% on pitavastatin 1 to 4 mg with discontinuation due to AEs in 3.6%, 3.4% and 4.3% in 1 mg, 2 mg and 4 mg groups. The most common reason was myalgia. Discontinuation due to AEs was similar to the lower doses of the comparators and less than with their higher doses.

In the short term studies (Group 1), the TEAE rate was 50.5%, 35.3% and 39.4% in the 1, 2 and 4 mg pitavastatin groups, respectively, compared to 54.3% in placebo, 37.2% in atorvastatin, 38.1% in simvastatin and 52.8% in pravastatin groups. There was a dose dependent increase in TEAEs with doses of 8 to 64 mg. The AE profile was as would be expected with a statin, with pitavastatin 4 mg showing nasopharyngitis (4.3%), myalgia (3.1%), headache (2.9%), constipation (2.2%), nausea (1.4%), diarrhea (1.9%), back pain (1.4%), influenza (1.3%), arthralgia (1.2%) and fatigue (1%). Myalgia showed dose dependent increases within the 1-4 mg range. Beyond 4 mg, dose dependent increases were seen in liver and muscle events, amongst others. TEAEs were similar to comparator statins (simvastatin, atorvastatin, pravastatin) but myalgia rates were more frequent with pitavastatin than the lower atorvastatin groups (1.9%, 2.8% and 3.1% in the 1, 2 and 4 mg pitavastatin doses versus 1.4% with placebo, 0.8-2.0% with atorvastatin 10 mg-40 mg, 8.3% with atorvastatin 80 mg, 2.8% and 3.9% with simvastatin 20 mg and 40 mg, and 2.1% to 2.9% with pravastatin 10 mg to 40 mg). Cataracts were not seen on pitavastatin and eye disorders were less than placebo in the short term studies with long term cataract rate at 0.2%.

The adverse events of interest with statins are muscle, liver and renal disorders.

The risk of rhabdomyolysis was present with doses of 8 mg and above where there were 9 cases in the Phase II program while no cases were reported with the 1 to 4 mg doses.55 In the long term analysis (Group 3), musculoskeletal and connective tissue disorders had a rate of 11.0% and 13.3% in the 2 and 4 mg dose groups. This was slightly higher than in the short term studies (Group 1); 8.5% and 8.0% for 2 and 4 mg, respectively. These rates were similar to the other statins except for a higher rate seen with atorvastatin 80 mg (19.8%). In Group 1, symptomatic myopathy (muscle pain, spasm or weakness) occurred in 8.6% and elevated CK without myopathy symptoms was frequent with mild elevations (1 to <10 times) in 27.5%, moderate (≥10 times to <50 times) in 0.3% and marked elevation (≥50 times) in 0.03%. The rate of CK elevation between 1 to <10 times ULN was not greater than placebo. The rate of higher CK levels was no more than with the comparators. In Group 1, the incidence of rhabdomyolysis/myopathy43 with 2 and 4 mg pitavastatin was 0.136 and 0.122 per patient year, respectively, compared to 0.061, 0.102 and 0.130 for atorvastatin 10 mg, 20 mg and 40 mg, and 0.259 and 0.148 for simvastatin 20 mg and 40 mg. Postmarketing experience showed 56 reports of serious rhabdomyolysis/myopathy up to July 2009.

Hepatobiliary disorders were not elevated compared to placebo in Group 1 (0.1% versus 0.5%) while in Group 3 the rate increased to 0.7%. In Group 3, the rate of increased ALT >3x ULN was 0.3% and 0.7% in the 2 and 4 mg dose groups, respectively. Liver enzyme elevations were dose dependent and the rate of ALT >3x ULN was higher with pitavastatin (0.1% to 0.5%) than with pravastatin (0%) and atorvastatin (0%) however the comparator groups were not at maximum doses. Postmarketing experience showed 39 serious hepatobiliary disorders in Japan from 2003-2009.

55 Sponsor comment: “There is a risk of rhabdomyolysis with therapeutic doses of all statins but that it is very rare. There were no cases of serious rhabdomyolysis or rhabdomyolysis requiring hospitalisation at doses lower than 32 mg in the program.”
The rate of renal and urinary disorders was not higher than the placebo group and comparable to the other statins. With high doses of pitavastatin (32 and 64 mg) there was a risk of haematuria. The most frequent TEAEs were abnormally frequent urination (0.3%) and haematuria (0.2%) which appeared related to the high pitavastatin doses. The incidence of acute renal failure TEAEs was 0.005 and 0.002 patients per patient year for the 2 and 4 mg doses compared to 0.024 and 0.013 for simvastatin 20 and 40 mg. There was a small change in the urine protein: creatinine ratio.

There were 6 deaths in the clinical program in pitavastatin patients that were considered unrelated. There have been 2 deaths reported from post marketing surveillance; one from rhabdomyolysis and one from interstitial pneumonia. There were 45 SAEs in pitavastatin treated patients in the short term core studies with a rate of 1.3% compared to 1.6% for atorvastatin, 3.0% for simvastatin, 1.3% for pravastatin and 0.5% for placebo. The SAE rate increased with pitavastatin doses of 8 mg and above. Most SAEs were cardiovascular disease related and at the 1 to 4 mg doses there were no SAEs related to elevated ALT, AST, CK or rhabdomyolysis. In Group 3 the SAE rate was 2.6% and 3.0% in the 2 and 4 mg groups, respectively, which was similar to other statins.

There were no other notable haematology or biochemistry findings. ECG findings were unremarkable and there was no evidence of QT prolongation in the Thorough QT trial.

There was an increased frequency of AEs and SAEs in the elderly which included an increased risk of rhabdomyolysis/myopathy\(^4\) (6.6% versus 2.3% with 2 mg) which did not appear to be dose dependent. There was also a slight increase in renal failure (0.3% versus 0% on 2 mg). Most subjects were of Caucasian origin. Subjects from South Asian had a lower rate of TEAEs in general although myopathy in those treated with 4 mg was higher. Assessment of safety by baseline LDL-C, NCEP category, primary diagnosis, diabetes or hypertension, BMI or gender did not reveal significant differences.

The Japanese postmarket surveillance study of 2 years duration had 28,969 patient years of exposure with 11,454 at 1 mg, 17,336 at 2 mg and 119 patient years at 4 mg. During the 2 years, 42.5% of patients discontinued with 7.4% reported as discontinued due to adverse events. Adverse Drug Reactions (ADRs) were reported in 10.4% of patients and 0.13% had a serious ADR. There were no deaths. The most frequent ADRs were increased CK (2.7%), increased AST (1.8%), increased ALT (1.5%), myalgia (1.1%) and increased GGT (1.0%). The most frequent serious ADRs were hepatobiliary events (0.04%). There were 36 cataract associated AEs and 2 cases of rhabdomyolysis (0.01%).

**Risk management plan**

The Office of Product Review has accepted the RMP, Version 4.0 (July 2010) for pitavastatin including the sponsor’s response from 4 August 2011 which was considered acceptable. There were no outstanding matters.

**Risk-benefit analysis**

**Delegate considerations**

**Efficacy**

The sponsor submitted a comprehensive data package of nonclinical and clinical studies. The clinical studies were conducted in accordance with the EU guideline on lipid disorders and included adult patients, elderly patients, primary hypercholesterolemia, mixed dyslipidaemia, heterozygous familial hypercholesterolemia, Type II diabetics, patients with risk factors for CHD and comparative data with simvastatin, atorvastatin and pravastatin. The minimal effective dose was 1 mg and the maximum was 4 mg due to
safety concerns at 8 mg. Pitavastatin demonstrated statistically significant reductions in lipid parameters. From the pooled analysis following 12 weeks of treatment, pitavastatin 1, 2 and 4 mg reduced LDL-C by approximately 31%, 38% and 43% respectively. LDL-C target attainment by NCEP criteria at Week 12 was 83%, 70% and 82%, respectively, and by EAS criteria it was 60%, 64% and 81%, respectively, for the 3 doses. Reductions were also seen in TC, TG, non-HDL-C and Apo-B along with a small increase in HDL. Compared to other stains, pitavastatin 1 mg was superior to pravastatin 10 mg in the elderly; pitavastatin 2 mg was non inferior to atorvastatin 10 mg in non diabetics and superior to simvastatin 20 mg and pravastatin 20 mg in the elderly; and pitavastatin 4 mg was superior to pravastatin 40 mg in the elderly, non inferior to atorvastatin 20 mg in non diabetics, non inferior to simvastatin 40 mg in those with high CHD risk and non inferior to atorvastatin 20 mg in the Type II diabetics. A slightly greater response was seen on LDL-C reduction in the elderly and in females. Efficacy was seen across subgroups of BMI, NCEP risk categories, baseline LDL levels, hypertension, diabetes and primary diagnosis. Long term studies demonstrated maintenance of effect at just over 40% reduction in LDL-C on pitavastatin 4 mg.

**Safety and RMP**

The nonclinical studies demonstrated a similar safety profile to other statins. Exposure to pitavastatin was for a mean 37 weeks on the 4 mg dose in the current Australian submission but postmarket data from Japan provided supportive data with no new safety signals; although limited exposure to 4 mg. Adverse events typically associated with statins were seen that were comparable to other statins including hepatic, muscle and renal events. No cases of rhabdomyolysis were seen on 1-4 mg doses but 2 reports have occurred postmarketing. Elderly patients had a higher risk of adverse events. Patients with moderate renal impairment had increase exposures. Cyclosporine and erythromycin had strong interactions and are therefore contraindicated. The Phase II clinical studies indicated that 8 mg of pitavastatin had increased safety concerns with an increased rate of SAEs, of treatment discontinuation, of CK, AST and ALT elevation and of haematuria and therefore must not be used.

**HeFH**

The data supporting this group is limited but a beneficial effect was seen in Study NK-104-09.

**Food effect**

Food reduces $C_{\text{max}}$ by 43% and delays $T_{\text{max}}$ from 1 to 2 hours but AUC remains unchanged. The sponsor has proposed the tablets can be taken with or without food. Given that pitavastatin AUC remains unchanged and the tablets are for treating a chronic disease that has lipid monitoring and does not depend on peak concentrations, then the proposed PI statement on taking the tablets without regard to meals is acceptable. A regular pattern is recommended.

**Indication**

Some changes to the indication are recommended to provide a simpler statement in line with other statins approved in Australia and which removes the endpoints (LDL-C and TC) to the Clinical Trials section of the PI. Since triglyceride reductions were not a primary endpoint in the trials, then it is recommended, in line with other statins, that reference to mixed dyslipidaemia is removed from the indication but the trials included in the Clinical Trials section of the PI. The standard statement on secondary causes of hypercholesterolemia is also recommended.

**Data deficiencies**

There was a lack of clinical outcome studies for beneficial effects on cardiovascular morbidity and mortality but given the acceptance of LDL lowering as a surrogate measure
and the wide use of statins then this should be acceptable but the sponsor should commit to undertaking these studies post approval. There was no data in severe renal impairment without haemodialysis, severe hepatic impairment, patients taking protease inhibitors, children, adolescents or homozygous familial hypercholesterolemia. Patients with secondary dyslipidaemias were excluded. The maximal doses of comparator statins were not used in the pivotal studies therefore it is unclear exactly how 4 mg pitavastatin would compare with 80 mg simvastatin, 80 mg atorvastatin or 40 mg atorvastatin.

**Conditions of registration**

The following should be conditions of registration:

The submission to the TGA as Category 1 submissions when available, the final study reports investigating patients with severe renal impairment and the drug interaction study with lopinavir/ritonavir.

The submission to the TGA as a Category 1 submission when available, the final study report from the EU observational study relating to statin risks.

**Summary**

Overall the submission appears approvable with demonstrated efficacy and an acceptable safety profile.

The Delegate proposed to approve this submission by Abbott Products Pty Ltd to register Livalo (pitavastatin) based on the quality, safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above in the Risk/Benefit Discussion:

Livalo is indicated as an adjunct to diet for the treatment of adult patients with primary hypercholesterolemia, including heterozygous familial hypercholesterolemia, when the response to diet and other non-pharmacological measures is inadequate.

Prior to initiating therapy with Livalo, secondary causes of hypercholesterolemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

The sponsor should address the following issues in the pre Advisory Committee on Prescription Medicines (ACPM) response:

a. Are there any clinical outcome studies being conducted on cardiovascular morbidity or mortality?

b. Please confirm if the RMP includes intensive active monitoring of the known risks and expedited reporting of major muscle and hepatic events.

c. Please clarify how many patients on pitavastatin, by dose, were exposed for >1 year.

The ACPM’s advice was requested on the following issue:

Are the efficacy and safety data and our acceptance of LDL lowering as a surrogate measure from other statins sufficient to not require a clinical outcome study for pitavastatin prior to approval?
Response from sponsor

Comments on the delegates proposed action

1. **Indication:** Some changes to the indication are recommended to provide a simpler statement in line with the other statins approved in Australia and which remove the endpoints (LDL-C and TC) to the clinical trials section of the PI.

Abbott Australasia concurred with the Delegate’s recommendation to align the indication with the other statins approved in Australia and proposed the following revised indication:

“Livalo is indicated as an adjunct to diet for the treatment of adult patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia when the response to diet and other non-pharmacological measures is inadequate. Prior to initiating Livalo, secondary causes of hypercholesterolaemia (such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.”

2. **Are there any clinical outcome studies being conducted on cardiovascular morbidity or mortality?**

Please be advised that there are several investigator initiated clinical outcome studies assessing the cardiovascular morbidity and mortality of pitavastatin. A tabulated summary of these studies has been included with our response. As noted by the clinical evaluator, the clinical development program for Livalo was conducted in accordance with the EU guideline on lipid disorders and included adult patients, elderly patients, primary hypercholesterolaemia, mixed dyslipidaemia, heterozygous familial hypercholesterolaemia, Type II diabetic patients, patients with risk factors for coronary heart disease (CHD) and included comparative data with simvastatin, atorvastatin and pravastatin. In accordance with this guideline and as per the US PI for pitavastatin Abbott Australasia propose the addition of the following statement to the PI: “The effect of Livalo on cardiovascular morbidity and mortality has not been determined.”

3. **Please confirm if the RMP includes intensive active monitoring of the known risks and expedited reporting of major muscle and hepatic events.**

Please be advised that the EU RMP includes expedited reporting of all serious adverse events, including major muscle and hepatic events.

4. **Please clarify how many patients on pitavastatin, by dose, were exposed for >1 year.**

The number of patients receiving pitavastatin for more than 1 year (adjusted for drop-outs) in the long term studies sponsored by Kowa are summarised in Table 34 below.

**Table 34. Patient exposure for >1 year to pitavastatin.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients receiving pitavastatin for &gt;1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK-104-09</td>
<td>32, 1200, 77</td>
</tr>
<tr>
<td>NK-104-307</td>
<td>378, 1200, 77</td>
</tr>
<tr>
<td>NK-104-308</td>
<td>109, 77, 60</td>
</tr>
<tr>
<td>NK-104-309</td>
<td>141, 60</td>
</tr>
<tr>
<td>NK-104-310</td>
<td>1559, 60</td>
</tr>
</tbody>
</table>

* Subjects entering these studies were previously treated for 12 weeks.

5. **Conditions of registration**

a. The submission to the TGA as a Category 1 submission when available the final study reports investigating patients with severe renal impairment and the drug interaction study with lopinavir/ritonavir.
b. The submission to the TGA as a Category 1 submission when available the final study report from the EU observational study relating to statin risks.

Abbott Australasia provided an assurance that the abovementioned documents will be submitted to the TGA in due course, and accepts this as a condition of registration for Livalo.

**Conclusion**

Abbott Australasia concurred with the Delegate’s recommendation to approve Livalo (pitavastatin) tablets for the following indication:

“Livalo is indicated as an adjunct to diet for the treatment of adult patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia when the response to diet and other non-pharmacological measures is inadequate. Prior to initiating Livalo, secondary causes of hypercholesterolaemia (such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaeas, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.”

**Advisory committee considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, advised the following:

**Efficacy**

The five Phase III 12 week trials demonstrated statistically significant reductions in lipid parameters after 12 weeks of treatment. Maintenance of this efficacy effect was seen in the 7 long term studies of 44 to 104 weeks duration. Non inferiority of safety and efficacy in pitavastatin compared to atorvastatin, simvastatin or pravastatin was also demonstrated in many of the target populations. It was noted that the maximal doses of comparator statins were not used in the pivotal studies.

**Safety**

There were no safety signals of concern noted. The nonclinical studies demonstrated a similar safety profile to other statins. Postmarket data from Japan was supportive. Beyond 4 mg, the trial data showed dose dependent increases in hepatic, renal and muscle events. The minimal effective dose was 1 mg and the maximum was 4 mg due to safety concerns at 8 mg. There was an increased frequency of adverse events in the elderly and patients with moderate renal impairment had increased exposures.

In line with contraindications for cyclosporine and erythromycin use due to dramatic effects on pharmacokinetics, tacrolimus should also be contraindicated.

It was noted that the sponsor had agreed to the Delegate’s modified indication in their pre ACPM response.

The ACPM was of the view that, although the surrogate endpoint of a relative reduction in LDL cholesterol is acceptable within the TGA adopted EMA guidelines, ideally a lipid-modifying agent should demonstrate an effect on the prevention of cardiovascular morbidity and mortality. The sponsor should commit to undertaking these studies post approval.

The ACPM agreed with the Delegate’s specific conditions of registration:

- The submission to the TGA when available of the final study reports investigating patients with severe renal impairment and the drug interaction study with lopinavir/ritonavir.
• The submission to the TGA when available of the final report from the EU observational study relating to statin risks.

• The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for pitavastatin (Livalo) would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Livalo film coated tablets containing pitavastatin (as calcium) 1 mg, 2 mg and 4 mg indicated for:

An adjunct to diet for the treatment of adult patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia, when response to diet and other non-pharmacological measures is inadequate.

Prior to initiating therapy with Livalo, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

Specific conditions applying to these therapeutic goods

1. The submission to the TGA, as evaluable data within the context of Category 1 applications, when available, of the final study reports (and/or any interim study reports, if relevant) of the clinical trial investigating patients with severe renal impairment and the drug-drug interaction study with lopinavir/ritonavir.

2. The submission to the TGA, when available, of the final study report (and/or any interim study reports, if relevant) of the EU observational study relating to statin risks.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.