



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Sitagliptin phosphate monohydrate + Simvastatin

Proprietary Product Name: Juvicor

Sponsor: Merck Sharp and Dohme (Australia)
Pty Ltd

Date of first round report: 11 March 2012

Date of second round report: 21 June 2012

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, 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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
CMI	consumer medicine information
DPP	dipeptidyl peptidase 4
FDC	fixed dosage combination
GIP	gastric inhibitory peptide
GLP-1	glucagon like peptide-1
HMG CoA	hydroxy-methyl glutaryl coenzyme A
HbA1c	haemoglobin A1c
HPS	Heart Protection Study
LS	least squares
MSD	Merck Sharp and Dohme
PI	product information
PD	pharmacodynamics
PK	pharmacokinetics
SCS	summary of clinical safety
SOC	system organ class
T2DM	Type 2 diabetes mellitus
TGA	Therapeutic Goods Administration
WAES	Worldwide Adverse Experience System

1. Clinical rationale

This is extensively described in the letter of application at 1.0.1 and in other parts of the submission. The product is proposed as a therapeutic tool to help achieve improved clinical outcomes for patients with T2DM. Sitagliptin is documented to improve glycaemic control and is registered for therapeutic use in T2DM. Simvastatin is documented to reduce the atherogenic components of plasma cholesterol and in consequence to reduce the incidence of related cardiovascular events. Macrovascular disease is a major cause of morbidity in T2DM and it is documented that its clinical effects can be lessened by pharmacological control of both plasma glucose and cholesterol. Accordingly, therapeutic guidelines recommend lower targets for plasma cholesterol in patients with T2DM, as well as a higher threshold for the introduction of therapeutic agents such as statins. This is also reflected in the guidelines for subsidy of these drugs through the PBS.

As a result of the above factors, the sponsor identifies that there is a substantial population of Australian T2DM patients who are either already receiving or would justify the administration of the combination of sitagliptin and a statin. The submission argues that the availability of a combination of these two therapeutic classes would improve the convenience of, and compliance with, such combination treatment. Although not stated, it is also evident that such a combination product might imply a cost reduction for patients.

The choice of the specific substances comprising this fixed combination product is influenced by the sponsoring company's history of innovation in both therapeutic classes. Sitagliptin was the first member of the class of DPP4 inhibitors introduced for therapeutic use in the past decade. Much earlier, the company's products simvastatin and its immediate predecessor lovastatin were the first HMG-CoA reductase inhibitors introduced for clinical use, and the landmark 4S study (3) employing simvastatin was the first demonstration of improved cardiovascular outcomes with use of these drugs.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The dossier was reviewed in electronic form. It is well indexed and readily navigated.

The submission contained the following clinical information:

- Module 5
 - 7 clinical pharmacology studies, listed below, which specifically support the submission and provide data upon which this evaluation report is based

Table 1. List of Clinical Pharmacology Studies

Study type	Protocol number
Biopharmaceutic studies	
MK-0431D Tablet formulation study	P154
MK-0431D Tablet definitive bioequivalence study	P153
MK-0431D Tablet food effect study	P155
MK-0431D Tablet definitive bioequivalence study	P255
Pharmacokinetic studies	
Simvastatin interaction study	P025
Sitagliptin interaction study	P168
Digoxin interaction study	P169

Component of original sitagliptin filing

2.1.1. Studies 153, 255, 155, 025 and 168 are regarded as pivotal.

- Additionally, there are included reports of 18 studies and 5 extensions thereof supporting various aspects of the efficacy/safety of sitagliptin. These, with the addition of study 801, constitute the 19 studies referred to on pages 6 and 7 of the letter of application as supporting the efficacy and safety of the product. **They are regarded as supportive only** as none involves the administration of the applicant product itself and are derived from the original development program for sitagliptin. The majority have been previously evaluated by TGA, but 10 (P 040, 047, 049, 051, 052, 053, 061, 064, 079; and 801 which is listed separately as reference 1996 at 5.3.5.4), along with 7 of the extension studies, have not. Summaries of all these studies (except 801) appeared in the form of a tabular listing.
- There are 208 documents containing analyses of various aspects of safety in relation to the concomitant use of simvastatin and sitagliptin and two literature references on safety aspects.
- Module 1
 - Application letter, application form, draft Australian PI and CMI
 - Certification regarding good manufacturing practice
 - Details regarding overseas regulatory status
 - At 1.12, a note regarding paediatric use or the lack thereof and justification for a waiver of the need for a paediatric development program
 - Documentation of a TGA waiver having been granted with regard to the need for a risk management plan.
- Module 2

Clinical Overview, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety, synopses of all individual studies and literature references.

2.2. Paediatric data

The submission did not include paediatric data. Paediatric use is excluded by the indications. Additionally, the sponsor points out that simvastatin is not indicated for use in children, the combination is accordingly unlikely to be used in a substantial number of paediatric patients, and therefore a waiver from the requirement for a paediatric development program is justified.

2.3. Good clinical practice

Apart from isolated episodes of non-compliance, none serious, documented in the study reports, the principles of good clinical practice appear to have been followed throughout the included trials.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 2 shows the studies relating to each pharmacokinetic topic.

Table 2. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	Bioequivalence† - Single dose	P154 P153 P255
	Food effect	P155
PK interactions	Sitagliptin on simvastatin PK	P025
	Simvastatin on sitagliptin PK	P168
	Sitagliptin + simvastatin on digoxin PK	P169

† Bioequivalence of different formulations.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

3.2.1. Physicochemical characteristics of the active substance

As noted in the Sponsor's summaries in Module 2, the reports of studies P154 and P153, the formulations employed for the two active substances in this fixed combination are identical

with those used in the Sponsor's products Januvia (sitagliptin) and Zocor (simvastatin). As these are both Australian-approved products, further detail of this aspect has not been sought.

3.2.2. Pharmacokinetics in healthy subjects

3.2.2.1. Bioavailability

3.2.2.1.1. Absolute bioavailability

No data are included in this submission. If necessary, reference could be made to the registration applications for the parent products Januvia and Zocor.

3.2.2.1.2. Bioequivalence of clinical trial and market formulations

Formulation [information redacted] used in studies P153, P255 and P155 is identical with the for-market formulation except for the colourant in the film coating [information redacted]. It is noted, that on 18 July 2011, the sponsor requested TGA review of four waivers, including one as a biowaiver for this minor formulation variation.

3.2.2.1.3. Bioequivalence of different dosage forms and strengths

Bioequivalence of the combination tablet with equivalent dosage given as coadministered Januvia (sitagliptin) and Zocor (simvastatin) was tested at the 100 mg sitagliptin/80 mg simvastatin dose (Study P153) and at the 100 mg/10 mg dose (Study P255). At both dose levels, good evidence of bioequivalence was obtained. The Sponsor proposes that these studies be taken as validating bioequivalence for the intervening 100 mg/20 mg and 100 mg/40 mg strengths, under the principle of "bracketing". Given the satisfactory outcome of the two included studies, the fact that only one dose level of sitagliptin is involved, and the previously established linearity of dose response for simvastatin (4), this approach is considered valid. It should be noted that the 100 mg sitagliptin/80 mg simvastatin strength is not proposed for marketing.

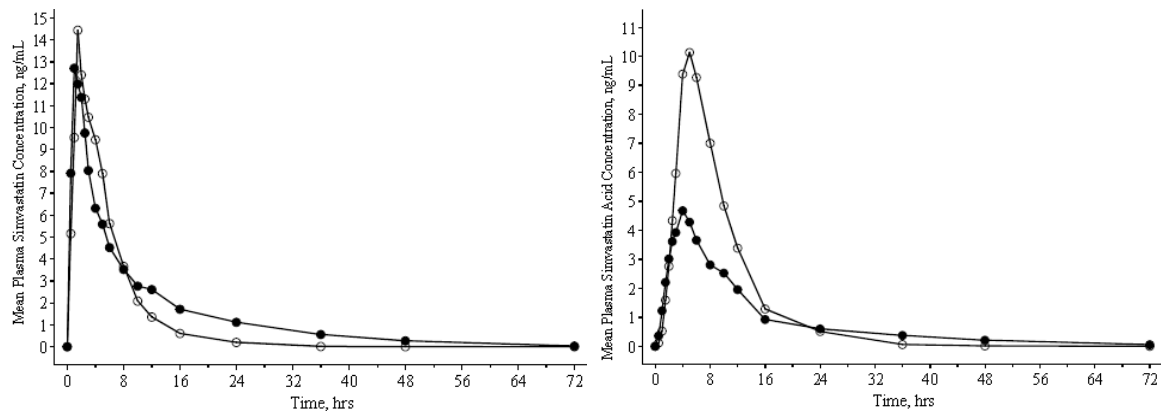
3.2.2.1.4. Bioequivalence to relevant registered products

Januvia and Zocor are the relevant Australian-registered products to which bioequivalence of the Juvicor combination tablet has been established, as already noted above.

3.2.2.1.5. Influence of food

In the food effect Study P155, the PK characteristics of the sitagliptin component of the combination tablet clearly remained unaltered whether the medication was given fasting or following the ingestion of food, in this case a high-fat meal. With regard to simvastatin, however, some changes were observed. Although the presence of a "substantial effect", as defined in the study protocol, was excluded by the 90% CI for the GMR fed/fasting of simvastatin AUC remaining within the rather wide predefined limits of (0.50, 2.00), there does appear to have been an effect. Figure 1 shows the time-concentration profiles following administration of MK-0431D 100 mg/80 mg for simvastatin (left panel) and simvastatin acid (right panel). The closed circles illustrate the profiles with the drug given in the fasting state, and the open circles with it given together with a high-fat meal.

Figure 1. Time-concentration profiles following administration of MK-0431D 100 mg/80 mg for simvastatin (left panel) and simvastatin acid (right panel)



Simvastatin acid is the principal active metabolite of simvastatin (see discussion at 4.2.2.1.9.1 below) and as such plays a major role in its pharmacodynamic effect. The summary PK for both simvastatin components are shown in the Table 3.

Table 3. Summary PK for both simvastatin components

Pharmacokinetic Parameter	MK-0431D Fed			MK-0431D Fasted			MK-0431D Fed/Fasted		rMSE ¹
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
Staglipitin									
AUC _{0-∞} [†] (nM·hr)	32	7266	(6907, 7643)	32	7263	(6904, 7640)	1.00	(0.98, 1.02)	0.0374
AUC _{0-t_{max}} [†] (nM·hr)	32	7163	(6808, 7536)	32	7165	(6810, 7539)	1.00	(0.98, 1.02)	0.0385
C _{max} [†] (nM)	32	764	(689, 846)	32	809	(731, 897)	0.94	(0.87, 1.03)	0.2003
T _{max} [‡] (hr)	32	2.3	(0.5, 6.0)	32	2.0	(0.5, 5.0)			
Apparent terminal t _{1/2} [‡] (hr)	32	12.9	2.7	32	12.6	2.8			
Simvastatin									
AUC _{0-∞} [†] (ng/mL·hr)	32	67.39	(55.76, 81.45)	32	88.76	(73.44, 107.27)	0.76	(0.64, 0.90)	0.3886
C _{max} [†] (ng/mL)	32	16.89	(13.61, 20.97)	32	14.08	(11.35, 17.48)	1.20	(0.97, 1.48)	0.4896
T _{max} [‡] (hr)	32	2.0	(0.5, 6.0)	32	1.5	(0.5, 5.0)			
Simvastatin Acid									
AUC _{0-∞} [†] (ng/mL·hr)	32	67.67	(54.36, 84.23)	32	49.27	(39.58, 61.33)	1.37	(1.16, 1.63)	0.4022
C _{max} [†] (ng/mL)	32	9.33	(7.44, 11.70)	32	4.31	(3.44, 5.41)	2.16	(1.84, 2.55)	0.3842
T _{max} [‡] (hr)	32	5.0	(2.3, 8.0)	32	4.0	(2.0, 12.0)			

¹ rMSE: Root mean square error on log-scale from linear mixed effect model. When multiplied by 100, provides estimate of the pooled within-subject coefficient of variation.
[†] Back-transformed least-squares mean and CI from mixed effect model performed on natural log-transformed values; GMR = Geometric least-squares mean ratio (MK-0431D Fed/MK-0431D Fasted).
[‡] Median (min, max) reported for T_{max}.
[‡] Harmonic mean, jack-knife standard deviation reported for apparent terminal t_{1/2}.
 GM = Geometric Least-Squares Mean; CI = Confidence Interval.

The quantification of the increased exposure to simvastatin acid in the fed state evident above in the right-hand panel of Figure 1 is that mean C_{max} is increased by 116% and mean AUC by 37%. In the study report, the interpretation of this is that "the high-fat meal increased the C_{max} of simvastatin acid without commensurate increases in the AUC of simvastatin acid or in the AUC or C_{max} of simvastatin". The interpretation of the simvastatin acid AUC data as "no increase" is based on the broad predefined limits for 90% CI (0.50, 2.00). In reality, the increase in AUC is consistent with the 116% increase in C_{max} and may well be biologically and perhaps clinically significant; whether this might be so is difficult to judge in the absence of pharmacodynamic data. The discussion in the study report offers no discussion of this observation, which may be a new finding; it is stated that "data on the effect of a high-fat meal on simvastatin, administered alone, are not available". In the approved PI for Zocor¹ a study is described in which the level of

¹ Approved product information for Zocor. <<https://www.ebs.tga.gov.au/>>

simvastatin metabolites (measured as HMG CoA reductase inhibitors) was measured and was not affected when simvastatin was administered immediately before a test meal (fat content not specified).

The clinical overview likewise interprets the food effect on simvastatin acid PK as "*not likely to have a meaningful clinical effect*" and this is translated into the statement in the PI that "*because coadministration of a high-fat meal with Juvicor had no clinically meaningful effect on the pharmacokinetics of sitagliptin or simvastatin, Juvicor may be administered with or without food*". The conclusion of "no clinically meaningful effect" appears to be a subjective judgement of doubtful scientific validity. If, for example, this increased exposure occurred in the setting of coincident consumption of grapefruit juice or coadministration of other CYP3A4 inhibiting substances, it is very likely that the level of risk of muscle events including rhabdomyolysis would be increased.

In summary, the data presents some evidence that administration of the combination tablet with a high-fat meal results in increased exposure to simvastatin beta-hydroxy acid. Hypothetically, this might relate to altered gastric pH or other conditions favouring increased hydrolysis of simvastatin. It is in principle unlikely that this phenomenon is specific to the combination tablet. The limited information available may implicate the fat content of the meal. The Sponsor should be asked whether any further information is available which might clarify the situation.

3.2.2.1.6. *Dose proportionality*

Dose proportionality for Juvicor (simvastatin component) rests on the data for the existing product Zocor and the principle of bracketing employing data from studies P153 and P2 55, as outlined above.

3.2.2.1.7. *Bioavailability during multiple-dosing*

Not applicable.

3.2.2.1.8. *Effect of administration timing*

No data is provided on any difference in PK, with particular reference to sitagliptin, resulting from the recommended time of administration in the evening by comparison with the data in the supporting studies when the drug is given in the morning. The possible implications of this are outlined in Submission details and discussed further below at *Evaluator's overall conclusions on pharmacodynamics*.

3.2.2. *Metabolites identified in humans*

3.2.2.2.1. *Active metabolites*

The TGA approved PI for Zocor¹ identifies simvastatin as an inactive lactone which, after oral ingestion, is hydrolysed to the beta-hydroxyacid form. It is this, together with four additional active metabolites, which inhibits HMG CoA reductase. It is stated that in dose proportionality studies, there was no substantial deviation from linearity of AUC of inhibitors with respect to the parent compound. It is further stated that the plasma profile of inhibitors (metabolites) was not affected when simvastatin was administered immediately before a test meal.

3.3. **Pharmacokinetic interactions**

3.3.1. **Pharmacokinetic interactions demonstrated in human studies**

The submission includes three studies which investigate actual or potential drug-drug interactions relevant to the application. These are P025, P168 and P169. While each of these studies involves the coadministration of sitagliptin and simvastatin in some way, none involves the administration of the combination tablet.

The bounds for 90% CI of (0.50, 2.00) prespecified in these drug/drug interaction studies so as to exclude what is described as a clinically meaningful effect might be seen as somewhat generous, allowing as they do for up to a twofold increase or a halving in exposure to drug A in the event that its PK is affected by drug B. The safety or otherwise of such a margin would depend on the characteristics of the drug affected. A rationale for the selection of these endpoints is provided in the report of Study P168 which examines the potential for an impact of simvastatin coadministration on PK of sitagliptin. The justification provided is that in Phase III clinical studies of sitagliptin (specific study not referenced), the efficacy and safety of a 200 mg once daily dose was similar to that observed with the approved clinical dose of 100 mg once daily; and that in dose ranging Study PN014, while 100 mg daily was maximum effective, 50 mg was also "efficacious".

Study P025 examines the effect of sitagliptin on the PK of simvastatin. It employs the same bounds for the 90% CI of (0.50, 2.00) referred to above in respect of P168, but without any justification or explanation. The study was carried out some six years earlier than P168, predating the development of the combination tablet, and should be seen in the context of the **potential** coadministration of sitagliptin and simvastatin as opposed their **deliberate** coadministration in the same formulation. Nevertheless, tolerance of a potential two fold exposure to simvastatin should be questioned in relation to a drug with a wide range of doses administered in clinical practice, within which range dosage is sometimes determined by individual estimations of risk against potential benefit. Such an increase in simvastatin exposure was not revealed in the data analysis for Study P025 in which the point estimates for coadministration/simvastatin alone varied, amongst the various parameters measured, between 0.80-1.12 with the widest variation from unity in the 90% CI being (0.51, 1.26) for C_{max} of simvastatin. In view of these observed data, the conclusion of the study that there was not a clinically important effect, and that dosage adjustment of simvastatin need not be considered, is accepted.

As noted above, Study P168 examines the reciprocal situation of whether simvastatin influences sitagliptin PK. The AUC, whether measured to infinity or last observation, and C_{max} for sitagliptin remained unchanged with coadministration, the GMRs for all parameters being close to unity with little variance. Lack of significant interference with the PK of either component of the coadministered medication by the other is therefore confirmed.

Study P169 examines the effect of coadministration of simvastatin 80 mg and sitagliptin 100 mg on the PK of digoxin, in light of the fact that each drug individually has been demonstrated to have such an effect. The study report cites PK interaction studies done during the earlier development programs for the two drugs which showed, in coadministration with sitagliptin, an 11% increase in the AUC and 18% increase in C_{max} for digoxin; and with simvastatin, a 19 % increase in AUC and no change for C_{max} although the data for the latter were highly variable so that the 90% CI fell outside the prespecified comparability bounds of (0.80, 1.25). In line with this, the PI for both Zocor and Januvia contain a cautionary statement advising monitoring of patients on digoxin.^{1, 2} The data from Study P169 likewise showed a significant increase in the digoxin exposure following a single oral dose of digoxin 0.5 mg coadministered with 80 mg simvastatin (Zocor) and 100 mg sitagliptin (Januvia) tablets at steady state. GMR (coadministration/digoxin alone) with 90% CI was 1.26 (1.13, 1.41) for AUC and 1.41 (1.20, 1.66) for C_{max}. These increases of 26% for AUC and 41% for C_{max} approximately represent addition of the individual drug effects described above.

² Approved product information for Januvia. <<https://www.ebs.tga.gov.au/>>

3.4. Evaluator's overall conclusions on pharmacokinetics

The Sponsor has provided good evidence that the proposed combination tablet is bioequivalent to its component substances simvastatin and sitagliptin coadministered as separate tablets, across the dose range proposed. The comparator preparations used in the studies supporting this conclusion are Australian registered products.

Evidence is produced that each of the component drugs is free of influence on the PK of the other.

Both simvastatin and sitagliptin have been previously documented to influence, by different mechanisms, the PK of digoxin so as to moderately increase its exposure. With coadministration, it is shown that these effects are additive. An appropriate comment is included in the proposed PI.

With regard to the possible food effect described above, if the conclusion is supported that increased simvastatin acid exposure occurs specifically with a high-fat meal, there might be a case for including a cautionary note about this finding in the PI; although perhaps the ultimate point is that patients being treated with simvastatin should not be having a high-fat meal in any case.

4. Pharmacodynamics

4.1. Summary of pharmacodynamics (PD)

While no pharmacodynamic studies are included in the submission, the issue of the time course of the PD action of sitagliptin is felt to be of potential relevance in relation to the change from morning to evening administration of this component of the combination tablet, which is imposed by its dosing schedule.

4.1.1. Mechanism of action

Sitagliptin is a member of the class of inhibitors of DPP4, an enzyme system responsible for the in-vivo degradation of incretin hormones (GLP-1 and GIP). This action leads to an increase in the level of these hormones and consequently insulin secretion in the fed state, and thereby improves glycaemic control in T2DM in which disorder the incretin response to feeding is deficient. These actions are well described in the literature (for example³) and in studies which supported the initial Australian registration of sitagliptin, as summarised in the clinical evaluation report for that application.

4.1.2. Time course of pharmacodynamic effects

The PD action of DPP4 inhibitors such as sitagliptin has been quantified by measuring the percent inhibition of DPP4 in plasma or by measuring, in comparison with placebo, the effect of the drug on the rise in GLP-1 following a meal or a glucose load. The time course of this action has relevance to the present submission; if there is a significant variance in the level of these actions over the 24 hour dosing interval, this might impact on post-prandial glycaemic response at various times of the day. A possible effect of this nature would depend on the exact timing of administration of the drug, which is not specified other than that it is to be given in the evening. If given before the evening meal and there is a peak of DPP4 inhibition in the acute phase after administration (note that C_{max} for sitagliptin occurs 1-4 hours post dose), an increase in

³ Pharmacokinetics and pharmacodynamic effects of the oral DPP-4 inhibitor sitagliptin in middle-aged obese subjects. Herman GA, Bergman A, Liu F, Stevens C, Wang AQ, Zeng W, Chen L, Snyder K, Hilliard D, Tanen M, Tanaka W, Meehan AG, Lasseter K, Dilzer S, Blum R, Wagner JA J Clin Pharmacol. 2006 Aug;46(8):876-86

glycaemic efficacy might be seen and most importantly might aggravate the already described potential for hypoglycaemia in the situation of coadministration with sulphonylureas. Alternatively, if the drug is taken before bed, and the level of DPP4 inhibition diminishes over the latter part of the 24 hour period, glycaemic efficacy following the evening (usually main) meal the following day might be **decreased**.

The essential issue is whether there is significant within-period of variation in the level of DPP4 inhibition following once daily dosage with sitagliptin. Information available to this evaluation on this point is limited. PD studies supporting the initial registration of sitagliptin are reviewed in the relevant CER. In Study P001C1, administration of single doses of sitagliptin to healthy volunteers inhibited plasma DPP4 in a dose-dependent fashion. Within the proposed dose range, inhibition was overall some 10% greater at 12 hours than at 24 hours post dose. With sitagliptin administration, GLP-1 concentrations were also demonstrated to be increased following meals administered at 4 hours, 10 hours and 24 hours post dose. There is no comment about any difference between the time intervals, and this would be of interest. Possibly of most significance is Study P005 undertaken in T2DM patients as reported in the CER. Plasma GLP-1 and GIP were measured following glucose challenge either 2 hours or 24 hours after single doses of sitagliptin. With 200 mg dosage, approximately twofold increases in these hormones occurred at both time intervals. With 25 mg dose, however, there was a two fold increase with a glucose load given at two hours post dose, but approximately 1.3 fold at 24 hours post dose. Whether such a within-period variation in the PD action of sitagliptin might occur with therapeutic doses at steady state is not clear from this data.

A 2008 study reporting the PD action of a novel xanthine based DPP4 inhibitor⁴ suggests that DPP4 inhibition is not fully maintained over 24 hours with comparator drugs including sitagliptin.

In summary, there is some evidence of time dependency of the PD action of sitagliptin during the dosing period. It appears unlikely that the quantum of this is sufficient to impact on the clinical action of sitagliptin resulting from a change to evening administration, but an effect of this nature cannot be completely excluded.

4.2. Evaluator's overall conclusions on pharmacodynamics

As described above, substitution of MK-0431D for separate administration of its component substances simvastatin and sitagliptin involves a change in the timing of administration of sitagliptin from morning to evening. Section III.1.2 of the EMEA guidelines on fixed combination products (9) states that under these circumstances "..... (the Sponsor) *should demonstrate that the change in timing of administration of one of the components of the combination does not affect the pharmacodynamic effect of any of the constituents of the combination. Therefore, in addition to the demonstration of a similar pharmacokinetic profile, a noninferiority pharmacodynamic study assessing the effect of the combination as compared with those components administered at their usual dose time is expected.*"

In the draft PI, in a section reproduced verbatim from the Januvia PI, it is stated that "*in Phase II studies, sitagliptin 50 mg twice a provided no additional glycaemic efficacy compared to 100 mg once daily*". This is the only information which can be found in the application related to variation in dosage schedule, apart from a brief statement on dosage timing, unsupported by data, in the Summary of Clinical Efficacy. No data is provided regarding the impact, or lack of

⁴ (R)-8-(3-amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a novel xanthine-based dipeptidyl peptidase 4 inhibitor, has a superior potency and longer duration of action compared with other dipeptidyl peptidase-4 inhibitors. Thomas L, Eckhardt M, Langkopf E, Tadayyon M, Himmelsbach F, Mark M. J Pharmacol Exp Ther. 2008 Apr;325(1):175-82. Epub 2008 Jan 25

impact, of giving the daily dose in the evening. As noted under *Time course of Pharmacodynamic effects* above, the possibility of a variation in glycaemic efficacy resulting from this change in dosage timing cannot be excluded.

The Sponsor should either comply with the EMEA recommendation regarding the performance of a PD study, or at a minimum justify non-performance of such a study with further data of the type discussed above under *Time course of Pharmacodynamic effects*.

5. Dosage selection for the pivotal studies

No Phase III studies involving the administration of the fixed dosage combination tablet are included in the submission. Evidence for efficacy and safety rests firstly on the pivotal biopharmaceutical and bioequivalence studies reviewed in earlier sections of this evaluation report, and secondly on interpretive summaries provided in the submission, based on data from the clinical development programs supporting registration of the parent products Januvia (sitagliptin) and Zocor (simvastatin) from which this fixed combination product is derived. The Phase III studies on which the summaries are based are reviewed in the following section.

6. Clinical efficacy

The Sponsor's case for demonstrating efficacy of the Juvicor combination tablet is based on the following set of arguments, copied from the summary of clinical efficacy:

Bridging of the efficacy observed in the sitagliptin and simvastatin development programs to MK-0431D is supported by:

1. *Demonstration of bioequivalence between the MK-0431D FDC tablets and the coadministration of corresponding doses of sitagliptin and simvastatin.*
2. *Demonstration of the absence of a clinically meaningful effect of sitagliptin on the pharmacokinetic properties of simvastatin.*
3. *Demonstration of the absence of a clinically meaningful effect of simvastatin on the pharmacokinetic properties of sitagliptin.*
4. *Data from individual sitagliptin studies showing generally neutral effects of sitagliptin on serum cholesterol levels.*
5. *Data from simvastatin and sitagliptin studies showing generally neutral effects of simvastatin/statins on glycaemic control in patients with T2DM.*

Points 1-3 have already been covered above under *Pharmacokinetics*, to the satisfaction of this evaluation.

Points 4 and 5 are addressed by the Sponsor referring to and providing analyses of a total of 19 sitagliptin efficacy studies as listed in their letter of application and described above. Although some of these studies have been previously evaluated for TGA, the data on plasma cholesterol and other lipid levels has not received detailed attention in previous evaluation reports, so brief descriptive summaries of all 19 are provided in the following section.

6.1. Supportive phase III studies

The following summaries appear in the order in which the studies are listed in the Sponsor's letter of application. Each study was conducted under the sponsorship of MSD as part of the development programs for the drug substances sitagliptin and simvastatin which make up the applicant FDC. All of the studies were conducted on populations of T2DM patients at various international sites. The purpose of the summaries is to describe the objectives and conduct of

each study, the treatments administered, and to confirm that each was conducted in accordance with good clinical practice and appropriate scientific principles. For the purpose of this report, it is not felt necessary to repeat these aspects or to detail the study outcomes in these summaries. In all of the studies, the principal efficacy outcomes relate to glycaemic control and these data, HbA1c in particular, form the basis for an overall analysis undertaken by the Sponsor of glycaemic response to sitagliptin according to use or non-use of statins as described below in the section *Analysis of Phase 3 study outcomes and the sponsor's case for efficacy*; these outcomes are presented in the summaries of the individual studies below. The other efficacy outcome of interest is the lipid data which is summarised by individual study below along with information on the numbers of subjects and treatments administered.

The safety data from all 19 studies has been pooled by the sponsor and forms the basis for the Summary of Clinical Safety, as described below in the *Clinical Safety* section of this report.

6.1.1. Previously evaluated studies

Study 019 was a multicentre, randomised, double-blind study evaluating the safety and efficacy of sitagliptin versus placebo in T2DM patients with inadequate glycaemic control on pioglitazone therapy, conducted in 2004-2005 at 71 international sites.

Study 035 was a multicentre, randomised, double-blind, placebo-controlled study which evaluated the safety and efficacy of sitagliptin by comparison with placebo added to the treatment of T2DM patients with inadequate control on glimepiride alone or in combination with metformin, conducted in 2005-2000 77⁵ international sites.

6.1.1.1. Previously evaluated studies with subsequent extensions

Study 010, a multicentre, double-blind randomised trial initiated in 2003 was evaluated previously as its initial 12 week phase in which the T2DM subjects were divided into six groups taking either placebo, glipizide or one of four trial doses of sitagliptin (5, 12.5, 25 or 50 mg twice daily). Enrolled subjects were required to have unsatisfactory diabetes control (HbA1c 6.5-10%) on either diet alone or a single hypoglycaemic agent which was then withdrawn during the run-in period. Following the initial 12 week study, there were two extension studies, the first of 40 weeks (reported as Study P010x1) and the second of a further 54 weeks, reported as Study P010c2. Throughout both these extensions subjects who had been receiving glipizide in the initial 12 week phase were maintained on this drug in the dose, between 5 and 20 mg daily, to which they have been titrated during the initial phase. Subjects on either placebo or any of the sitagliptin dosages were switched to sitagliptin 100 mg daily in the morning and maintained on this dose throughout the rest of the study, which therefore became an active control design. The mean fall from baseline in HbA1c at 106 weeks was similar in the sitagliptin group (-0.39%) and the glipizide group (-0.42%). The lipid data, for the previously unevaluated 40 week extension study only (see comment below), are shown in Tables 4A-D.

⁵ Erratum: 74

Table 4A. Mean % change from baseline, plasma total cholesterol. Comparison of sitagliptin and placebo treated subjects

Study ID	Week	Background Therapy	Mean % change from baseline (SE)			
			Sitagliptin	n	Placebo	n
P019	24	pioglitazone	2.6 (1.3)	151	2.9 (1.3)	162
P035	54	glimepiride ± metformin	3.0 (1.4)	142	-0.9 (1.6)	111
P021	104	diet ⁶	4.2 (1.3)	182	n/a	
P040	18	diet/exercise	2.9 (0.8)	329	3.9 (1.1)	158
P047	24	diet ⁷	2.2 (1.8)	71	3.8 (1.9)	57
P051	24	insulin ± metformin	1.7 (1.1)	277	3.0 (1.1)	286
P052	54	metformin + rosiglitazone	2.5 (1.5)	161	4.3 (2.0) ⁸	83
P053	30	metformin	2.3 (1.9)	89	6.9 (2.6)	82
P064v1	24	pioglitazone	-0.0 (1.2)	237	1.5 (1.2)	231
P064x1	54	pioglitazone	-2.2 (1.4)	149	-0.4 (1.4)	142
P079	18	metformin	-4.2 (0.8)	481	-3.8 (0.8)	470
801	24	metformin	4.9*	86	11.3*	83

*Variance data for difference from baseline not given in reference 1996 which is the source of this report.

⁶ Erratum: diet/exercise

⁷ Erratum: diet/exercise

⁸ Erratum: 4.9 (2.5)

Table 4B. Mean % change from baseline, plasma LDL cholesterol. Comparison of sitagliptin and placebo treated subjects

Study ID	Week	Background Therapy	Mean % change from baseline (SE)			
			Sitagliptin	n	Placebo	n
P019	24	pioglitazone	5.8 ⁹ (2.3)	150	4.5 (2.0)	162
P035	54	glimepiride ± metformin	4.5 (2.6)	136	-0.9 (2.5)	107
P021	104	diet ¹⁰	5.5 (2.0)	182	n/a	
P040	18	diet/exercise	8.0 (1.4)	325	6.5 (2.0)	158
P047	24	diet ¹¹	7.1 (3.7)	71	28.7 (21.1)	57
P051	24	insulin ± metformin	4.1 (1.9)	276	6.0 (2.0)	286
P052	54	metformin + rosiglitazone	6.2 (2.6) ¹²	161	9.7 (3.6) ¹³	83
P053	30	metformin	7.4 (3.6)	89	12.1 (4.2)	82
P064v1	24	pioglitazone	3.2 (2.8)	217	2.7 (1.8)	217
P064x1	54	pioglitazone	0.8 (2.5)	148	1.9 (2.5)	142
P079	18	metformin	-0.8 (1.5)	476	-4.8 (1.3)	470
801	24	metformin	11.4*	86	16.7*	83

*Variance data for difference from baseline not given in reference 1996 which is the source of this report.

⁹ Erratum: 6.6

¹⁰ Erratum: diet/exercise

¹¹ Erratum: diet/exercise

¹² Erratum: 5.9 (2.5)

¹³ Erratum: 11.2(4.9)

Table 4C. Mean % change from baseline, plasma HDL cholesterol. Comparison of sitagliptin and placebo treated subjects

Study ID	Week	Background Therapy	Mean % change from baseline (SE)			
			Sitagliptin	n	Placebo	n
P019	24	pioglitazone	1.3 (1.3)	151	0.6 (1.3)	162
P035	54	glimepiride ± metformin	-1.3 (1.3)	142	6.2 (1.5)	111
P021	104	diet ¹⁴	3.3 (1.0)	182	n/a	
P040	18	diet/exercise	4.0 (1.2) ¹⁵	329	5.3 (1.5) ¹⁶	158
P047	24	diet ¹⁷	0.6 (1.6)	71	1.9 (1.2)	57
P051	24	insulin ± metformin	1.7 (1.2)	277	1.7 (0.8)	286
P052	54	metformin + rosiglitazone	-1.2 (1.2)	161	1.5 (1.8) ¹⁸	83
P053	30	metformin	-0.1 (1.5)	89	2.4 (1.7)	82
P064v1	24	pioglitazone	11.4 (1.5)	236	12.7 (1.3) ¹⁹	231
P064x1	54	pioglitazone	- 845 (1.9) ²⁰	148	13.2 (1.8)	142
801	24	metformin	4.3*	86	1.8*	83

*Variance data for difference from baseline not given in reference 1996 which is the source of this report.

¹⁴ Erratum: diet/exercise

¹⁵ Erratum: 1.7 (1.5)

¹⁶ Erratum: 1.3 (1.1)

¹⁷ Erratum: diet/exercise

¹⁸ Erratum: (2.1)

¹⁹ Erratum: 12.0

²⁰ Erratum: 8.5

Table 4D. Mean % change from baseline, plasma triglyceride. Comparison of sitagliptin and placebo treated subjects

Study ID	Week	Background Therapy	Mean % change from baseline (SE)			
			Sitagliptin	n	Placebo	n
P019	24	pioglitazone	3.0 (3.3)	151	13.7 (4.4)	162
P035	54	glimepiride ± metformin	16.0 (4.4)	142	0.1 (4.7)	111
P021	104	diet ²¹	9.2 (3.4)	182	n/a	
P040	18	diet/exercise	7.7 (4.5)	329	14.2 (7.7)	158
P047	24	diet ²²	-2.3 (34.4)*	71	-4.5 (36.1)*	57
P051	24	insulin ± metformin	-4.2 (40.9)**	277	2.2 (43.3)**	286
P052	54	metformin + rosiglitazone	13.7 (5.8)	161	2.0 (7.2) ²³	83
P064v1	24	pioglitazone	-19.9 (38.0)**	237	-12.0 (42.0)**	231
P064x1	54	pioglitazone	-17.4 (34.2)**	149	-15.1 (43.7)**	142
P079	18	metformin	-8.4 (45.0)**	481	-2.1 (46.4)**	470
801	24	metformin	-4.8***	86	11.9***	83

*Data given as median (SD) results of non-parametric analysis (table 14-27 of study report), see comment in text.

**Data given as median (SD) results of rank analysis as pre-specified in study statistical plan.

***Variance data for difference from baseline not given in reference 1996 which is the source of this report.

Study 014 was very similar in design to 010 except that the comparator group received metformin rather than glipizide. The data from the extension studies for 010 and 014 are shown jointly in the reports. Mean fall from baseline in HbA1c in the metformin group after 106 weeks was 0.52%. The lipid data for the long-term extension of the study are again shown in Tables 5 A-D. The 106 week data have not been tabulated as the actively treated groups from studies 010/014 have been pooled, but do not appear significantly different from the 52 week data.

²¹ Erratum: diet/exercise

²² Erratum: diet/exercise

²³ Erratum: 2.9 (5.1)

Table 5A. Mean % change from baseline, plasma total cholesterol. Active controlled studies.

Study ID	Week	Background Therapy	Comparator	Mean % change from baseline (SE)			
				Sitagliptin	n	Comparator	n
P010x1	52	diet ²⁴	glipizide	6.1 (SD15.3)	69	2.1 (SD18.4)	58
P014x1	52	diet ²⁵	metformin	3.2 (SD15.9)	95	-1.8 (2.8)	23
P020	104	metformin	glipizide	3.4 (0.9)	374	3.8 (1.5)	155
P023	54	diet ²⁶	pioglitazone	2.0 (1.6)	149	6.9 (2.1)	65
P024	104	metformin	glipizide	4.0 (1.2)	250	-0.2 (1.4) ²⁷	255
P036	54	diet ²⁸	metformin	1.6 (1.7)	96	-3.0 (1.6)	75
P036x1	104	diet ²⁹	metformin	1.3 (2.4)	47	3.5 (3.3)	37
P049	24	diet ³⁰	metformin	5.8 (0.9)	441	2.0 (1.0)	427

²⁴ Erratum: diet/exercise²⁵ Erratum: diet/exercise²⁶ Erratum: diet/exercise²⁷ Erratum: (1.0)²⁸ Erratum: diet/exercise²⁹ Erratum: diet/exercise³⁰ Erratum: diet/exercise

Table 5B. Mean % change from baseline, plasma LDL cholesterol. Active controlled studies.

Study ID	Week	Background Therapy	Comparator	Mean % change from baseline (SE)			
				Sitagliptin	n	Comparator	n
P010x1	52	diet ³¹	glipizide	9.2 (SD24.7)	68	3.6 (SD 30.5)	58
P014x1	52	diet ³²	metformin	6.2 (SD24.3)	95	-3.4 (5.0)	23
P020	104	metformin	glipizide	4.1 (0.9) ³³	374 ³⁴	-1.8 (1.1) ³⁵	155
P023	54	diet ³⁶	pioglitazone	6.3 (3.0)	148	8.6 (3.4)	65
P024	104	metformin	glipizide	8.4 (2.8)	250	-1.0 (2.9) ³⁷	255
P036	54	Diet ³⁸	metformin	0.2 (2.1)	94	-9.8(3.2) ³⁹ (3.2)	75
P036x1	104	Diet ⁴⁰	metformin	-2.6 (3.2)	45	2.8 (4.6)	37
P049	24	diet ⁴¹	metformin	11.6 (1.9)	441	2.1 (1.7)	426

³¹ Erratum: diet/exercise³² Erratum: diet/exercise³³ Erratum: 7.1 (1.9)³⁴ Erratum: 373³⁵ Erratum: 5.2 (2.5)³⁶ Erratum: diet/exercise³⁷ Erratum: (1.7)³⁸ Erratum: diet/exercise³⁹ Erratum: 8.4 (3.1)⁴⁰ Erratum: diet/exercise⁴¹ Erratum: diet/exercise

Table 5C. Mean % change from baseline, plasma HDL cholesterol. Active controlled studies

Study ID	Week	Background Therapy	Comparator	Mean % change from baseline (SE)			
				Sitagliptin	n	Comparator	n
P010x1	52	diet ⁴²	glipizide	2.2 (SD11.4)	69	2.1 (SD30.3) ⁴³	58
P014x1	52	diet ⁴⁴	metformin	2.8 (SD15.8)	95	4.6 (2.9)	23
P020	104	metformin	glipizide	4.1 (0.9)	374	-1.8 (1.1)	155
P023	54	diet ⁴⁵	pioglitazone	0.9 (1.1)	148	13.8 (2.6)	65
P024	104	metformin	glipizide	9.7 (4.2) ⁴⁶	250	13.3 (5.2) ⁴⁷	255
P036	54	Diet ⁴⁸	metformin	1.4 (1.5)	95	9.0 (3.0) ⁴⁹	75
P036x1	104	Diet ⁵⁰	metformin	7.3 (2.6)	45	11.2 (2.6)	37
P049	24	diet ⁵¹	metformin	6.4 (0.8)	440	6.9 (0.8)	427

⁴² Erratum: diet/exercise⁴³ Erratum: (13.3)⁴⁴ Erratum: diet/exercise⁴⁵ Erratum: diet/exercise⁴⁶ Erratum: 4.2 (1.0)⁴⁷ Erratum: 1.5 (0.7)⁴⁸ Erratum: diet/exercise⁴⁹ Erratum: (3.3)⁵⁰ Erratum: diet/exercise⁵¹ Erratum: diet/exercise

Table 5D. Mean % change from baseline, plasma triglyceride. Active controlled studies

Study ID	Week	Background Therapy	Comparator	Mean % change from baseline (SE)			
				Sitagliptin	n	Comparator	n
P010x1	52	diet ⁵²	glipizide	10.4(SD45.2)	69	7.1 (37.6) ⁵³	58
P014x1	52	diet ⁵⁴	metformin	5.2 (SD 40.5)	95	5.9 (7.8)	23
P020	104	metformin	glipizide	6.1 (2.2)	374	17.2 (4.6)	155
P023	54	diet ⁵⁵	pioglitazone	5.7 (3.0)	149	6.7 (7.6)	65
P024	104	metformin	glipizide	9.7 (3.4)	250	11.7 (2.9)	255
P036	54	Diet ⁵⁶	metformin	17.5 (7.0)	96	4.9 (4.7)	75
P036x1	104	Diet ⁵⁷	metformin	13.1 (7.4)	47	8.6 (9.1)	37
P049	24	diet ⁵⁸	metformin	-3.7 (37.7)*	441	-1.2 (41.6)*	427

*Data given as median (SD) results of rank analysis (table 11-14 of study report), as pre-specified in study statistical plan.

Study 020 was a randomised, multicentre double-blind study evaluating safety and efficacy of sitagliptin as add-on treatment for T2DM patients inadequately controlled on metformin therapy. While there was a placebo-control group in the originally evaluated 24 week study, this group was switched to glipizide for the 104 week extension study which therefore becomes active controlled. The HbA1c data comparing the two groups are irrelevant for the purpose of this report although that from the sitagliptin treated arm is validly included by the sponsor in their analysis by statin use as reported below.

Study 021 was a multicentre randomised, placebo-controlled (in the initial 24 week phase), double-blind study to evaluate safety and efficacy of sitagliptin as monotherapy in T2DM patients inadequately controlled on diet. Two sitagliptin dosage levels were employed, 100 mg daily and 200 mg daily, throughout the study including the 104 week extension reported here during which all subjects were treated with sitagliptin and there was no placebo control group. For the purpose of tabulating the lipid data in Tables 4 A-D, only that of the 100 mg group relevant to this application have been included.

Study 023, similar to Study 021, was a double blind study of sitagliptin 100 mg or 200 mg daily as monotherapy with an initial 18 week placebo-controlled period. In this case, during the 36 week extension to a total of 54 weeks, the placebo group was switched to pioglitazone 30 mg so for the purpose of comparing HbA1c and lipid data, this becomes an active-controlled study.

Study 024 was a multicentre double-blind randomised study comparing sitagliptin with glipizide as add-on therapy for T2DM patients inadequately controlled on metformin. The primary efficacy parameter of HbA1c change was assessed at 52 weeks and the study extended

⁵² Erratum: diet/exercise

⁵³ (SD)

⁵⁴ Erratum: diet/exercise

⁵⁵ Erratum: diet/exercise

⁵⁶ Erratum: diet/exercise

⁵⁷ Erratum: diet/exercise

⁵⁸ Erratum: diet/exercise

to 104 weeks with all subjects remaining in the same treatment arms. The lipid data, being active controlled, are shown in Tables 5A-D

Study 036 was a double blind study of the safety and efficacy of coadministration of sitagliptin and metformin in T2DM patients inadequately controlled on diet and exercise. In the initial 24 week phase as previously evaluated for TGA, there was a placebo group. For the 30 week extension to week 54, this group was placed on metformin so that in the extension period there are six groups taking either sitagliptin alone, metformin alone, or the combination of both at various dose levels. For the purpose of tabulating the lipid data at Tables 5A-D, the sitagliptin monotherapy group is compared with the placebo (now on metformin) group in this active-controlled phase of the study. Data from a further extension to 104 weeks listed as study report 036x1, is also shown.

6.1.2. Studies not previously evaluated for TGA

Study 040 was a multinational, double-blind, randomised, parallel group, placebo-controlled study of the efficacy and safety of sitagliptin 100 mg daily, given as monotherapy, compared with placebo, and conducted in 2006-2007. 530 T2DM subjects were randomised to sitagliptin or placebo in a 2:1 ratio at 28 sites in China, India and Korea. Recruited subjects with inadequate glycaemic control (HbA1c 7.5-11%) were on diet alone or, with modified enrolment criteria, on existing oral therapy which was withdrawn during the run-in period. The double-blind randomised study period was of 18 weeks duration. The primary efficacy parameter was the change in HbA1c which was -0.71% in the sitagliptin and +0.31% in the placebo groups respectively, a between treatment difference of 1.03% ($p < 0.001$). The comparative lipid data for the groups is shown in Tables 4A-D.

Study 047 was a further double-blind, placebo-controlled randomised study of sitagliptin 100 mg daily as monotherapy, of essentially similar design to 040 with regard to the study plan and inclusion criteria (HbA1c 7.0-10%). In this case the study population was community dwelling elderly (65 years or older) T2DM patients recruited at 60 US sites. The study was conducted in 2006-2008 with a double-blind period of 24 weeks. Mean (SE) fall from baseline in HbA1c was 0.33 (0.08) for the sitagliptin group, compared with a mean of 0.39 (0.10) in the placebo group (between treatment group difference with 95% CI, -0.70 (-0.94, -0.47), $p < 0.001$). The lipid data is shown in Tables 4A-D. The study report indicates that nonparametric analysis of the triglyceride data was prespecified. It is presumed that this relates to high-end outliers in the study population which was significantly more obese than that of Study 040.

Study 049 was a multicentre, double-blind, randomised, controlled study comparing sitagliptin 100 mg daily with metformin as initial combination therapy for T2DM. Subjects were between 18 and 78 years old and were required to be off all oral hypoglycaemic therapy for four months prior to screening and have HbA1c between 6.5% and 9.0%. The study was conducted at 121 sites in 26 countries during 2007-2008. After 24 weeks, mean (SE) change from baseline HbA1c was -0.42 (0.03)% for sitagliptin and -0.57 (0.03)% for metformin, demonstrating noninferiority of sitagliptin on the basis of pre-established criteria. Lipid profile data for this active controlled study are shown in Tables 5A-D. It is noted that total and LDL cholesterol rose more in the sitagliptin than in the metformin patients and that this difference appears to be statistically significant. The metformin patients lost on average 1.2 kg body weight by comparison with the sitagliptin patients.

Study 051 was a multicentre, randomised, double blind trial of the efficacy and safety of sitagliptin 100 mg daily compared with placebo in the control of T2DM in patients receiving insulin with or without metformin, conducted at 100 international sites between 2007-2008. The primary efficacy parameter, change in HbA1c at Week 24, showed a fall (LS mean, 95% CI) of -0.59 (-0.702⁵⁹, -0.48)% with sitagliptin and -0.03 (-0.14, 0.08)% for placebo. The between

⁵⁹ Erratum: 0.70

treatment difference of -0.56 (-0.70, -0.42)% was significant ($p < 0.001$). The lipid data is shown in Tables 4A-D.

Study 052 was a multicentre, randomised, placebo-controlled trial to assess efficacy and safety of the addition of sitagliptin 100 mg daily to the treatment of T2DM patients inadequately controlled (HbA1c 7.5%-11%) on the combination of metformin ≥ 1500 mg/day and rosiglitazone ≥ 4 mg/day. It was conducted in 41 international sites during 2006-2008. After a double-blind period of 18 weeks, HbA1c fell by a mean of 1.03% in the sitagliptin group and 0.31% in the placebo group; the treatment difference (LS mean, 95% CI) was -0.72 (-0.95, -0.49), $p < 0.001$. This difference was maintained at 54 weeks when it was -0.77 (-1.04, -0.50). Placebo-controlled lipid data at the 54 week point is shown in Tables 4A-D.

Study 053 was a multicentre, double-blind, randomised study to evaluate safety and efficacy of sitagliptin as add-on therapy to metformin in T2DM patients inadequately controlled on metformin monotherapy (HbA1c 8%-11%). It was conducted at 24 international sites during 2006-2007. At week 18, HbA1c had fallen by a mean of 1.00% in the sitagliptin group and 0.02% in the placebo group, the treatment difference (LS mean, 95% CI) being -1.02 (-1.36, -0.67), $p < 0.001$. This difference was maintained at 30 weeks when it was -1.01 (-1.4, -0.6), $p < 0.001$. Placebo-controlled lipid data at 30 weeks is shown in Tables 4A-D.

Study 061 is not a Phase III study. It is described as a phase 1 double-blind, randomised, placebo-controlled clinical trial to study the safety, efficacy and mechanism of action of sitagliptin and pioglitazone in patients with T2DM who have inadequate glycaemic control on diet and exercise. This 12 week study was the subject of a presentation entitled "*initial combination therapy with sitagliptin and pioglitazone: complementary effects of post-prandial glucose and islet cell function*", published in the abstracts of the 2009 International Diabetes Federation. While of scientific interest, the study does not include HbA1c as a parameter of glycaemic efficacy, nor plasma lipids as an outcome parameter, and has therefore not been evaluated for the purpose of this evaluation.

Study 064 was a multicentre, double-blind, randomised, placebo-controlled trial to study the efficacy and safety of initial combination therapy using sitagliptin 100 mg and pioglitazone 30 mg daily as explored in the pharmacodynamic Study 061 described above. It was conducted at 53 international sites between 2007-2009. T2DM patients 18 years or above on diet alone with HbA1c 8%-12% were randomised to receive either sitagliptin 100 mg or matching placebo, together with pioglitazone 30 mg daily, for a double-blind period of 24 weeks. As reported in **064v1**, HbA1c fell at 24 weeks by 2.38% in the active and by 1.49% in the placebo group, the treatment difference attributable to sitagliptin (LS mean, 95% CI) being -0.89 (-1.13, -0.65)%, $p < 0.001$. At 24 weeks, the pioglitazone dose was increased to 45 mg and treatment continued for a further 30 weeks. The results of this extension are reported as **064x1**. Mean HbA1c, which was 7.11% in the combination and 7.97% in the pioglitazone alone group at 24 weeks, fell at 54 weeks to 7.07% and 7.57% respectively, the treatment difference now being -0.51 (-0.76, -0.26)%. Placebo-controlled lipid data at 24 and 54 weeks is shown in Tables 4A-D.

Study 079 was a Phase III randomised, active comparator study to assess the efficacy of a FDC of sitagliptin and metformin as initial therapy for drug naive T2DM subjects, by comparison with metformin alone. It was conducted between 2007 and 2009 at 229 sites, all in the US except for 5 in Puerto Rico. At 18 weeks, mean HbA1c fell by 2.37% with the combination therapy by comparison with 1.76% in those on metformin alone, a treatment difference (LS mean, 95% CI) of -0.60 (-0.78, -0.43)%, $p < 0.001$. At week 44 HbA1c values in both groups remained closely similar with the treatment difference now being -0.48 (-0.67, -0.30)%. Although this is referred to as an active comparator study, a placebo was used for the sitagliptin component and the lipid data is therefore regarded as placebo-controlled. Data (excluding HDL which was not provided) for the 18 week assessment only is included in Tables 4A-D. Data provided in the study report for the 44 week assessment did not exclude patients given other hypoglycaemic agents as rescue therapy and is therefore regarded as less robust.

Study 801, as noted above, is not amongst the studies in CTD format (its electronic folder is empty) but is included in the form of literature reference 1996, a paper by Scott and colleagues from the Christchurch school of medicine. This was a three-arm study in which sitagliptin 100 mg, rosiglitazone 8 mg or placebo were given in double-blind fashion as add-on therapy in T2DM patients inadequately controlled (HbA1c 7%-11%) on metformin monotherapy. For the purpose of this evaluation, the rosiglitazone arm is irrelevant. The data tabulated in the literature reference indicates that at 18 weeks, HbA1c had fallen by 0.73% in the sitagliptin and 0.22% in the placebo groups respectively, the treatment difference (LS mean, 95% CI) being -0.51 (-0.70,-0.32)%. Plasma lipid data at 24 weeks are also presented and are included in Tables 4A-D of this report.

6.1.3. Analysis of phase III study outcomes and the sponsor's case for efficacy

The summaries presented in the previous section confirm that glycaemic efficacy of sitagliptin has been demonstrated in a variety of therapeutic settings including those which comprise the therapeutic indications proposed in the application for the FDC, and that the 19 Phase III studies submitted constitute a valid source of glycaemic (HbA1c) efficacy data for the Sponsor's analysis of glycaemic efficacy by statin use/non-use as described in point 5 above, and discussed further below.

Evaluator note: studies 040, 047, 049, 064 and 079 on sitagliptin used as monotherapy or initial combination therapies with metformin or pioglitazone and 051 in combination with insulin provide data on glycaemic efficacy which could support its use in these indications, which are not currently registered in Australia. It is important to emphasise that these studies have not been rigorously evaluated for this purpose which is not part of the brief for this clinical evaluation.

Point 4 of the Sponsor's argument on efficacy emphasises "generally neutral effects of sitagliptin on serum cholesterol levels". The data on plasma lipid profiles in the submitted Phase III studies which are summarised in the Tables 4 and 5, particularly the 11 which contain a placebo control arm, support this statement. The changes from baseline in total, LDL and HDL cholesterol vary by little more than 1-2 % between the sitagliptin and placebo groups in almost all cases, and in no instance was a significant difference detected. The data on changes in triglyceride is difficult to interpret, with apparent changes in either direction in different studies. The inherently wide variability of serum triglyceride in T2DM subjects is probably responsible.

Point 5 receives the most attention in the efficacy analysis. One reason for this is the finding, in a recent meta-analysis of large statin studies, of a small but significantly increased incidence of T2DM. Reference is given for this meta-analysis in the Summary on Clinical Efficacy, but it could not be located in the documentation: this is not regarded as a major problem. Assessment of any effect of simvastatin on glycaemia or the therapeutic (glycaemic) effect of sitagliptin has been addressed in the following ways:

- a. Examination of any change in HbA1c in T2DM patients randomised to simvastatin. Reference is made to the Heart Protection Study (HPS), a landmark study of statin use, in which a random sample of 1087 participants was selected to undergo HbA1c measurement at baseline and after an average 4.6 years of follow-up. No difference was observed between simvastatin 40 mg daily and placebo in this respect. Additionally, in the entire T2DM population of the HPS (n 4867) no difference between active and placebo groups was observed in patterns of use of antidiabetic therapy. In one of the sponsor's studies of simvastatin use in combination with a thiazolidinedione (MK-0733-P187), HbA1c was also an outcome measure and showed no difference between simvastatin and placebo groups.
- b. Analysis of the glycaemic efficacy of sitagliptin in subgroups of simvastatin users, statin users and non-statin users. This was conducted using data from the 19 studies of sitagliptin use which are summarised above. Statistical analysis of the data is inherently difficult as this is a retrospective analysis of the subgroups indicated above,

and the groups were not stratified by statin use at randomisation. The confidence limits overlap widely. The data is best presented in the following plots of change from baseline in HbA1c with 95% CI, following sitagliptin use, by subgroup of simvastatin users, statin users and non-statin users.

Figure 2. Change from baseline in HbA1c with 95% CI, following sitagliptin use, by subgroup of simvastatin users, statin users and non-statin users

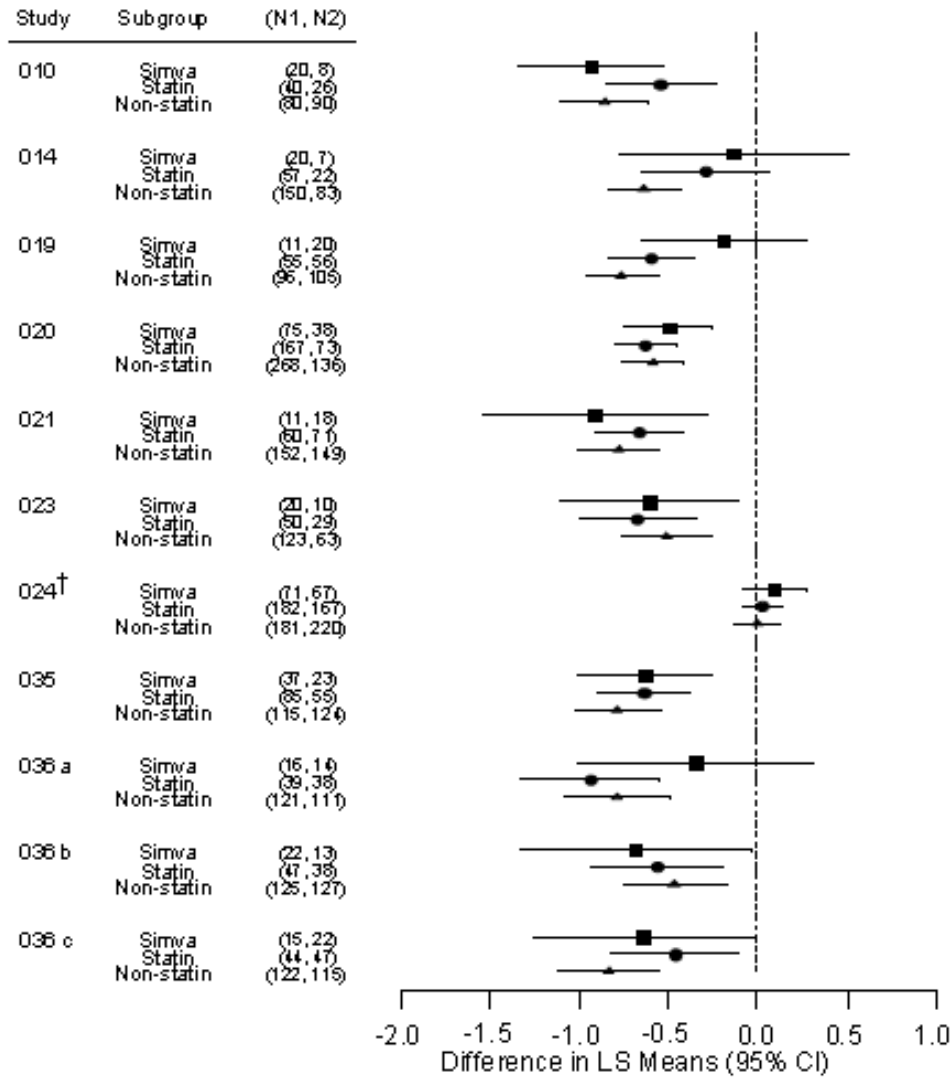
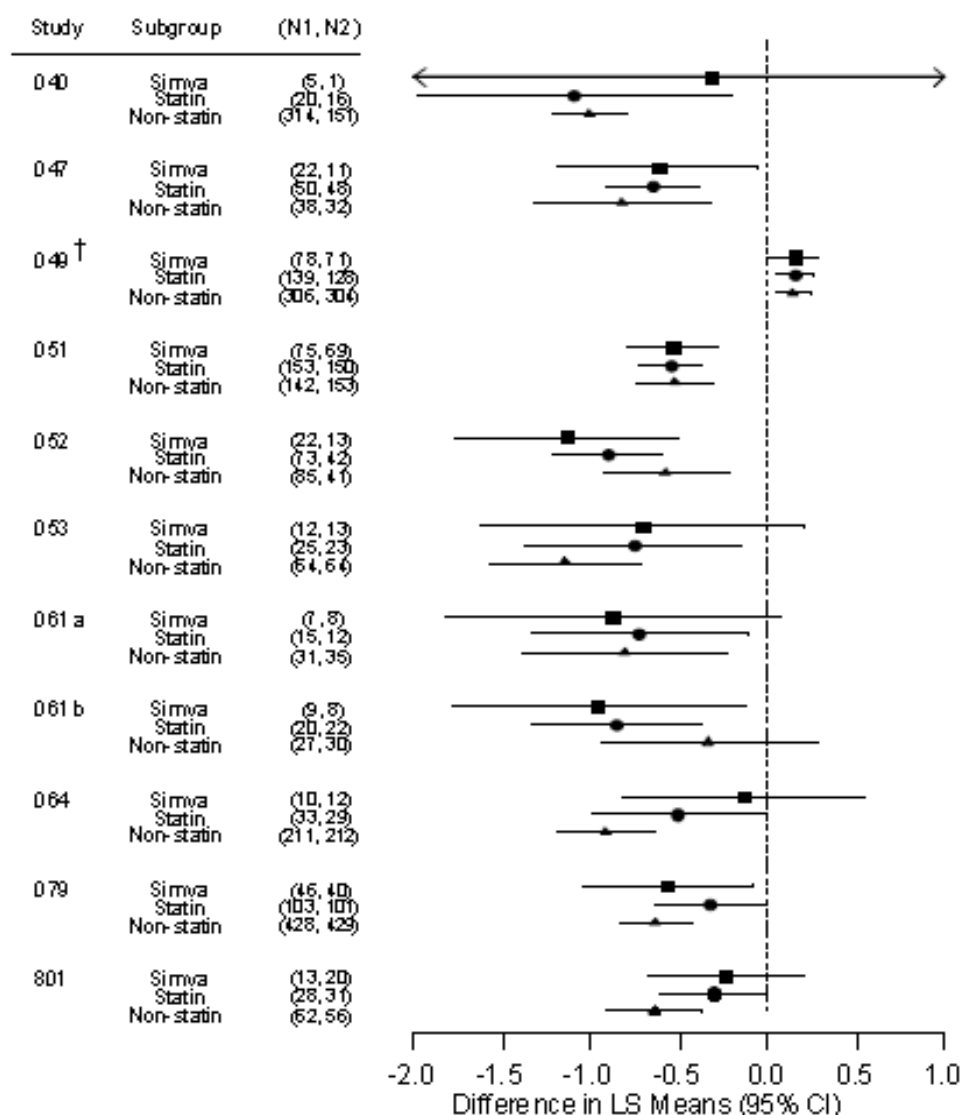


Figure 2 continued. Change from baseline in HbA1c with 95% CI, following sitagliptin use, by subgroup of simvastatin users, statin users and non-statin users



There is no overall trend towards impairment of glycaemic response by statin or simvastatin use.

- c. Analysis of HbA1c change in patients initiating simvastatin or statin use during efficacy studies conducted as part of the sitagliptin development program, as compared with those who took these drugs during the entire study period as shown above in Figure 2. The results for these patients are listed in appendix 2.7.3 of the Summary [not in this AusPAR]. No consistent difference in glycaemic control as reflected by HbA1c change was observed in this group.

The combination of the above 3 approaches provide adequate justification that the glycaemic efficiency of sitagliptin in T2DM is not impaired by its coadministration with simvastatin.

6.1.4. Evaluator's conclusions on clinical efficacy

Given the adequate demonstration of bioequivalence of MK-0431D (Juvicor fixed combination tablet) with its component substances sitagliptin and simvastatin coadministered as separate tablets, and the demonstration that these two drugs were free of mutual PK interaction when coadministered, the task of the Sponsor was to demonstrate that the therapeutic efficacy of the two components, for their respective indications, is maintained during coadministration. This

has been adequately addressed by the strategy summarised under points 4 and 5 in the previous section. It is therefore the conclusion of this evaluation that:

- the therapeutic efficacy of sitagliptin for glycaemic control in T2DM is unimpaired by its coadministration with simvastatin;
- the therapeutic efficacy of simvastatin for control of hypercholesterolaemia in T2DM patients is unimpaired by its coadministration with sitagliptin; and that
- with the proviso that efficacy of the sitagliptin component of the combination tablet might be influenced by pharmacodynamic factors relating to its being administered in the evening as outlined above in section 5, efficacy of both of the above drugs is equivalent whether coadministered in the form of MK-0431D (Juvicor) or as the separate formulations Januvia and Zocor.

A further proviso is that the conclusion regarding the therapeutic efficacy of simvastatin remaining unimpaired during coadministration with sitagliptin rests on the pharmacokinetic data showing no interaction, and on there being no known plausible mechanism by which sitagliptin might interfere with simvastatin's biological action. A pharmacodynamic interaction study to firmly exclude that possibility has not been performed.

A further aspect of efficacy is that of compliance. Improved compliance can, in turn, improve efficacy both in individual patients and in an epidemiological sense. Compliance with this product, by comparison with separately taking its component substances, has not been directly studied, but the Sponsor provides an analysis of the compliance advantage gained by its combination lipid-lowering product Vytorin (simvastatin/ezetimibe). This averaged 12.2% over a range of comparator therapies requiring compliance with two separate lipid-lowering medications. Juvicor shares some characteristics with Vytorin, as a fixed dosage combination used in patients with a chronic metabolic disorder, usually asymptomatic, in whom long-term therapy is required. Extrapolation of these data to the clinical use of Juvicor therefore has some basis.

7. Clinical safety

The only safety observations relating directly to administration of the combination tablet MK-0431D are those undertaken in the small population of healthy subjects who received mostly single doses of the product during the pharmacokinetic/bioequivalence studies described above. These data revealed no safety issues of concern regarding the product itself - as opposed to its interaction with digoxin, described in Study P169 and which is the subject of a comment and a question below - but do not constitute an exposure population adequate or relevant for safety assessment.

For the reasons described in the efficacy evaluation of this report, safety assessment depends on analysis of data provided by the Sponsor arising from the development programs for the parent products Januvia (sitagliptin) and Zocor (simvastatin). These data, derived from the studies summarised in the section *Supportive Phase III studies*, using the approach of assessing safety and tolerability of the coadministration of sitagliptin and simvastatin in this pool of sitagliptin studies. It is assumed that the reciprocal of this approach has not been employed for the reason that sitagliptin was not available at the time simvastatin was under development. An additional approach used is to assess potential class effect of statins by examining the data of patients who were coadministered sitagliptin and a statin in a pool of sitagliptin studies.

The individual safety and adverse event profiles for sitagliptin and simvastatin are well documented and the only issues requiring consideration are whether any of the known safety concerns for either drug are amplified by coadministration with the other, and whether any additional adverse events have been identified exclusively in the coadministration setting.

As the Sponsor of both component products at the innovator stage, the applicant has ready access to comprehensive data on which this safety assessment is based.

Altogether the database for this safety assessment comprised 3665 patients randomised to sitagliptin or placebo who were also co-administered at least one dose of any statin during the treatment period. Of these, 1582 had at least one dose of simvastatin specifically. Other oral hypoglycaemic agents were taken by 507, including 339 on metformin and 68 on a thiazolidinedione.

A summary of reported AE by system organ class (SOC) in patients belonging to the all statins population, exposed or not exposed to sitagliptin 100 mg daily, appears below.

Table 6. Summary of AEs by System Organ Class (SOC).

	Sitagliptin 100 mg		Non-Exposed	
	n	(%)	n	(%)
Patients in population	1,939		1,726	
With one or more conditions	1,923	(99.2)	1,711	(99.1)
With no conditions	16	(0.8)	15	(0.9)
Blood and lymphatic system disorders	78	(4.0)	69	(4.0)
Cardiac disorders	434	(22.4)	390	(22.6)
Congenital, familial and genetic disorders	63	(3.2)	49	(2.8)
Ear and labyrinth disorders	122	(6.3)	108	(6.3)
Endocrine disorders	193	(10.0)	172	(10.0)
Eye disorders	403	(20.8)	352	(20.4)
Gastrointestinal disorders	604	(31.2)	531	(30.8)
General disorders and administration site conditions	200	(10.3)	185	(10.7)
Hepatobiliary disorders	128	(6.6)	88	(5.1)
Immune system disorders	300	(15.5)	287	(16.6)
Infections and infestations	415	(21.4)	345	(20.0)
Injury, poisoning and procedural complications	168	(8.7)	146	(8.5)
Investigations	318	(16.4)	269	(15.6)
Metabolism and nutrition disorders	1,750	(90.3)	1,530	(88.6)
Musculoskeletal and connective tissue disorders	769	(39.7)	713	(41.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	162	(8.4)	153	(8.9)
Nervous system disorders	574	(29.6)	528	(30.6)
Pregnancy, puerperium and perinatal conditions	6	(0.3)	7	(0.4)
Psychiatric disorders	353	(18.2)	351	(20.3)
Renal and urinary disorders	307	(15.8)	235	(13.6)
Reproductive system and breast disorders	329	(17.0)	299	(17.3)
Respiratory, thoracic and mediastinal disorders	385	(19.9)	353	(20.5)
Skin and subcutaneous tissue disorders	306	(15.8)	248	(14.4)
Social circumstances	166	(8.6)	138	(8.0)
Surgical and medical procedures	756	(39.0)	620	(35.9)
Vascular disorders	1,365	(70.4)	1,236	(71.6)
NULL	5	(0.3)	3	(0.2)

Every patient is counted a single time for each applicable specific condition. A patient with multiple conditions within a system organ class is counted a single time for that system organ class.
A system organ class or specific condition appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

No difference attributable to coadministration of sitagliptin with simvastatin can be observed in the incidence of this wide spectrum of events.

Exposure or non-exposure to sitagliptin was also examined in relation to various categories of AE, including serious AE and those requiring discontinuation, with regard to events occurring concurrently and specifically with simvastatin use, as shown in Table 7.

Table 7. Exposure or non-exposure to sitagliptin in relation to various categories of AE (including serious AE and those requiring discontinuation) with regard to events occurring concurrently and specifically with simvastatin use

Treatment	n	%	Difference in % vs Non-Exposed
			Estimate (95% CI) [†]
Patients in population			
Sitagliptin 100 mg	827		
Non-Exposed	755		
with one or more adverse events			
Sitagliptin 100 mg	531	(64.2)	
Non-Exposed	474	(62.8)	0.4 (-4.2, 5.0)
with no adverse events			
Sitagliptin 100 mg	296	(35.8)	
Non-Exposed	281	(37.2)	-0.4 (-5.0, 4.2)
with drug-related adverse events			
Sitagliptin 100 mg	135	(16.3)	
Non-Exposed	135	(17.9)	-2.0 (-5.8, 1.7)
with serious adverse events			
Sitagliptin 100 mg	59	(7.1)	
Non-Exposed	59	(7.8)	-0.9 (-3.6, 1.8)
with serious drug-related adverse events			
Sitagliptin 100 mg	0	(0.0)	
Non-Exposed	1	(0.1)	-0.2 (-0.8, 0.3)
who died			
Sitagliptin 100 mg	2	(0.2)	
Non-Exposed	5	(0.7)	-0.5 (-1.5, 0.3)
discontinued due to an adverse event			
Sitagliptin 100 mg	27	(3.3)	
Non-Exposed	32	(4.2)	-1.2 (-3.2, 0.8)
discontinued due to a drug-related adverse event			
Sitagliptin 100 mg	10	(1.2)	
Non-Exposed	11	(1.5)	-0.3 (-1.5, 1.0)
discontinued due to a serious adverse event			
Sitagliptin 100 mg	13	(1.6)	
Non-Exposed	12	(1.6)	-0.1 (-1.5, 1.3)
discontinued due to a serious drug-related adverse event			
Sitagliptin 100 mg	0	(0.0)	
Non-Exposed	0	(0.0)	0.0 (-0.5, 0.5)

[†] Based on Miettinen & Numminen method stratified by study; if no patients are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Again, no influence of coadministration with sitagliptin is seen on any of these AE patterns in patients taking simvastatin.

An analysis of simvastatin dose-specific populations does not suggest a dose dependent trend in adverse events.

The incidence of AE known to be associated with statin use, in particular, was assessed in relation to concomitant sitagliptin use. The incidence of muscle AE in statin treated patients, sitagliptin exposed and not exposed, is shown in the following table.

Table 8. The incidence of muscle AE in statin treated patients, sitagliptin exposed and not exposed

Treatment	n	%	Difference in % vs Non-exposed	
			Estimate (95% CI) [†]	p-Value [†]
Patients in population				
Sitagliptin 100 mg	1112			
Non-exposed	971			
Muscle Events				
Sitagliptin 100 mg	6	(0.5)		
Non-exposed	3	(0.3)	0.3 (-0.4, 1.0)	0.372

[†] Based on Miettinen & Numminen method stratified by Study.
Muscle adverse event includes the terms: myopathy, myositis, blood creatine phosphokinase increased, myoglobinaemia, myoglobinuria and rhabdomyolysis.
The Other Statins Population includes patients who were treated with at least 1 dose of study medication, took at least one dose of a statin other than simvastatin, and did not take simvastatin at any time during the Treatment Period.

No difference attributable to coadministration is observed.

Similar findings apply to the AE of serum CPK increased concurrently with simvastatin use (2/827 on sitagliptin, 0/755 non-exposed), or with any statin (8/1939 on sitagliptin, 4/1726 non-exposed). The numerical incidence of abnormalities is consistently higher in the sitagliptin group but the numbers are very small and the p-values for the comparison never approach significance.

Minor and variable changes in liver function test values were observed in the data analysis. Given the one-sided nature of the statistical analysis, there is a tendency for these to be attributed to the statin component if the analysis does not reveal a statistical difference between statin/sitagliptin and statin/placebo. Visual inspection of the data suggest that influence of sitagliptin cannot be excluded. The overall incidence of abnormalities is low and not exceeding that seen with many commonly used drugs, and is not felt to constitute a clinical problem.

Similar analyses of routine clinical chemistry and haematology parameters did not reveal any abnormal patterns of significance in the coadministration population.

There was no specific analysis of AE incidence in the subpopulation of patients taking other antidiabetic therapy in addition to sitagliptin and simvastatin.

7.1. Deaths and other serious adverse events

Of the 3691 patients in the pooled safety analysis, 13 died during the study period; 7 of them in the simvastatin any dose population. The report states that narratives for all deaths and non-fatal serious adverse experiences can be found at 5.3.6: 2281. This section and reference could not be located and appears not to be included in the electronic submission. This is not considered to be a problem as the number and distribution of deaths, given the size and nature of the study population and the duration of the studies, is consistent with expectation.

7.2. Electrocardiograph

A single subject in drug interaction Study P169 developed non-specific S-T/T wave changes within six hours following a single 0.5 mg dose of digoxin on the background of steady state therapy with sitagliptin 100 mg and simvastatin 80 mg. His plasma digoxin 1-2 hours following drug administration was 2.16 nmol/L and within the therapeutic range. The event, which resolved spontaneously and was not followed by any clinical sequelae, was classified as unrelated to study drug but particularly given the timing, this must be regarded as uncertain. It is known that patients taking digoxin vary considerably in their sensitivity to the drug, as drug-related morbidity exhibits a poor relationship with plasma digoxin levels⁶⁰ The overall finding of this study that the demonstrated increases of digoxin exposure of 26% in AUC and 41% in Cmax are "*not clinically meaningful*" is questionable particularly in view of the degree of inter-individual variation.

7.3. Postmarketing experience

There is no post marketing experience with the applicant product. However the sponsor has undertaken a review of post marketing data with regard to the safety profile of sitagliptin and concomitant statin therapy. The Worldwide Adverse Experience System (WAES) database was searched for spontaneous reports submitted for patients taking sitagliptin and concomitant therapy with either simvastatin, atorvastatin or rosuvastatin. A total of 444 (122), 420 (147),

⁶⁰Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. Adams KF Jr, Patterson JH, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, Gheorghide M. Am Coll Cardiol. 2005;46(3):497.

and 164 (55) adverse events (serious AE in parentheses) were reported for these three combinations respectively. The data is of limited use because it is uncontrolled. A number of events known to be associated with statin therapy, including a small number of serious myopathic events, were described. Amongst the reported AE were 2 events described as drug-drug interactions. Both can be identified as likely to be attributable to the statin component of the treatment without a role of sitagliptin being attributed. Importantly, there is no trend evident in the data for an unusual or not previously observed form or pattern of AE.

7.4. Evaluator's overall conclusions on clinical safety

The sponsor has conducted a detailed analysis of the AE profile for the combined use of sitagliptin and simvastatin. This analysis was carried out on pooled data of controlled trials in which the possibility of AE is actively explored; the likelihood of under-reporting of unusual events is therefore low. The overall result of the analysis shows no qualitative or quantitative pattern of AEs not attributable to the known effects of the separate components of the product. Significant AE patterns include effects known to occur with statin use, including muscle disorders and related biochemical abnormalities, and liver function abnormalities. The incidence of these events was not increased in those taking sitagliptin as well as simvastatin or any statin: in summary, the side-effect profile of the combination is basically that of the statin component with no evidence of any amplification due to coadministration of the two drugs.

The ECG event possibly related to increased exposure to digoxin in Study P169, and the overall results of that study showing increased exposure from the additive effects of simvastatin and sitagliptin, is in the opinion of this evaluator more significant than the study authors consider. A comment and related question are given below.

These conclusions on clinical safety need to be seen in the context that they represent an assessment of the risks associated with coadministration of sitagliptin and simvastatin, rather than the combination tablet as such. These two drugs are in common use in the target population of T2DM patients with high plasma cholesterol and in many cases the use of Juvicor will take the form of a substitution for existing therapy with both agents. However, it should be noted that as sitagliptin is not at this time authorised for first-line treatment in Australia, patients using Juvicor would by definition be using another antidiabetic agent. As noted above, there has been no specific analysis of safety for such multiple combinations and if the application is approved this should be a specific requirement for ongoing pharmacovigilance.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of Juvicor in the proposed usage are:

- Improved glycaemic control of T2DM, as specified in the indications and supported by data for the parent product Januvia (sitagliptin); the benefit is no more and no less than that applying to sitagliptin for which the benefit profile is well-established, including additional benefits in terms of parameters such as beta cell function which are suggested and supported by the data.
- Reduction in LDL cholesterol levels as a result of the simvastatin component of the combination, and with long-term use a consequent reduction in cardiovascular events. Again, the benefit is no more and no less than that attributable to simvastatin given alone.

- An additional benefit may be attributable to improvement in compliance as outlined under *Clinical Efficacy*. Obviously this benefit will only apply to that proportion of patients who take the medicine more regularly because of its combination nature.

8.2. First round assessment of risks

The risks of Juvicor in the proposed usage are those attributable to the adverse effect profile of the component drugs sitagliptin and simvastatin. These are products in common use and with well-established safety profiles which need not be detailed in this report. As outlined under *Clinical Safety*, there is no evidence of significant risks attributable to their coadministration or to their combination in a single formulation. Consistent with this, it is understood that TGA is not requiring a specific risk management plan for the combination product.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of Juvicor, given the proposed usage, appears favourable but cannot be properly assessed without answers to the questions on PK (meal effect) and PD (time of day effect) (see below), which may impact on the safety of the product.

9. First round recommendation regarding authorisation

The findings of this evaluation have raised a number of questions, listed below, which **preclude an immediate recommendation for authorisation**. Pending resolution of these matters, the product may nevertheless be a suitable and worthwhile addition to the therapeutic armamentarium for the common comorbidities of Type 2 diabetes associated with dyslipidaemia.

If and when the application is approved, safety monitoring of the use of sitagliptin/simvastatin in combination with other oral hypoglycaemic agents should be a requirement for pharmacovigilance.

10. Clinical questions

10.1. Pharmacokinetics

The Sponsor should be asked to comment on the suggestion that the food (high-fat meal) effect on simvastatin PK demonstrated in Study P155, particularly the marked increase in exposure to the active hydroxyacid metabolite, might be clinically significant, particularly in the potential situation of coadministration of a CYP3A4 inhibitor, and whether they have further data which may clarify the situation. Note that this situation is potentially applicable to other formulations of simvastatin, not just the fixed combination tablet.

10.2. Pharmacodynamics

The Sponsor should be asked to justify the non-performance of a pharmacodynamic study in relation to dosage timing of sitagliptin, as outlined in under *Pharmacodynamics*.

10.3. Efficacy

No questions except insofar as the question on pharmacodynamics might influence efficacy.

10.4. Safety

No questions except that implied by the suggested change in the PI statement regarding the effect of the combination therapy on digoxin PK [this discussions has not been included as it is beyond the scope of this AusPAR].above.

11. Second round evaluation of clinical data submitted in response to questions

The sponsor's responses to these questions are summarised and discussed in the following sections of this Second round report.

12. Second round benefit-risk assessment

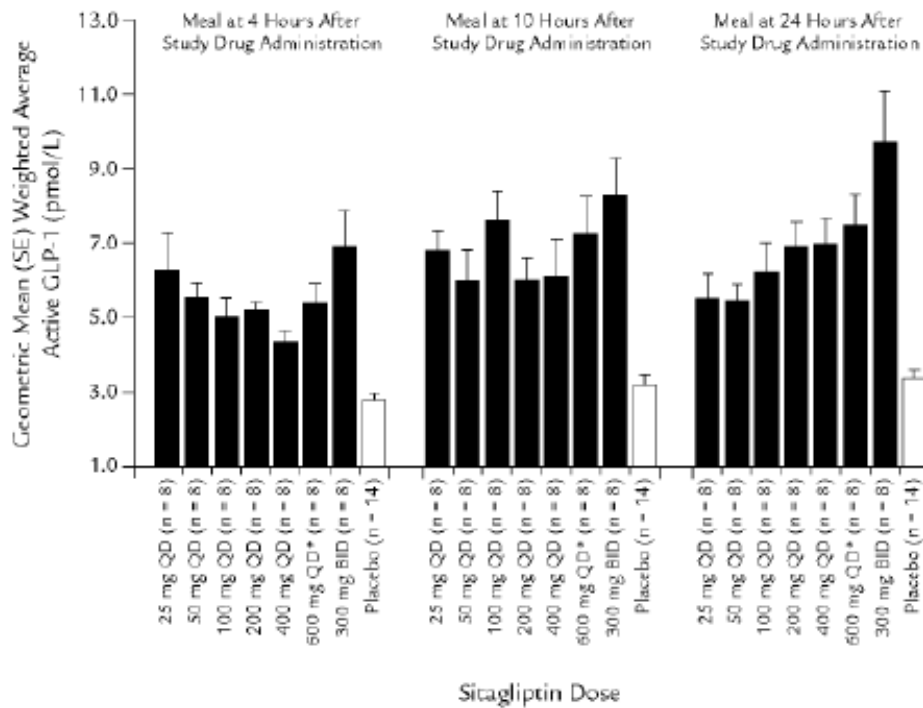
12.1. Second round assessment of benefits

Questions 14.2 and 14.3 relate to the efficacy of the sitagliptin component of the combination tablet, the issue being whether the shift from morning to evening administration of sitagliptin, imposed by the obligation to give the product in the evening because of its simvastatin component, has any impact on its efficacy.

The sponsor's response to these questions provides data from studies conducted in the development program for sitagliptin and can be summarised as follows:

PK of sitagliptin is suggested to be similar with morning and evening administration. A table is shown giving 12 hour trough concentrations following evening dosing which are some 25% higher than those following morning dosing, with confidence intervals for the ratio not crossing unity, despite which it is suggested that these differences would not be "*clinically meaningful*". More importantly, evidence is quoted that 80% inhibition of DPP4 is maintained 24 hours following the 100 mg dose at steady state.

The most relevant data appears in the sponsor's letter and is reproduced as Figure 3below:

Figure 3. Geometric Mean Weighted Average Active GLP-1 versus Sitagliptin dose

The enhancement of GLP-1 response to feeding is the key PD response to DPP4 inhibition. Whether there is an improvement in glycaemia is in turn dependent on the remaining level of beta cell function, but it is the GLP-1 response which should be used as a measure of PD action, particularly with regard to the present question of whether that action is preserved over the 24 hour period following drug administration. The above shows clearly that this response is similar at 10 hours and 24 hours following all dosing levels including the 100 mg dose for this product.

These data effectively answer the concerns expressed in the first round evaluation regarding a potential time of day effect with regard to dosing, and **are accepted as adequate justification for not having carried out a specific pharmacodynamic study with evening administration.**

Whether the efficacy of sitagliptin is preserved with evening as opposed to morning administration might also be affected by compliance. This is not strictly a second round issue, as the point was not raised in the first-round report, but it is felt necessary to make some comment about this. A brief review of the literature provides some support^{61,62} for what clinicians would intuitively suspect, which is that compliance with morning administration of medication is in general superior to that for evening administration. This, therefore, might be regarded as a factor having a negative influence on the benefit of the combination tablet with respect to its sitagliptin component. On the other hand, it has been argued by the sponsor that compliance might be **improved** by the use of the combination tablet, presumably due to factors of cost and convenience, as discussed above under Clinical Efficacy in this report.

⁶¹ Compliance and compliance-improving strategies in hypertension: the Japanese experience. Fujii J, Seki A. J Hypertens Suppl. 1985 Apr;3(1):S19-22.

⁶² A study of medication-taking and unobtrusive, intelligent reminding. Hayes TL, Cobbinah K, Dishongh T, Kaye JA, Kimel J, Labhard M, Leen T, Lundell J, Ozertem U, Pavel M, Philipose M, Rhodes K, Vurgun S. Telemed J E Health. 2009 Oct;15(8):770-6.

12.2. Second round assessment of risks

Question 14.1 has two components: firstly, it asks for a response to the point that the food effect on simvastatin PK evident in Study P155 did not receive adequate comment in the original submission (see discussion under *Pharmacokinetics*); and secondly that the apparent increase in simvastatin metabolite PK might have safety implications.

In its response, the sponsor agrees that there is an evident food effect but presents a number of arguments against this being clinically significant. Reference is made to a study which shows that simvastatin acid (measured in Study P155) comprises only 25% of active HMG CoA reductase inhibitors and it is argued that the increase in the remaining active inhibitors may have been more modest, but this is speculative rather than based on any actual data.

With regard to the suggestion that the food effect might pose an additional risk in the setting of concomitant use with CYP3A4 inhibitors, the sponsor draws attention to safety provisions in the current PI for Zocor, the sponsor's simvastatin-only product which is the source of the simvastatin clinical data used for bridging purposes as outlined above in section *Clinical Efficacy* above. These consist of precautionary statements and dosage limitations in particular situations of concomitant use, and are particularly relevant as the sponsor has now submitted revised PI for the applicant products incorporating changes which bring it into line with the existing approved PI for simvastatin (Zocor).

It was pointed out in the first-round report of this evaluation that this apparent food effect, along with its possible attendant safety risks, could be presumed to apply to other formulations of simvastatin, e.g. Zocor. The sponsor's response concurs with this and makes the case that any such safety issue might be reflected in adverse reactions, particularly muscle related side-effects, reported in the safety studies and ongoing pharmacovigilance of Zocor. It is suggested that no such pattern of risk has been evident. Presuming that information available to TGA agrees with that assessment, this is seen as a valid argument. Because there is no evidence of PK interaction between the components of Juvicor, there should be no need to discriminate between Juvicor and other simvastatin formulations such as Zocor on safety grounds relating to simvastatin exposure.

12.3. Second round assessment of benefit-risk balance

The concerns expressed in the first-round report regarding the possible impact of food effect on safety (risk), and a possible efficacy (benefit) issue relating to evening administration have been adequately addressed as noted above. In view of these considerations, the benefit-risk balance of the combination sitagliptin/simvastatin tablet (Juvicor) is seen as equivalent to that of the two medications administered as separate tablets, and therefore satisfactory in the context of the application.

The potential effect of evening by comparison with morning administration on compliance, as noted under *Pharmacokinetics*, is a minor hypothetical concern with regard to the benefit of the product, but potentially counteracted by the sponsor's argument that compliance might be enhanced by the combination nature of the product.

13. Second round recommendation regarding authorisation

It is now the recommendation of this evaluation that **the combination sitagliptin/simvastatin product Juvicor is suitable for authorisation** for the indications stated in the application.

As recommended in the first-round report, safety monitoring of the use of sitagliptin/simvastatin in combination with other oral hypoglycaemic agents should be a requirement for pharmacovigilance.

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