**Omarigliptin**

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**Table 1. Timelines relating to the development of omarigliptin**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>2010</td>
<td>Phase I studies with MK-3102 (omarigliptin) commence</td>
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<tr>
<td>2012</td>
<td>First patients recruited into phase III studies including a cardiovascular outcome trial: MK-3102-018</td>
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<tr>
<td>2014</td>
<td>First phase III results with omarigliptin presented</td>
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<td>2015</td>
<td>Oumarigliptin approved and launched in Japan</td>
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<tr>
<td>2016</td>
<td>Merck announces that it will no longer be filing for a licence in the United States and Europe; the cardiovascular outcome trial is terminated</td>
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**Introduction**

Dipeptidyl peptidase-4 (DPP-4) inhibitors have been available for use in the management of diabetes mellitus since 2006. These drugs are normally administered once daily. Recent drug developments have been focused on creating longer-acting inhibitors.

Omarigliptin is one example of a long-acting DPP-4 inhibitor which is administered once weekly as either monotherapy or as add-on therapy for optimisation of glycaemic control. It has been licensed for use in Japan since 2015 but its phase III development programme in Europe and the United States has been halted for undisclosed commercial reasons.

**Pharmacology**

Omarigliptin is a competitive, reversible inhibitor of DPP-4 which is cleared by excretion into the urine. It is structurally different from currently available once-daily dosing DPP-4 inhibitors.

It is rapidly absorbed after administration, with time to maximum concentration ranging from 0.5–4 hours. The terminal half-life of omarigliptin was greater than 100 hours which allows for once-weekly administration. Steady state of the drug is achieved after two to three doses. Both pre-clinical and clinical studies have demonstrated significant inhibition of DPP-4 activity with an associated increase in active GLP-1 levels.

**Trials of safety and efficacy in diabetes**

To date, there are two published trials which give useful information on the possible clinical use of omarigliptin.

In a 12-week, dose-ranging phase II clinical trial, 685 subjects were randomised to placebo or five different doses of omarigliptin. Eligible participants were aged 18–70 years old with type 2 diabetes mellitus and a BMI of 20–43kg/m². Exclusion criteria included renal impairment, significant cardiovascular or liver disease and prior treatment with a DPP-4 inhibitor or GLP-1 analogue. A follow-on study over 66 weeks was commenced on completion of the base study to assess long-term safety and tolerability. The primary endpoint was change in HbA1c with secondary endpoints of 2-hour post meal glucose and fasting blood glucose.

Participants were randomised into receiving placebo or omarigliptin at 0.25mg, 1mg, 3mg, 10mg or 25mg once weekly. Participants could receive additional treatment during the base study with metformin if glycaemic targets were not met. All groups who received omarigliptin demonstrated a reduction in HbA1c at 12 weeks from baseline in a dose-dependent way (HbA1c changes: +0.14%, -0.14%, -0.36%, -0.35%, -0.53% and -0.57% for 0.25mg, placebo, 1mg, 3mg, 10mg and 25mg once weekly, respectively). There was a -0.72% (-0.93%
During the extension study, those participants randomised to omari- glptin had a dose increase to 25mg once weekly. The placebo group was switched to blinded pioglitazone initially, which was then converted to blinded metfor min based on the safety concerns of pioglitazone.3

Rescue therapy during the extension study was with glimepiride. In all, 485 patients were entered into the extension study with 374 patients completing the 66-week follow up. HbA1c measurements in the 25mg weekly omarigliptin group had deteriorated slightly compared to week 12 measurements (-0.34% at week 78 vs -0.57% at week 12). This trend was seen across all groups receiving omarigliptin. The group receiving placebo and add-on therapy with pioglitazone then metformin were noted to have a marked improvement in HbA1c at week 78 (-0.73% at week 78 vs +0.14% at week 12).

There was no statistical difference in body weight observed between the placebo group and the omarigliptin groups. The incidence of adverse events recorded during the initial 12-week study was similar across all study cohorts. There were no cases of pancreatitis in the initial 12-week study and there was one case in the extension study in a patient taking omarigliptin which was deemed to be secondary to gallstones. With respect to hypoglycaemic episodes, there were three cases in the placebo group and five recorded episodes in the groups randomised to omarigliptin. None of these episodes were severe. In the extension study, no episodes of hypoglycaemia were recorded in the placebo/metformin group, while 14 occurred in the pooled omarigliptin group (two severe episodes).

During the extension study, there were five deaths (one in the placebo group and four in the pooled omarigliptin group); none were deemed related to the drug.

The phase III development programme for omarigliptin was set to include 10 clinical trials recruiting approximately 8000 patients with type 2 diabetes, including a cardiovascular outcomes trial. The O-QWEST (Omarigliptin Q Weekly Efficacy and Safety in Type 2 Diabetes) trial compared the efficacy of omarigliptin 25mg once weekly vs sitagliptin 100mg once daily in patients inadequately controlled on metformin therapy. Inclusion criteria included patients with type 2 diabetes mellitus aged over 18 with an HbA1c between 6.5–9% (48–75mmol/mol). This double-blinded, randomised controlled trial lasted 24 weeks. In total, 642 subjects were recruited: 322 randomised to omarigliptin 25mg once weekly and 320 randomised to sitagliptin 100mg once daily. Data were collected regarding HbA1c, fasting plasma glucose, blood, weight and adverse events.

At week 24 there was no significant difference between the changes in HbA1c measurement (percentage omarigliptin -0.47 vs sitagliptin -0.43).3 On completion of the study, no statistically significant differences were noted in the percentage of subjects attaining optimal glycaemic control in both groups (54.4% omarigliptin vs 52.4% sitagliptin).4 The incidence of adverse events was 36.3% in the omarigliptin cohort and 40.6% for the sitagliptin cohort. There was one episode of severe hypoglycaemia recorded in a patient receiving omarigliptin. There were no cases of pancreatitis recorded during the study period. No changes were observed in blood pressure or ECG monitoring.

Discussion
Compliance with medication in chronic disease has been shown to be related to the number of medications and dosing frequency. A once-weekly preparation may be more appealing to patients with improvement in adherence and overall improved disease control. Omarigliptin has been shown to be non-inferior in glycaemic control in comparison to a currently licensed DPP-4 inhibitor.5 It has been demonstrated to be well tolerated during clinical trials with, importantly, a weight neutral effect and a low incidence of hypoglycaemia. However, despite being available in Japan for clinical use and well on in terms of development, the pharmaceutical company has decided not to pursue a licensing authorisation in Europe and the United States, citing commercial reasons. No other information regarding this decision has been made public. (Table 1.)

Declaration of interests
Dr Galloway has no conflicts of interest to declare.
Professor Fisher has received payment for lectures and advisory boards from MSD.
Professor McKay has received payment for lectures and advisory boards from MSD.

References