National Horizon Scanning Centre

Rimonabant (Acomplia) for type 2 diabetes

December 2007

This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Rimonabant (Acomplia) for type 2 diabetes

Target group
- Type 2 diabetes – add-on therapy with or without metformin.

Technology description
Rimonabant (Acomplia, SR141716) is the first in class oral selective antagonist of cannabinoid type 1 (CB1) receptors. If licensed it would be used with or without metformin, as an add-on to current management. Rimonabant is already licensed as an adjunct to diet and exercise in the management of obese patients (BMI ≥ 30 kg/m²), or overweight patients (BMI > 27 kg/m²) with associated risk factors, such as type 2 diabetes (who may be taking oral anti-diabetes medication or insulin) or dyslipidaemia. For adults the recommended dosage is 20 mg twice daily.

Innovation and/or advantages
If licensed for type 2 diabetes, rimonabant may reduce glycated haemoglobin (HbA₁c) levels, thereby helping to reduce risk of long-term microvascular complications. This would be expected in addition to reductions in weight and waist circumference.

Developer
Sanofi-Aventis.

Place of use
- Home care e.g. home dialysis
- Community or residential care e.g. district nurses, physio
- Secondary care e.g. general, non-specialist hospital
- Tertiary care e.g. highly specialist services or hospital
- General public e.g. over the counter
- Primary care e.g. used by GPs or practice nurses
- Emergency care e.g. paramedic services, trauma care
- Other:

Availability, launch or marketing dates, and licensing plans:
Phase III clinical trials.

NHS or Government priority area:
This topic is relevant to the National Service Framework for Diabetes.

Relevant guidance
- NICE technology appraisal in development: Rimonabant for the treatment of overweight and obese patients. Expected date of issue to be confirmed¹.
- NICE clinical guideline: Management of type 2 diabetes – managing blood glucose levels. 2002².
- NICE clinical guideline in development: type 2 diabetes (update). Expected date of issue April 2008. This is an update of the following guidelines: type 2 diabetes – retinopathy, renal disease, blood glucose, management of blood pressure and blood lipids.
Clinical need and burden of disease

In England and Wales an estimated 2,018,000 people have diabetes, with type 2 diabetes accounting for more than 85%. Type 2 diabetes is characteristically a disease of the middle aged or elderly yet increasing being seen in younger patients (in particular in ethnic minority groups). Patients with diabetes have an average reduction in life expectancy of 5-10 years. Cardiovascular disease accounts for around 60% of all deaths from diabetes and is the most common complication of type 2 diabetes. The risk of myocardial infarction and stroke is two to five times higher for individuals with type 2 diabetes than in the general population. Further diabetic complications include nephropathy, retinopathy, foot ulceration and erectile dysfunction.

Existing comparators and treatments

- In people with diabetes who are overweight, and whose blood glucose is inadequately controlled using lifestyle interventions alone, metformin should normally be considered as the first-line glucose-lowering therapy. Metformin should also be considered as an option for first-line or combination therapy for people who are not overweight.
- When metformin is not tolerated or is contraindicated, or in people who are not overweight, the insulin secretagogues (including sulphonylureas and the rapid-acting insulin secretagogues - nateglinide and repaglinide) should be considered as a first-line option.
- People should be offered glitazones (pioglitazone, rosiglitazone) as oral combination therapy if they are unable to take metformin and insulin secretagogues as combination therapy, or if their HbA1c levels remain unsatisfactory despite an adequate trial of metformin with insulin secretagogues.
- In most patients diabetes progresses and many will eventually need insulin to maintain satisfactory blood glucose levels.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial name or code</th>
<th>NCT00029848</th>
<th>NCT00257257</th>
<th>NCT00288236</th>
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<tr>
<td>RIO-Diabetes study</td>
<td>SERENADE, phase III</td>
<td>ARPEGGIO, phase III</td>
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<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Sanofi-Aventis</th>
<th>Sanofi-Aventis</th>
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<tbody>
<tr>
<td>Status</td>
<td>Published¹⁷</td>
<td>Conference abstract¹⁴,¹⁵</td>
<td>Completed, unpublished¹⁶</td>
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<tr>
<td>Location</td>
<td>International</td>
<td>USA</td>
<td>International</td>
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<tr>
<td>Design</td>
<td>Randomised, double-blind placebo-controlled</td>
<td>Randomised, double-blind, placebo-controlled</td>
<td>Randomised, placebo-controlled, double-blind</td>
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<tr>
<td>Participants in trial</td>
<td>n=1,047 overweight or obese; HbA1c 6.5-10%; on metformin or sulphonylurea for at least 3 months. Randomised to placebo; rimonabant 5 mg or 20 mg per day</td>
<td>n=278 treatment-naïve. Randomised to rimonabant 20 mg or placebo.</td>
<td>n=300 inadequately controlled with insulin.</td>
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<tr>
<td>Follow-up</td>
<td>1 year</td>
<td>6 months</td>
<td>48 weeks</td>
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<tr>
<td>Primary outcome</td>
<td>Weight change</td>
<td>Change in HbA1c</td>
<td>Change in HbA1c</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>HbA1c, HDL cholesterol, triglyceride, fasting glucose and insulin, C-reactive protein, leptin, waist circumference and blood pressure</td>
<td>Fasting glucose and insulin, C-peptide, homeostasis model assessment, body weight, HDL-cholesterol, triglycerides, blood pressure, safety</td>
<td>Fasting glucose, total daily insulin dose, body weight, waist circumference, HDL-cholesterol, triglycerides, safety</td>
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</table>
### Key results

<table>
<thead>
<tr>
<th>Intention to treat analysis – rimonabant 20 mg vs. placebo:</th>
<th>Rimonabant vs. placebo. Reduction in body weight: 7 kg vs. 2.9 kg (p&lt;0.001). HbA1c: 0.9% reduction vs. 0.4% (p=0.0009). Reduced waist circumference: 6.4 cm vs. 2.4 cm (p&lt;0.0001) HDL-cholesterol increase: 10.4% vs. 3.1% (p&lt;0.0001) Triglyceride: 18.3% decrease vs. 4.5% increase (p=0.0024)</th>
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<tbody>
<tr>
<td>Reduction in weight: 5.3 kg vs. 1.4 kg (p&lt;0.001). Waist circumference reduction: 5.2 cm vs. 1.9 cm (p&lt;0.0001). HbA1c: 0.6% reduction vs. 0.1% increase (p&lt;0.0001).</td>
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### Expected reporting date

- N/A

### Adverse effects

| Adverse effects leading to discontinuation, mainly due to depressed mood disorders (3%), nausea (1.5%) and dizziness (0.9%) | Most common side effects with rimonabant vs. placebo: dizziness (10.9% vs. 2.1%), nausea (8.7% vs. 3.6%), upper respiratory tract infection (7.2% vs. 2.7%), anxiety (5.8% vs. 3.6%) and depressed mood (5.8% vs. 0.7%) |

### Trial name or code

<table>
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<tr>
<th>NCT00546325 REASSURE</th>
<th>NCT00478972 SOLO</th>
<th>ISRCTN63367873 CARDIO-REDUSE</th>
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### Sponsor

- Sanofi-Aventis
- Sanofi-Aventis
- Care and Public Health Research Institute (the Netherlands) and Sanofi-Aventis

### Status

- Ongoing (enrolment commenced October 2007)
- Ongoing (enrolment commenced May 2007)
- Ongoing (commenced enrolment September 2006)

### Location

- Japan
- The Netherlands

### Design

- Randomised, double-blind
- Randomised, double-blind, placebo-controlled.
- |

### Participants in trial

<table>
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<tr>
<th>n=382 (expected); currently taking metformin and sulfonylurea. HbA1c between 7% and 9% inclusive, BMI between 27kg/m² and 40kg/m².</th>
<th>n=306; inadequately treated with diet and exercise alone. HbA1c between 7% and 10% inclusive. BMI &gt; 25 kg/m²</th>
</tr>
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<tbody>
<tr>
<td>n=600 (expected); waist circumference more than 88 or 102 cm in women and men. Diabetes or impaired fasting blood glucose &gt;6.1 mmol/l.</td>
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</table>

### Follow-up

- 48 weeks
- 36 weeks
- 12 months

### Primary outcome

- HbA1c; hypoglycaemia
- HbA1c; body weight.
- Waist circumference, plasma glucose, HbA1c.

### Secondary outcomes

- Insulin sensitivity, fasting glucose, hypoglycaemia, BMI, waist and hip circumference, weight, quality of life, lipid measures, fasting insulin, Fasting plasma glucose, waist circumference, triglycerides and HDL-cholesterol and safety.
- Lipid profile, body weight, blood pressure, smoking, QALYs and costs

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*Information received from company*
<table>
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<tr>
<th>Expected reporting date</th>
<th>Planned 2009&lt;sup&gt;b&lt;/sup&gt;</th>
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<table>
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<tr>
<th>Trial name or code</th>
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<th>NCT00458081</th>
<th>NCT00449605, phase III.</th>
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<tr>
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<td>Status</td>
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<td>Ongoing</td>
<td>Ongoing (enrolment commenced March 2007)</td>
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<tr>
<td>Location</td>
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<td>International.</td>
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<tr>
<td>Participants in trial</td>
<td>n=450 (expected); BMI ≥ 25 kg/m²; HbA&lt;sub&gt;1c&lt;/sub&gt; ≥ 7.0 % and ≤ 10.0 %. Randomised to rimonabant or placebo in combination with sulfonylurea or an alpha glucosidase inhibitor.</td>
<td>n=550 (expected); diabetic or dyslipidaemia with or without other cardiometabolic risk factors; abdominal obesity and microalbuminuria. Randomised to rimonabant 20 mg or placebo</td>
<td>n=500 (expected); BMI ≥27kg/m² HbA&lt;sub&gt;1c&lt;/sub&gt;≥7% and ≤9% with metformin. Randomised to Rimonabant or glimepiride.</td>
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<tr>
<td>Follow-up</td>
<td>1 year</td>
<td>1 year</td>
<td>1 year</td>
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<tr>
<td>Primary outcome</td>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt;; body weight</td>
<td>Microalbuminuria.</td>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt;.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Fasting glucose, waist circumference, triglycerides and HDL-cholesterol and safety</td>
<td>Albuminuria, weight, waist circumference, BMI, lipid parameters, glycaemia control, proinflammatory markers, glomerular filtration rate, blood pressure, quality of life and safety.</td>
<td>Body weight and HDL-cholesterol.</td>
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<tr>
<td>Expected reporting date</td>
<td>Planned 2009</td>
<td>-</td>
<td>-</td>
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<th>TOCCATA&lt;sup&gt;20&lt;/sup&gt;</th>
<th>RESONATE&lt;sup&gt;20&lt;/sup&gt;</th>
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<td>Design</td>
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<td>Randomised, double-blind, placebo-controlled&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Randomised, double-blind, active-control&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>Status</td>
<td>Ongoing - study began in Q1 2007</td>
<td>Planned to begin Q1 2008</td>
<td>Planned to begin Q1 2008</td>
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<tr>
<td>Participants in trial</td>
<td>Rimonabant versus sulfonylurea with metformin</td>
<td>Rimonabant versus placebo in combination with metformin</td>
<td>Rimonabant versus sitagliptin in combination with metformin</td>
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<tr>
<td>Follow-up</td>
<td>9 months&lt;sup&gt;c&lt;/sup&gt;</td>
<td>36 weeks&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9 months&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Primary outcome</td>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>HbA&lt;sub&gt;1c&lt;/sub&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Secondary outcomes</td>
<td>Fasting glucose, body weight, triglycerides and</td>
<td>Fasting glucose, body weight, HDL-cholesterol and</td>
<td>Waist circumference, fasting glucose, HDL-cholesterol,</td>
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</tbody>
</table>

<sup>b</sup> Information received from company
<sup>c</sup> Information received from company


Estimated cost and cost impact

For the licensed indication of obesity, rimonabant at 20 mg per day costs approximately £570.

Potential or intended impact – speculative

Patients

- Reduced morbidity
- Reduced mortality or increased survival
- Quicker, earlier or more accurate diagnosis or identification of disease
- Other:
- Non identified

Services

- Increased use
- Service reorganisation required
- Staff or training required
- Decreased use
- Other:
- None identified

Costs

- Increased unit cost compared to alternative
- New costs:
- Increased costs: more patients coming for treatment
- Savings:
- Increased costs: capital investment needed
- Other:

References

14 Controlled Trials Register. Hwww.controlled-trials.com/mrct/trial/135027/rimonabantH (accessed 24/10/07)

British National Formulary, number 54. September 2007

Controlled Trials Register. Hwww.controlled-trials.com/mrct/trial/144989/rimonabantH (accessed 24/10/07)

Controlled Trials Register. Hwww.controlled-trials.com/mrct/trial/337091/rimonabantH (accessed 24/10/07)
