Phentermine/topiramate (Qnexa) for weight loss and maintenance of weight loss

April 2011

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Phentermine/topiramate (Qnexa) for weight loss and maintenance of weight loss

Target group
- Obesity: weight loss and maintenance of weight loss in conjunction with a mildly hypocaloric diet in adult obese patients (BMI \( \geq 30\)kg/m\(^2\)) or overweight patients (BMI \( \geq 27\)kg/m\(^2\)) with weight-related co-morbidities.

Technology description
Phentermine/topiramate (Qnexa, VI-0521) is an oral low-dose combination of immediate-release phentermine and prolonged-release topiramate. Phentermine is a US licensed appetite suppressant, while topiramate is an anti-convulsant, licensed in the US and EU for the treatment of generalised seizures and migraine prophylaxis, with weight loss properties. VI-0521 is intended for the treatment of obesity, including weight loss and maintenance of weight loss in obese and overweight adult patients. VI-0521 is administered orally once daily, initially at a low-dose combination of 3.75mg phentermine and 23mg topiramate for 7 to 14 days, increased to a target treatment mid-dose of 7.5mg phentermine and 46mg topiramate for 90 days. Dose and length of treatment period depends on the percentage of weight loss and weight loss goal\(^1\).

VI-0521 is also in phase II development for the treatment of obese patients with type 2 diabetes and treatment of patients with sleep apnoea syndrome.

Innovation and/or advantages
If licensed, VI-0521 would provide an additional pharmacological therapy for inducing and maintaining weight loss in adult patients with obesity or weight-related comorbidities, in an area where pharmacological options are limited.

Developer
Vivus Inc.

Availability, launch or marketing dates, and licensing plans
In phase III clinical trials.

NHS or Government priority area

Relevant guidance
- NICE technology appraisal in development. Lorcaserin hydrochloride for the treatment of adults who are obese and treatment of adults who are overweight who have at least one obesity related comorbidity. Expected date of issue to be confirmed\(^2\).
- NICE public health guideline. Dietary interventions and physical activity interventions for weight management before, during and after pregnancy. 2010\(^3\).
- NICE clinical guideline. Type 2 diabetes. 2008\(^5\).
• NICE clinical guideline. Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. 2006, amended 2010.6
• SIGN. Management of obesity. 2010.7
• National Obesity Forum. Guidelines on management of adult obesity and overweight in primary care. 2010.8

Clinical need and burden of disease
In adults, a body mass index (BMI) of 25 to 29.9 kg/m² is considered overweight, a BMI of 30 to 39.9 kg/m² obese and a BMI of >40 kg/m² morbidly obese. BMI may require some interpretative caution, as risk factors such as waist circumference, ethnicity and other co-morbidities may also need to be considered.

In Europe being overweight and obesity are responsible for around 80% of cases of type 2 diabetes, 35% of cases of ischaemic heart disease and 55% of hypertensive disease in adults. Together these conditions cause more than 1 million deaths and 12 million life years of ill health each year. It is estimated that in Europe, 1 in 13 annual deaths may be related to excess weight. These figures indicate the substantial burden that obesity has on national health care costs.

England has some of the highest levels of obesity in Europe, with 66% of men and 57% of women being overweight or obese in 2008.10 If this trend continues the Foresight Report estimates that by 2015, 36% men and 28% women will be obese.11,6 Health Survey England data suggests that this upward trend in children might now be flattening out.

Existing comparators and treatments
Obesity is a chronic condition and its management should be lifelong, requiring lifestyle changes which may involve the wider family as well as the patient. Conventional weight management programmes aim for a 10% weight loss in 3 months to achieve significant health benefits.8

The National Obesity Forum guidelines recommend that treatment or advice should be offered to the following patient groups:8
• Patients with a BMI ≥30 kg/m².
• Patients with a BMI ≥28 kg/m² with comorbidities.
• Patients with any degree of overweight coinciding with diabetes, other severe risk factors or serious disease (e.g. raised cardiovascular risk or sleep apnoea).
• Patients who self-refer, where appropriate.
• Parents of families with more than one obese or overweight member may need special consideration and more intensive support.

Currently, orlistat is the only medicine indicated for the promotion of weight loss as an adjunctive therapy within a weight management programme. Combination therapy with multiple anti-obesity drugs is contraindicated by manufacturers.8,9 In January 2010, the EMA suspended the product licence for sibutramine due to an increased risk of
cardiovascular events. This product is no longer recommended for the promotion of weight loss\textsuperscript{12}.

### Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
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<tbody>
<tr>
<td>EQUIP, OB-302, NCT00554216; VI-0521 or placebo; phase III.</td>
<td>VIVUS Inc.</td>
<td>Complete, published in abstract.</td>
<td>Trial registry\textsuperscript{13}, FDA briefin...</td>
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<tr>
<td>CONQUER, OB-303, NCT00553787; VI-0521 or placebo; phase III.</td>
<td>VIVUS Inc.</td>
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<td>Trial registry\textsuperscript{16} abstract...</td>
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<tr>
<td>SEQUEL, OB-305, NCT00796367; VI-0521 or placebo; phase III extension.</td>
<td>VIVUS Inc.</td>
<td>Complete, unpublished.</td>
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<tr>
<th>Follow-up</th>
<th>Primary outcome</th>
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<tbody>
<tr>
<td>Treatment period 56 weeks. Follow up every 2 weeks for initial 4 weeks and then monthly for following 52 weeks.</td>
<td>Weight loss at week 56.</td>
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<td>Weight loss at week 56.</td>
<td></td>
</tr>
<tr>
<td>Treatment period 52 weeks. Follow up every month for 52 weeks.</td>
<td>Weight loss at week 108.</td>
<td></td>
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</tbody>
</table>
### Secondary outcomes

| Improvement in obesity-associated comorbidities, absolute weight loss, reduction in waist circumference, improvement in quality of life (IWQOL\textsuperscript{a}-Lite, SF-36\textsuperscript{b}). |
| Improvement in HbA1c\textsuperscript{c} and other obesity-associated comorbidities, absolute weight loss, reduction in waist circumference, improvement in quality of life (IWQOL-Lite, SF-36). Change in medication for comorbidities; type 2 diabetes progression. |
| Improvement in HbA1c and other obesity-associated comorbidities, absolute weight loss, reduction in waist circumference, improvement in quality of life (IWQOL-Lite, SF-36). Change in medication for comorbidities; type 2 diabetes progression. |

### Key results

| Weight loss at week 56 for low-dose, high-dose and placebo groups respectively: ≥5% weight loss achieved by 45%, 67% and 17%; ≥10% weight loss achieved by 19%, 47% and 7% (ITT\textsuperscript{d} analysis; all p-values <0.001). |
| Weight loss at week 56 for mid-dose, high-dose and placebo groups respectively: ≥5% weight loss achieved by 62%, 70% and 21%; ≥10% weight loss achieved by 37%, 48% and 72%; ≥15% weight loss achieved by 19%, 29% and 3%\textsuperscript{e} (ITT\textsuperscript{e} analysis; all p-values <0.001). HbA1c significantly reduced in VI-0521 groups compared with placebo (p<0.05). |
| Weight loss at week 108 for mid-dose, high-dose and placebo groups respectively: ≥5% weight loss achieved by 75%, 79% and 30%; ≥10% weight loss achieved by 50%, 54% and 12% (ITT\textsuperscript{e} analysis; all p-values <0.001). |

### Expected reporting date

- April 2011.

### Adverse effects (AEs)

For low dose, high dose and placebo groups respectively: completion rate 61%, 66% and 53%; discontinuation due to AEs 11%, 16% and 8%; severe AEs 2.5%, 2.0% and 2.3%. AEs included paresthenia, dry mouth, constipation, upper respiratory infection, headache, nasoparyngitis and dysgeusia.\textsuperscript{f}

For mid dose, high dose and placebo groups respectively: completion rate 75%, 74% and 62%; discontinuation due to AEs 12%, 19% and 9%; severe AEs 2.8%, 4.3% and 3.8%. AEs included dry mouth, paresthenia, constipation, upper respiratory infection, dysgeusia, insomnia and headache.\textsuperscript{f}

For mid dose, high dose and placebo groups respectively: completion rate 83% for all doses and 86% placebo; discontinuation due to AEs 3.9%, 4.1% and 2.6%; severe AEs 2.6%, 4.1% and 4.0%. AEs included constipation, tingling, dry mouth, dysgeusia, insomnia.\textsuperscript{f}

### Trial

| EQUATE, OB-301, NCT00563368; VI-0521, phentermine alone, topiramate alone or placebo; phase III. | OB-201, VI-0521, phentermine alone, topiramate alone or placebo; phase II. |

### Sponsor

VIVUS Inc.

### Status

Complete and published in abstract.

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\textsuperscript{a} IWQOL = Impact of Weight on Quality of Life questionnaire.

\textsuperscript{b} SF-36 = Short-form health survey questionnaire with 36 questions.

\textsuperscript{c} HbA1c = Glycosylated haemoglobin A1c.

\textsuperscript{d} ITT = Intention To Treat.

\textsuperscript{e} Results provided by manufacturer.
### Source of information
- Trial registry, FDA briefing document, abstract and manufacturer.
- FDA briefing document and manufacturer.

### Location
- USA.
- USA.

### Design
- Randomised, placebo controlled.
- Randomised, placebo controlled.

### Participants and schedule
- n=756; adults (≤70 yrs); obese (BMI 30-45kg/m²); excludes type 2 diabetes. Randomised to VI-0521 mid-dose (phentermine 7.5mg and topiramate 46mg) or high-dose (phentermine 15mg and topiramate 92mg), topiramate 46mg, topiramate 92mg, phentermine 7.5mg, phentermine 15mg or placebo, all given orally once daily.
- n=200; adults aged 18 to 60 years; obese/overweight (BMI 30-50kg/m²); non-diabetics. Randomised to VI-0521 (phentermine 15mg and topiramate 100mg), phentermine 15mg, topiramate 100mg or placebo all given orally once daily.

### Follow-up
- Treatment period 28 weeks. Follow up every 2 weeks for initial 4 weeks and then monthly for following 24 weeks.
- Treatment period 24 weeks. Follow up every 2 weeks for initial 4 weeks and then monthly for following 20 weeks.

### Primary outcome
- Weight loss at week 28.
- Weight loss at week 24.

### Secondary outcomes
- Absolute weight loss, improvement in obesity-associated comorbidities (blood pressure, glycaemia), reduction in waist circumference, improvement in quality of life (IWQOL-Lite).
- Absolute weight loss, improvement in obesity-associated comorbidities (blood pressure, glycaemia), reduction in waist circumference, improvement in quality of life (IWQOL-Lite).

### Key results
- Weight loss at week 28 for VI-0521 mid-dose or high-dose, phentermine 7.5mg, phentermine 15mg, topiramate 46mg, topiramate 92mg or placebo groups respectively: ≥5% weight loss achieved by 62%, 66%, 43%, 46%, 39%, 49% and 15%; ≥10% weight loss achieved by 39%, 41%, 12%, 21%, 19%, 24% and 7% (ITT analysis; all p-values <0.0001).
- Weight loss at week 24 for VI-0521, phentermine alone, topiramate alone and placebo groups respectively: ≥5% weight loss achieved by 82%, 38%, 50% and 14%; ≥10% weight loss achieved by 50%, 14%, 16% and 8% (ITT analysis; all p-values <0.0001).

### Adverse effects (AEs)
- For VI-0521 mid-dose or high-dose, phentermine 7.5mg, phentermine 15mg, topiramate 46mg, topiramate 92mg or placebo groups respectively: completion rate 73%, 69%, 73%, 74%, 72%, 72% and 68%; discontinuation due to AEs 15.1%, 21.3%, 9.2%, 10.2%, 7.5%, 16.8% and 7.3%; severe AEs 0.9%, 0.9%, 1.8%, 0.9%, 0% 0.9% and 0%. AEs included paresthesia, dry mouth, dysgeusia, constipation, dizziness and insomnia.
- For VI-0521, phentermine alone, topiramate alone and placebo groups respectively: completion rate 92%, 76%, 86% and 62%; discontinuation due to AEs 1 out of 50 patients for VI-0521 and 3 out of 50 patients for all other groups; no severe AEs reported; most common AEs included decreased appetite, paresthesia, increased satiety, dysgeusia, increased urinary frequency and headache.

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**Estimated cost and cost impact**

The cost of VI-0521 is not yet known. Phentermine is not currently licensed in the UK. Topiramate is licensed for the treatment of generalised seizures and migraine prophylaxis, for this indication, with 60 tablets of topiramate 100mg costing £12.52.

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^ Results provided by manufacturer.
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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Period: 28 day</th>
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<tr>
<td>Orlistat</td>
<td>120mg with each main meal (maximum dose 360mg daily)</td>
<td>£31.63</td>
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</tbody>
</table>

Claimed or potential impact – speculative

Patients

☐ Reduced mortality or increased length of survival
☐ Reduction in associated morbidity or improved quality of life for patients and/or carers
☐ Quicker, earlier or more accurate diagnosis or identification of disease
☐ Other:
☐ None identified

Services

☐ Increased use
☐ Service organisation
☐ Staff requirements
☐ Decreased use
☐ Other:
☐ None identified

Costs

☐ Increased unit cost compared to alternative
☐ New costs: Additional treatment option.
☐ Increased costs: more patients coming for treatment
☐ Savings: decreased use of medications for obesity-related co-morbidities.
☐ Increased costs: capital investment needed
☐ Other:
☐ None identified

Other issues

☐ Clinical uncertainty or other research question identified:
  Safety of longer term use not yet established. Comparison of relative role of type 2 diabetes therapeutic agents is currently unclear.
☐ None identified

References

1 U.S. Food and Drug Administration, [www.fda.gov](http://www.fda.gov), VI-0521(Qnexa) advisory committee briefing document, NDA 022580, 15 July 2010.
2 National Institute for Health and Clinical Excellence. Lorcaserin hydrochloride for the treatment of adults who are obese and treatment of adults who are overweight who have at least one obesity related co-morbidity. Technology appraisal in development. Expected date of issue to be confirmed.


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