Zucapsaicin (Civamide) for episodic cluster headache

SUMMARY

Zucapsaicin (Civamide) is a synthetically produced vanilloid receptor subtype-1 (TRPV-1) agonist and neuronal calcium channel blocker. It is intended for the treatment of episodic cluster headache (CH). In clinical trials zucapsaicin has been administered intranasally at 0.01% 20µg twice daily for 7 days (0.1 ml to each nostril).

CH is a primary headache disease characterised by recurrent (1-3 per day) short-lasting attacks (15 to 180 minutes) of excruciating unilateral periorbital pain accompanied by ipsilateral autonomic signs (lacrimation, nasal congestion, ptosis, miosis, lid oedema, and eye redness). CH is thought to be one of the most painful conditions an individual can experience. It is estimated that CH affects approximately 1% of all people at some time in their life. CH has a circannual and circadian periodicity, attacks being clustered in bouts that can occur during specific months of the year.

Anyone can be affected by CH, but approximately 8 out of 10 people who have them are men and most are smokers. Prevalence is estimated at 0.5-2 per 1,000 population. In England during 2012, there were 1,205 hospital admissions, resulting in 1,732 bed days and 1,366 finished consultant episodes.

Zucapsaicin has completed two phase III clinical trials, with one phase III clinical trial planned, all assessing mean percent change in the number of CHs per week during a three week observation compared with placebo.
TARGET GROUP

- Episodic cluster headaches (CH)

TECHNOLOGY

DESCRIPTION

Zucapsaicin (Civamide) is a synthetically produced vanilloid receptor subtype-1 (TRPV-1) agonist and neuronal calcium channel blocker. It is intended for the treatment of episodic CH. In clinical trials zucapsaicin has been administered intranasally at 0.01% 20µg twice daily for 7 days (0.1 ml to each nostril).

Zucapsaicin (topical) is currently licensed in Canada for treatment of osteoarthritic pain.

Zucapsaicin is also in phase III development for post-herpetic neuralgia of the torso (topical). It is also in phase II development for Crohn's disease (oral), keratoconjunctivitis sicca (intranasal), and post-herpetic neuralgia of the trigeminal nerve (intranasal).

INNOVATION and/or ADVANTAGES

If licensed, zucapsaicin will offer an additional treatment option for this patient group.

DEVELOPER

Winston Pharmaceuticals Inc.

AVAILABILITY, LAUNCH OR MARKETING

Currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

CH is a primary headache disease characterised by recurrent (1-3 per day) short-lasting attacks (15 to 180 minutes) of excruciating unilateral periorbital pain accompanied by ipsilateral autonomic signs (lacrimation, nasal congestion, ptosis, miosis, lid oedema, and eye redness). CH is thought to be one of the most painful conditions an individual can experience. CH has a circannual and circadian periodicity, attacks being clustered in bouts that can occur during specific months of the year. Alcohol is the only known dietary trigger for CH, but it is believed that overheating may also be a trigger (such as exercising in a hot room, or having a hot bath) and strong smelling substances such as solvents, perfumes and petrol as well as napping may also trigger CH attacks. During bouts, attacks may happen at precise hours and are especially prevalent during the night. During the attacks, patients tend to be restless, as opposed to migraine where a sufferer tends to avoid unnecessary movement.

CH may be episodic or chronic, depending on the presence of remission periods (pain-free period between two cluster bouts). Remission from episodic CH may last longer than one
month whereas for chronic CH, remission may last less than one month\textsuperscript{2,5}. Episodic CH may be up to six times more common than chronic CH\textsuperscript{6}. CH is associated with trigeminovascular activation and neuroendocrine and vegetative disturbances, however the precise causative mechanisms remain unknown\textsuperscript{1}. Involvement of the hypothalamus has been confirmed, which may explain, at least in part, the cyclic aspects of CH\textsuperscript{1}. The disease is thought to be familial in about 10\% of cases\textsuperscript{1}.

**CLINICAL NEED and BURDEN OF DISEASE**

Anyone can be affected by CH, but approximately 8 out of 10 people who have them are men and most are smokers. Prevalence is estimated at 0.5-2 per 1,000 population\textsuperscript{1,3}. It is estimated that CH affects approximately 1\% of all people at some time in their life\textsuperscript{7}. Many patients do not see their general practitioner due to a knowledge gap in primary care about this disorder\textsuperscript{a}. In England during 2012, there were 1,205 hospital admissions, resulting in 1,732 bed days and 1,366 finished consultant episodes (ICD-10 G44.0)\textsuperscript{8}.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE clinical guideline. Headaches. (CG150). September 2012\textsuperscript{4}.
- NICE quality standard. Headaches in young people and adults (QS42). August 2013\textsuperscript{9}.

**Other Guidance**

- NHS Clinical Knowledge Summary. Headache – cluster. 2012\textsuperscript{6}.
- Evers S, Áfra J, Frese A \textit{et al.} Cluster headache and other trigemino- autonomic cephalgias. 2011\textsuperscript{10}.
- British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 2010\textsuperscript{11}.
- Scottish Intercollegiate Guidelines Network. Diagnosis and management of headache in adults (CG107). November 2008\textsuperscript{12}.

**EXISTING COMPARATORS and TREATMENTS**

Although short-lasting, CH is excruciatingly painful. Because of the frequency of attacks, disability during a cluster period can be considerable. Whilst CH may spontaneously enter long-term remission, there is no prospect of a curative medical intervention at present. The ultimate attainable goal of treatment is total attack cessation or suppression. More realistically, the aim for most patients is to shorten the cluster period and to reduce the frequency and/or severity of attacks. As the biological nature of the underlying mechanism of CH is poorly understood, prophylactic methods are given empirically\textsuperscript{10}.

The following interventions may be used in the acute treatment of episodic CH\textsuperscript{5,6,7,10}:

- Oxygen therapy
  - 100\% oxygen at a flow rate of at least 12 litres per minute with a non-rebreathing mask and a reservoir bag and provision of home and ambulatory oxygen.

\textsuperscript{a} Expert clinical opinion.
• Triptan (subcutaneous)
  o sumatriptan 6mg (licensed)
• Triptan (nasal)
  o sumatriptan 20mg (unlicensed for this indication)
  o zolmitriptan 5mg (unlicensed for this indication)
  o intranasal local anaesthetics – lidocaine (unlicensed for this indication)\(^b\)

The following interventions may be used in the prophylactic treatment of episodic CH\(^4,6,7,11,13\):

First line
• Verapamil - (80mg three times a day, gradually increased up to 960mg daily in 3-4 divided doses, according to response) (unlicensed for this indication).
• Prednisolone – as monotherapy or in combination with verapamil during verapamil titration, 60-100mg, once daily for 2-5 days. Dose reduction is initiated after 2-5 days and continued, in 10mg decrements each second or third day, so that treatment is discontinued after 2-3 weeks (unlicensed for this indication).

Second line
• Lithium carbonate – may be considered if verapamil is not effective (800-1,600mg daily <12 weeks duration (unlicensed for this indication).
• Ergotamine – used on an intermittent basis is an alternative for patients with short cluster length, but it should not be used for prolonged periods.

Efficacy and Safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00033839, zucapsaicin vs placebo, phase III.</td>
<td>Winston laboratories Inc.</td>
<td>Complete, published.</td>
<td>Abstract(^14), trial registry(^15), manufacturer.</td>
<td>USA</td>
<td>Randomised, placebo-controlled.</td>
<td>n=60; aged ≥18 years; ≥2 years history of episodic CH; ≥2 previous episodes; expected duration of cluster period is ≥6 weeks but &lt;16 weeks; ≥1 but not &gt;8 headaches on each of the 3 days immediately prior to treatment. Randomised to zucapsaicin (intranasally) 0.01%, or placebo (sodium chloride 10%) (intranasally) twice daily for 1 week.</td>
<td></td>
</tr>
<tr>
<td>NCT00069082, zucapsaicin vs placebo, phase III.</td>
<td>Winston Laboratories Inc.</td>
<td>Complete but unpublished.</td>
<td>Trial registry(^16), manufacturer.</td>
<td>USA</td>
<td>Randomised, placebo-controlled.</td>
<td>n=60; aged ≥18 years; ≥2 years history of episodic CH; ≥2 previous episodes; expected duration of cluster period is ≥6 weeks but &lt;24 weeks; ≥1 but not &gt;8 headaches on each of the 3 days immediately prior to treatment. Randomised to zucapsaicin (intranasally) 0.01%, or placebo (sodium chloride 10%) (intranasally) twice daily for 1 week.</td>
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<tr>
<td>NCT01341548, zucapsaicin vs placebo, phase III.</td>
<td>Winston laboratories Inc.</td>
<td>Planned.</td>
<td>Trial registry(^17), manufacturer.</td>
<td>USA</td>
<td>Randomised, placebo-controlled.</td>
<td>n=180 (planned); aged ≥18 years; ≥2 year history of episodic CH with ≥2 previous episodic CH periods; current cluster period is expected to last ≥5 weeks but not &gt;24 weeks; ≥1 but not &gt;8 CHs daily on each of the three days of the baseline period; good health; no use of systemic steroids to treat the current cluster episode. Randomised to zucapsaicin (intranasally) 0.01% 20µg/dose, 0.1ml to each nostril twice daily for 7 days, or placebo (intranasally) twice daily for 7 days.</td>
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\(^b\) Expert clinical opinion.
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<tr>
<th>Follow-up</th>
<th>Active treatment for 7 days, follow-up 6 weeks.</th>
<th>Active treatment for 7 days, follow-up 6 weeks.</th>
<th>Active treatment for 7 days, follow-up 21 days.</th>
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<tr>
<td>Primary outcome/s</td>
<td>Mean percent change in the number of CHs per week in the first 3 weeks of the observation period.</td>
<td>Mean percent change in the number of CHs per week in the first 3 weeks of the observation period.</td>
<td>Change in number of CHs per week from baseline to week 3 of post-treatment observation period.</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Mean CH severity; mean CH duration; requirement for acute medications.</td>
<td>Mean CH severity; mean CH duration; requirement for acute medications.</td>
<td>Change in number of CHs per week from baseline to individual weeks 1, 2 and 3 of the post-treatment observation period.</td>
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<tr>
<td>Key results</td>
<td>Reduction in number of headaches in the zucapsaicin group at weeks 1, 2 and 3 of the post-treatment observation period was 40.3%, 48.7% and 66.6% vs 18.9%, 18.7% and 37.7% in the control group. Mean percent change in number of headaches was not statistically significant between groups: 49.9% vs 21.2% reduction (p=0.067) for zucapsaicin and control respectively. There was no difference between treatment groups in the severity or duration of CH. The percentage of CH requiring acute medication remained relatively constant throughout the study and was not statistically different between groups 63-64% for zucapsaicin vs 62-66% for control.</td>
<td>Not reported.</td>
<td>-</td>
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<tr>
<td>Adverse effects (AEs)</td>
<td>There were more AEs reported in the zucapsaicin group, primarily related to local drug effects e.g. transient nasal burning. No AEs were related to the physical examination of the nose and oropharynx or vital sign measurements. There were 71 and 41 reported AEs for the zucapsaicin and control groups respectively. There were no reportable drug-related serious adverse events (SAEs). Four subjects withdrew</td>
<td>Not reported.</td>
<td>-</td>
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during the treatment period after 2-5 doses due to intolerability of the study drug.

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<tr>
<th>Expected reporting date</th>
<th>Previously reported as Jan 2004.</th>
<th>Estimated primary completion date Apr 2016.</th>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of zucapsaicin is not yet known. The cost of selected comparator treatments for the treatment and prophylaxis of CH are shown below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit cost</th>
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<tbody>
<tr>
<td>Sumatriptan (Imigran) SC</td>
<td>6mg/0.5mL (may be repeated once, after at least 1 hour if headache recurs: max dose = 12mg in 24 hours).</td>
<td>Treatment pack (2 x 0.5mL prefilled syringes and auto injector) = £42.47. Refill pack (2 x 0.5mL prefilled cartridges) = £40.41</td>
</tr>
<tr>
<td>Verapamil hydrochloride</td>
<td>80mg three times daily 960mg daily in three divided doses.</td>
<td>£2.15</td>
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<td></td>
<td></td>
<td>£84.60</td>
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<tr>
<td>Prednisolone</td>
<td>60mg once daily 100mg once daily</td>
<td>£41.04c</td>
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<td>£40.00</td>
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</tbody>
</table>

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: improved patient convenience (intranasal administration as opposed to subcutaneous triptan)d.
- No impact identified

**Impact on Services**

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other: None identified

**Impact on Costs**

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
  - Other: uncertain unit cost compared to existing treatments.
  - Other reduction in costs: this is a treatment that patients can self-administer at home and may therefore be more cost-effective than if they attend A+E or are admitted to hospital.
- None identified

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c Assumes wastage.
d Expert clinical opinion.
Other Issues

☑ Clinical uncertainty or other research question identified: expert comments that the duration and severity of each CH bout is difficult to predict. Large numbers of participants are required to show efficacy in clinical trials. It is difficult to do placebo controlled studies with zucapsaicin because blinding is difficult even with active placebo.

☑ None identified

REFERENCES


11 British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache.3rd edition (1st revision), September 2010.


15 ClinicalTrials.gov. A phase III study of Civamide nasal solution (zucapsaicin) for the treatment of episodic cluster headache.

* Expert clinical opinion.
16 ClinicalTrials.gov. Intranasal Civamide for episodic cluster headache.
17 ClinicalTrials.gov. Civamide nasal solution for cluster headache (ECH).