Intepirdine for Alzheimer’s disease – add on therapy

NIHR HSRIC ID: 3668

Lay summary

*Intepirdine* is a new drug to treat Alzheimer's disease in people with mild to moderate symptoms. Intepirdine is taken by mouth with donepezil, a drug that is already used in some patients with Alzheimer’s disease. Intepirdine causes the release of chemicals in the brain which may improve cognition and function. At the moment, there are no drugs that treat the underlying problem that causes Alzheimer’s disease and no known cure.

*This briefing 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 or commissioning without additional information.*

*This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.*
### TARGET GROUP

- Alzheimer’s disease (AD): mild to moderate – add on therapy; in combination with donepezil.

### TECHNOLOGY

#### DESCRIPTION

Intepirdine (RVT-101; SB-742457; GSK 742457) is a serotonin 6 receptor antagonist which causes the release of acetylcholine and other neurotransmitters that may improve cognition and function in AD. It is intended to be used in addition to donepezil, an acetylcholinesterase inhibitor. In the phase III clinical trial, intepirdine is administered orally at 35mg once daily for 24 weeks in combination with donepezil\(^1\).

Intepirdine does not currently have Marketing Authorisation in the EU for any indication. Intepirdine is in phase II clinical trials for dementia with Lewy bodies.

#### INNOVATION and/or ADVANTAGES

If licensed, intepirdine will offer an additional treatment option for mild to moderate AD.

### DEVELOPER

Axovant Sciences Ltd.

### AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

### PATIENT GROUP

#### BACKGROUND

Dementia is a chronic progressive mental disorder, which is largely irreversible and characterised by a widespread impairment of mental function\(^2,3\). It adversely affects higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. AD is the most common form of dementia. It is a degenerative cerebral disease with characteristic neuropathological and neurochemical features\(^3\).

AD is usually insidious in onset and develops over several years. People with AD may find it increasingly difficult to undertake everyday activities such as shopping, socialising, communication, and recognising people and places. In the later stages of the disease, physical impairments can include problems with eating (including dysphagia), incontinence, unsettled behaviour, and behaviour that challenges. AD may also be associated with loss of confidence and feelings of fear, confusion, apathy, stigma and depression. The effects of AD are heterogeneous and vary from patient to patient\(^1\).
A common tool to measure cognitive functioning is the mini mental state examination (MMSE). The MMSE is scored out of 30. Although scores of 24 or less are strongly associated with dementia in an appropriate clinical context, scores of >24 can be seen in some people with mild dementia. A score of ≥20 suggests mild dementia, 13 – 20 suggests moderate dementia, and ≤12 indicates severe dementia. On average, the MMSE score of a person with Alzheimer's declines about two to four points each year.

**CLINICAL NEED and BURDEN OF DISEASE**

The number of people with dementia in the UK is estimated to be 850,000, representing 1.3% of the UK population. AD accounts for around 60% of all dementia cases. The UK incidence of AD in people over the age of 65 years was an estimated 4.9 per 1,000 person-years in 2011. Approximately 64% of people with AD are estimated to have mild to moderate disease.

In 2014-15, there were 4,866 hospital admissions in England due to AD (ICD-10 G30), resulting in 9,364 finished consultant episodes and 318,152 bed days. Expert opinion suggests the number of hospital admissions related to Alzheimer's disease may be higher than this figure as many patients are admitted for a different reason but AD is a significant factor. Expert opinion also suggests that AD is associated with longer durations of hospital stay and, for many diseases, worse outcomes. In 2014 in England and Wales, 11,298 deaths were registered in which Alzheimer’s disease was the underlying cause of death (ICD-10 G30).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
- NICE guideline. Older people with social care needs and multiple long-term conditions (NG22). November 2015.
- NICE guideline. Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset (NG16). October 2015.

---

*Expert personal opinion*
CURRENT TREATMENT OPTIONS

There is currently no disease modifying treatment for AD. Treatment aims to promote independence, maintain function, and treat symptoms, including non-cognitive (such as hallucinations, delusions, anxiety, marked agitation and associated aggressive behaviour), cognitive, behavioural, and psychological symptoms\(^2\). Non-pharmacological management options include: cognitive stimulation, social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home nursing and personal care, community services (such as meals-on-wheels), befriending services, day centres, respite care and care homes\(^2,3\). Pharmacological options for mild to moderate AD include acetylcholinesterase inhibitors such as donepezil, galantamine and rivastigmine, and the N-methyl-D-aspartate antagonist memantine. These drugs can temporarily reduce some symptoms of the condition in some people\(^5,6\).\(^\text{b}\)

\(^{b}\) Expert personal opinion
## EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>MINDSET Study, NCT02585934, RVT-101-3001; interpirdine vs placebo, both in combination with donepezil; phase III.</th>
<th>MINDSET extension, NCT02586909, RVT-101-3002; interpirdine in combination with donepezil; phase III extension.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Axovant Sciences Ltd.</td>
<td>Axovant Sciences Ltd.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry¹, manufacturer.</td>
<td>Trial registry¹⁶, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA, Canada and Australia.</td>
<td>USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Open label.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=1150 (planned); aged 50-85 yrs; Alzheimer’s disease (AD); receiving ongoing donepezil therapy for AD; mini-mental state examination (MMSE) score 12-24 at screening; Hachinski Ischaemia score ≤4 at screening; reliable caregiver to report on status; no vascular dementia; no other forms of dementia; no history of significant psychiatric illness.</td>
<td>n=1150 (planned); aged 50-85 yrs; pts that have completed last on-treatment visit of the MINDSET study.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to interpirdine 35mg oral once daily; or placebo oral once daily; both in combination with 5mg or 10mg donepezil.</td>
<td>Pts receive interpirdine 35mg oral once daily.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 24 wks, follow-up 24 wks.</td>
<td>Active treatment for 52 weeks, follow-up 52 weeks.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Alzheimer’s disease assessment scale - cognitive subscale 11 items (ADAS-Cog-11) score; Alzheimer’s disease cooperative study - activities of daily living (ADCS-ADL) scale score.</td>
<td>Adverse events; changes in physical examinations, vital sign measurements, electrocardiograms (ECGs) or routine laboratory assessments.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Clinical global impression of change - plus caregiver input (CIBIC+); neuropsychiatric inventory (NPI) total score; EQ-5D Visual Analogue Scale (EQ-5D-VAS); adverse events (AEs); changes in clinical examinations, ECGs and routine laboratory assessments; resource utilisation in dementia (RUD) Lite, Dependence Scale.</td>
<td>RUD Lite, Dependence Scale.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as October 2017.</td>
<td>Study completion date reported as June 2018.</td>
</tr>
</tbody>
</table>

---

Trial | NCT00710684, AZ3110868; interpirdine vs placebo, both in combination with donepezil; phase II. | NCT00708552, AZ3110865; interpirdine vs donepezil vs placebo; phase II. | NCT00224497, AZ3100603; interpirdine vs placebo; phase II. |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Published.</td>
<td>Published.</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Publication¹⁷, trial registry¹⁸, manufacturer.</td>
<td>Publication¹⁷, trial registry¹⁸, manufacturer.</td>
<td>Publication²⁰, trial registry²¹, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not UK), USA, Canada, Argentina, Australia and Chile.</td>
<td>EU (not UK), Russian Federation, Mexico, Republic of Korea and Chile.</td>
<td>EU (not UK), Chile, Republic of Korea, New Zealand, Russian Federation, South Africa.</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Participants</td>
<td>n=684; aged 50-85 yrs; probable mild-to-moderate Alzheimer's disease; ≥6 mnths of donepezil therapy with stable dosing for at least 2 mnths; a regular caregiver to oversee compliance and report on status; no vascular dementia; no hypersensitivity to sunlight; no history of seizures.</td>
<td>n=576; aged 50-85 yrs; probable mild-to-moderate Alzheimer's disease; a regular caregiver to oversee compliance and report on status; no vascular dementia; no other CNS disorder that could be interpreted as a cause of dementia; no history of seizures, loss of consciousness or significant head trauma; no photosensitivity.</td>
<td>n=371; aged 50-85 yrs; probable mild-to-moderate Alzheimer's disease as determined by the NINCDS-ADRDA and DSM-IV criteria with an MMSE score of 12-26; no other causes of dementia such as vascular damage, depression, bipolar affective disorder, schizophrenia, syphilis, vitamin B12 deficiency or thyroid deficiency; no known hypersensitivity to sunlight or seizures.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to intepirdine 15mg or 35mg oral; or placebo; all once daily and in combination with donepezil (5-10mg).</td>
<td>Randomised to intepirdine 15mg or 35mg oral once daily; placebo; or donepezil (5-10mg).</td>
<td>Randomised to intepirdine 5mg, 15mg or 35mg oral; or placebo.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 48 wks, follow-up 48 wks.</td>
<td>Active treatment 24 wks, follow-up 24 wks.</td>
<td>Active treatment 24 wks, follow-up 24 wks.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Cognition and function measured using the Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog) score; Clinical Dementia Rating-Sum of Boxes (CDR-SB).</td>
<td>Cognition and function. ADAS-Cog score; CIBIC+ score.</td>
<td>Cognition and function. ADAS-Cog score; CIBIC+ score.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Safety and tolerability; pharmacokinetics and exploratory pharmacogenetics; ADCS-ADL; Repeatable Battery for Assessment of Neuropsychological Status (RBANS); MMSE. No quality of life measurement included in trial outcomes.</td>
<td>Safety and tolerability; pharmacokinetics and exploratory pharmacogenetics. ADCS-ADL; RBANS; MMSE; Cornell scale for depression in dementia. No quality of life measurement included in trial outcomes.</td>
<td>Behavioural symptoms; activities of daily living (ADL); caregiver burden; safety and tolerability; PK and dose response profiling; efficacy related to apolipoprotein E (ApoE) status; NPI; disability assessment for dementia (DAD); MMSE; Alzheimer’s carer’s quality of life instrument (ACQLI).</td>
</tr>
<tr>
<td>Key results</td>
<td>At wk 48: ADAS-Cog – a statistically significant improvement with intepirdine 35mg vs placebo (difference of 1.6 points, P=0.024). CDR-SB - no statistically significant difference.</td>
<td>At wk 24: ADAS-Cog – no significant differences with intepirdine 35 mg or 15 mg, or donepezil vs. placebo. CIBIC+ - no statistically significant differences</td>
<td>At wk 24: ADAS-Cog – no significant difference with intepirdine 35mg vs. placebo. CIBIC+ - a statistically significant improvement with intepirdine 35mg vs placebo (p=0.047).</td>
</tr>
</tbody>
</table>
Horizon Scanning Research & Intelligence Centre

<table>
<thead>
<tr>
<th>AD/CS-ADL – a non-statistically significant increase with intepirdine 35mg vs. placebo (p= 0.088). RBANS and MMSE - no significant differences vs placebo.</th>
<th>observed with intepirdine vs. placebo. MMSE – no statistically significant differences with intepirdine vs. placebo. ADCS-ADL, RBANS, CSDD – no statistically differences for intepirdine, placebo or donepezil.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effects (AEs)</td>
<td>Cumulative incidence of on-treatment AEs 60% at wk 48, proportion reporting any on-treatment AEs similar across the treatment groups. Most AEs mild-to-moderate intensity. The most common AEs were headache, nasopharyngitis, diarrhoea, dizziness and influenza. The incidence of drug-related AEs, AEs leading to withdrawal, and serious adverse effects (SAEs) similar across treatment groups: 7%–13%; 7%–9%; 8%–12% respectively. 10 deaths reported (35mg, n=4; 15mg, n=5; placebo, n=1). None of the deaths considered to be drug related. Changes in haematology, clinical chemistry, urinalysis, vital signs, and ECG parameters generally small, not clinically relevant, and comparable across treatment groups.</td>
</tr>
</tbody>
</table>

| Expected reporting date | - | - | - |

**Trial**

NCT00348192, AZ3106242; intepirdine vs donepezil vs placebo; phase II.

NCT02910102, RVT-101-2003; intepirdine vs placebo; phase II.

**Sponsor**

GlaxoSmithKline.

Axovant Sciences Ltd.

**Status**

Published.

Ongoing.

**Source of information**

Publication, trial registry, manufacturer.

Trial registry, manufacturer.

**Location**

EU (incl UK), Chile and Russian Federation.

USA.

**Design**

Randomised, placebo-controlled.

Randomised, placebo-controlled.
| Participants | n=198; probable mild-to-moderate Alzheimer’s disease as determined by the NINCDS-ADRDA and DSM-IV criteria with an MMSE score of 12-24; no other causes of dementia such as vascular damage, depression, bipolar affective disorder, schizophrenia, syphilis, vitamin B12 deficiency or thyroid deficiency; no other medication; no conditions which might be exacerbated by exposure to donepezil; no known hypersensitivity to sunlight or seizures. | n=40 (planned); aged 50-89 yrs; a clinical diagnosis of Alzheimer’s disease; MMSE score 14-26; gait impairment; stable background acetylcholinesterase inhibitor therapy. |
| Schedule | Randomised to intepirdine 15mg or 35mg oral; donepezil 5 or 10mg; or placebo, all once daily. | Randomised to oral intepirdine 35mg or placebo; both once daily. |
| Follow-up | Active treatment for 24 wks, follow-up 24 wks. | Active treatment 12 wks, follow-up 12 wks. |
| Primary outcome/s | Cognition and function; ADAS-Cog; CIBIC+. | Quantitative gait measurements based on computerized gait assessment tools. |
| Secondary outcome/s | Behavioural symptoms; ADL; caregiver burden; safety and tolerability; pharmacokinetic profiling; efficacy related to ApoE and 5-Hydroxytryptamine Receptor 6 (HTR6) status; NPI; DAD; MMSE; cerebral transit time; ACQLI. | AEs. |
| Key results | At week 24: drug-placebo treatment differences in CIBIC+ score -0.17 for intepirdine and -0.28 for donepezil; drug-placebo treatment differences in ADAS-Cog score -0.4 for intepirdine and -1.2 for donepezil. All treatments were generally safe and well tolerated. | - |
| Adverse effects (AEs) | On-treatment AEs reported by 35% of subjects. The most frequent AEs were nasopharyngitis, headache, urinary tract infection, upper abdominal pain, and nausea. | - |
| Expected reporting date | - | Estimated primary completion date September 2017. |

**ESTIMATED COST and IMPACT**

**COST**

The cost of intepirdine is not yet known. The cost of other selected treatments specifically licensed for Alzheimer’s disease are listed in the following table.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost for 28 days' treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (5mg)</td>
<td>5mg once daily for one month then increased to a maximum of 10mg if necessary.</td>
<td>£1</td>
</tr>
<tr>
<td>Galantamine (8mg)</td>
<td>4mg twice daily for 4 weeks then increased to 8mg twice daily for 4 weeks; maintenance 8-12mg twice daily.</td>
<td>£25</td>
</tr>
<tr>
<td>Rivastigmine (1.5mg)</td>
<td>Initially 1.5mg twice daily, increased in steps of 1.5mg twice daily at intervals of at least 2 weeks.</td>
<td>£7</td>
</tr>
<tr>
<td>Memantine (10mg)</td>
<td>Initially 5mg once daily, increased in steps of 5mg at weekly intervals to a maximum of 20mg daily.</td>
<td>£2</td>
</tr>
</tbody>
</table>

### IMPACT - SPECULATIVE

#### Impact on Patients and Carers
- [ ] Reduced mortality/increased length of survival
- [ ] Reduced symptoms or disability
- [ ] Other
- [ ] No impact identified

#### Impact on Health and Social Care Services
- [x] Increased use of existing services: *expert opinion suggests that there might be an increased need for monitoring due to the side effect burden of intepirdine*.
- [ ] Decreased use of existing services
- [ ] Re-organisation of existing services
- [ ] Need for new services
- [ ] Other
- [x] None identified: *intepirdine is administered as an oral medication which could be initiated in secondary care with GPs taking over after an initial period or it could be initiated in primary care. Expert opinion suggests that there would be little effect on services*.

#### Impact on Costs and Other Resource Use
- [x] Increased drug treatment costs: *expert opinion suggests that there would be little prospect for cost savings based on the benefits seen in phase II studies*.
- [ ] Reduced drug treatment costs
- [ ] Other increase in costs
- [ ] Other reduction in costs
- [ ] Other
- [ ] None identified

#### Other Issues
- [x] Clinical uncertainty or other research question identified: *expert opinion suggests that it is likely that any effect of intepirdine would be small as patients would already have an increase in the neurochemical used and the loss of neurones mean there would be a ceiling effect of the treatment. However it should be noted that a small effect on a larger number of people may address the disease burden*.
- [x] None identified

---

[c] Expert personal communication
REFERENCES


