R&D pipeline review
part II

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Levosimendan for Low Cardiac Output Syndrome

Partner Tenax Therapeutics
Levosimendan development in US by Tenax Therapeutics

Development of levosimendan for Low Cardiac Output Syndrome (LCOS)

- Phase 3 LEVO-CTS trial to evaluate the efficacy of levosimendan in reducing morbidity/mortality in cardiac surgery patients with reduced ejection fraction
- Data read out early 2016*
- Fast track status granted by FDA and protocol approved under SPA

Possibility to include sepsis shock as an additional indication?

- Collaboration with Imperial College London for LeoPARDS trial
- Data read out in 2016*
- More information: [www.leopards-trial.org](http://www.leopards-trial.org)

*) [www.tenaxthera.com](http://www.tenaxthera.com)
LEVO-CTS & LeoPARDS trials

Levosimendan

### LEVO-CTS trial
- A Double-Blind, Randomized, Placebo-Controlled Study of Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass
- 760 patients, approximately 60 centers
- ClinicalTrials.gov identifier: NCT02025621

### Low Cardiac Output Syndrome

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
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### LeoPARDS trial
- Double-blind randomized placebo controlled LeoPARDS trial to study the effect of levosimendan in septic shock
- Levosimendan for the prevention of acute organ dysfunction in sepsis
- Investigator initiated study performed in UK ICUs
- Trial has enrolled over 300 of the estimated 516 patients
- Discussions ongoing with FDA about the possibility to include the data for US regulatory filing

Levosimendan Low Cardiac Output Syndrome
Dexmedetomidine for treatment of pain

Partner Recro Pharma
Dexmedetomidine development for acute post-operative pain by Recro Pharma

- Phase II trial to study the effect and safety of intranasal formulation of dexmedetomidine in adult patients undergoing bunionectomy surgery in US
- Possibility to avoid many of the side-effects associated with opioids
- Primary efficacy endpoint is summed pain intensity difference SPID48, over 48 hours starting on post op day 1.
- As a result of interim analyses in April, the total enrollment was reduced to 170 patients (was 200-250 pts)
- Top-line results will be reported by mid-year 2015*

*) www.recropharma.com

ClinicalTrials.gov identifier: NCT02284243
ORM-12741 for Alzheimer’s disease

In collaboration with Janssen
ORM-12741

• Highly potent and selective alpha-2C adrenoceptor antagonist
• Rodent models predict beneficial effects on cognition and neuropsychiatric symptoms (NPS)
• Phase 1 studies (healthy subjects)
  - Possible to administer orally
  - Well tolerated
  - Displacement of an alpha-2C PET tracer
• Phase 2a study in AD patients
  - Positive signals of efficacy in
  - Episodic and working memory
  - and
  - Neuropsychiatric symptoms

ClinicalTrials.gov identifier: NCT01324518
Phase 2 study on efficacy of ORM-12741 in AD

ORM-12741 (alpha-2c adrenoceptor antagonist)  |  Alzheimer’s disease  I  IIa

Improved formulation for the next Phase 2 study
- New formulation improving pharmacokinetic (PK) properties of ORM-12741 has been developed
- Phase 1 PK studies conducted to confirm qualities of the new formulation
- The improved formulation will be used in the next Phase 2 study

Objectives
- To evaluate efficacy of ORM-12741 on agitation & aggression and other neuropsychiatric symptoms
- To evaluate efficacy of ORM-12741 on cognitive performance
- To evaluate safety

Design and methodology
- Randomised, double-blind, placebo-controlled, parallel-group, Phase 2 study
- Patients with mild to moderately severe Alzheimer’s disease
- 2 dose levels of ORM-12741 and placebo

Sample size
- 100/group = ~300
Treatment of Parkinson’s disease with levodopa

- Levodopa is the most effective medicine for treating PD
- As PD progresses, most people will eventually require the use of levodopa (85% of PD patients receive levodopa)
- However, like all medicines, levodopa is not perfect - short acting levodopa can lead to motor complications
- Longer acting levodopa with more stable plasma concentrations is an unmet need for PD treatment

**Short acting levodopa**
- Dyskinesia
- Wearing-off

**Too much levodopa can cause involuntary movements**

**Effect of levodopa can fade and PD symptoms can return**
New COMT-inhibitor ODM-104 for Parkinson’s disease treatment

ODM-104 (more effective COMT inhibitor) | Parkinson’s disease
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- In phase I*, ODM-104 has been in well tolerated and superior to entacapone by improving COMT inhibition and levodopa pharmacokinetics in man
- Optimized carbidopa component further improves ODM-104 effect with double action on levodopa PK - levodopa exposure (AUC) increased over 30% when compared to entacapone
- Orion Pharma is currently developing a next generation PD product enabling the optimization of levodopa/carbidopa together with ODM-104
- Preparations for a phase II Proof-of-Concept study are ongoing. ODM-104 product will be compared with Stalevo® (levodopa/carbidopa/entacapone combination) in 66 PD patients with end-of-dose wearing-off symptoms

*) ClinicalTrials.gov identifier: NCT01840423
Increased levodopa exposure\(^1\) reduces OFF-time\(^2\) in PD patients during different LD/AADCi \(\pm\) COMTi\(^3\) treatments q.i.d - A change from Stalevo\(^4\)

<table>
<thead>
<tr>
<th>COMTi Dose</th>
<th>Sinemet(^5) AUC(^1)</th>
<th>Sinemet(^5) OFF(^2)</th>
<th>Stalevo AUC</th>
<th>Stalevo OFF</th>
<th>Carbidopa+(^6) AUC</th>
<th>Carbidopa+(^6) OFF</th>
<th>ODM-104 AUC</th>
<th>ODM-104 OFF(^11)</th>
<th>ODM-104 with carbidopa+(^7) AUC</th>
<th>ODM-104 with carbidopa+(^7) OFF(^12)</th>
</tr>
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<tbody>
<tr>
<td>100 mg</td>
<td>0.74(^8)</td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg</td>
<td>1.0</td>
<td>1.0</td>
<td>1.26</td>
<td>1.20</td>
<td>1.26</td>
<td>-</td>
<td>1.32</td>
<td>In PoC study</td>
<td></td>
<td></td>
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</table>

\(^1\) Levodopa AUC 0-16 h*ng/ml in healthy subjects
\(^2\) Reduction of daily OFF-time, hours by patient diary
\(^3\) Levodopa/aminoacid decarboxylase inhibitor \(\pm\) cathecol–omethyltransferase inhibitor
\(^4\) Levodopa/carbidopa + entacapone in combination or in separate tablets
\(^5\) Levodopa/AADCi (standard levodopa branded or generics)

\(^6\) Carbidopa optimized + entacapone 200 mg (ODM-101)
\(^7\) ODM-104 + optimized carbidopa
\(^8\) Kuoppamäki et al 2014
\(^9\) Kuoppamäki 2009
\(^10\) Trenkwalder et al 2013
\(^11\) ODM-104 not studied alone
\(^12\) To be studied
The target indication of ODM-104 is Parkinson’s disease with end-of-dose motor fluctuations - the same as the currently approved indications of Comtess®/Comtan® and Stalevo®.

- Levodopa + carbidopa
- Levodopa + carbidopa + Comtess® / Comtan® (entacapone)
- Stalevo® (levodopa + carbidopa + entacapone)
- ODM-104 + levodopa & carbidopa
Target: First/Best-in-class GABA B PAM molecule for the treatment of Essential tremor
Essential Tremor

- Chronic, slowly progressive postural and/or kinetic tremor, usually affecting both upper extremities
  - May initially be intermittent and then becomes persistent
  - May also affect the head, voice, jaw, lips and face
  - Tremor amplitude is highly variable, worsened by emotion, hunger, fatigue and temperature

- Affects patients quality of life, social and employment prospects

- Most common movement disorder
  - 8 times more common than Parkinson's Disease
  - Prevalence 0.5-1.5%, >40 yr 4%
  - Usually starts in middle age or later, but possible also earlier in life
Unmet needs in Essential Tremor

Approximately 50% fail on current treatments due to efficacy or side-effects

- Mainly treated with generic beta-adrenergic blockers (propranolol) and anticonvulsants (primidone)

Deep Brain Stimulation (DBS) used for last option for the treatment of severe patients

Current R&D activity is low

- SAGE-547, a GABA-A PAM, in clinical phase as an infusion
- Some non-drug therapies in development for more severe cases
GABAB PAM (gamma-aminobutyric acid B positive allosteric modulator)

Positive allosteric modulator: a ligand that binds to a distinct (allosteric) site on the receptor and hereby increases the activity of the endogenous agonist.

Decrease of GABA activity in several brain areas in essential tremor which could be ameliorated by a GABAB PAM.

Advantages of a PAM:
- A more physiological approach
- Better safety and selectivity
- Less side-effects
- Avoiding development of tolerance through receptor desensitization
ODM-106 shows efficacy and safety in Essential tremor

- Alleviates tremor in essential tremor animal model (harmaline-induced tremor)
- No signs of development of tolerance after repeated doses
- No sedative or other CNS side-effects in preclinical models
- Well tolerated in the preclinical safety studies
- Efficacy also shown in parkinsonian tremor, levodopa-induced dyskinesia and pain models
- Phase I FIMPAM trial ongoing

ClinicalTrials.gov identifier: NCT02393950
Target: Best-in-class TRPA1 antagonist molecule for the treatment of Neuropathic pain
Neuropathic Pain

Caused by a lesion or disease affecting the somatosensory nervous system

- Trauma, infection, cancer, anti-cancer treatments, etc.

Causes distress and suffering

- Very high impact on quality of life
- Sleep, enjoyment of life, work and earning are all affected

Prevalence 3.3-8.2%
Unmet needs in Neuropathic Pain

High unmet need as currently available treatments only work as monotherapy in < 30% of those treated

Treatment options include serotonin-noradrenaline reuptake inhibitors, (duloxetine, venlafaxine) tricyclic antidepressants, pregabalin, gabapentin, opioids, tramadol, carbamazepine, botulinum toxin A, capsaicin patches and lidocaine patches

Most patient use several medications concomitantly

Various molecules with novel mechanism of action in phase 2 development
TRPA1 antagonist (Transient Receptor Potential Ankyrin 1)

TRPA1 receptors are expressed on pain neurons and when activated sends signals of pain in humans

Highly competitive target with very difficult chemistry

Advantages of TRPA1 antagonist

• Robust functional antagonism
• High selectivity
• Less side-effects
• No tolerance to repeated dosing
ODM-108 shows efficacy and safety in Neuropathic pain

- ODM-108 blocks pain in several animal models of pain (STZ in figure, SNI, CFA)
- No CNS side-effects seen in preclinical models
- Well tolerated in the preclinical safety studies
- Phase I FIMTRIP trial ongoing

ClinicalTrials.gov identifier: NCT02432664
Target:
Best symptomatic treatment for Amyotrophic Lateral Sclerosis (ALS)
Amyotrophic lateral sclerosis - ALS

- Orphan disease with prevalence of
  - ~0.4 patients/10,000
- Degeneration of motoneurons leads to skeletal muscle weakness and diaphragm failure
- Causes premature death (3 years median survival time from symptom onset)
- Decreases Quality of Life of both patient and caregiver
- No symptomatic treatments for muscle weakness available

A clear unmet need in ALS for a drug that improves endurance and function at the level of diaphragm/skeletal muscle force
Data supporting development of ODM-109 for ALS

Levosimendan enhances force generation of diaphragm muscle fibers obtained from a rat model of heart failure and from COPD and non-COPD patients (ex vivo experiments)

Levosimendan improves human diaphragm function in healthy subjects \textit{in vivo}

Levosimendan and its long-acting metabolite OR-1896 show a positive effect on skeletal muscle function (endurance) in Myasthenia Gravis rat model functionally mimicking ALS

By increasing skeletal muscle force and endurance, levosimendan has potential to improve respiratory function, muscle fatigue and QoL in ALS patients
Levosimendan increases calcium sensitivity by binding selectively to troponin C in cardiac and skeletal muscles

<table>
<thead>
<tr>
<th>Effect/parameter</th>
<th>Levosimendan</th>
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<tbody>
<tr>
<td>Calcium sensitization (troponin C)</td>
<td>+</td>
</tr>
<tr>
<td>Affects fast muscle fibers</td>
<td>+</td>
</tr>
<tr>
<td>Affects slow muscle fibers</td>
<td>+</td>
</tr>
<tr>
<td>ATP/oxygen sparing effect</td>
<td>+</td>
</tr>
<tr>
<td>Long-acting metabolite</td>
<td>+</td>
</tr>
<tr>
<td>Crossing BBB</td>
<td>-</td>
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<tr>
<td>PK interaction with riluzole</td>
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LEVALS study - levosimendan in ALS patients

ODM-109 (oral levosimendan) | ALS
---|---
I | II

- The first phase II study aims to demonstrate beneficial effects on respiratory function
- Double-blind, cross-over design with 3 treatment periods
- Cross-over part of the study is followed by an open-label part for 6 months - an opportunity to study long term effects
- The study will recruit approx. 50-60 patients in Europe

Levosimendan potentially delays the need for respiratory support and improves QoL in ALS patients by increasing skeletal muscle force

Regulatory considerations for ODM-109

- Possibility to seek parallel orphan designation in EU and US
- Several options for fast track designation