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## R&D Presentation for Investors after Q1 2017

**ORION**

Building well-being. Together.

# Disclaimer

This presentation contains forward-looking statements which involve risks and uncertainty factors. These statements are not based on historical facts but relate to the Company's future activities and performance. They include statements about future strategies and anticipated benefits of these strategies.

These statements are subject to risks and uncertainties. Actual results may differ substantially from those stated in any forward-looking statement. This is due to a number of factors, including the possibility that Orion may decide not to implement these strategies and the possibility that the anticipated benefits of implemented strategies are not achieved. Orion assumes no obligation to update or revise any information included in this presentation.

# Focus areas of Orion's R&D

## Proprietary Products



- CNS
- Oncology
- Respiratory (Easyhaler® product family)

## Animal Health



Orion utilises the R&D of proprietary products to develop new medicines for animals

## Fermion



- APIs to Orion's proprietary products
- Generic APIs
- Contract development for pharmaceutical companies

## Orion Diagnostica



- QuikRead test system
- GenRead test system

# Together we can achieve more in R&D

Research

Early development

Late stage development

Target identification and validation

8-24 mo

Hit to Lead generation

12-24 mo

Lead optimisation

18-36 mo

Candidate selection, preclinical development

12-24 mo

Phase I

12-14 mo

Phase II

12-36 mo

Phase III

18-48 mo

Collaboration with partners

Collaboration with partners



AsahiKASEI








## Clinical development pipeline

# Key clinical pharmaceutical development projects 1/2

Project	Indication	PHASE			Registration
Easyhaler® salmeterol-fluticasone	Asthma, COPD	Bioequivalence study			Registration
Darolutamide (ODM-201) <sup>1)</sup>	Prostate cancer (nmCRPC)	I	II	III	
Darolutamide (ODM-201) <sup>1)</sup>	Prostate cancer (mHSPC)	I	II	III	
Levosimendan <sup>2)</sup>	Low Cardiac Output Syndrome	I	II	III	

<sup>1)</sup> In collaboration with Bayer <sup>2)</sup> Partner: Tenax Therapeutics, Inc.



	= Phase completed
	= Phase ongoing
	= Status changed

More info about R&D projects at: <http://www.orion.fi/en/rd/orion-rd/pipeline/>

## Key clinical pharmaceutical development projects 2/2

Project	Indication	PHASE			Registration
ODM-109 (oral levosimendan)	ALS	I	II		
ORM-12741 (alpha-2c adrenoceptor antagonist) <sup>3)</sup>	Alzheimer's disease	I	IIa		
ODM-104 (more effective COMT inhibitor)	Parkinson's disease	I	II		
ODM-203 (targeted FGFR+VEGFR inhibitor)	Solid tumours	I	II		
ODM-207 (BET protein inhibitor)	Cancer	I			

<sup>3)</sup> In collaboration with Janssen Pharmaceuticals

 = Phase completed  
 = Phase ongoing

More info about R&D projects at: <http://www.orion.fi/en/rd/orion-rd/pipeline/>



## Darolutamide (ODM-201)

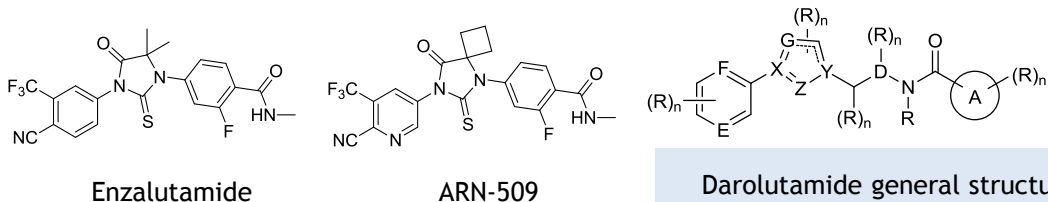
A novel second generation androgen receptor (AR) antagonist for the treatment of prostate cancer  
In collaboration with Bayer.



# Darolutamide (ODM-201): Partnership with Bayer - Financial terms

- Orion and Bayer will jointly develop darolutamide, with Bayer contributing a major share of the costs of future development
- Bayer will commercialise darolutamide globally and Orion has the option to co-promote darolutamide in Europe
- Orion is eligible to receive milestone payments from Bayer upon achievement of certain development, tech transfer and commercialization milestones
- Orion will receive substantial royalties on future sales
- Orion will be responsible for manufacturing of the product

# Darolutamide (ODM-201) has a unique profile



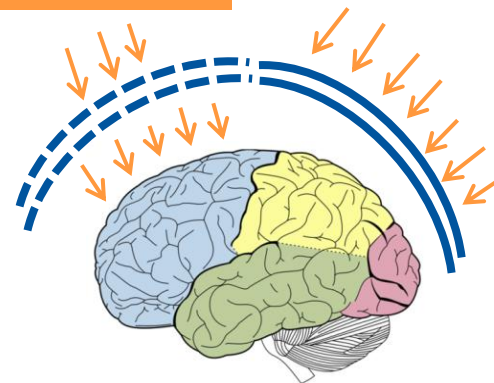
Compound	AR affinity Ki (nM)	Antagonism IC50 (nM)				Proliferation VCaP IC50 (nM)
		WT AR	AR (F876L)	AR (T877A)	AR (W741L)	
Bicalutamide	12	150	218	957	Agonist	
Enzalutamide	86	155	Agonist	296	>10000	400
ARN-509	68	168	Agonist	1130	>10000	300
Darolutamide	9	65	66	1782	1500	500

- Darolutamide blocks the function of androgen receptor in both biochemical and cell assays with equal or better potency compared to enzalutamide and ARN-509
- Low likelihood for brain entry demonstrated in preclinical models

Enzalutamide 19%\*

ARN-509 29%\*

Darolutamide 3% \*\*



\*Refs. Clegg et al, 2012; Forster et al, 2011  
 \*\* Rat autoradiography (QWBA confirms brain/plasma ratio of 14C-ODM-201 related radioactivity was 0.04-0.06, indicating negligible penetration to the brain)

# Darolutamide (ODM-201): Phase III study ongoing in non-metastatic castration resistant prostate cancer (nmCRPC)

Darolutamide (ODM-201)

Prostate cancer (nmCRPC)

I

II

III

- nmCRPC patients who are at high risk for developing metastatic disease are included (n=1,500)
- Primary endpoint
- Darolutamide over placebo in metastasis-free survival (MFS)
- Secondary endpoints
- Overall survival, time to first symptomatic skeletal event (SSE), time to first initiation of cytotoxic chemotherapy, time to pain progression, and to characterize the safety and tolerability of darolutamide.
- Estimated completion in 2018



[ClinicalTrials.gov identifier:  
NCT02200614](https://clinicaltrials.gov/ct2/show/study/NCT02200614)

# Darolutamide (ODM-201): Phase III study in metastatic hormone sensitive prostate cancer (mHSPC)

Darolutamide (ODM-201)

Prostate cancer (mHSPC)

I

II

III

- ARASENS is a randomized, double-blind, placebo-controlled multicenter study
- Approximately 1,300 patients are randomized (1:1 ratio) to receive either darolutamide or placebo in combination with an ADT of investigator's choice (LHRH agonist/antagonists or orchiectomy), started  $\leq 12$  weeks before randomization. Six cycles of docetaxel will be administered after randomization.
- Primary endpoint: overall survival
- Secondary endpoints: time to castration-resistant prostate cancer, time to initiation of subsequent antineoplastic therapy, symptomatic skeletal event free survival, time to first symptomatic skeletal event, time to initiation of opioid use, time to pain progression, time to worsening of physical symptoms of disease and safety.

[ClinicalTrials.gov identifier: NCT02799602](https://clinicaltrials.gov/ct2/show/study/NCT02799602)

The logo for ARASENS features a stylized blue and green arch above the word "ARASENS" in a bold, blue, sans-serif font. A small yellow star is positioned above the letter 'A'.

A photograph of laboratory glassware, including two Erlenmeyer flasks and a beaker, on a metal tray. The image is overlaid with a blue gradient. The text is positioned in the lower right area of the image.

## ODM-203

A unique and selective dual FGFR+VEGFR inhibitor for FGFR-dependent tumors

## Angiogenic indications with altered FGFR signalling

Tumor type	Genomic alterations of FGFRs and FGFs
Breast (luminal)	~35% (FGFR1 amp, FGFR2 amp, FGFR4 amp, FGFs)
NSCLC-SCC	~20% (FGFR1 amp, FGFR2 amp)
Bladder (invasive)	~15% (FGFR3 fusions, FGFR1 amp, FGFs)
Prostate	~14% (FGFR1 amp, FGFR2&3 fusions)
Colorectal	~10% (FGFR1 amp, FGFR3 mut)
Endometrial	~10% (FGFR2 mut)
Gastric	~7% (FGFR2 amp)
Renal	~6% (FGFR4 amp)

# ODM-203 has strong in vivo antitumor activity

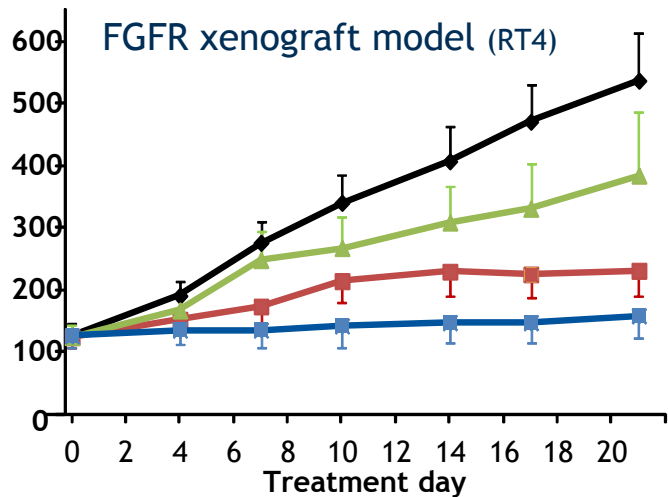
ODM-203 (targeted FGFR+VEGFR inhibitor)

Solid tumours

I

II

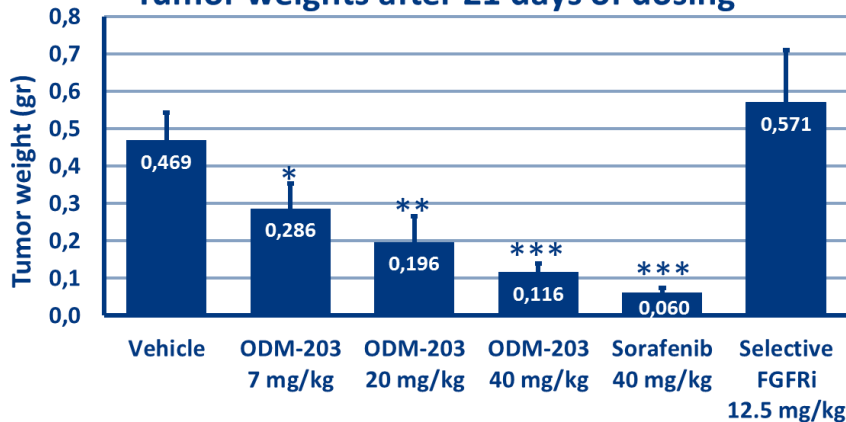
[ClinicalTrials.gov identifier:  
NCT02264418](https://ClinicalTrials.gov/ct2/show/study/NCT02264418)



◆ Vehicle control p.o.    ■ Selective FGFRi (12.5 mg/kg)  
▲ ODM203 (20 mg/kg)    ■ ODM203 (40 mg/kg)

Angiogenic kidney cancer model (Renca)

Tumor weights after 21 days of dosing





**ODM-207**  
BET protein inhibitor



# ODM-207

ODM-207 (BET protein inhibitor)

Cancer

I

- ODM-207 is an investigational small molecule that has a unique chemical structure designed to block the growth of cancer cells through potent and selective inhibition of BET family proteins. In preclinical studies, ODM-207 has shown antiproliferative effects in several haematological and solid tumour cell lines.



# ORM-12741 for Alzheimer's disease

alpha-2c adrenoceptor antagonist

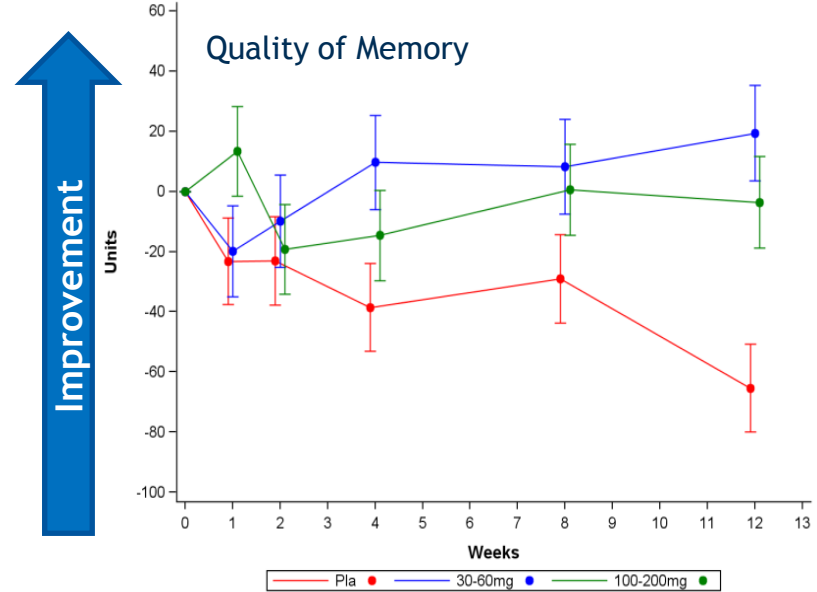
In collaboration with Janssen

# ORM-12741 - collaboration with Janssen

- Licence agreement announced on 19 December 2013 (includes ORM-12741 and other compounds)
- Orion received USD 31 million upfront payment which is mainly used against current ongoing additional Phase IIa study costs
- Orion is eligible to receive milestone payments from Janssen upon successful completion of certain development and commercialisation events, as well as royalties on future sales
- Orion has exclusive commercialisation rights in Europe
- Janssen has worldwide exclusive license to develop ORM-12741 and an exclusive right to commercialise it outside Europe
- Orion and Janssen will co-fund the development after an additional Phase IIa study is completed successfully by Orion

# 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
  - Neuropsychiatric symptoms



# Phase 2 study on efficacy of ORM-12741 in AD

[ClinicalTrials.gov identifier: NCT02471196](https://clinicaltrials.gov/ct2/show/study/NCT02471196)

ORM-12741 (alpha-2c adrenoceptor antagonist)

Alzheimer's disease

I

IIa

- New formulation improving pharmacokinetic (PK) properties of ORM-12741 is used in the current 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



## ODM-104

more effective COMT inhibitor

# New COMT-inhibitor ODM-104 for Parkinson's disease treatment

ODM-104 (more effective COMT inhibitor)

Parkinson's disease

I

II

- 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
- Phase II: ODM-104/optimized carbidopa/long-acting levodopa will be compared with Stalevo® (levodopa/carbidopa/entacapone combination) in PD patients with end-of-dose wearing-off symptoms
- [ClinicalTrials.gov identifier: NCT02764125](https://clinicaltrials.gov/ct2/show/study/NCT02764125)

A blue-tinted photograph of laboratory glassware, including two Erlenmeyer flasks and a beaker, on a metal tray. The background is blurred, showing a person in a white lab coat. The text is overlaid on the right side of the image.

**ODM-109**  
Oral levosimendan  
Best symptomatic treatment for Amyotrophic Lateral Sclerosis (ALS)



# LEVALS study - levosimendan in ALS patients

ODM-109 (oral levosimendan)

ALS

I

II

- Although the trial did not achieve its primary objective (oral levosimendan did not improve respiratory function against placebo measured by Slow Vital Capacity), the findings were, however, promising. Based on the findings, Orion is planning to continue the development programme.
- 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
- 66 patients in Europe

[ClinicalTrials.gov Identifier: NCT02487407](https://clinicaltrials.gov/ct2/show/study/NCT02487407)

## Regulatory considerations for ODM-109

- The US Food and Drug Administration (FDA) has granted ODM-109 Orphan Drug Designation
- Several options for fast track designation



# Levosimendan for Low Cardiac Output Syndrome

Partner Tenax Therapeutics

# Levosimendan development in the US by Tenax Therapeutics

Levosimendan

Low Cardiac Output Syndrome



- Phase 3 LEVO-CTS trial evaluated the efficacy of levosimendan in reducing morbidity/ mortality in cardiac surgery patients with reduced ejection fraction
- According to the preliminary findings, the trial did not achieve its primary objectives. Tenax has announced that it will continue analysing the findings and will discuss the trial results and possible continuance of development work with the US Food and Drug Administration (FDA).
- Fast track status granted by FDA and protocol approved under SPA
- More information [www.tenaxthera.com](http://www.tenaxthera.com)

[ClinicalTrials.gov identifier: NCT02025621](https://clinicaltrials.gov/ct2/show/study/NCT02025621)



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