R&D presentation for investors

Updated on 6 February 2019

ORION
Building well-being

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.

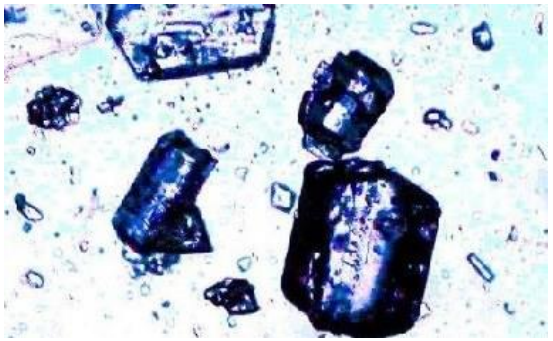
Focus areas of Orion's R&D

Proprietary products

- Central nervous system
- 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

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

Building the R&D future success

2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 | 2026

- Innovation system
- Competence base
- Therapy area work

ROADMAP

ODM-207
ODM-109
ODM-203
ODM-104
ODM-208
tiotropium
Darolutamide

Bringing treatments to patients addressing unmet needs also in the future require capability to discover and develop less validated targets, new treatment concepts and increasing collaboration with academic partners

Orion's R&D vision for the future

Brain power and muscle of a Big Pharma, the agility of a small biotech.

A preferred partner for other pharma companies and research institutions.

Increased visibility within the academic community and capabilities to recruit and retain "the best and the brightest".

A balanced pipeline that can deliver clinically meaningful differentiation and patient benefit long-term.

Capability to deliver novel proprietary small molecule therapeutics and biologics.

A significant contributor to the global scientific community.

Clinical development pipeline

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Orion's key clinical drug development projects

Project	Indication	Phase	Registration
Easyhaler® tiotropium	COPD	Bioequivalence study	
Darolutamide [1)]	Prostate cancer (nmCRPC)	I, II, III	
Darolutamide [1)]	Prostate cancer (mHSPC)	I, II, III	
ODM-109 (oral levosimendan)	ALS	I, II, III	
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	
ODM-208 (CYP11A1 inhibitor)	Prostate cancer (CRPC)	I	

[1)] In collaboration with Bayer

= Completed
= Ongoing
= Status changed

More information on R&D projects:
https://www.orion.fi/en/rd/orion-rd/pipeline/

Darolutamide

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

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Orion and Bayer's phase III trial of darolutamide for non-metastatic castration-resistant prostate cancer: Primary endpoint was met

- Darolutamide significantly extended metastasis-free survival compared to placebo. The safety and tolerability were consistent with previously published data.
- The full data will be presented at the ASCO GU on 14 February 2019. An abstract will be published on 11 February 2019.
- Bayer is having discussions with health authorities regarding the submission for marketing authorisation application.
- Darolutamide has been granted Fast Track designation by the U.S. Food and Drug Administration (FDA). If the process proceeds as planned, the sales could in the best-case scenario start in the US already at the end of 2019.
- Phase III ARASENS trial for metastatic prostate cancer continues.

Financial impacts of darolutamide

- Bayer covered the majority of the development costs and has the right to commercialize darolutamide globally. Orion has the option of co-promoting in Europe. Orion will manufacture the product.
- **Milestone payments** upon first commercial sales: EUR 45 million in USA, EUR 20 million in the EU and EUR 8 million in Japan.
- **Tiered royalties on product sales** approximately 20%, including production revenue.
- **Potential one-off payments** if certain sales targets are met.

Two trials with Bayer on darolutamide

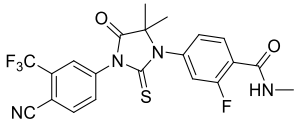
ARAMIS
Androgen Receptor inhibiting Agent for Metastatic-free Survival

- Patients: men with non-metastatic, castration-resistant prostate cancer treated with androgen deprivation therapy (hormonal therapy) and at risk of developing metastatic disease
- Treatment: 600 mg of darolutamide or matching placebo twice a day
- Endpoints:
  - Primary: metastasis-free survival, defined as time between randomization and evidence of metastasis or death from any cause
  - Secondary: Overall survival, time to first symptomatic skeletal event, time to first initiation of cytotoxic chemotherapy, time to pain progression, and to characterize the safety and tolerability of darolutamide
- Status: Trial completed, primary endpoint met. The full data presented at ASCO GU on 14 February.

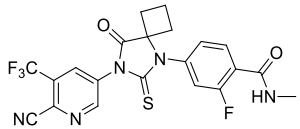
ARASENS

- Patients: men with metastatic, hormone-sensitive prostate cancer
- Treatment: Darolutamide with androgen deprivation therapy and six cycles of docetaxel (chemotherapy)
- Endpoints:
  - Primary: Darolutamide over placebo in overall survival
  - Secondary: Time to castration resistance, time to antineoplastic therapy, time to first symptomatic skeletal event, time to initiation of opioids, time to pain progression, and to characterize the safety and tolerability of darolutamide
- Status: Recruitment finalized, estimated completion of the trial in 2022.

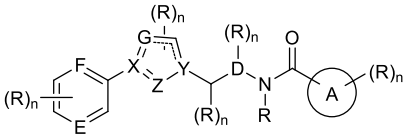
Darolutamide has a unique profile (Phase II trial)



Enzalutamide



ARN-509



Darolutamide general structure

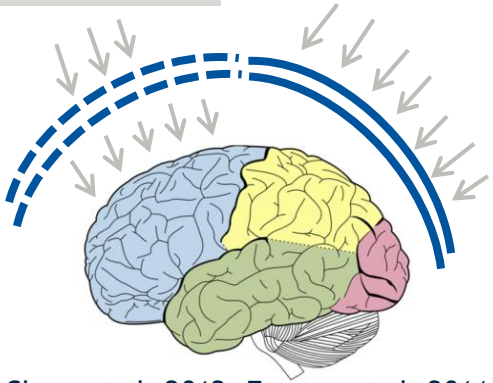
Compound	AR affinity Ki (nM)	Antagonism IC50 (nM)				Proliferation VCaP IC50 (nM)
		WT AR	AR (F876L)	AR (T877A)	AR (W741L)	
Bicalutamide	12	150	218	957	Agonist	
Enzalutamide	86	155	Agonist	296	>10000	400
ARN-509	68	168	Agonist	1130	>10000	300
Darolutamide	9	65	66	1782	1500	500

- 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 at 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 clinical studies

Study	Phase	Populations	N	Daily Dose (mg)	Status	ClinicalTrials.gov identifier
ARADES	I/II	mCRPC* • Chemo/CYP17 naïve • Post chemo/ CYP17 naïve • Post CYP17	134	200-1,800	Completed	NCT01317641
ARADES ext	II	mCRPC* • Chemo/CYP17 naïve • Post chemo/ CYP17 naïve • Post CYP17	76	200-1,800	Completed	NCT01317641
ARAFOR	I	Chemo-naïve mCRPC*	30	1,200	Ongoing	NCT01784757
ARIADME	I	Healthy subjects	12	300	Completed	NCT02418650
ARAMIS	III	nmCRPC**	1500	1,200	Completed	NCT02200614
ARASENS	III	mHSPC***	1300	1,200	Ongoing	NCT02799602

* metastatic Castration Resistant Prostate Cancer
** non-metastatic Castration Resistant Prostate Cancer
*** metastatic Hormone Sensitive Prostate Cancer

ODM-109

Best symptomatic treatment for Amyotrophic Lateral Sclerosis (ALS)

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ODM-109: Oral levosimendan for ALS

- First patients recruited in July for the Phase III clinical trial (REFALS).
- By enhancing respiratory muscle function in ALS patients, orally administered levosimendan can help maintain breathing capacity and benefit overall functioning of ALS patients.
- Orion is investing approximately EUR 60 million over three years in the trial.
- The aim is to apply for marketing authorisation in the US and Europe.
- Levosimendan has been granted an Orphan Drug Designation in the US and in the EU.
- It is a molecule originally developed by Orion for the treatment of acute decompensated heart failure. Simdax has been in the market for this indication since 2000.

ODM-109 (ALS): REFALS phase III trial

450 patients

- Levosimendan 1-2mg/day (300 patients)
- Placebo (150 patients)

Approx. 100 clinical sites

- US, Canada, Western Europe, Australia

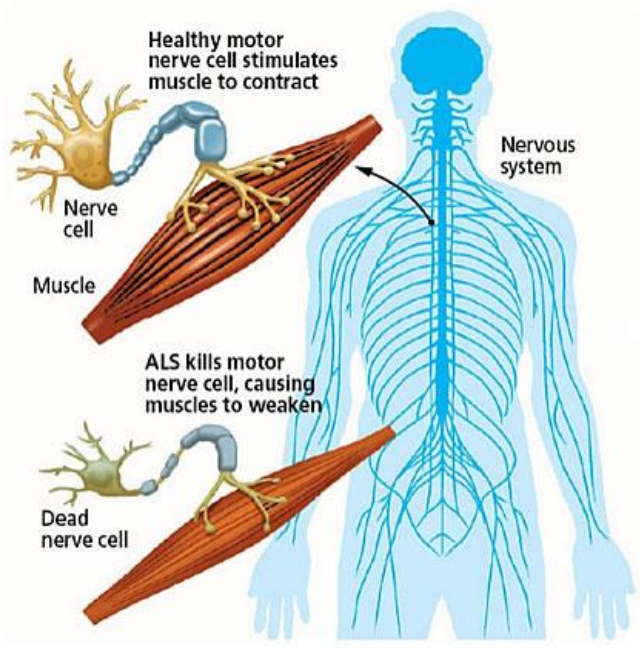
Primary endpoints

- 12 weeks: Slow vital capacity (Breathing capacity compared to normal subjects)
- 48 weeks: ALS functional rating scale (Overall assessment of ALS symptoms)

www.clinicaltrials.gov: NCT03505021

ODM-109: Oral levosimendan for ALS

- ALS (Amyotrophic lateral sclerosis) is a fast progressing and fatal neurodegenerative disease:
  - Leads to diaphragm and skeletal muscle weakness and eventually paralysis and death typically due to respiratory failure.
  - No symptomatic treatments for muscle function available.
- Levosimendan is developed for symptomatic treatment for muscle weakness, the main symptom of ALS:
  - Levosimendan has shown positive effect on diaphgram muscle function in experimental studies in animals and in humans.
  - Positive signal from a small phase II study in ALS patients.



Picture from: ALS Foundation for life
http://www.alsfoundation.org/learn/

ALS (Amyotrophic lateral sclerosis) as a rare disease

1–2/ 100,000	~16,800	~12,500	~450–500
Incidence	Patients in the US in 2017	Patients in Europe	Patients in Finland

Promising findings from LEVALS phase II study completed in 2016

- The cross-over part of Phase II clinical trial with orally administered levosimendan (ODM-109) for treatment of patients
- The first phase II study aimed to demonstrate beneficial effects of levosimendan on respiratory function of ALS patients.
- Double-blind, cross-over design with 3 treatment periods.
- Cross-over part of the study followed by an open-label part for 6 months – an opportunity to study long term effects.

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 *in vivo*.
- Levosimendan 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.

*)QoL = Quality of Life

ODM-104

New COMT-Inhibitor for Parkinson's Disease

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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 compared with Stalevo® (levodopa/carbidopa/entacapone combination) in PD patients with end-of-dose wearing-off symptoms.
- The Phase II trial was completed in Q2/2018. The primary endpoint was met. The results are being analysed and Orion is looking for a possible partner. Decision-making will also consider investment opportunities in other R&D projects.

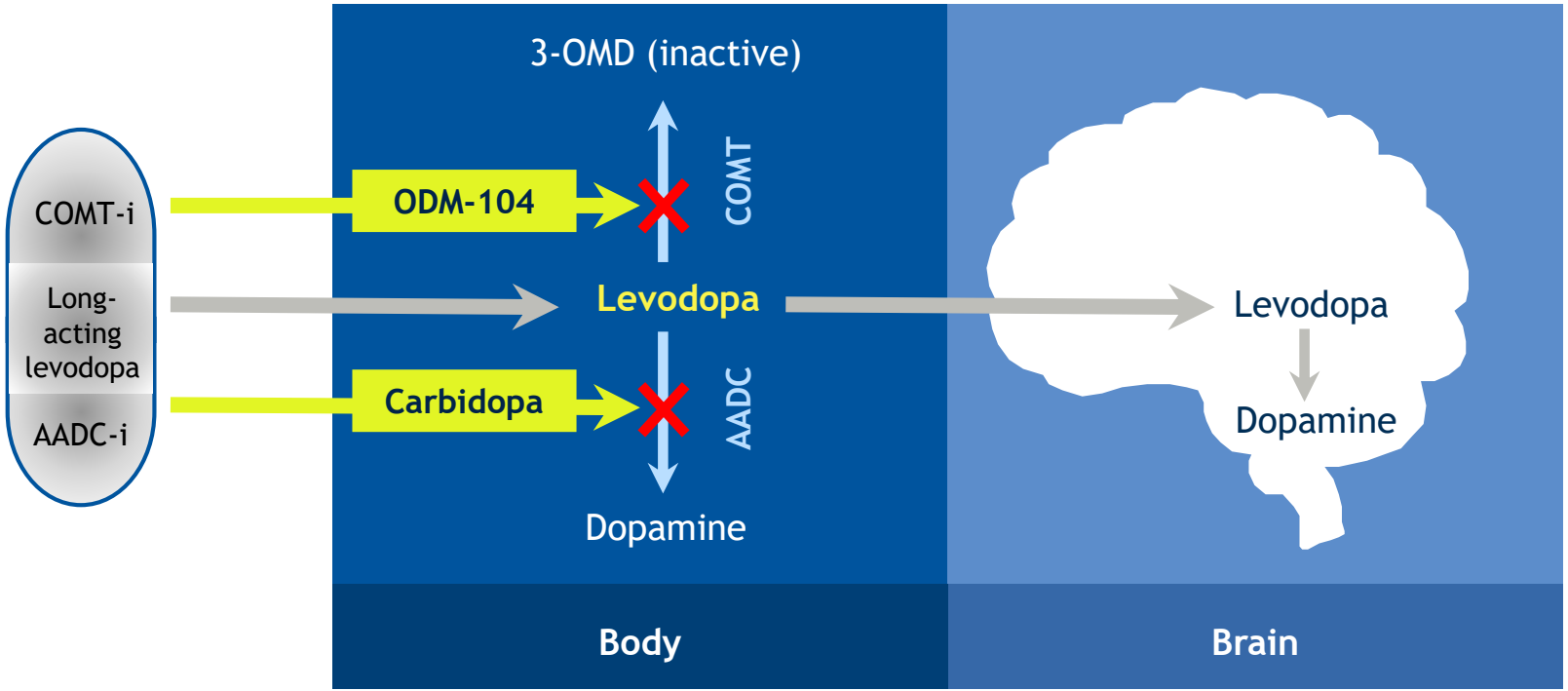
ClinicalTrials.gov identifier: NCT02764125

* Area Under the Curve

Treatment of Parkinson’s disease with levodopa

- Levodopa is the most effective medicine for treating Parkinson’s disease (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.

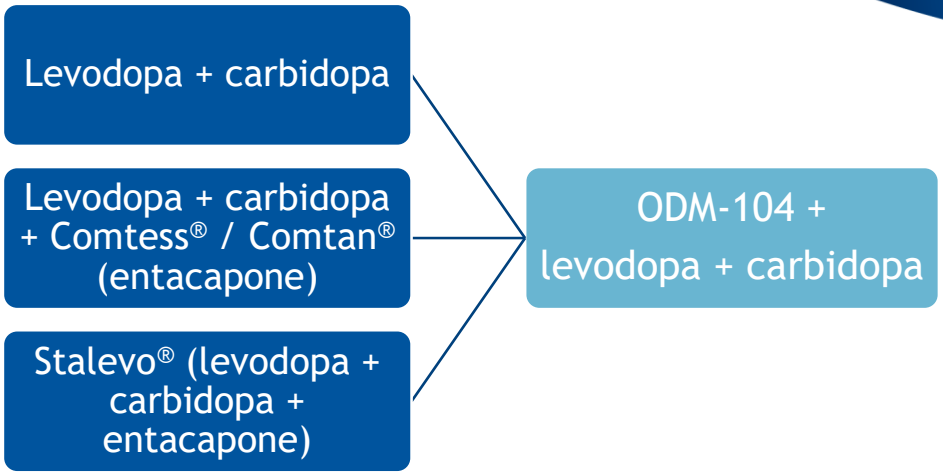
Levodopa elimination can be reduced and treatment effect improved by inhibiting breakdown enzymes AADC and COMT



AADC = Aromatic amino acid decarboxylase COMT = Catechol-O-methyltransferase 3-OMD = 3-O-Methyldopa

Target indication

- 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®.
- Patients on levodopa/AADC inhibitor treatment with or without entacapone can be directly switched to the new combination product (ODM-104/optimized carbidopa/long-acting levodopa).



ODM-203

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

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Angiogenic indications with altered FGFR* signalling

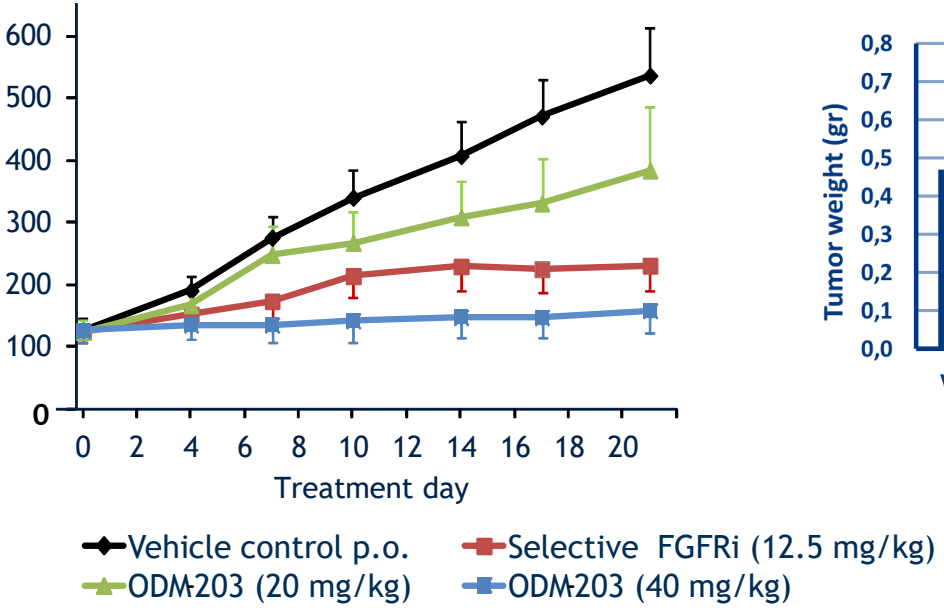
Tumor type	Genomic alterations of FGFRs and FGFs
Breast (luminal)	~35% (FGFR1 amp, FGFR2 amp, FGFR4 amp, FGFs)
NSCLC-SCC	~20% (FGFR1 amp, FGFR2 amp)
Bladder (invasive)	~15% (FGFR3 fusions, FGFR1 amp, FGFs)
Prostate	~14% (FGFR1 amp, FGFR2&3 fusions)
Colorectal	~10% (FGFR1 amp, FGFR3 mut)
Endometrial	~10%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

* Fibroblast Growth Factor Receptor

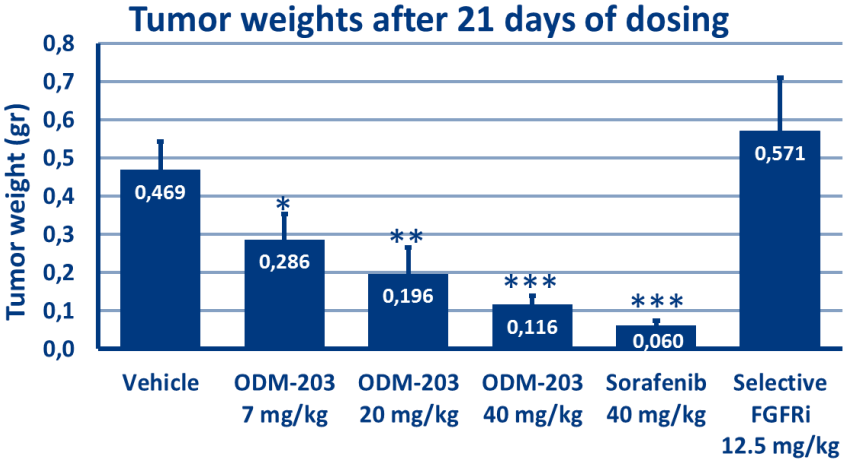
ODM-203 has strong in vivo antitumor activity

ODM-203 (targeted FGFR+VEGFR inhibitor)	Solid tumours	I	II

FGFR xenograft model (RT4)

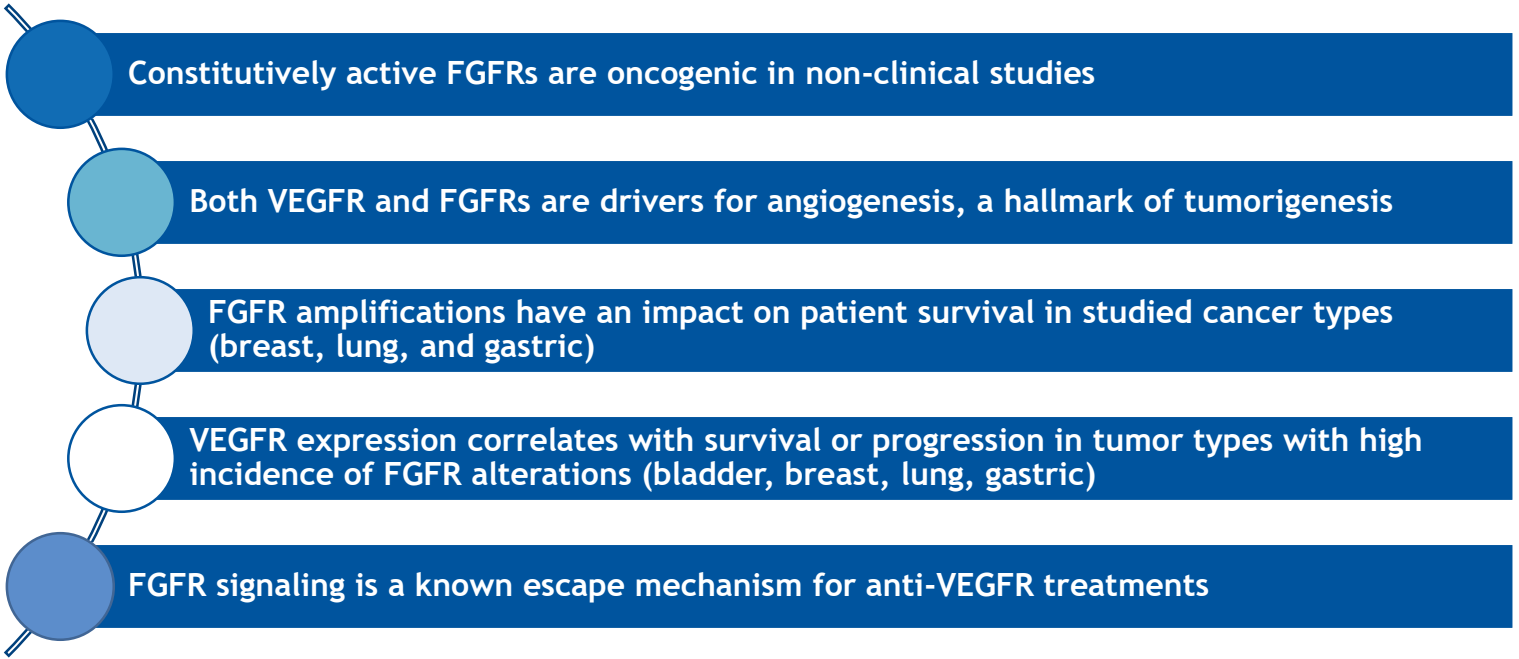


Angiogenic kidney cancer model (Renca)



ClinicalTrials.gov identifier: NCT02264418

Rationale for combining FGFR* and VEGFR** inhibition



* Fibroblast Growth Factor Receptor
** Vascular Endothelial Growth Factor Receptor

ODM-203 – current status

ODM-203 (targeted FGFR+VEGFR inhibitor)	Solid tumours	I	II

KIDES trial with Phase II expansion ongoing

- The trial is investigating
  - Safety and tolerability of ODM-203 in subjects with advanced solid tumours
  - Efficacy of ODM-203 in slowing the growth of solid cancerous tumours in patients in which FGFR changes in cancerous tumours have been detected

ClinicalTrials.gov identifier: NCT02264418

ODM-207

Unique BET inhibitor for solid tumors

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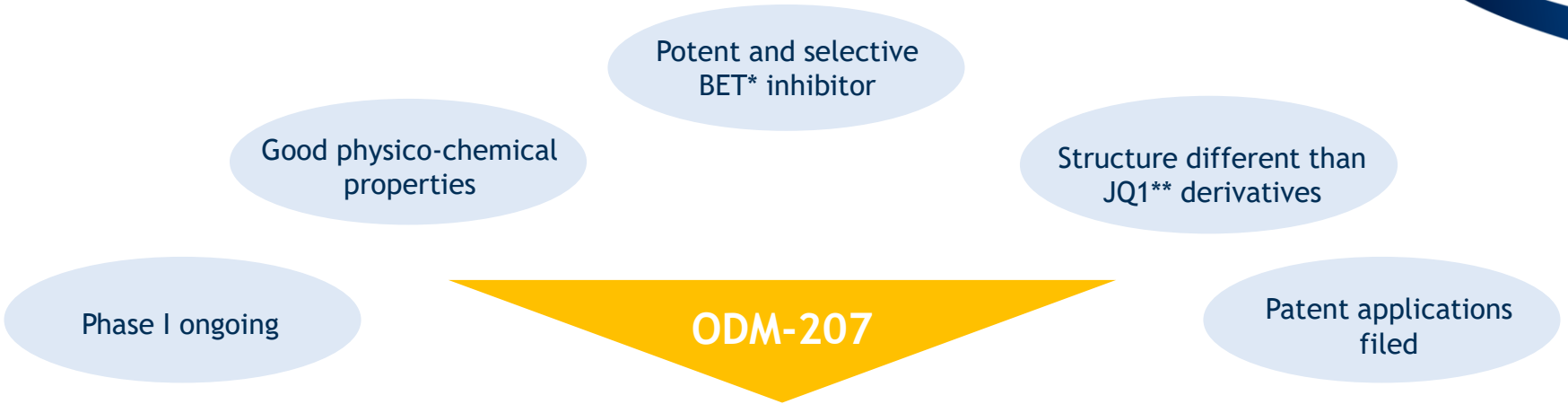
ODM-207 – A unique BET* inhibitor for solid tumours



- 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.

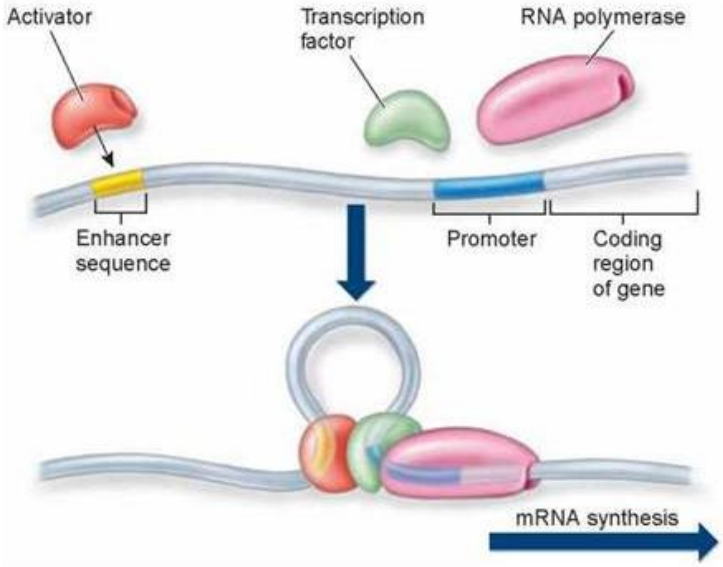
* Bromodomain and Extra-Terminal
** JQ1 is a BET inhibitor reference compound

Target: BET proteins which regulate expression of oncogenes

- BET proteins occupy regulatory elements of DNA (superenhancers) in many key oncogenes
  - They increase the expression target oncogenes
- BET target genes include: **Myc**, MycN

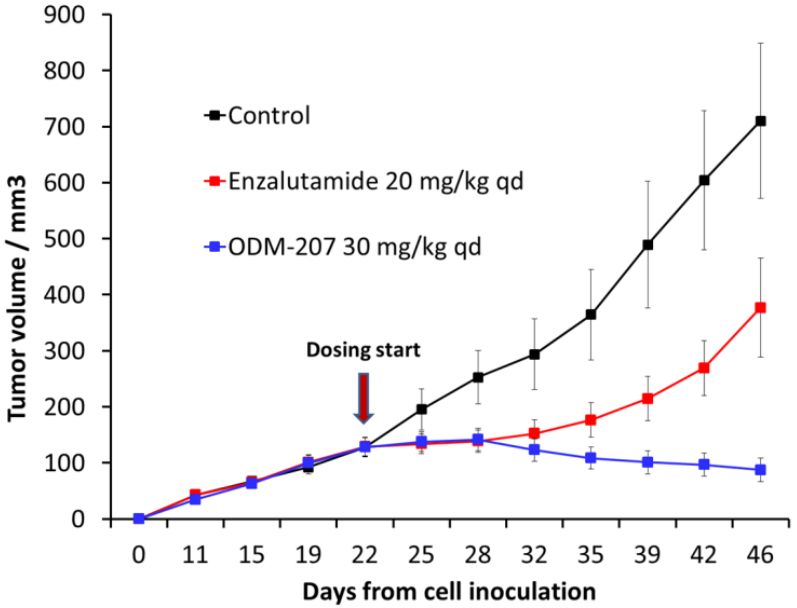
ODM-207

- Binds to BET proteins
- Inhibits transcription of key oncogenes such as Myc and MycN in many cancers



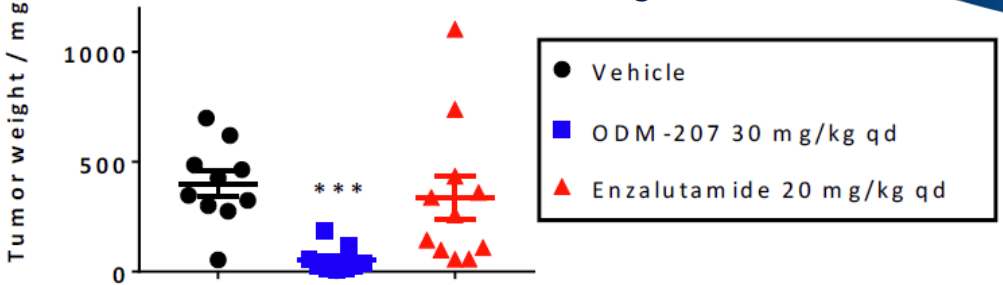
ODM-207 inhibits the tumour growth in enzalutamide-resistant 22Rv1 prostate cancer xenograft

Effect of ODM-207 on tumour volumes

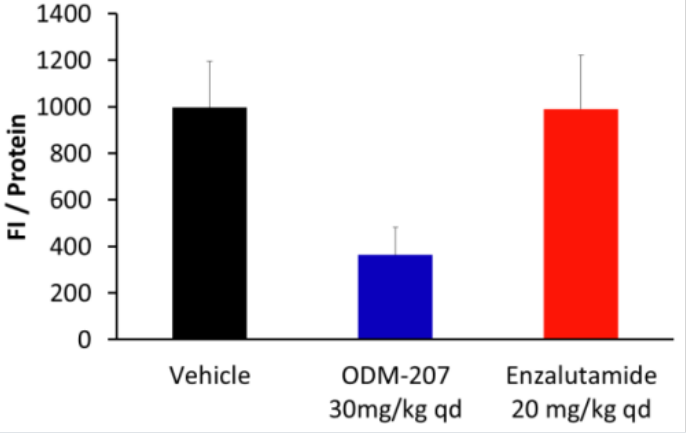


From poster Björkman et al., presented in EORTC-NCI-AACR in 11-12/2016

Effect of ODM-207 on tumour weights



ODM-207 inhibits Myc in *in vivo* efficacy study



ODM-207 – current status

ODM-207 (BET protein inhibitor)	Cancer	I

BETIDES phase I/II trial ongoing

- The trial is investigating
  - PK, safety and tolerability, and antitumour activity of ODM-207 in subjects with advanced solid tumours

ClinicalTrials.gov identifier: NCT03035591

ODM-208

Pan-steroid hormone synthesis inhibitor (CYP11A1 inhibitor) for castration-resistant prostate cancer

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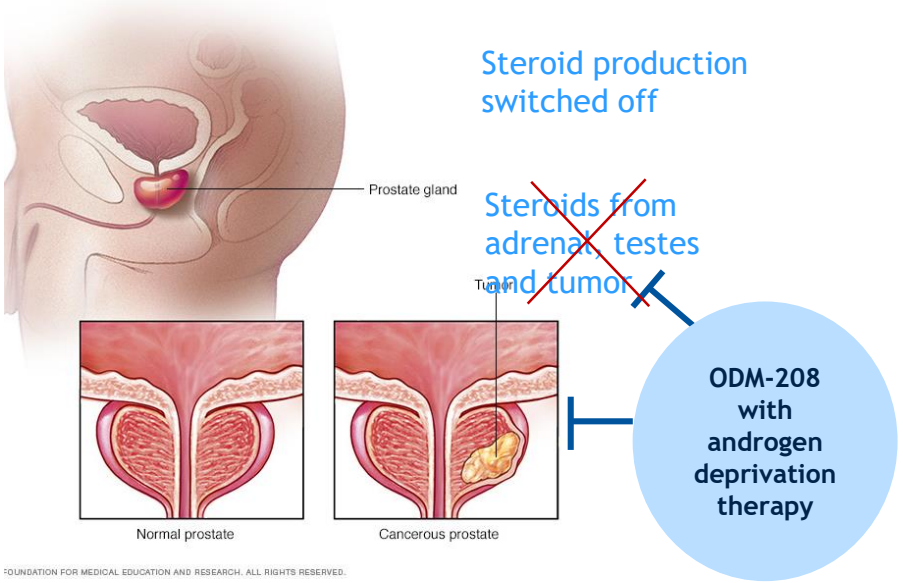
ODM-208: Pan-steroid hormone synthesis inhibitor (CYP11A1 inhibitor) for castration-resistant prostate cancer

- Steroid hormones stimulate the growth of hormonally regulated cancers, such as most breast prostate and breast cancers.
- Hormonal treatments have proven highly effective, but drug resistance will often eventually emerge and cancer will start growing again.
- Preclinical studies have shown that ODM-208 is an agent that inhibits the synthesis of steroids hormones. It has potential efficacy also for those cancers that have become resistant to the standard hormonal treatments.
- The steroid hormones that are needed and do not promote cancer growth, are replaced with additional medication.



Easyhaler product family

for treatment of asthma and COPD

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Orion's Easyhaler®
is a dry-powder inhaler developed in-house

- Diverse treatment options for asthma and COPD by utilizing the same inhaler technology.
- Orion has developed Easyhaler-adapted dry powder formulations of several well-known generic active substances:
  - salbutamol, beclometasone, budesonide, formoterol, salmeterol and fluticasone
- Key benefits:
  - Dosing accuracy and consistent deposition
  - Easy to teach, learn and use
  - A wide range of products

Salmeterol-fluticasone Easyhaler®
The sixth member of the product family launched

- In March 2018, Orion received positive conclusions for the salmeterol-fluticasone Easyhaler under the decentralised EU marketing authorisation procedure.
- The national approval procedures started in 23 EU countries.
- First product deliveries started in October 2018.
- In the combined formulation, fluticasone acts as an anti-inflammatory agent and salmeterol acts as a long-acting bronchodilator.

The seventh product, tiotropium, is in development

- Bioequivalency study started in Q1/2018.
- The product is developed for European markets.
- Tiotropium is a long-acting anticholinergic bronchodilator used in the treatment of chronic obstructive pulmonary disease.

Easyhaler product family is expanding

EASYHALER

1984
The idea of Easyhaler is born

1993
Salbutamol Easyhaler

1994
Beclometasone Easyhaler

2002
Budesonide Easyhaler

2004
Formoterol Easyhaler

2014
Bufomix Easyhaler

2018
Salmeterol-Fluticasone Easyhaler

2018
Tiotropium development started

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