EVGEN PHARMA PLC

Investor Presentation

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Company summary

- Clinical stage drug development company with a new class of pharmaceuticals
- Focused on the development of well-tolerated, stable, sulforaphane-based compounds that:
  - inhibit the STAT3 pathway – a target for reducing cancer proliferation and metastases; and
  - activate the Nrf2 pathway – a target for reducing neurodegeneration
- World-wide exclusive licence to an IP estate covering novel compositions and manufacturing
- Lead product, SFX-01, is in two Phase II trials (oncology and neurology) utilising two separate mechanistic targets with expected read-outs around the end of 2018
- Preclinical pipeline from a library of novel derivatives of sulforaphane
- Business model looks to license post-Phase II or potentially Phase III (for orphan indications)
Sulforaphane modulates STAT3 and Nrf2 presenting opportunities in both oncology and neurology

Improving outcomes for patients with neurodegenerative conditions


Improving outcomes for patients becoming resistant to cancer therapies

Pipeline

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<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Preclin</th>
<th>Phase I</th>
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<tr>
<td>SFX-01</td>
<td>Subarachnoid Haemorrhage</td>
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<td>SFX-01</td>
<td>Metastatic Breast Cancer (ER+)</td>
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<td>SFX-01</td>
<td>Investigator-Initiated Studies e.g. Triple Negative Breast Cancer, Ischaemic Stroke</td>
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- Potential for different formulations to establish more than one product line based on SFX-01
- Completion of Phase I studies in healthy human volunteers means that SFX-01 is Phase II-ready for other indications
- Pipeline further supported by a library of novel derivatives of sulforaphane (SFX-02 to SFX-42) in early preclinical development
Growth in sulforaphane publications and strong academic collaborations support the scientific fundamentals.
SFX-01 in Estrogen-Receptor Positive (ER+) Metastatic Breast Cancer
Metastatic estrogen-receptor positive (ER+) breast cancer

- ER+ breast cancer is the most prevalent breast cancer sub-type
- Metastatic breast cancer (also known as “Advanced” or “Stage 4”) means that the cancer has spread to other parts of the body
- 5-year survival rates are 22\%\textsuperscript{1}
- First-line hormone therapy can provide c.15 months of progression free survival\textsuperscript{2}
- This has now been extended to c.25 months, by the combination of hormone therapy with CDK4/6 inhibitors\textsuperscript{2}
- Poor options thereafter and new therapies needed

\textsuperscript{1}American Cancer Society; \textsuperscript{2}Palbociclib and Letrozole in Advanced Breast Cancer (2016) N Engl J Med
Market landscape in metastatic estrogen receptor positive (ER+) breast cancer

- Incidence of ER+ metastatic breast cancer is approximately 130,000\textsuperscript{1} in US and Europe
- CDK4/6 inhibitors are now first line treatment, in combination with hormone therapy
- Pfizer (Ibrance\textsuperscript{®}/palbociclib), Novartis (Kisqali\textsuperscript{®}/ribociclib) and Eli Lilly (Versenio\textsuperscript{®}/abemaciclib) are the key players with sales forecasts of $4.4bn, $0.3bn and $0.17bn respectively in 2018\textsuperscript{e}\textsuperscript{2}
- CDK4/6 inhibitor sales forecast to reach c.$9bn by 2021\textsuperscript{e}\textsuperscript{2}
- However, all patients will ultimately become resistant to CDK4/6 inhibitors
- Potential of SFX-01 after CDK4/6 inhibitor therapy: a unique mechanism of action and a more favourable side-effect profile

\textsuperscript{1} Evgen estimate derived from: The American Cancer Society’s estimates for 2016 US breast cancer incidence; The Metastatic Breast Cancer Network; Brufsky, Cancer Treatment Review, Vol 59, Sept 2017
\textsuperscript{2} Biopharm Insight Consensus Broker Forecasts
SFX-01 presents a unique mechanism of action in the metastatic breast cancer therapy landscape

**Aromatase inhibitors**
Anastrazole, Letrozole, Exemestane

**ER modulators**
Tamoxifen, Fulvestrant

**CDK4/6 inhibitors**
Palbociclib, Ribociclib, Abemaciclib

**mTOR inhibitors**
Everolimus

**STAT3**

**Cyclin D**

**Estradiol**

**CELL PROLIFERATION**

**TUMOUR RENEWAL**
**THERAPY RESISTANCE**
**IMMUNE EVASION**

SFX-01 targets cancer stem cells, deactivates STAT3 and reduces metastases

Li et al (2010) were the first to observe that sulforaphane reduces the size and number of primary mammospheres in human breast cancer cells (A); a property of cancer stem cells (CSCs)

In ER+ PDX tumours, SFX-01 reduces CSCs (AACR, 2015), deactivates STAT3 (B) and eliminates metastases to the lungs (C) - University of Manchester, unpublished data
Current clinical progress

- **STEM**: SFX-01 treatment and evaluation in patients with metastatic breast cancer
- A European, multi-centre, Phase II trial on 60 patients evaluating SFX-01 as an adjunct to failing hormone therapy (i.e. the “salvage” setting)
- Hormone resistant “all-comers”: tamoxifen, aromatase inhibitors or fulvestrant
- Chief Investigator: Dr Sacha Howell at Manchester’s Christie NHS Foundation Trust
- Primary Endpoints: Safety and Clinical Benefit Rate (stable or responsive disease at 6 months)
- Interim read-out H1 2018 and final read-out around end of 2018
- Compassionate use programme accepted first patient in June 2017
Commercial opportunity and monetisation

- Substantial market opportunity – CDK4/6i sales projected to reach c.$9bn by 2021e¹
- License and/or co-develop SFX-01 as second-line therapy to CDK4/6i
- Up-front payment potential of c.$50m² (although some deals e.g. AstraZeneca/Innate up-front of $250m for antibody in combination with AZ’s immuno-oncology assets)
- Double digit royalties
- Licensees – Big Pharma or large biotechs, opportunity to enhance existing second-line therapies following CDK4/6i failure

¹Biopharm Insight Consensus Broker Forecasts
²IMS Pharma Deals: Review of 2016
SFX-01 in Subarachnoid Haemorrhage
Aneurysmal subarachnoid haemorrhage (aSAH)

- Defined by bleeding in the outer layers of the brain due to a ruptured brain aneurysm
- 40% to 50% die within 30 days and for the survivors c.50% will have long-term cognitive impairment
- Delayed cerebral ischaemia (DCI) occurs days after the aSAH, causing brain tissue death and is associated with poorer patient outcomes
- Current standard of care is nimodipine (approved over 20 years ago) - new pharmacological treatments are needed to prevent and treat DCI
SAH market landscape

- Annual incidence of c.50,000 in the EU and c.40,000 in US*
- Current standard of care, nimodipine, reduces calcium-dependent smooth muscle contraction but its precise mechanism of action in SAH is unknown
- Nimodipine side-effects include unusually fast or slow heart beats and systemic hypotension is a risk factor that requires monitoring
- No new drug treatment since the 1980s to address effects of the DCI
- SFX-01 is believed to be the only Nrf2-activator in the clinic for any acute neurological indication and is safe and very well tolerated
- Evgen apart, thin development pipeline - benign competitive landscape

*Extrapolated from *Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends.* De Rooij et al. (2007) J Neurol Neurosurg Psychiatry
SFX-01 provides neuroprotection via the activation of the Nrf2 pathway

Improving outcomes for patients with neurodegenerative conditions

Oxidative stress and inflammation

Cytoprotective proteins

SFX-01 provides neuroprotection via the activation of the Nrf2 pathway.
In experimental SAH, sulforaphane upregulates Nrf2, reduces apoptosis and ameliorates motor deficits

“In the SUL [sulforaphane]-treated group, early brain damage such as brain edema, blood–brain barrier (BBB) impairment, cortical apoptosis, and motor deficits was significantly ameliorated compared with vehicle-treated SAH rats

Chen et al. (2011) J Neurosci Res
Furthermore, sulforaphane reduces the delayed cerebral ischaemia and improves behavioural scores.

“SFN [sulforaphane] has a therapeutic benefit in post-SAH, and this may be due to elevated Nrf2-ARE pathway activity and inhibition of cerebral vascular proinflammatory cytokine expression.”

Zhao et al. (2016) Brain Res
Current clinical progress

- **SAS**: SFX-01 After Subarachnoid Haemorrhage – a Phase II, double-blind, placebo-controlled trial on 90 patients (45 in test and placebo arm respectively)
- Administered alongside the calcium channel antagonist, nimodipine
- Primary Endpoints: improved blood flow (ultrasound) associated with the DCI, levels of drug in plasma and cerebral spinal fluid & safety
- Secondary endpoints: cognitive measures at 3 and 6 months
- Chief Investigator: Mr Diederik Bulters, Consultant Neurosurgeon, Wessex Neurological Centre in Southampton
- Read-out around end of calendar year 2018
- **Orphan designation** granted by FDA
Commercial opportunity and monetisation

- Potential peak sales of $500m+ (c.f. $1.7bn for EG1962\textsuperscript{1}) as SAH orphan drug
- License and/or co-develop post-Phase IIb (2019) to fund pivotal Phase III
  - Up-front payment potential post-Phase IIb of >$70m\textsuperscript{2} and post-Phase III of >$150m\textsuperscript{2}
  - Royalty rates estimated in high teens
- Broader deal for stroke increases value and bio-dollars
- Licensees - companies interested in SAH/stroke or targeting Nrf2 pathway. Likely to be large biotech or specialty pharma

\textsuperscript{1}Credit Suisse Research Report, 26 Oct 2015 – Edge Therapeutics
\textsuperscript{2}IMS Pharma Deals: Review of 2016 – averages for 2015 and 2016
Evgen is building a stabilised sulforaphane platform (Sulforadex®) with multiple commercialisation routes

Strong preclinical data and mechanistic evidence for broad utility in oncology and neurodegenerative diseases. Benign and well-tolerated

Lead product, SFX-01, is in two Phase II trials (ER+ metastatic breast cancer and subarachnoid haemorrhage), with read-outs around the end of 2018

Monetisation horizon from 2019 via licensing/co-development

World-wide exclusive license to an IP estate covering novel compositions and manufacturing

Preclinical pipeline from a library of novel derivatives of sulforaphane asserts leadership position around this new class of pharmaceuticals
Barry Clare, Chairman
Former main Board member of Boots Company plc and Chairman UHSM Foundation Trust

Dr Stephen Franklin, CEO
Founder of Evgen Pharma and former CEO of Provexis plc and former Principal Executive with ANGLE plc

Richard Moulson, CFO
Former CFO of Intercytex Group Plc, ReNeuron Group plc and Cobra Therapeutics Ltd

Dr Marc d’Abbadie, NED
Investor Director at SPARK Impact and formerly with Inventages, Technikos and McKinsey and Co

Dr Sue Foden, NED
NED and Chair of the Remuneration Committee at Vectura plc and has previously Chaired Bergenbio

Dr Alan Barge, NED
Former CMO of ASLAN Pharmaceuticals and former VP and Head of Oncology and infection at AstraZeneca
Sulfuraphane, a Dietary Component of Broccoli/Broccoli Sprouts, Inhibits Breast Cancer Stem Cells

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Abstract

**Purpose**—The existence of cancer stem cells (CSCs) in breast cancer has profound implications for cancer prevention. In this study, we evaluated sulfuraphane, a natural compound derived from broccoli/broccoli sprouts, for its efficacy to inhibit breast CSCs and its potential mechanism.

**Experimental Design**—Aldefluor assay and mammosphere formation assay were used to evaluate the effect of sulfuraphane on breast CSCs in vitro. A NOD/SCID xenograft model was employed to determine whether sulfuraphane could target breast CSCs in vivo, as assessed by Aldefluor assay and tumor growth upon cell re-implantation in secondary mice. The potential mechanism was investigated utilizing Western blotting analysis and \(\beta\)-catenin reporter assay.

**Results**—Sulfuraphane (1–5 \(\mu\)M) decreased aldehyde dehydrogenase (ALDH)-positive cell population by 65%–80% in human breast cancer cells \((P < 0.01)\), and reduced the size and number of primary mammospheres by 8–125-fold and 45%–75% \((P < 0.01)\), respectively. Daily injection with 50 mg/kg sulfuraphane for two weeks reduced ALDH-positive cells by more than 50% in NOD/SCID xenograft tumors \((P = 0.003)\). Sulfuraphane eliminated breast CSCs in vivo, thereby abrogating tumor growth after re-implantation of primary tumor cells into the secondary mice \((P < 0.01)\). Western blotting analysis and \(\beta\)-catenin reporter assay showed that sulfuraphane down-regulated Wnt/\(\beta\)-catenin self-renewal pathway.

**Conclusions**—Sulfuraphane inhibits breast CSCs and down-regulates Wnt/\(\beta\)-catenin self-renewal pathway. These findings support the use of sulfuraphane for chemoprevention of breast cancer stem cells and warrant further clinical evaluation.
Sulforadex targets breast cancer stem-like cells in patient-derived cells and xenograft tumours

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Sulforadex abrogates tamoxifen enrichment for cells with cancer stem cell properties in patient-derived xenograft tumours

**CONCLUSION**

Sulforadex may be of value in combination with anti-estrogens to overcome endocrine resistance of ER+ tumours

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**Figure 5:** A) BB3RC31 and HBCx34 patient derived xenografts treated in vivo for 14 days with sulforadex (300mg/kg/day, oral gavage) in the presence or absence of tamoxifen (10mg/kg/day, oral gavage). HBCx34 model was kindly provided by Dr Elisabetta Marangoni (Institute Curie, Paris). B) Quantification of Ki67 expression determined by immunohistochemistry showing that tamoxifen but not SFX significantly decreases proliferation marker Ki67. C) Percentage of ALDH-positive cells was determined with ALDEFLUOR assay. ALDH-positive cells were discriminated from ALDH-negative cells using the ALDH inhibitor, DEAB. Mouse cells were excluded from the FACS analysis with anti-mouse MHC Class I (H-2Kd) antibody. D) Mammosphere formation efficiency was determined on day 7-9 and calculated by dividing the number of mammospheres formed (≥ 50μm) by the original number of single cells seeded (500 cells/cm²) and is expressed as the mean percentage of mammosphere formation. Representative micrographs are shown (scale bar 50 μm). Data are represented as mean ± SEM. * p < 0.05; ** p < 0.01
**Abstract**

Nrf2-ARE pathway reportedly plays a protective role in several central nervous system diseases. No study has explored the role of the Nrf2-ARE pathway in cerebral vasospasm (CVS) after subarachnoid hemorrhage (SAH). The purpose of the present study was to investigate the activation of the cerebral vascular Nrf2-ARE pathway and to determine the potential role of this pathway in the development of CVS following SAH. We investigated whether the administration of sulforaphane (SFN, a specific Nrf2 activator) modulated vascular caliber, Nrf2-ARE pathway activity, proinflammatory cytokine expression, and clinical behavior in a rat model of SAH. A two-hemorrhage protocol was used to generate an animal model of SAH in male Sprague-Dawley rats. Administration of SFN to these rats following SAH enhanced the activity of the Nrf2-ARE pathway and suppressed the release of proinflammatory cytokines. Vasospasm was markedly attenuated in the basilar arteries after SFN therapy. Additionally, SFN administration significantly ameliorated two behavioral functions disrupted by SAH. These results suggest that SFN has a therapeutic benefit in post-SAH, and this may be due to elevated Nrf2-ARE pathway activity and inhibition of cerebral vascular proinflammatory cytokine expression.
Role of the Nrf2-ARE Pathway in Early Brain Injury After Experimental Subarachnoid Hemorrhage

Gang Chen,1 Qi Fang,2 Jian Zhang,1 Dai Zhou,1,* and Zhong Wang1,*

The nuclear factor erythroid 2-related factor 2 and antioxidant-response element (Nrf2-ARE) pathway is a key regulator for modulating inflammation and oxidative damage, which are involved in the pathogenesis of early brain injury (EBI) after subarachnoid hemorrhage (SAH). Previous studies have demonstrated that Nrf2-ARE pathway play neural protective roles in traumatic brain injury, cerebral ischemia, and intracerebral hemorrhage models; however, it has not been investigated whether, and to what degree, the Nrf2-ARE pathway is induced by SAH, and the role of the Nrf2-ARE pathway in development of EBI following SAH remains unknown. Experiment 1 sought to investigate the time course of Nrf2-ARE activation in the cortex in the early stage of SAH. In experiment 2, we assessed the effect of sulforaphane (SUL; a specific Nrf2 activator) on regulation of the Nrf2-ARE pathway in the SAH model and evaluated the impact of SUL on EBI after SAH. The rat SAH model was used injection of 0.3 ml fresh arterial, nonheparinized blood into the prechiasmatic cistern over 20 sec. As a result, Nrf2 and its target gene product, heme oxygenase-1 (HO-1), were up-regulated in the cortex after SAH and peaked at 24 hr post-SAH. After intraperitoneal SUL administration, the elevated expression of Nrf2-ARE-related factors such as Nrf2, HO-1, NAD(P)H:quinone oxidoreductase 1 (NQO1), and glutathione S-transferase-α1 (GST-α1) was detected in the cortex at 48 hr following blood injection. In the SUL-treated group, early brain damage such as brain edema, blood–brain barrier (BBB) impairment, cortical apoptosis, and motor deficits was significantly ameliorated compared with vehicle-treated SAH rats. Our results suggest that the Nrf2-ARE pathway is activated in the brain after SAH, playing a beneficial role in EBI development, possibly through inhibiting cerebral oxidative stress by inducing antioxidant and detoxifying enzymes. © 2011 Wiley-Liss, Inc.

Key words: early brain injury; subarachnoid hemorrhage; Nrf2

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