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Evgen Pharma

Harnessing the clinical potential of sulforaphane

Evgen is a virtual pharmaceutical company focused on the development of a synthetic version of a natural product, sulforaphane, which is known to modulate key signalling pathways involved in cellular protection and inflammation. Evgen's proprietary technology, Sulforadex, creates new and stable variants of sulforaphane, enabling it to be used as a therapeutic for the first time. Its lead candidate, SFX-01, has entered Phase II clinical trials for both subarachnoid haemorrhage (SAH) and ER+ metastatic breast cancer with an expected read out of results in 1H 2018.

- **Strategy**: Evgen is focused on the clinical development of synthetic and stable variants derived from sulforaphane using its proprietary technology, Sulforadex. Lead candidate SFX-01 is entering Phase II trials for both SAH and breast cancer, both strategic entry portals for other uses in neurology and oncology.

- **Sulforaphane:** An established natural product known to modulate signalling pathways involved in cellular protection (oxidative stress response) and inflammation. However, use of sulforaphane as a therapeutic has been held back by its instability, a problem resolved using the Sulforadex technology.

- **SFX-01:** First of a potential series of stable synthetic variants of sulforaphane. Patient recruitment has commenced, and is about to commence, for Phase II clinical trials in subarachnoid haemorrhage and ER+ metastatic breast cancer respectively. Headline results are expected during 1H 2018.

- **Risks:** As with all drug development companies, there is a risk that products will fail in clinical trials. However, sulforaphane has been through a number of encouraging clinical trials despite its stability and dosing limitations. Therefore, Evgen's risk profile is arguably reduced.

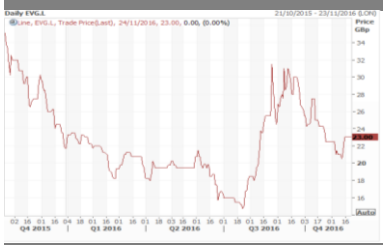
- **Investment summary:** SFX-01 would be entering multi-billion dollar global markets which are currently unsatisfied. There is also potential use in other indications. Evgen intends to out-license its drugs to the pharmaceutical majors for global commercialisation. The enterprise value afforded Evgen by the market does not reflect properly the development stage and lower than usual risk profile of SFX-01.

Financial summary and valuation

Year end March (£000)	2014	2015	2016E	2017E	2018E
Sales	0	0	0	0	0
SG&A	-312	-338	-980	-1,010	-1,050
R&D	-484	-612	-3,029	-2,181	-3,054
EBITDA	-789	-942	-4,002	-3,183	-4,096
Underlying EBIT	-796	-950	-4,010	-3,191	-4,104
Reported EBIT	-1,246	-2,434	-4,135	-3,322	-4,241
Underlying PBT	-1,853	-1,733	-3,999	-3,187	-4,106
Statutory PBT	-2,303	-3,217	-4,124	-3,318	-4,244
Underlying EPS (p)	-6.2	-3.3	-4.9	-3.9	-5.0
Statutory EPS (p)	-7.8	-6.3	-5.1	-4.1	-5.2
Net (debt)/cash	-903	7,126	3,264	543	-3,221
Capital increases	0	8,565	0	0	0

Source: Hardman & Co Life Sciences Research

Pharmaceuticals & Biotech



Source: Eikon Thomson Reuters

Market data

EPIC/TKR	EVG
Price (p)	23.0
12m High (p)	35.0
12m Low (p)	15.0
Shares (m)	73.1
Mkt Cap (£m)	16.8
EV (£m)	9.7
Free Float*	50%
Market	AIM

**As defined by AIM Rule 26*

Description

Evgen is a virtual pharmaceutical company using its proprietary technology, Sulforadex, to create new synthetic and stable variants of the natural product, sulforaphane. Lead product, SFX-01, is now in two Phase II trials

Company information

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Key shareholders

Directors	3.2%
North West Fund	22.1%
Rising Stars	16.3%
AXA	8.9%
South Yorkshire	5.2%
Seneca	4.8%

Events

5 Dec	Interims
4Q-16	Phase II breast cancer
May-17	Finals
Jun-17	AGM

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Executive summary

Virtual drug development company focused on natural products

Founded in 2007, and first financed in 2008, Evgen is a virtual drug development company focused on the clinical development of pharmaceuticals based on natural products. In 2010, Evgen secured the intellectual property right for Sulforadex, the technology that enables the manufacture of a synthetic and stable version of a natural product called sulforaphane.

Sulforaphane

Sulforaphane is of great scientific interest...

...but limited by its instability at ambient temperature

Enzymatic degradation of glucoraphanin, which is found naturally in cruciferous vegetables such as the brassica family (broccoli, cabbage, sprouts etc.) in response to damage – insect attack or chewing by animals – results in the formation of sulforaphane. This small molecule has a reactive isethionate (ITC) group and a sulphoxide group at opposite extremities of a carbon chain. Sulforaphane attracted huge interest after it was discovered in 1992 to possess an anti-cancer properties; since when there have been over 1,500 scientific research publications and numerous clinical trials using frozen botanical extracts. However, whilst sulforaphane can be manufactured synthetically, it is an incredibly unstable chemical that needs to be stored at -20°C and under an inert atmosphere, making it unsuitable for use as a drug.

Sulforadex® technology

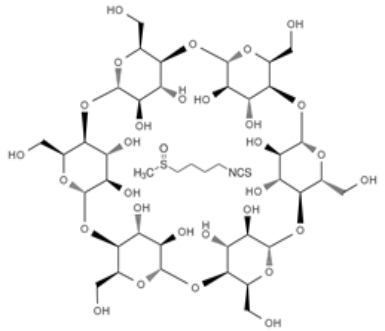
Sulphoradex technology overcomes the inherent instability of sulforaphane

Sulforadex is the technology that overcomes the considerable problem of high instability occurring with ITC products. Synthetic sulforaphane is encapsulated within a sugar ring structure, called α-cyclodextrin, to create a viable formulation that is stable at ambient temperature, which for the first time enables sulforaphane to be used as a therapeutic. Evgen is using its proprietary Sulforadex technology to stabilise compounds that are renowned for their high reactivity and instability, and prone to decomposition under normal conditions used during the manufacturing process. Therefore, this technology provides for the first time, a stable synthetic source of sulforaphane, a natural product known to be effective in multiple indications. This stabilisation process would also applicable to, and required by, other new chemical variants based on sulforaphane.

SFX-01

The first product developed by Evgen using its Sulforadex technology is SFX-01, which is a white solid that has proved to be stable at ambient temperatures for a period of at least two years. This allows accurate and repeatable dosing of sulforaphane (300mg of SFX-01 is equivalent to 46.5mg of sulforaphane).

SFX-01



Source: Evgen

Potential indications for sulforaphane

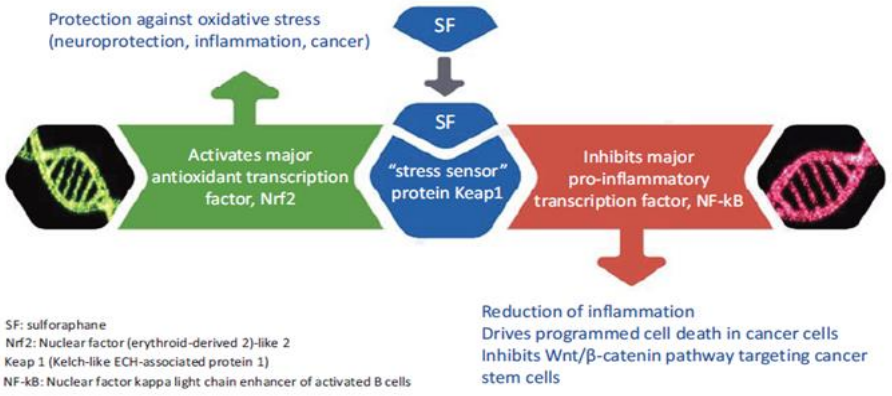
- Cancer and cancer prevention
- Cardiovascular disease prevention
- Subarachnoid haemorrhage
- Autism
- Asthma and COPD
- Type II diabetes
- Schizophrenia
- Oxidative stress prevention

Source: Company reports; Hardman & Co Life Sciences Research

Sulforaphane has been shown to be a potent modulator of key signalling pathways

This non-exhaustive significant spread of indications, is due to the fact that sulforaphane is a potent modulator of the stress sensor protein Keap1, controlling both the Nrf2 and NF-κB signalling pathways, which are the main cellular regulators. While sulforaphane activates Nrf2, bringing protection against oxidative stress, it also down-regulates the pro-inflammatory transcription factor, and increases programmed cell death in cancer cells.

Sulforaphane mechanism of action



Source: Evgen

Research publications and clinical studies, which claim to have used sulforaphane, are mostly using a frozen broccoli sprout extract that contains only an approximate level of the active ingredient. With the Sulforadex technology, illustrated by SFX-01, Evgen can synthesise and stabilise sulforaphane in a solid form, that can be readily and accurately (in terms of dose) used as a therapeutic.

Clinical trials

SFX-01 proved to be safe, well tolerated with a no serious side effects

After completing pre-clinical safety and toxicology package, Evgen used the numerous precedent *in vitro* and *in vivo* data already published to gain acceptance from the MHRA for Phase I trials. Two Phase I clinical trials in healthy subjects, aimed at assessing the safety and tolerability of SFX-01 were performed and results were compared to published data with extracts of sulforaphane. SFX-01 was shown to have excellent pharmacokinetics, with bioavailability of approximately 80%. The results helped to determine the dosing regimen for subsequent trials, i.e. twice daily dosing of 300mg SFX-01.

Clinical trial timetable

Drug	Indication	2016	2017
SFX-01	Metastatic Breast Cancer	Phase II	
SFX-01	Subarachnoid Haemorrhage	Phase II	
SFX-01	Multiple Sclerosis	Preclinical Studies	
New SFX analogues	Various	Preclinical Studies	

Source: Evgen Pharma

Evgen has sufficient funds to conduct two Phase II clinical trials in subarachnoid haemorrhage (SAH) and oestrogen receptor-positive (ER+) metastatic breast cancer, indications with high unmet medical need. Both trials are strategic entry portals to further therapeutic markets in neurology and oncology.

Phase II in Subarachnoid Haemorrhage

SFX-01 is in Phase II in subarachnoid haemorrhage ...

Evgen has initiated a Phase II trial in patients suffering an aneurismal subarachnoid haemorrhage, with its first subject recruited in April 2016. The principal investigator is Mr Diederik Bulters, Consultant Neurosurgeon at University Hospital Southampton NHS Foundation Trust.

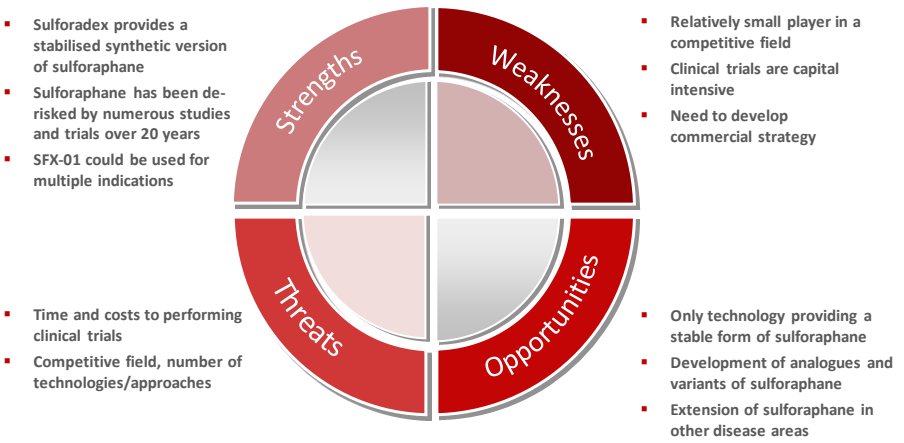
The study will assess safety, tolerability, pharmacodynamics (PD) and pharmacokinetics (PK) of SFX-01, with evaluation of clinical benefit as measured by ultrasonography of blood in the brain. The study will recruit 90 patients in total within 48 hours of experiencing the haemorrhage. All the patients will receive the current standard of care, nimodipine, with 45 additionally receiving SFX-01.

Phase IIa in ER+ breast cancer

… and in Phase IIa in metastatic breast cancer

Commencement of patient recruitment for a Phase IIa trial with SFX-01 in ER+ metastatic breast cancer is imminent. At the time of writing, ethical approval had been received for the first site to start the programme. This trial will investigate SFX-01 in combination with three different hormone-based therapies in 60 ER+ patients, divided equally into three cohorts. The primary objectives are to evaluate safety and tolerability after up to 24 weeks of dosing, and clinical benefit (tumour size) in patients starting to demonstrate resistance to their hormone therapy.

SWOT analysis



Source: Hardman & Co Life Sciences Research

Investment conclusion

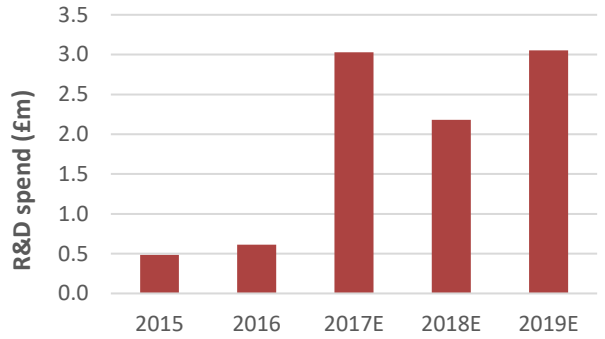
With SFX-01, Evgen is targeting a multi-billion markets…

Evgen is targeting two areas of high unmet medical need. There is little to treat the 80,000 patients per annum that suffer a subarachnoid haemorrhage. Evgen has already secured market exclusivity in the US (orphan drug designation) for a condition where there has been no improvement *via* drug therapy for over 20 years. Breast cancer affects nearly 600,000 women annually in US and Europe. Evgen has also completed its pre-clinical evaluation in multiple sclerosis. Based on conservative assumptions about pricing, Hardman estimates that the market opportunity in SAH and metastatic breast cancer is $1.7bn and $4.1bn respectively. Therefore, SFX-01 would be entering markets with multi-billion dollar potential.

… which is not reflected in its market capitalisation

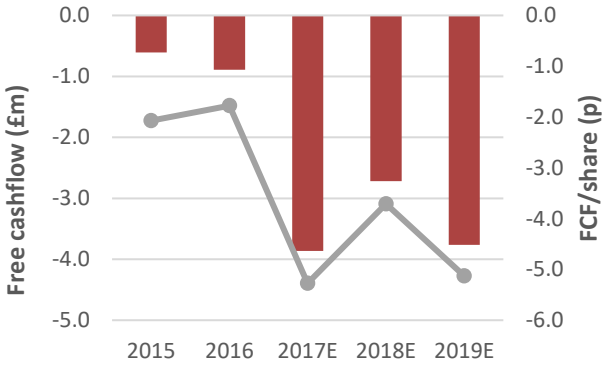
The stock is trading on a market capitalisation of £15m and an EV of £10m which is well below the average of a peer group of companies at a similar stage of clinical development and operating in a comparable therapeutic field (relative EV range 3.0x to 27.4x; average 14.4x). The underlying potential of SFX-01 coupled with the reduced level of risk, due to the huge number of supportive publications and trials with sulforaphane despite its dosing and stability limitations, suggests that a positive outcome in one or both of Evgen's Phase II trials would result in substantial returns for shareholders.

R&D investment



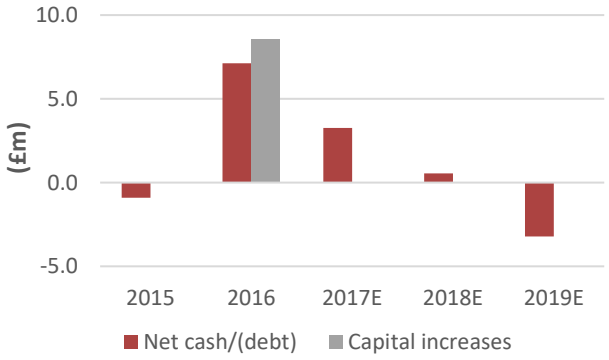
- Investment in R&D has been ramped up to fund the Phase II trial programmes with SFX-01
- Costs have been spread over the expected lifetime of the clinical trial
- Evgen has sufficient funds to complete both Phase II clinical trials with SFX-01 in metastatic breast cancer and subarachnoid haemorrhage

Free cashflow



- Cashflow is driven by the corporate overhead (SG&A) and R&D investment
- Timing differences might occur between accrued tax credits on R&D spend and actual receipts from HMRC

Balance sheet



- Evgen raised £8.5m in fiscal 2016 in a pre-IPO funding round (£2.0m) and at the time of the IPO (£7.0m gross)
- Evgen had net cash of £7.1m at 31st March 2016
- Average monthly burn in fiscal 2017 is ca.£320k

Source: Company data; Hardman & Co Life Sciences Research

Evgen Pharma – the Company

Evgen is a drug development company focused on the clinical development of pharmaceuticals based on natural products.

Corporate history

In 2010, Evgen secured the rights for Sulforadex, the first stabilising formulation of synthetic sulforaphane

Evgen was founded in 2007 by Dr Stephen Franklin in collaboration with two venture capital investors (Enterprise Ventures and Imprimatur Capital), with the strategic objective of securing intellectual property rights relating to natural products that could have a disruptive impact in healthcare. First funding was secured in 2008. After in-depth evaluation of a number of diverse opportunities, management secured the intellectual property rights to the Sulforadex technology from PharmAgra Labs in 2010 and 2011, via an exclusive option then exclusive worldwide licence, respectively. This technology enabled, for the first time, the manufacture of a synthetic and stabilised form of the natural product, sulforaphane.

Sulforaphane attracts huge interests for its potential therapeutic effect

Sulforaphane is produced by enzymatic degradation of glucoraphanin in cruciferous vegetables such as the brassica family (broccoli, cabbage, sprouts etc.) in response to damage – e.g. insect attack or chewing by animals. Interest in sulforaphane has been intense since it was discovered in 1992 to have anti-cancer properties.[1] Since then, there have been over 1,500 scientific research publications and several clinical trials on frozen botanical extracts. However, whilst sulforaphane can be manufactured synthetically, it is an incredibly unstable chemical that needs to be stored at -20°C under an inert atmosphere, making it unsuitable for use as a drug.

Sulforadex is the technology that overcomes this considerable disadvantage. Synthetic sulforaphane is encapsulated within a sugar ring structure, called α-cyclodextrin, to create a viable formulation that is stable at ambient temperature.

Evgen conducted Phase I studies proving the safety and stability of SFX-01

Since inception, Evgen has raised £13m, using the proceeds for pre-clinical development work and to undertake clinical trials. Evgen has conducted two Phase I clinical studies that established the safety and tolerability profile of SFX-01 in healthy patients. The first study used a single ascending dose regimen which resulted in minor side effects (gastric irritation and nausea) and identified the Maximum Tolerated Dose. These findings allowed Evgen to optimise the dosing regimen by splitting the dose into a twice-daily administration of 300mg of SFX-01. In the second trial, these improvements eliminated the side-effects.

Evolution of Evgen

Date	Event
2007	Foundation of Evgen as a corporate vehicle to source new technology
2010	Sulforadex technology held under option agreement
2011	Series A funding, exercise of option agreement and exclusive worldwide licence
2013	Acquisition of an option to acquire right to novel Sulforaphane analogues from the Spanish Research Council and the University of Seville
2014	Phase I completed
Oct-2015	IPO of Evgen Group on AIM, raising gross funds of £7.0m
Nov-2015	Exercise of option and worldwide exclusive rights to novel sulforaphane analogues
Apr-2016	Phase II in subarachnoid haemorrhage

Source: Company reports; Hardman & Co Life Sciences Research

[1] Zhang et al., *Proc. Natl. Acad. Sci. U.S.A*, 1992, **86**(6), 2399-2403

Evgen underwent an IPO in October 2015 to raise sufficient funds to support a programme of two Phase II clinical trials of SFX-01 in breast cancer and subarachnoid haemorrhage.

Strategy

Evgen is focused on the clinical development of SFX-01 initially for two indications: breast cancer and subarachnoid haemorrhage. Phase II trials have been initiated in 2016 for both indications.

Evgen's strategy is to develop Sulforadex in multiple medical indications

Evgen is also contemplating another indication which has a high unmet medical need: multiple sclerosis (and similar neurodegenerative conditions where oxidative stress and the Nrf2 pathway are pivotal), which is currently at the pre-clinical stage of development. No decision has been made whether to progress this further or if this is the optimum neurology indication.

For commercialisation, Evgen has the capacity to formulate SFX-01 in distinct product formats adapted for each therapeutic need (capsule and solid tablet) which will enable the company to establish differential pricing for different indications.

In addition to conducting its own research on SFX-01, Evgen has entered into strategic pre-clinical collaborations with prestigious institutions around the world. These alliances will support Evgen's area of expertise as well as extending the knowledge of SFX-01 and its potential use in other conditions.

Under an exclusive worldwide licence with the University of Seville and the Spanish National Research Council, Evgen has acquired rights to the next generation of sulforaphane analogues; the intension being to harness these equally unstable compounds using the Sulforadex technology. This has extended Evgen's IP position and could facilitate further segmentation of the markets in oncology, neurology and other inflammatory diseases.

Sulforadex® – SFX-01

The considerable disadvantage of sulforaphane is its instability – when synthesised, it is a yellow liquid that needs to be held at -20°C under an inert gas. This has been overcome successfully by its complexation with α–cyclodextrin, using the Sulforadex technology, resulting in a powder formulation that has proven to be stable at room temperature. As a pharmaceutical preparation, it is known as SFX-01.

The technology

Sulforadex

Sulforadex enables for the first time the stabilisation of sulforaphane...

Evgen secured exclusive rights to the core Sulforadex technology from its originators, PharmaAgra and Lalilab, in 2010. This technology represents the expertise that provides a scalable synthesis and, more importantly, the concomitant stabilised form of sulforaphane within an α-cyclodextrin ring.

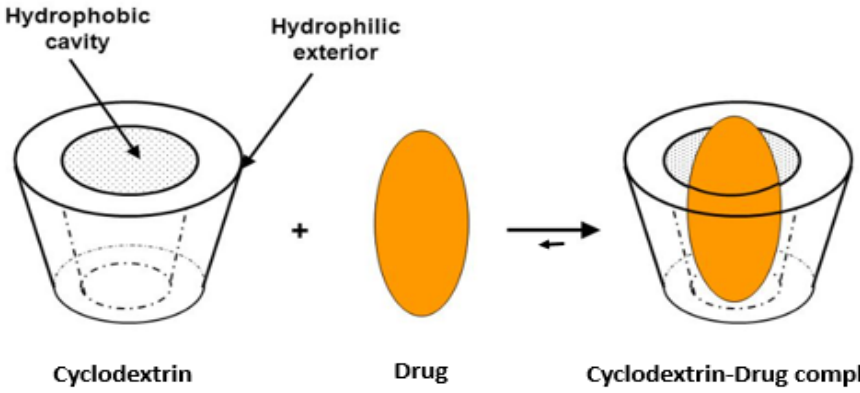
During the manufacturing process, α-cyclodextrin acts both as a catalyst for the synthesis of sulforaphane and as a stabiliser. The new complex formed can be isolated easily, being a solid, and provides a stable synthetic form of sulforaphane. This process can also be used for the synthesis of other sulforaphane analogues.

Cyclodextrin

... using a well-known excipient...

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a slightly lipophilic central cavity. Cyclodextrins are able to form water-soluble inclusion complexes with many lipophilic water-insoluble drugs. Drug molecules, that are usually lipophilic, enter naturally into the central cavity.

Formation of cyclodextrin-drug conjugate



Source: Mohammad Issa in SlidePlayer

Surprisingly, and central to the invention in terms of the patent position, sulforaphane, as a lipophilic entity, has formed the complex. The cyclodextrin used in the manufacturing process is a well-known excipient present in many commercialised drugs. In aqueous solution, drug molecules located within the central cavity are in dynamic equilibrium with free drug molecules.

...that has many benefits

Cyclodextrins can be used to reduce or prevent gastrointestinal irritation, reduce or eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions within a formulation, or to convert oils and liquid drugs into microcrystalline or amorphous powders – as is the case for SFX-01.

In the pharmaceutical industry, cyclodextrins have mainly been used as complexing agents to increase various biophysical factors:

Characteristics of cyclodextrin

- Increase dissolution rate
- Increase stability
- Increase bioavailability
- Enhanced solubility of poorly soluble molecules
- Low toxicity, therapeutically inert
- Mask bitter taste of drug
- Mask unpleasant/obnoxious odour
- Prevent volatility of the drug
- Antidote for metal poisoning
- Prevent skin irritation
- Simple to manufacture
- Low cost

Source: Hardman & Co Life Sciences Research

SFX-01

SFX-01 is Evgen's first product in clinical development

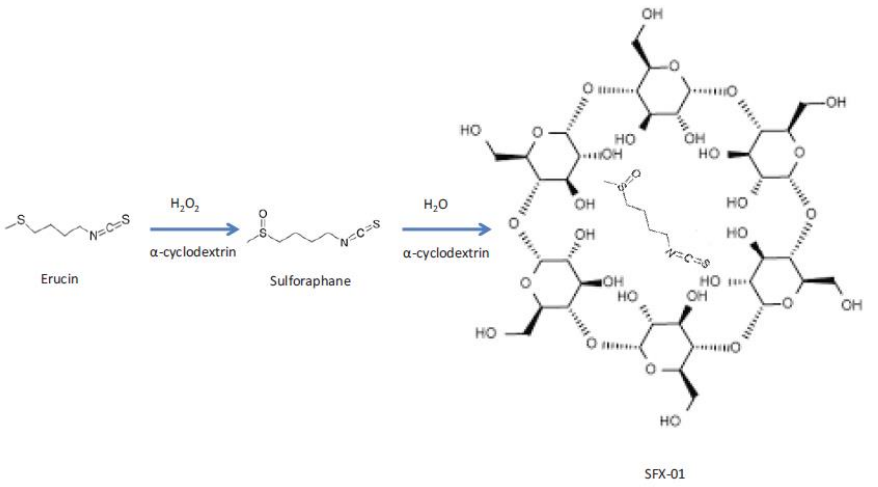
SFX-01 is a synthetic form of sulforaphane stabilised by an α-cyclodextrin ring and is the codename for the first product to use the Sulforadex technology.

Manufacture

SFX-01 is easily obtained as a solid in two synthetic steps

SFX-01 is manufactured using a proprietary two-step chemical process, starting with a small commercially available chemical called erucin. During the reaction, the α-cyclodextrin acts as both a catalyst for the synthesis of sulforaphane and, as the reaction conditions are altered, sulforaphane becomes stable and in solid form through the formation of a complex.

Synthesis of SFX-01



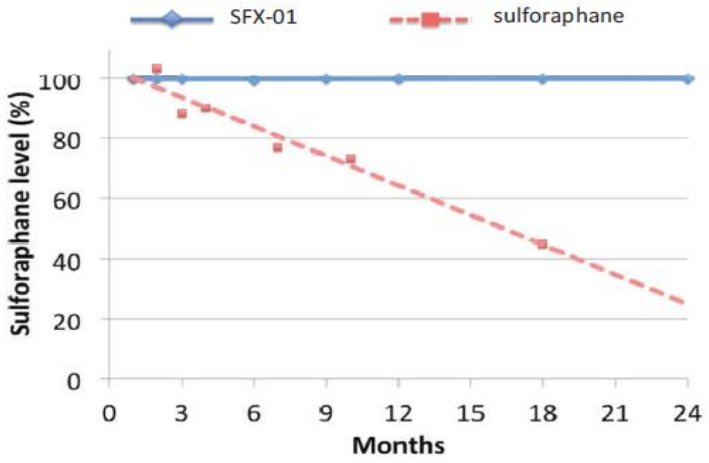
Source: Evgen Pharma

Stability

SFX-01 enables the stabilisation of sulforaphane over a period of 2 years

This innovation has enabled the development of a scalable manufacturing process of an active pharmaceutical ingredient (API) with enhanced stability at room temperature. Sulforaphane is inherently unstable at ambient temperatures and must be stored at -20°C under inert atmosphere in order to maintain its integrity. The following graph represents a two year stability study, comparing SFX-01 with pure sulforaphane at room temperature. This experiment demonstrates clearly the improved stability of SFX-01, keeping its integrity over the whole period compared with regular sulforaphane that constantly degrades over time.

Two year stability of solid SFX-01



Source: Evgen Pharma

The significance of this stable powder API is crucial, as it enables for the first time, the use of sulforaphane as a viable product. Also, the favourable manufacturing economics means that, for the first time, a regular capsule or tablet pharmaceutical sulforaphane product is viable and can be used effectively as a drug.

Phase I clinical trials

Phase I clinical trials gave confidence in SFX-01 and defined the therapeutic dose

Evgen used the numerous precedent *in vitro* and *in vivo* data already published to gain acceptance from the MHRA for Phase I trials. Evgen also conducted two Phase I clinical trials in healthy subjects, aimed at assessing the safety and tolerability of SFX-01 and compared it to published data on sulforaphane.

SFX-01 successfully completed animal safety and toxicology testing without any adverse effects up to an equivalent dose of 700mg per day in man, with the selected therapeutic dose being 300mg twice a day (300mg of SFX-01 corresponds to 46.5mg of sulforaphane). SFX-01 has been shown to have excellent pharmacokinetics in man and bioavailability of 79% in rat.

When sulforaphane is released from the α-cyclodextrin ring in the gastrointestinal tract, it has the same half-life in the body as regular sulforaphane, and has been demonstrated to be equipotent to regular sulforaphane in all head-to-head tests undertaken by Evgen. The studies showed that SFX-01 behaves in the same manner as sulforaphane in humans. No adverse events were recorded with SFX-01.

On-going clinical trials

Evgen is progressing two Phase II clinical trials in oncology and neurology

Following the IPO in October 2015, raising £7m (gross), Evgen has sufficient capital to complete two Phase II clinical trials. Its initial focus will be oncology and neurology:

- Phase IIa in metastatic breast cancer
- Phase II in subarachnoid haemorrhage

Clinical trial timetable

Drug	Indication	2016	2017
SFX-01	Metastatic Breast Cancer	Phase II	
SFX-01	Subarachnoid Haemorrhage	Phase II	
SFX-01	Multiple Sclerosis	Preclinical Studies	
New SFX analogues	Various	Preclinical Studies	

Source: Evgen Pharma

SFX-01: Phase II in metastatic breast cancer

SFX-01 as an anti-cancer agent

SFX-01 shows chemo-protection ...

Sulforaphane has been studied extensively in a number of scientific research papers demonstrating that it may be an effective chemo-protective and therapeutic agent against a vast number of tumours.[2] Sulforaphane is thought to exert its cytoprotective properties through the modulation of Phase I and Phase II enzymes that are active in the initiation phase of carcinogenesis. In several *in vitro* and *in vivo* studies sulforaphane was shown to:

- Inhibit Phase I enzymes, thereby blocking the initiation of chemically-induced carcinogenesis
- Induce Phase II enzymes that detoxify the cell and protect against carcinogens

... and triggers apoptosis in tumour cells

Sulforaphane has been proven also to stop the cell cycle at the G2/M stage in a dose-dependent manner in xenograft and cellular cancer models, triggering cell apoptosis[3]. The precise mechanism of the cytostatic and cytotoxic effects of sulforaphane have not been described fully and are likely to arise from a broad spectrum of activity across a number of targets.

Collaboration with Cancer Research UK

Since 2012, Evgen and the Cancer Research UK Manchester Institute have been collaborating in the field of ER+ metastatic breast cancer and the role of cancer stem cells (CSCs). This fruitful collaboration has highlighted the role of SFX-01 in reducing the number of CSCs in patient-derived breast cancer tissue in xenograft models. The experiments were conducted with SFX-01 in combination with conventional hormone therapy and were shown to reduce the population of hormone independent CSCs.

Resistance in breast cancer treatments

Endocrine therapy to block the ER pathway is highly effective, but its usefulness is limited by common intrinsic and acquired resistance. Multiple mechanisms responsible for endocrine resistance have been proposed[4] and include the presence and progression of hormone-independent breast CSCs. Such events occur in ca.50% of patients. It is thought that, while the hormonal treatment is affecting cancer cells, it leaves the CSCs untouched allowing them to proliferate. This ultimately brings the cancer into relapse and permits the tumour to become hormone-independent.

[2] Lenzi et al., *Cancer Treat. Res*. 2014, 159, 207-223.
[3] Suppipat et al., *PLoS One*, 2012, 7(12), e5 1251.
[4] Clarke et al., *Mol. Cell. Endocrinol.*, **2015**, 418, 220-234.

Phase IIa clinical trial

Evgen has received the all clear to start its Phase IIa trial in metastatic breast cancer...

Evgen received a positive recommendation from the UK's regulatory agency for the commencement of a Phase IIa trial with SFX-01 in metastatic breast cancer. The STEM (**S**FX-01 **T**reatment & **E**valuation in Patients with **M**etastatic Breast Cancer) programme is a multicentre study and is now ready to receive its first patient and will investigate SFX-01 in combination with three different hormone-based therapies in ER+ patients. Sixty patients will be enrolled in three cohorts, following their current therapy:

- **Cohort 1**: SFX-01 (300mg twice daily) + Aromatase inhibitors
- **Cohort 2**: SFX-01 (300mg twice daily) + Tamoxifen
- **Cohort 3**: SFX-01 (300mg twice daily) + Fulvestrant

The primary objectives are to evaluate safety and efficacy in patients that start to show resistance to their current hormone therapy. The trial will assess the effect of SFX-01 on tumour size (as measured by RECIST criteria) in patients that have been shown to have tumours that are starting to progress after an initial benefit on hormone therapy alone.

... with expected read-out in mid-2018

Patients will receive SFX-01 for up to 24 weeks in addition of their current treatment, and will have the choice of whether to continue therapy at the end of the trial period. The study read-out is estimated to be mid-2018, although an earlier read-out from one of the arms is possible as the study is open label.

SFX-01: Phase II in SAH

SFX-01 for subarachnoid haemorrhage

A phase II trial with SFX-01 in patients enduring subarachnoid haemorrhage started in April 2016

Evgen is targeting the population affected by aneurysm SAH. It is not attempting to cure blood leakage or prevent SAH but to prevent the oxidative stress and the toxicity caused by free haemoglobin from the haemorrhage that usually occurs after the brain incident.

Administration of sulforaphane has been shown to reduce inflammation and neurological deficits in rats after intracerebral haemorrhage[5] and subarachnoid haemorrhage. Nrf2 deficient mice are significantly more prone to the neurological deficits of haemorrhagic brain injury.

Phase II clinical trial

A Phase II trial, **S**FX-01 **A**fter **S**ubarachnoid Haemorrhage (SAS), has been initiated in patients suffering an aneurysmal subarachnoid haemorrhage with the first subject recruited in April 2016. The study is being led by the principal investigator, Mr Diederik Bulters, Consultant Neurosurgeon at the University Hospital Southampton NHS Foundation Trust. It aims to assess the safety, tolerability, pharmacodynamics (PD) and pharmacokinetics (PK) of SFX-01. Evaluation of the clinical benefit will be measured by ultrasonography of blood flow in the brain.

Read out in mid-2018

The trial will recruit 90 patients in total, with 45 receiving SFX-01 and all the patients receiving nimodipine, the current standard of care. Patients will be administered SFX-01 (300mg b.d., corresponding to 93mg of sulforaphane) as capsules or as a suspension *via* a nasogastric tube for up to 28 days, within 48h of experiencing SAH. The read-out is estimated around mid-2018, although the addition of further study sites could expedite this.

[5] Zhao et al., *Stroke*, **2007**, 38(12), 3280-6.

SFX-01 in Phase II Clinical Trial – NCT02614742	
Primary outcome measures	**Secondary outcome measures**
► Toxicity: evaluate the safety of up to 28 days of SFX-01 dosed at up to 96mg of sulforaphane per day (300mg bid)	► Assessment of clinical outcome with the modified Rankin scale* (at 7, 28, 90 and 180 days)
► Detection of sulforaphane in cerebrospinal fluid	► Sulforaphane plasma PK at 300mg bid SFX-01
► Measurable reduction of middle cerebral artery flow velocity after 7 days	► Sulforaphane level in cerebrospinal fluid with 300mg twice-a-day SFX-01
	► Determine if up to 28 days treatment with SFX-01 increases serum haptoglobin (HP) levels
	► Determine if up to 28 days treatment with SFX-01 can reduce the incidence of Delayed Cerebral Ischaemia

** scale for measuring the degree of disability and dependence of people who have suffer a stroke or other cause of neurological disability*
Source: ClinicalTrials.gov; Hardman & Co Life Sciences Research

Pre-clinical assessment of SFX-01 in multiple sclerosis

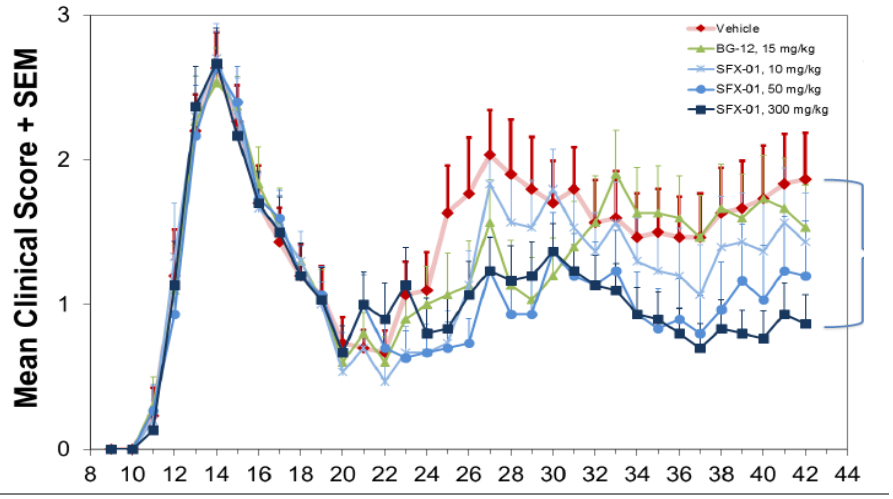
SFX-01: pre-clinical study in multiple sclerosis

Multiple sclerosis (MS) is a condition of the nervous system that affects the coating around nerve fibres, called myelin. Myelin is a substance that protects nerve fibres, helping messages to travel quickly and smoothly between the brain and the rest of the body. In MS, the immune system mistakes myelin for a foreign body and attacks it. Oxidative stress secondary to cell-mediated inflammation plays an important role in the pathology of MS. According to the MS society, 100,000 are affected in the UK, 400,000 in the US and an estimated 2.5 million are affected globally.[6]

To date, there is no cure for MS with approved medications attempting only to prevent relapses of symptoms. ß-interferon was approved first for the treatment of relapsing remitting MS. More recently, Tecfidera (Biogen) has been approved in the US and Europe to treat relapsing MS and has been shown proven to reduce some measures of disease activity, including relapses and development of brain lesions, as well as to slow disability progression over time.

Pre-clinical assessment

EAE mouse model



BG-12 = Tecfidera
Source: Evgen Pharma

[6] www.healthline.com

SFX-01 shows superiority in-vivo compared to Tecfidera

By upregulating the Nrf2-mediated anti-oxidant protective mechanisms and inhibiting NF-κB-mediated inflammatory responses, SFX-01 is thought to have a dual therapeutic potential in MS. In a mouse autoimmune encephalomyelitis (EAE) model which replicates some features of MS, SFX-01 was shown to have a superior effect compared to Tecfidera. A dose dependent effect and higher level of activation of Nrf2 was observed with SFX-01, with significant clinical and histological evidence of superiority compared to Tecfidera. SFX-01 appears to produce a maximum effect in the course of the disease by enabling superior neurological recovery during the chronic stage after relapse.

Conclusion

At this juncture, although the pre-clinical findings in multiple sclerosis look very encouraging, no decision has been made, nor does the company have the resources, to move SFX-01 forward into the clinic for MS. Indeed, nor has a decision been made about whether MS would be Evgen's optimal neurological indication.

Intellectual property

Sulforadex is strongly protected by 3 patent families

Evgen intellectual property is divided into three distinct patent families protecting Sulforadex, SFX-01 and potential analogues:

- **Compositional IP:** Patents, applications and know-how licensed exclusively from US partner. Granted in US, Canada, Australia. Pending in Europe and Japan – Expiry: 2028
- **Process IP:** Stabilised sulforaphane with two further applications awaiting international examination, same major territories as above but also extending geographical reach to Brazil, China and India – Expiry: 2033
- **Compositional analogues IP:** Novel sulforaphane analogues. Patents, application and know-how licensed exclusively from the Spanish National Research Council and University of Seville. Granted in Spain and pending in Australia, Canada, China, Europe, Japan and US – Expiry 2033

Manufacture

Evgen does not currently have, nor does it plan to acquire, the infrastructure or capability internally to manufacture SFX-01 for use in clinical studies.

Evgen has a contract with PharmAgra Labs (United States), the originator of the technology, for the bulk supply of SFX-01 for clinical trial purposes. Under the terms of that agreement, Evgen has issued a non-exclusive sub-licence back to PharmAgra Labs so that they can manufacture SFX-01 for clinical trial purposes. Importantly, Evgen retains all manufacturing rights and can use any manufacturer at any time for clinical trial supplies, and, in due course, industrial scale commercial batches.

Sulforaphane is manufactured using a simple two-stage synthesis from readily available starting materials and is concurrently complexed *in situ* with α-cyclodextrin to form SFX-01.

For commercial production, Evgen intends to transfer the manufacturing to a larger partner, and the clinical trial supply manufacturing agreement is constructed to facilitate this transfer.

Evgen has the ability to formulate SFX-01 in two distinct product formats:

- **Capsule** – For use in SAH; patients unable to take the drug orally, the active ingredient will be solubilised in saline and perfused via a nasogastric tube
- **Solid tablet** – For use in longer-term treatment indications

These distinct formulations may allow Evgen to establish differential pricing for different indications.

Using the API produced by PharmAgra Labs (under licence from Evgen), Evgen has retained the services of a UK-based contract manufacturing company to produce clinical trial supplies of SFX-01 capsules for its SAS and STEM trials.

PharmAgra Labs

PharmAgra Labs is a small privately held Contract Research Organisation based in North Carolina that provides R&D and medicinal chemistry solutions. The company has cGMP production facilities and the ability to manufacture kilo scale API for clinical trials.

Evgen signed the Licence Agreement for SFX-01 (intellectual property and know-how) on an exclusive worldwide basis from PharmAgra Labs for $50,000 upfront payment and subsequent $100,000 and $150,000 milestones based on successful Phase II and Phase III trial outcomes, respectively. The licence terms included topical applications (with the exclusion of skin cancer), which have been retained by PharmaAgra. Under the terms of the contract, PharmAgra Labs is entitled to a maximum of $6m on regulatory approvals (across all indications) and royalties up to 3.5% based on future net sales. In addition, the Licence Agreement provides for sub-licensing at higher royalty rates. The principal terms are consistent with those usually observed in this sector.

Pre-clinical collaborations

Several pre-clinical collaborations support Evgen's targeted market as well as other potential indications

In addition to conducting its own research on SFX-01, Evgen has entered into strategic pre-clinical collaborations with prestigious institutions around the world. Having the technology to stabilise sulforaphane for the first time is a major attraction for many leading research teams studying the Nrf2 and NF-κB signalling pathways. These alliances will support Evgen's area of expertise as well as extending the use and the knowledge of SFX-01 into other conditions.

Pre-clinical collaborations

Date	Institution	Objective
2012	Paterson Institute for Cancer Research, Manchester, UK	*In vitro* and *in vivo* effects of SFX-01 on breast cancer stem cells and mechanism of action
2013	Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, US	*In vitro* and *in vivo* effects of SFX-01 in Acute Lymphoblastic Leukaemia (ALL)
2013	King's College, University of London, UK	Identification of SFX-01 molecular targets using an antibody that recognises sulforaphane-protein adducts
2013	Royal Veterinary College, University of London, UK	Effect of SFX-01 on *in-vivo* models of osteoarthritis joint disease
2014	Duke University, Durham, North Carolina,US	Effect of SFX-01 on *ex-vivo* models of sickle cell anaemia
2015	University of Liverpool, UK	Mechanism of action of SFX-01 and other sulforaphane analogues using an Nrf2 *in-vivo* model
2016	MayoClinic, Rochester, US	Regenerative medicine: repair of bone, cartilage, ligament and tendon tissue

Source: Evgen Pharma

Expanding pipeline with new compounds

In-licensing agreement to strengthen Sulforadex with analogues of sulforaphane

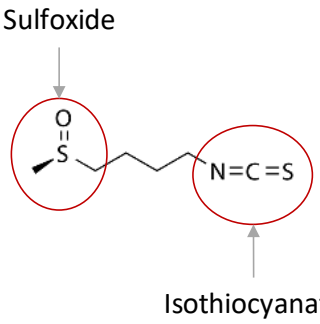
In November 2015, Evgen strengthened its intellectual property portfolio of compounds with the acquisition of exclusive worldwide licensing rights from the Spanish National Research Council and the University of Seville, to a wide range of analogues of sulforaphane; all of which can then potentially use the Sulforadex platform to stabilise them.

The in-licensing agreement extends and complements the IP position with rights to more than 60 new compounds with a view to taking the most promising into clinical development.

Under the terms of the worldwide licensing agreement, Evgen Pharma will make a modest upfront payment and one-off milestones when the first compound progresses through clinical development. Royalties on future sales of any marketed products will not exceed 1% of net sales.

Sulforaphane

Sulforaphane

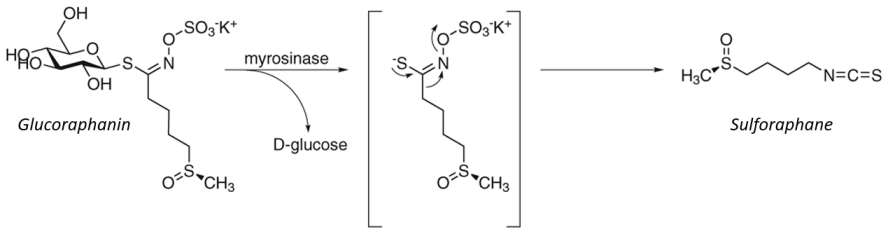


Source: Hardman & Co Life Sciences Research

Origin

Sulforaphane is now a well-known chemical consisting of a reactive isothiocyanate group and a sulfoxide group at opposite extremities of a carbon chain. Intact plants, particularly cruciferous vegetables such as broccoli, cauliflower, cabbage and Brussel sprouts, contain glucoraphanin which is the precursor of sulforaphane. Sulforaphane itself is generated from the enzymatic degradation of glucoraphanin. The enzyme responsible for the degradation is myrosinase, which is a plant defence-related enzyme capable of hydrolysing glucosinolates (i.e. glucoraphanin) into isothiocyanates (i.e. sulforaphane).

Natural biosynthesis of sulforaphane



Source: Hardman & Co Life Sciences Research

Sulforaphane is generated from the enzymatic decomposition of glucoraphanin

In cruciferous vegetables, myrosinase is stored in vesicles within the cells. When the plant experiences tissue damage, the enzyme is discharged from the vesicle and hydrolyses glucoraphanin which, in turn, releases glucose and generates sulforaphane. This conversion typically starts in the mouth when the plant is chewed, and continues in the digestive tract of animals as well as humans.

The natural main source of sulforaphane is broccoli

The main natural source of sulforaphane is broccoli plants, but quantities are quite modest and certainly not at therapeutic levels. Also, there is a large variation in the amount of sulforaphane produced in the guts by each individual person. On average, the amount of sulforaphane generated is as follows:

Conversion in the gut

In man, the conversion to sulforaphane can occurs in the gut with an average rate of 11%

Many reports have demonstrated the conversion of glucoraphanin into sulforaphane in human gut. A complete study, combining two distinct populations (Baltimore, USA and Qidong, China) measured the conversion of glucoraphanin to sulforaphane frozen broccoli sprout extract in the gut by microflora.[7] The authors concluded that the conversion varies enormously between the volunteers from 1% to 40%, with an average value of 11%. Also, the authors highlighted the large discrepancy for a single volunteer on different occasions, ranging from 2% to 40%. This proves that botanical extracts are not a suitable means of providing a therapeutic dose of sulforaphane.

Evgen is taking a conservative approach in the conversion rate with a higher value of 20%, corresponding to the average value for higher rate individuals.

[7] Fahel J.W. et al *Cancer Prev. Res*. **2012**, 5(4), 603-611.

To achieved the therapeutic dose, the daily intake of broccoli is 4.8kg!

In our calculations, knowing the quantity of glucoraphanin in Broccoli and Broccoli sprouts[8], the daily quantity of broccoli needed to achieve the therapeutic dose would be:

- **Broccoli:** 4.4kg based on 11% gut conversion (or 2.4kg with 20% conversion)
- **Broccoli sprout:** 0.287kg based on 11% gut conversion (or 0.158kg with 20% conversion)

Stability

In normal condition, sulforaphane is poorly stable...

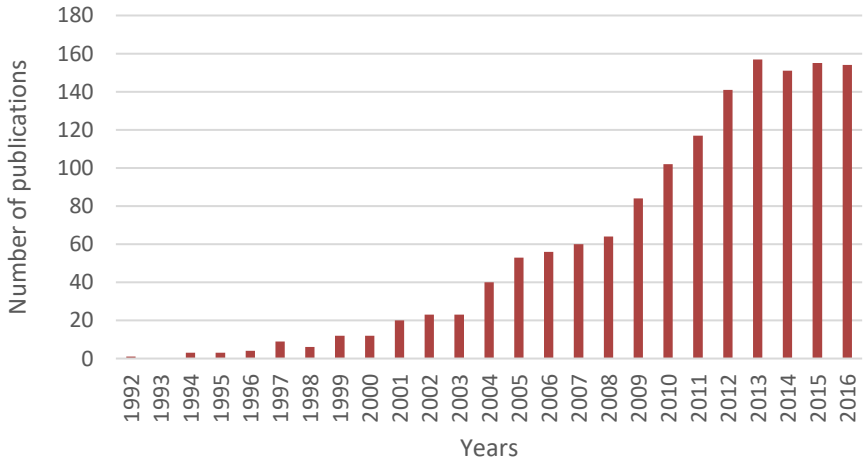
In its pure form, sulforaphane is a yellow oil unstable at ambient temperature, making it difficult to manufacture and impossible to be used as a drug. Multiple clinical trials have endeavoured to deliver sulforaphane by enzymatically treating broccoli sprouts extracts and then freezing the liquid preparation. However, the only registered clinical trials using synthetic sulforaphane are those with SFX-01.

Application

... but has attracted a huge scientific interest

Sulforaphane has attracted huge scientific interest since it was discovered to have and anti-cancer properties[1]. Particularly since 2004, a growing number of scientific research papers have been published worldwide, underlining the compound's medical potential in multiple diseases.

Sulforaphane in scientific publications



Source: PubMed, 17th October 2016

Sulforaphane has proved to be effective in many disease area

The development of a concentrated pure form of sulforaphane – of the sort that could be presented in a tablet or similar medicinal format – has been held back by its inherent instability. Despite this, several clinical trials[9] have being conducted using extracts in the following disease areas:

- Cancer
- Schizophrenia
- Autism
- Cardiovascular disease prevention
- Asthma and COPD
- Type II diabetes

[8] Fahel J.W. et al *PNAS* **1997**, 94(19), 10367-10372
[9] Clinicaltrials.gov

In published studies, plant extracts are used as the source of sulforaphane

All these studies have the same common point: use of broccoli and broccoli sprout extract in some form. Some studies specify sulforaphane but are actually delivering the precursor molecule in a dried botanical preparation. Others use enzymes to release sulforaphane, which then requires a liquid preparation to be frozen in advance of being administered in the clinic. All of them suffer from the fact that sulforaphane levels are low, or, when they are elevated, the extract becomes difficult to consume, by volume and by gastrointestinal side effects.

On the back of these publications, the use of broccoli and broccoli sprouts in various forms (powder, capsules, extracts) has been widely marketed in natural and health product shops. But the point is that these products contain no sulforaphane and only have the potential after digestion to produce sulforaphane at low doses with no proven clinical benefit.

Sulforaphane has been shown to have anti-cancer and neuroprotective qualities in a wide range of pre-clinical and/or clinical studies, for example breast cancer,[10] prostate cancer,[11] neurodegenerative disorders,[12] multiple sclerosis,[13] diabetes[14] and autism.[15] However, the daily dose of sulforaphane required to elicit these potential therapeutic effects is far greater than can practically and consistently be delivered from dietary sources.

Mechanism of action

Sulforaphane is a modulator of the anti-oxidant and inflammation response

Published literature on the mechanism of action of sulforaphane has focused largely on its ability to modulate two important pathways linked with the anti-oxidant and inflammation responses, Nrf2 and NF-κB, that have been implicated in both cancer[16] and neurodegenerative disease.[17] Whilst the anti-cancer effects of sulforaphane have been established since 1992, the neuroprotective effect of sulforaphane has more recently gained traction in published scientific literature. In recent years, sulforaphane has been shown in *in-vitro* and *in-vivo* studies to have neuroprotective effects in ischaemic stroke, traumatic brain injury, multiple sclerosis, Alzheimer's and Parkinson's disease, as well as autism.

The key regulator of both pathways is the stress sensor protein chaperone Keap1, on which sulforaphane is a modulator. Sulforaphane is one of the most potent naturally occurring modulators of Keap1, exhibiting high efficacy in the nanomolar range in cell culture. Its potency may reflect in part a capacity to accumulate in cells as an interchangeable conjugate with glutathione:

Sulforaphane upregulates the anti-oxidant response via Nrf2...

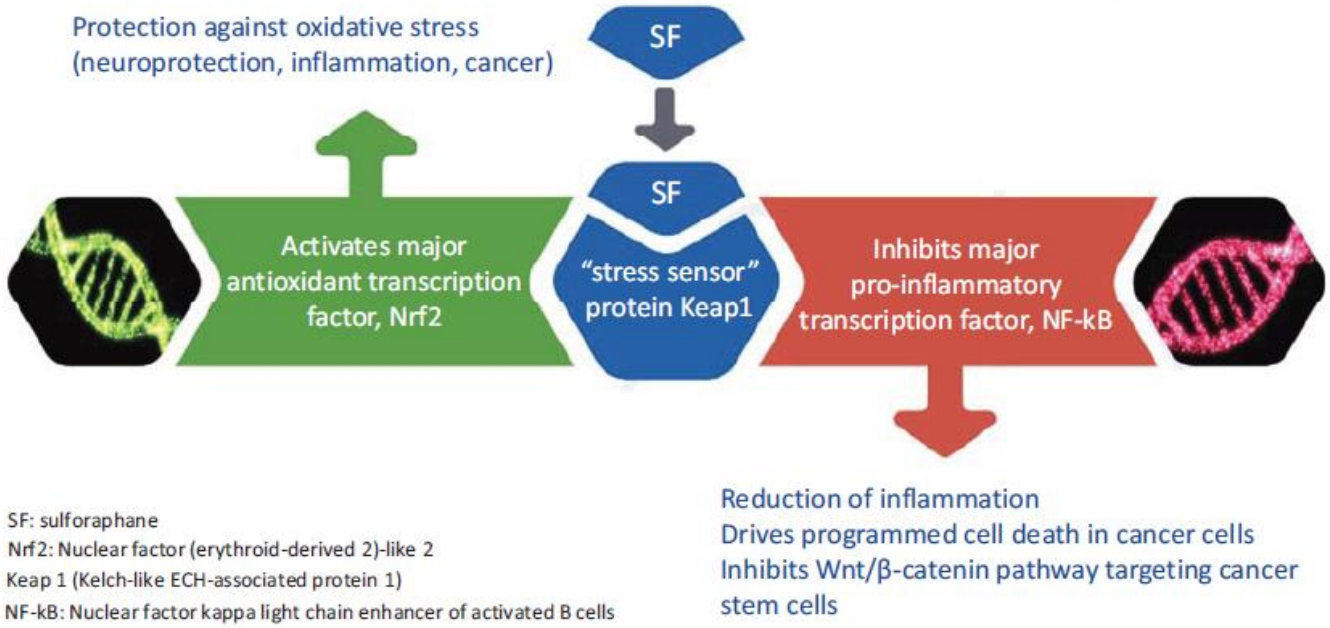
- **Upregulate transcription factor Nrf2, which drives the anti-oxidant response:** In normal conditions, Keap1 is able to block Nrf2 signalling by marking it for proteasomal degradation. Interaction of sulforaphane with Keap1 disrupts this function allowing accumulation of Nrf2 in the cell nucleus and activation of a transcriptional program to trigger the anti-oxidant response.

...and downregulates the inflammation response via NF-κB

- **Downregulate transcription factor NF-□B, which drives the inflammatory response:** Keap1 is a IKK binding partner, which is responsible for the down-regulation of NF-□B activation. By interacting with Keap1, sulforaphane is able to inhibit the activation of the NF-□B signalling by IKK and ultimately plays an important role in down-regulation of the expression of pro-inflammatory genes.

[10] Sun D. et al, *Clin Cancer Res.* **2010**, 16(9), 2580-2590.
[11] Traka, M.H. et al, *Drug Discov Today*, **2014**, 19(9), 1488-1492.
[12] An, L et al, *Int. J. Mol. Sci*. **2014**, 15, 14396-14410
[13] Guo L et al, *Exp. Neurol*. **2013**, 239-249.
[14] De Souza et al, **2016**, *Food Funct*. 7, 2060-2065.
[15] Zimmerman et al, *Proc Natl Acad Sci USA*, **2014**, 111(43), 15550-15555.
[16] I. Bellezza, et al, *Cancers*, **2010**, 2, 483-497.
[17] J.D Wardyn, et al, *Biochem. Soc. Trans*., **2015**, **43**(4), 621-626.

Sulforaphane mechanism of action



Source: Evgen Pharma

Nrf2 signalling pathway

The natural red-ox homeostasis balance

When the body is young and healthy, it is able to take care of the balance between cellular damage, repair and rejuvenation. One way of repairing damage is to produce anti-oxidants to balance and fight against the reactive oxygen particles generated during normal metabolic processes.

Nrf2 is the main regulator of the anti-oxidant response

Following through this idea, anti-oxidants are thought to reduce risk of certain pathological conditions such as cancer, diabetes, atherosclerosis, aging, and neurodegeneration. Anti-oxidant supplements have always been popular and available to the public in the belief that they will help to fight the potential damage caused by reactive oxygen molecules. These reactive elements are usually coming from metabolic reactions and stress conditions due to the external environment.

Such anti-oxidant supplements, including vitamin C and E found, for example, in fruit juices and berries, are used to neutralise free radicals and prevent the damage they cause. In this case, one molecule of anti-oxidant would neutralise one free radical. In normal unstressed conditions, only low-level concentrations of these compounds are required.

However, there will be times when the balance is not right. Too much anti-oxidant unbalances the redox homeostasis. This occurs in cancer cells, where accelerated metabolism and a high concentration of reactive oxygen is needed to maintain their high proliferation rate.

One way the cell takes care of repairing oxidative damage is to trigger the production of anti-oxidant enzymes through the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signal pathway. [18]

[18] Levonen et al, *Redox Biology*, **2013**, 45-49

Nrf2 signalling pathway

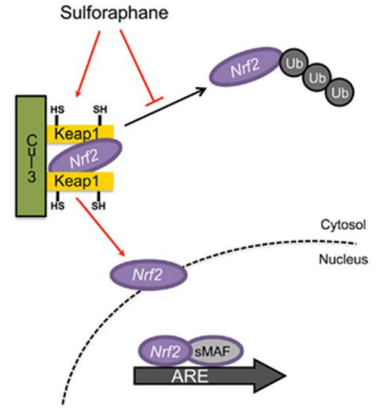
Nrf2 regulates the expression of anti-oxidant proteins that protect the body against oxidative damage triggered by injury and inflammation. Under normal and unstressed conditions, Nrf2 is localised in the cytoplasm and is kept in a dormant state through an interaction with its chaperone protein Keap1. It forms a complex with other proteins that keep it in this dormant state and with a short half-life, it is subsequently degraded rapidly by the same complex of proteins.

Under oxidative stress, this complex is disrupted, freeing the Nrf2 protein, which then can translocate into the cell nucleus and bond to a specific portion of DNA: the anti-oxidant response element (ARE). This location corresponds to the main upstream region of many antioxidative genes, and Nrf2 can trigger their transcription. Nrf2 gene products are typically characterised as Phase II detoxification enzymes and/or anti-oxidant enzymes. Production of anti-oxidant enzymes have sufficient power to neutralise up to one million free radicals per enzyme, every second. This one to one million ratio proves to be a far more effective approach in combating aging and disease than the production and the use of anti-oxidant molecules.

Sulforaphane activates the Nrf2 pathway

The protective qualities of sulforaphane are mediated by activation of Nrf2. Numerous scientific publications[19] describe sulforaphane as a key player in facilitating the dissociation of Nrf2 from the chaperone protein Keap1, which translocases into the nucleus and activate the anti-oxidant response.

Sulforaphane and Nrf2



Source: Frontier in Genetics

Modulators of the Nrf2 pathway

To date, only Biogen with Tecfidera has a marketed product activator of the Nrf2 pathway treating multiple sclerosis patients. There are few Nrf2 activators in clinical development at present. However, there is an increasing quantum of research around activators as potential treatments across a number of indications. A non-exhaustive list of pharmaceutical Nrf2 activators (not dietary supplements) is listed in the following table.

Activator of the Nrf2 pathway in clinical trials

Product	Company	Stage	Indication
Tecfidera – BG12	Biogen	Marketed	Multiple sclerosis
RTA408-omaveloxolone	Abbvie/Reata Pharma	Phase II	Mitochondrial myopathies
RTA408-omaveloxolone	Abbvie/Reata Pharma	Phase II	Friedreich's ataxia
RTA408-omaveloxolone	Reata Pharma	Phase I	Melanoma
RTA408-omaveloxolone	Reata Pharma	Phase I	Post-surgical corneal endothelial cell loss
Bardoxolone methyl	Kyowa Kirin/Reata Pharma	Phase I and II	Pulmonary hypertension indications
XP23829	Xenoport	Phase II - discontinued	Psoriasis, multiple sclerosis
ALKS8700	Alkermes	Phase II	Multiple sclerosis
CXA-10	Complexa	Phase I	Acute Kidney Injury

Source: Hardman & Co Life Sciences Research

[19] Boddupalli S, et al., *Front. Gene*. **2012**, 3:7

The NF-κB pathway

NF-kB controls many cellular protective events...

Nrf2 is also an essential in the inhibition of another major transcription factors called kappa-light chain-enhancer of activated B cells (NF-κB), which have an essential role in inflammation and innate immunity. Indeed, NF-κB controls the expression of a number of genes that regulate cell survival mechanism and immune responses[20]:

- Cell growth and proliferation
- Survival
- Apoptosis
- Stress responses to a variety of stimuli
- Embryogenesis

Aberrant NF-κB activation contributes to development of various autoimmune, inflammatory and malignant disorders including rheumatoid arthritis, atherosclerosis, inflammatory bowel diseases, multiple sclerosis and malignant tumours. Thus, inhibiting NF-κB signalling has potential therapeutic application in cancer and inflammatory diseases. NF-κB has been found to be highly expressed in tissues that are frequently subject to environmental and metabolic stresses such as lung, gastrointestinal tract, liver and kidney.

NF-κB and cancer

NF-κB is recognised increasingly as having a crucial role in many steps of cancer initiation and progression controlled by the well-known IKK enzymes. IKKs inactivate the NF-κB transcription factor by keeping it in an dormant state in the cytoplasm. Phosphorylation (activation) of IKK freeing the NF-κB complex, which enters into the nucleus where it can turn on gene expression (canonical pathway). NF-κB can also be activated through the non-canonical pathway that relies the processing of p100 protein instead of IKK.

Active NF-κB turns on the expression of genes that keep the cell proliferating and protect the cell from conditions that would otherwise cause apoptosis. Inhibition of NF-κB results in increased susceptibility to apoptosis leading to increased cell death.

In tumour cells, NF-κB is kept in an active state either due to a mutation in the protein itself or in the proteins that regulate its activity (e.g. IKKs).

NF-κB and inflammation

NF-κB is chronically activated in many inflammatory diseases[21], After activation of T- or B-cell receptors, through a cascade of phosphorylation events, NF-κB is activated and enters the nucleus to upregulate genes involved in T-cell proliferation, maturation and development leading to inflammation such as inflammatory bowel disease, arthritis, sepsis, gastritis, asthma, atherosclerosis, multiple sclerosis, COPD and others.

[20] Park M.H. et al, Cell, 2016, 5(2), 15
[21] Monaco, C.; *Proc. Natl. Acad. Sci. USA* **2004**, 101, 5634–5639

Commercial opportunity

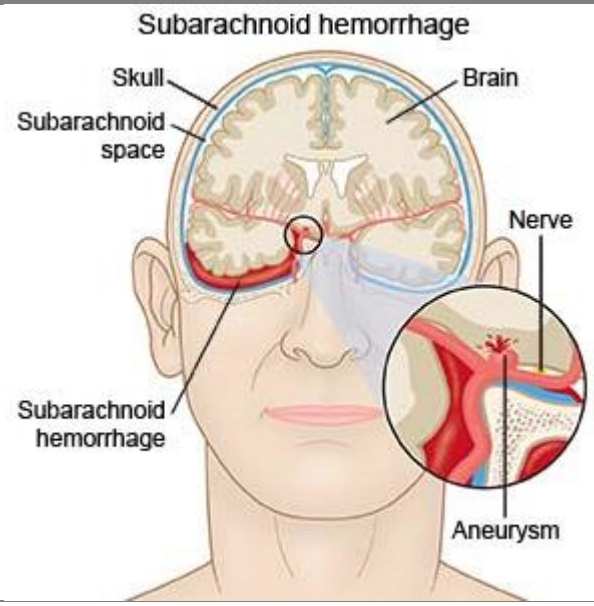
The proposed clinical development strategy for SFX-01 is focused on developing the drug for markets that currently have significant clinical needs and/or little competition with possible market exclusivity.

Subarachnoid haemorrhage

Subarachnoid haemorrhage is a life-threatening condition

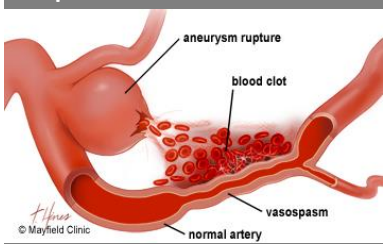
SAH is a life-threatening and catastrophic event caused by bleeding into the space surrounding the brain, the subarachnoid space, that corresponds to the area between the arachnoid membrane and the pia mater surrounding the brain. Usually, this space is filled with the cerebrospinal fluid for protection. SAH can also lead to a debilitating condition caused by oxygen deprivation through cerebral vasospasms and thus to impairment of brain functions and ultimately tissue death.

Subarachnoid haemorrhage



Source: Lone parenting website

Complications in SAH



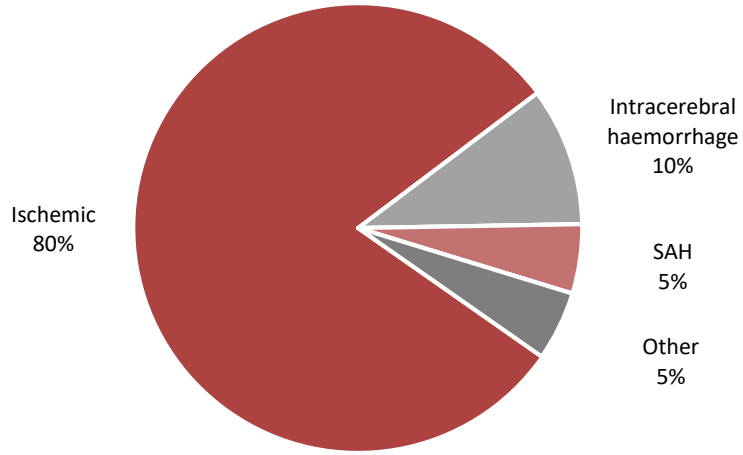
Source: Mayfield clinic

When blood is released into the space, it increases pressure, irritates surrounding tissues and induces vasospasm. Moreover, the vascular event deprives of oxygen the area of brain that previously received oxygen-rich blood, resulting in a stroke. In addition, the pressure exercised by the excess of blood creates a complication called vasospasm that narrows the inside diameter of nearby arteries that could cause a secondary stroke 5 to 10 days after SAH. The two main causes of SAH are:

- Ruptured cerebral aneurysm that could happened spontaneously (50%-80%, with women more affected)
- Head injury (10%)

The vascular incident is a very serious condition and accounts for around 5% of total number of strokes, with ischemic and intracerebral haemorrhage strokes accounting for 80% and 10%, respectively. Approximately 75% of these patients suffer permanent brain damage or die within 30 days due to all the side effects affecting patients.

Subarachnoid haemorrhage



Source: WHO

Symptoms

When SAH occurs, it is an emergency situation and necessitates hospitalisation in intensive care units for several days.

Symptoms of subarachnoid haemorrhage

- Sudden onset of a severe headache
- Nausea and vomiting
- Stiff neck
- Photophobia –sensitivity to light
- Type II diabetes loss of consciousness
- Seizures

Source: Medicine Today; Hardman & Co Life Sciences Research

Diagnosis

In addition to the physical and cognitive symptoms, SAH is diagnosed and confirmed following non-invasive or/and invasive procedures:

Computed Tomography (CT) scan: a non-invasive X-ray that provides detailed images of anatomical structures within the brain. It is especially useful for detecting blood in or around the brain. When a contrast is injected into the blood stream, the technology is called CT angiography (CTA) and aims to view the arteries. CTA provides the best pictures of blood vessels (through angiography) and soft tissues (through CT). If the CT scan does not show evidence of bleeding but the patient's symptoms are typical for SAH, a lumbar puncture may be performed.

Magnetic resonance imaging (MRI) scan is a non-invasive procedure that uses a magnetic field and radio-frequency waves to give a detailed view of the soft tissues of the brain. An MRA (Magnetic Resonance Angiogram) is the same non-invasive study, that examines the blood vessels in addition to structures of the brain.

Lumbar puncture is an invasive procedure in which the cerebrospinal fluid is collected *via* a hollow needle inserted into the subarachnoid space of the spinal canal for the detection of blood.

Angiogram is an invasive procedure in which a catheter is inserted into an artery and passed through the blood vessels to the brain. Once the catheter is in place, contrast dye is injected into the bloodstream and X-ray images are taken.

Available treatments

SAH suffers for no clinical development in 20 years...

To date, there has been no improvement in clinical outcomes for SAH for at least 20 years. Although early repair of ruptured aneurysms has improved overall outcomes, it remains a devastating disease, with mortality approaching 50% and less than 60% of survivors returning to functional independence.

Surgery: Two main procedures are used to repair the affected blood vessel and prevent the aneurysm from bleeding again:

- Neurosurgical clipping: after craniotomy, the neurosurgeon seals the aneurysm with a permanent tiny metal clip
- Endovascular coiling: a thin catheter is guided through the blood vessel to the aneurysm, then a platinum coil is passed through to seal the aneurysm

... with few medical options...

Medication: Pain relief will be used to relieve the severe headache pain associated with SAH (Morphine, codeine, paracetamol).

- Nimodipine is also used in SAH, not to repair the bleeding, but to prevent or reverse any eventual cerebral vasospasms following the event. Nimodipine blocks calcium channels on the walls of the blood vessels, causing the muscles in the wall to relax and the blood vessels to widen. This action helps to overcome the effects of vasospasm and avoid oxygen shortage to brain cells.
- Other medications include anti-convulsants to prevent seizures and anti-emetics

Burden for the healthcare system

... and is a huge burden for the healthcare system due to complications

In the US, it is believed that 30,000 to 35,000 patients are hospitalised, each year for aneurysm SAH. Due to the severity of the condition, they need to be in intensive care units. Approximately 75% of these patients suffer permanent brain damage or die within 30 days due to complications. Given the morbidity, the fact that patients affected by SAH need intensive care, and the cost of rehabilitation of survivors, the burden on the healthcare system is disproportionately high. This results in overall in-patient charges of more than £510m in the UK.[22]

After the ruptured aneurysm is surgically repaired, patients remain at risk of multiple complications that can occur after surgery, with cerebral vasospasm and delayed cerebral ischemia (DCI) being the most common and severe.

DCI is a clinical syndrome of focal neurological, cognitive deficits, or both, that occurs unpredictably in 30% of patients in 3 to 14 days after the initial haemorrhage. While re-bleeding from the aneurysm is still a significant complication in the hours after the initial bleed, DCI remains the single most important cause of mortality and morbidity in those patients who survive aneurysm treatment. DCI often leads to the death of brain tissue due to insufficient blood flow to certain areas of the brain.

The pathological mechanisms underlying DCI are still unclear and nimodipine remains the only therapeutic intervention proven to improve functional outcomes after SAH. This results to a significant economic burden to the hospital due to additional direct in-hospital costs per patient of approximately $50,000. In addition, the lifetime cost associated with chronically disabled patients presents a significant economic burden to the entire healthcare system.

[22] Rivero-Arias et al. Cost Effectiveness and Resource Allocation 2010, 8:6

Commercial market

Orphan Drug designation

Evgen secured the Orphan Drug designation in the US allowing market exclusivity

Due to the market size, SFX-01 is eligible for Orphan Drug designation in both the EU and US for, which would provide marketing exclusivity.

Regulation 141/2000 states that a drug shall be designated as an Orphan Drug if its sponsor can establish:

- that it is intended for diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in EU or less than 200,000 in US when the application is made; or
- that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in EU and US, and that without incentives it is unlikely that the marketing of the drug would generate sufficient return to justify the necessary investment; and
- that there exists no satisfactory method of diagnosis, prevention or treatment of the condition that has been authorised in the EU and US, if such method exists, the drug will be of significant benefit to those affected by that condition

Orphan drug designation exclusivity

	Europe	US
Patient populations	Less than 5 in 10,000 (1 in 2,000)	Less than 200,000 (1 in 1,500)
Market exclusivity	10 years from approval	7 years from approval
Reduced R&D cost	Assistance with development of the medicine Reduced fees for marketing-authorisation applications	50% tax credit in clinical trials conducted in the US R&D grants for Phase I to Phase III clinical trials User fees waived
Regulatory process	Fast track procedure	Fast track procedures

Source: Hardman & Co Life Sciences Research

Evgen has secured Orphan Drug status for SFX-01 already in the US (August 2016) and is in the process of applying for it in Europe.

Affected population

Market opportunity in just the US and EU is $1.7bn

The World Health Organization and published medical literature estimate that ca.600,000 individuals worldwide suffer an aneurysm SAH each year, with 30,000 to 35,000 being in the US and around 51,000 in Europe. All of these patients would potentially benefit from SFX-01. Based on an estimated price of $20,000 per course of treatment, this would equate to a market opportunity of $1,7bn.

Breast cancer

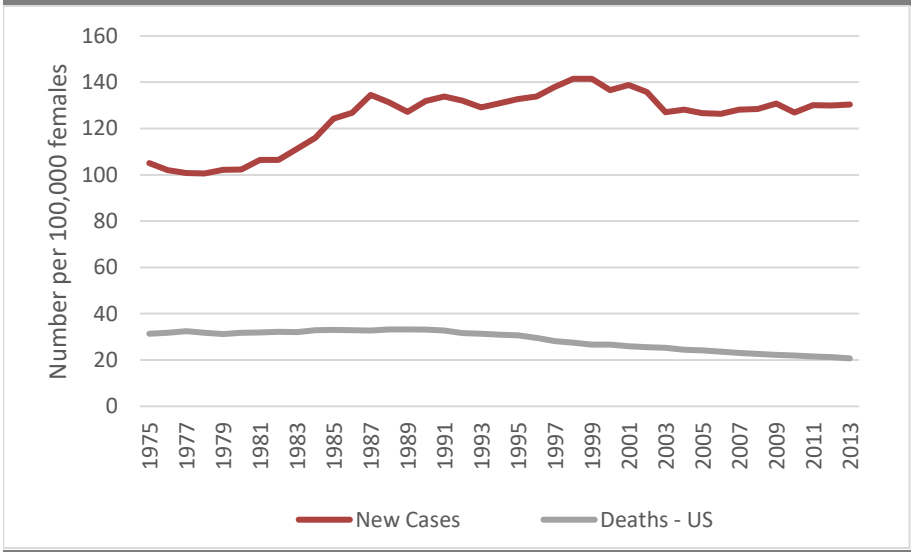
Breast cancer is the most common cancer globally with more than 3m women affected in the US in 2013 and with a five-year survival rate of 89.7%, benefiting from improved treatment regimens.[23] The decrease in the death rate is believed to be a combination of early diagnosis through screening programmes, coupled with increased awareness and more efficacious drugs.

Breast cancers are classified according to three categories:

- Hormone-receptor positive (ER-positive)
- HER2 positive
- Triple negative

[23] www.cancer.gov

Breast cancer per 100,000 females in the US



Source: www.cancer.gov, Hardman & Co Life Sciences Research

70% of breast cancer are ER-positive

ER-positive breast cancer

With SFX-01, Evgen is targeting the ER-positive breast cancer category. Studies show that approximately 70% of breast cancers are ER-positive and are then sensitive to hormonal therapy. Most ER-positive breast cancers are also progesterone receptor (PR)-positive.

Hormone-sensitive breast cancer cells express receptors that are activated when female sex hormones bind to them, causing changes in the expression of specific genes, and drive rapid proliferation.

After surgical removal of the breast tumour, doctors test samples for presence of hormone receptors in the cancer cells. If the tumour cells express oestrogen receptors, the cancer is defined as oestrogen receptor-positive (ER-positive). Similarly, if the tumour cells express progesterone receptors, the cancer is called PR-positive. ER+ breast cancer may grow more quickly than other breast cancer types, and is more likely to spread to other parts of the body.

The primary treatments for ER+ breast cancer are drugs which target the oestrogen receptor directly, or those which block the production of oestrogen in the body.

Type of hormonal therapy

Hormonal therapies are routinely used in patients who have ER+ breast cancer immediately after surgery. This approach is known as adjuvant therapy. Tamoxifen and aromatase inhibitors are the standards of care in the pre-and post-menopausal settings respectively. Both classes of agents have been shown to prolong the time to recurrence significantly, and to reduce the recurrence rate. In the metastatic setting, tamoxifen and LHRH antagonists are used in the pre-menopausal population, and aromatase inhibitors in the post-menopausal group. In the metastatic setting, resistance to first-line treatments inevitably develop in all cases, and second-line therapies such as the ER down-regulator fulvestrant (Faslodex) are used, or the second-generation aromatase inhibitor examestane.

The major classes of hormonal agents include:

- **Blocking ovarian function:** Ovaries are the main source of oestrogen in pre-menopausal women. Hence, ovarian ablation is the main treatment and can be done surgically or by radiation. Alternatively, the ovarian function can be suppressed temporally by interfering with the signal from the pituitary gland that stimulates the ovaries to produce oestrogen. These drugs are activators of gonadotropin-releasing hormone (GnRH) and luteinizing hormone-releasing hormone (LH-RH) receptors.

GnRH and LH-RH agonists				
Drug	**Generic name**	**Company**	**Target**	**Cumulative sales $m**
Zoladex	goserelin	AstraZeneca	GnRH, LH-RH	19,300
Lupron	leuprorelin	Takeda	GnRH	24,269

Source: Hardman & Co Life Sciences Research

- **Blocking oestrogen production:** Aromatase is an enzyme that is crucial in the production of oestrogen in the ovaries and in other tissues. By inhibiting the function of this enzyme, mainly in post-menopausal women, the oestrogen secretion is blocked and may stop the cancer growing and spreading.

Main aromatase inhibitors			
Drug	**Generic name**	**Company**	**Cumulative sales $m**
Femara	letrozole	Novartis	9,412
Arimidex	anastrozol	AstraZeneca	14,286
Aromasin	exemestane	Pfizer	3,465

Source: Hardman & Co Life Sciences Research

- **Blocking the oestrogen's effects:** Oestrogen receptor antagonists are used to prevent oestrogen from binding and stop its stimulatory effects. They are usually used for a long period (usually for 5 to 10 years) and also prevent cancer recurrence. The main drug is Nolvadex (tamoxifen) that is being used for more than 30 years and is now available generically.

Oestrogen receptor antagonists			
Drug	**Generic name**	**Company**	**Cumulative sales $m**
Nolvadex	tamoxifen	AstraZeneca	8,276
Evista	raloxifene	Lilly	14,503
Faslodex	fulvestrant	AstraZeneca	3,842

Source: Hardman & Co Life Sciences Research

All patients treated with hormonal agents in the metastatic setting eventually develop resistance to the treatment. A number of different mechanisms are implicated in the acquisition of resistance to endocrine therapy.

Resistance in breast cancer treatments

50% of patients relapse due to hormone-independent breast cancer CSCs

Endocrine therapy to block the ER pathway is highly effective, but its usefulness is limited by common intrinsic and acquired resistance. Multiple mechanisms responsible for endocrine resistance have been proposed[24] and include the presence and progression of hormone-independent breast CSCs. Such event is occurring in nearly 50% of patients treated. It is thought that, while the hormonal treatment is affecting cancer cells, it let the CSCs untouched and proliferate during treatment with hormonal agents. This ultimately bring the cancer to relapse and the tumour to become hormone-independent.

[24]R. Clarke, *Mol. Cell. Endocrinol.*, **2015**, 418, 220-234.

Affected population

Breast cancer is the most common cancer

Breast cancer is the most common cancer in women worldwide. It is believed that the number of new cases is 125:100,000 per year. In the US, 230,815 women were diagnosed with breast cancer in 2013, with 40,860 deaths. In Europe, the incidence is established at 358,967 in 2012. If we estimated that 70% of breast cancer is hormonal dependent, the following table shows Evgen's addressable market in Europe and in the US.

Breast cancer – addressable market

Country	Population	Addressable population
US	230,815	161,570
Europe	358,967	251,277
Total	**589,782**	**412,847**

Source: Hardman & Co Life Sciences Research

Big addressable market and conservative pricing still equates to an addressable market of $4.1bn

The breast cancer therapeutic market is mainly dominated by the generic drugs. There are approximately 25 drugs available to treat breast cancer and there is still an unmet need for new drugs that would overcome resistance and prevent recurrence of the disease. In 2013, the market was valued at nearly $10bn and it is expected to double in the next 10 years.[25] Assuming a very conservative price of $10,000 p.a. for SFX-01 and the addressable population shown in the table above, the market opportunity in breast cancer would be $4.1bn.

[25]http://www.pharmatimes.com/news/breast_cancer_drug_sales_will_almost_double_by_2023%2C_says_ims_1002558

Financials & Investment case

On flotation, the company changed its accounting period from July to June. Evgen is a virtual company with most of its activities being outsourced.

Profit & Loss

In the medium term, the P&L account will be driven by two numbers, the corporate overhead/administration costs (SG&A) and the investment in clinical trials.

- **SG&A** – The underlying corporate overhead is estimated to be about £1.0m and rising modestly. Since IPO, the company has added senior personnel to oversee the clinical trial programme
- **R&D** – Investment will rise sharply as a consequence of the Phase II trial programme for SFX-01 in SAH and breast cancer. Trial costs have been allocated evenly across the expected timelines
- **Tax credit** – Evgen is accruing and receiving tax credits from the UK government in relation to its R&D spend

Profit & Loss account

Year end March (£000)	2015	2016	2017E	2018E	2019E
Sales	0	0	0	0	0
COGS	0	0	0	0	0
SG&A	-312	-338	-980	-1,010	-1,050
R&D	-484	-612	-3,029	-2,181	-3,054
EBITDA	-789	-942	-4,002	-3,183	-4,096
Depreciation & Amortis.	-7	-8	-8	-8	-8
Licensing/Royalties	0	0	0	0	0
Underlying EBIT	**-796**	**-950**	**-4,010**	**-3,191**	**-4,104**
Share based costs	-155	-801	-125	-131	-138
Exceptional items	-295	-683	-683	0	0
Statutory EBIT	-1,246	-2,434	-4,135	-3,322	-4,241
Net financials	-1,057	-783	10	4	-3
U/L pre-tax profit	**-1,853**	**-1,733**	**-3,999**	**-3,187**	**-4,106**
Reported pre-tax	-2,303	-3,217	-4,124	-3,318	-4,244
Tax liability/credit	30	85	421	303	424
Tax rate	0	0	0	0	0
Underlying net income	**-1,823**	**-1,648**	**-3,578**	**-2,884**	**-3,682**
Statutory net income	-2,273	-3,132	-3,703	-3,015	-3,820
Ordinary shares:					
Period-end (m)	0.0	73.1	73.2	73.3	73.4
Weighted average (m)	29.2	49.8	73.1	73.2	73.3
Fully diluted (m)	36.2	58.3	81.6	81.7	81.8
Underlying basic EPS (p)	**-6.2**	**-3.3**	**-4.9**	**-3.9**	**-5.0**
Statutory Basic EPS (p)	-7.8	-6.3	-5.1	-4.1	-5.2
U/l Fully-diluted EPS (p)	**-5.0**	**-2.8**	**-4.4**	**-3.5**	**-4.5**
Stat. Fully-diluted EPS (p)	-6.3	-5.4	-4.5	-3.7	-4.7
DPS (p)	0.0	0.0	0.0	0.0	0.0

Source: Hardman & Co Life Sciences Research

Balance sheet

- **IPO** – Evgen raised £7.0m gross proceeds at IPO through an institutional Placing of Ordinary shares
- **Net cash** – At 31st March 2016, Evgen had net cash of £7.1m on its balance sheet

Balance sheet					
@ 31st March (£000)	**2015**	**2016**	**2017E**	**2018E**	**2019E**
Shareholders' funds	-358	7,087	3,509	625	-3,058
Cumulated goodwill	0	0	0	0	0
Total equity	-358	7,087	3,509	625	-3,058
Share capital	73	183	183	183	183
Reserves	-1,260	6,904	3,326	442	-3,241
Provisions/liabilities	0	0	0	0	0
Long-term loans	1,646	0	0	0	0
Short-term debt	3	0	0	0	0
less: Cash	163	5,120	1,258	-1,463	-3,221
less: Deposits	0	2,006	2,006	2,006	0
Invested capital	**-284**	**-39**	**245**	**81**	**163**
Fixed assets	1	6	3	-2	-6
Intangible assets	45	74	74	74	74
Inventories	0	0	0	0	0
Trade debtors	*6*	*3*	*3*	*3*	*3*
Other debtors	*111*	*79*	*79*	*79*	*79*
Tax credit/liability	*30*	*115*	*421*	*303*	*424*
Trade creditors	*-130*	*-86*	*-86*	*-86*	*-86*
Other creditors	*-347*	*-227*	*-248*	*-290*	*-325*
Debtors less creditors	-330	-116	168	9	95
Invested capital	**-284**	**-36**	**245**	**81**	**163**
Net cash/(debt)	**-903**	**7,126**	**3,264**	**543**	**-3,221**

Source: Hardman & Co Life Sciences Research

Cashflow

- In the near-term, the cashflow is driven entirely by R&D investment and SG&A spend from the P&L account
- Any changes in working capital are simply the result of timing differences between receipt of invoices and payment
- Being a virtual company, there is minimal capital expenditure
- Based on our forecasts, the company has sufficient cash to take it through to Phase II clinical results at the end of March 2018

Cashflow					
Year end March (£000)	**2015**	**2016**	**2017E**	**2018E**	**2019E**
Trading profit	-796	-950	-4,010	-3,191	-4,104
Depreciation/amort.	7	8	8	8	8
Inventories	0	0	0	0	0
Working capital	81	57	48	41	35
Other	0	0	0	0	0
Company op cashflow	**-708**	**-885**	**-3,953**	**-3,142**	**-4,061**
Net interest	0	0	10	4	-3
Tax paid/received	103	0	85	421	303
Operational cashflow	-605	-885	-3,858	-2,717	-3,760
Capital expenditure	-1	-6	-5	-3	-4
Free cashflow	**-606**	**-891**	**-3,862**	**-2,720**	**-3,764**
Dividends	0	0	0	0	0
Acquisitions	0	-36	0	0	0
Disposals	0	0	0	0	0
Cashflow after invest.	**-606**	**-927**	**-3,862**	**-2,720**	**-3,764**
Share repurchases	0	0	0	0	0
Share issues	0	8,565	0	0	0
Change in net debt	**-606**	**7,638**	**-3,862**	**-2,720**	**-3,764**
Hardman FCF/share (p)	-2	-2	-5	-4	-5
Opening net cash	-297	-903	7,126	3,264	543
Closing net cash	-903	7,126	3,264	543	-3,221

Source: Hardman & Co Life Sciences Research

Valuation

Peer group valuation

There are many specialty pharmaceutical companies with a very diverse range of market capitalisations. For our comparative valuation analysis, a group of quoted pharma companies with activities in a similar therapeutic field to that of Evgen – but excluding dietary supplements – have been selected, to provide a guide about the relative valuation. Most of these companies are also at a similar stage of clinical development to Evgen. This also provides an indication of valuation uplift potential when Evgen's products advance through each clinical development phase through to regulatory approval and commercial launch.

Reata Pharmaceuticals

Reata is focused on diseases that are involved in regulating cellular metabolism and inflammation. Reata is slightly ahead of Evgen, with two products in clinical development, which are modulators of the Nrf2 pathway. Bardoxolone methyl (partnered with AbbVie) is in Phase III clinical trials for the treatment of pulmonary arterial hypertension associated with connective tissue disease and in Phase II for four types of pulmonary hypertension as well as Phase II in patients with chronic kidney disease. The second product, Omaveloxolone (partnered with Kyowa Kirin), is in Phase II for multiple indications, including Friedreich's ataxia and mitochondrial myopathies and in evaluation in a Phase Ib/II in melanoma patients with the aim of enhancing the activity of the checkpoint inhibitors, ipilimumab and nivolumab. Omaveloxone is also in Phase II for prevention of corneal endothelial cell loss due to cataract surgery.

Edge Ttherapeutics

Edge is developing a new formulation for the generically available nimodipine using its proprietary technology called Precisa, a blend of polymers controlling the slow and sustained release of the drug. Edge has two product candidates that have the potential to target multiple indications associated with brain haemorrhage. EG-1962 is in Phase III trials in aneurysmal subarachnoid haemorrhage, with the drug administered through an external ventricular drain.

Diurnal

Evgen is under-valued compare to its peers

Diurnal is a virtual speciality pharmaceutical company developing new formulations for Adrenal Insufficiency disease in adults, and paediatrics. Diurnal has two products in Phase III clinical trials, Chronocort and Infacort, with commercial launch anticipated in 2018.

Verona Pharma

VRP is developing first-in-class drugs to treat unmet medical needs in respiratory disease. The company has been reporting consistently positive outcomes from a five stage Phase I/IIa programme which has de-risked RPL554 significantly. This drug has been shown to have strong bronchodilatory and anti-inflammatory effects with minimal side effects. New funds have been secured to support a broad programme of Phase II trials with RPL554 in hospitalised patients and to expand the programme into maintenance therapy, taking the drug into bigger commercial markets and retaining more of the value proposition

Peer group valuations

Company	Diurnal	Edge Therapeutics	Evgen Pharma	Reata Pharmaceuticals	Verona Pharma
Ticker	**DNL**	**EDGE**	**EVG**	**REATA**	**VRP**
Local currency (lc)	**£p**	**$**	**£p**	**$**	**£**
Share price	106.5	12.3	23.0	26.6	3.7
Shares in issue (m)	52.2	28.9	73.1	16.0	2,565.7
Market cap (lcm)	55.6	355.7	16.8	424.9	94.9
Mkt cap (£m)	**55.6**	**286.6**	**16.8**	**342.4**	**94.9**
Cash	30.1	112.8	7.1	95.7	40.0
Debt	-3.2	-14.8	0.0	0.0	0.0
EV (lcm)	28.7	257.7	9.7	329.3	54.9
EV (£m)	**28.7**	**207.7**	**9.7**	**265.4**	**54.9**
Relative EV	3.0x	21.4x	-	27.4x	5.7

lc = local currency
Prices taken at close of business on 28th November 2016
Source: Hardman & Co Life Sciences Research

Company matters

Registration

Incorporated in the UK with company registration number: 09246681

Liverpool Science Park Innovation Centre 2
146 Brownlow Hill
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L3 5RF

+44 (0) 151 705 3532

Website: www.evgen.com

Board of Directors

Board of Directors				
Position	**Name**	**Nominations**	**Remuneration**	**Audit**
Chairman	Barry Clare			
Chief Executive Officer	Dr Stephen Franklin			
Chief Financial Officer	John Bradshaw			
Non-executive director	Dr Alan Barge		M	M
Non-executive director	Dr Susan Foden		C	M
Non-executive director	Dr Marc d'Abbadie			C
Non-executive director	Dr Mark Wyatt		M	

M = member; C = chair
Source: Company reports

Barry Clare – Executive Chairman

Barry has over 20 years' experience in the healthcare industry. He was a main board director of the Boots Company plc and managing director of its successful consumer healthcare division, Boots Healthcare International, where he led the global expansion of a leading portfolio of brands including Nurofen, Strepsils and Clearasil. Since leaving Boots, he set up his own company, Clarat Partners LLP, and engineered several private equity backed transactions. He is also the Non-Executive Chairman of University Hospital of South Manchester Foundation Trust.

Dr Stephen Franklin – Chief Executive Officer

Stephen, the founder of Evgen Pharma, has over 20 years' commercial experience in life science industries, focusing on the commercialisation of new technology. He was the founder of Provexis plc, a nutraceutical company, and was its chief executive at the time of its admission to AIM in 2005. Prior to that, Stephen was a principal executive with ANGLE plc, the AIM quoted technology commercialisation company, having previously held a business development role with Manchester Biotech (now University of Manchester Innovation Company), one of the largest campus-based incubators in Europe; in these roles, he helped establish a portfolio of drug discovery and development businesses. Stephen has a BSc in Biology (York), a PhD in Applied Biochemistry (Nottingham) and an MBA with distinction (Nottingham). He is a Fellow of the Royal Society of Medicine and an alumni of the Royal Commission for the Exhibition of 1851.

John Bradshaw – Chief Financial Officer

John is a qualified chartered accountant with over 20 years' post-qualification experience working as a finance director for UK quoted and venture capital owned companies. John trained with Arthur Andersen, where he worked from 1986 until 1997, when he joined Gyrus Group plc as finance director ahead of its IPO. Since leaving Gyrus in 2001, John acted as finance director for Analysys Limited, TeraView Limited and HCEG plc and since 2006 has provided interim and part time finance director services to start-up and other venture capital funded companies, since 2012 through Bradshaw Daniel Limited. John is also a non-executive director of Ixico plc, where he serves as Chairman of the Audit Committee.

Dr Alan Barge – Non-Executive Director

Alan is a former chief medical officer of Singapore-based ASLAN Pharmaceuticals PTE. Up until 2011, he was vice-president and head of oncology & infection at AstraZeneca, a role in which he was responsible for the overall strategy in oncology and infection from drug discovery to proof-of-concept. He was also chairman of AstraZeneca's Therapy Area Portfolio Team and accountable for the design and delivery of all projects, including budgetary oversight. Prior to his career at AstraZeneca, Alan was European and global medical director for Amgen Inc.

Dr Susan Foden – Non-Executive Director

Susan has broad experience in executive and non-executive roles at both public and private companies and at funding organisations. Her current directorships include NED roles at BTG plc, BerGenBio AS and Vectura Group plc. From 2000 to 2003, Susan was an investor director with the London-based venture capital firm Merlin Biosciences Limited and, from 1987 to 2000, was chief executive officer of the technology transfer company Cancer Research Campaign Technology Limited. She studied biochemistry at the University of Oxford, obtaining an MA and a DPhil.

Dr Marc d'Abbadie – Non-Executive Director

Marc is an investor director at SPARK Impact, managers of the North West Fund for Biomedical. He was previously at Inventages, which manages one of the world's largest life-science focused venture capital funds with assets of $1.5bn, and Technikos, a medical device venture capital investor. Prior to being a consultant at McKinsey & Co., Marc was a research fellow at Trinity College Cambridge. He obtained his MA in Natural Sciences from Trinity College Cambridge and his PhD in Biochemistry from the MRC Laboratory of Molecular Biology, also in Cambridge.

Dr Mark Wyatt – Non-Executive Director

Mark is currently an investment director at Enterprise Ventures. He has more than 15 years' experience working in venture capital, having previously worked at Merlin Biosciences and Imperial Innovations, both specialist life science investors. He has Board level experience in both private and public companies. Mark has a PhD from the Glaxo Institute of Applied Pharmacology at Cambridge University. He is also a Sainsbury's Management Fellow in the Life Sciences, receiving his MBA from Warwick.

Senior management

Evgen has a number of senior executives that support the Board, providing considerable industry expertise, covering small molecule pre-clinical and clinical development, R&D and business development, analyse, safety, manufacturing and regulatory affairs.

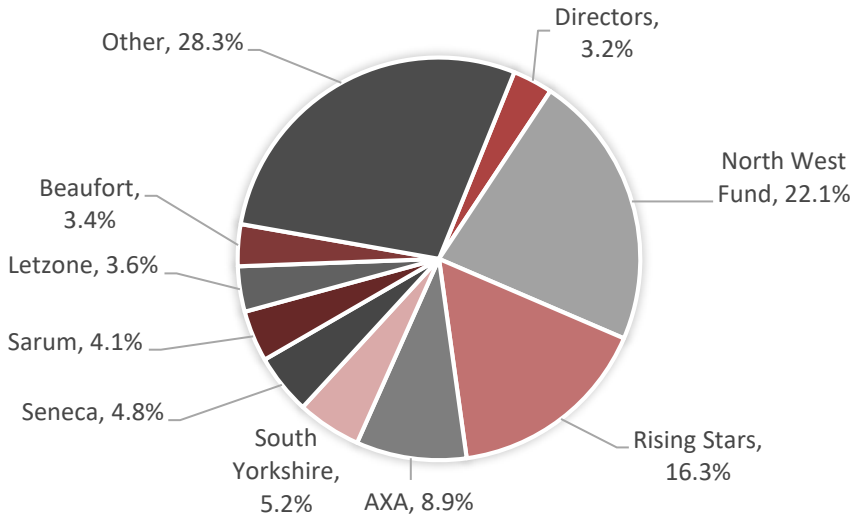
Senior management team	
Name	**Position**
Dr David Howat	Chief Development Officer
David Chadwick	Senior Clinical Study Manager
Dr Bob Holland	Medical Advisor, Neurology
Dr Tomas Morris	Medical Advisor, Oncology
Liz Jenkins	Regulatory consultant

Source: Company reports

Share capital

The company has 73,142,862 shares in issue. At the time of going to press, there were 8.47m options and 1.4m warrants in issue.

Major shareholders



Source: Company reports

Risks

Background

It goes without saying that investments in small early stage companies carry a significant risk and investors must be aware of this fact. In our opinion, the following risks are particularly relevant. Each of them could have an impact on time to reach market, cash flow breakeven and profitability.

Dilution risk

The company has sufficient cash to fund its ongoing clinical trial programme for SFX-01. Further capital will be required to extend this programme and for commercialisation. However, the company and products will be significantly de-risked by this point. There is no guarantee of either the size of any follow-on funding or the share price at which it will be done, raising the risk of dilution.

Commercialisation

The strategy of the company is to complete the clinical programme and then to out-licence the product for commercialisation, which might or might not lead to a trade sale. There is no certainty that such events will take place or the timing of such event should they occur.

Manufacturing and suppliers

The current strategy is to have all product supply out-sourced. Evgen is working with the originator of the technology for the supply of clinical trial material.

Patent robustness

As with all therapeutic products, there is risk that the intellectual property is insufficiently covered by the global patents, allowing a competitor to gain market access. However, in the case of Evgen, there is certain know-how also involved in the stabilisation process and commercial protection will be derived mostly from the marketing exclusivity periods associated with Orphan Drug designation.

Regulatory

As with all pharmaceutical and drug development companies, there is a regulatory risk. Protocols for clinical trials need to be approved. It is important for companies to liaise with regulators on a regular basis throughout the development programme. Protocols for clinical trials need to be planned carefully to ensure that, if the drug works, the results and statistical analysis will deliver the answer being sought.

Share liquidity

As with many small cap companies listed on AIM, there can be difficulty in buying and shares in volume. Market makers only guarantee prices in a very small number of shares

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Glossary

API	Active Pharmaceutical Ingredient
CSC	Cancer stem cells
ER+	Oestrogen-receptor positive breast cancer
EMA	European Medicines Agency
FDA	US Food & Drug Administration
MHRA	UK Medicines & Healthcare products Regulatory Agency
PR	Progesterone receptor
SAH	Subarachnoid haemorrhage
SAS	SFX-01 After Subarachnoid Haemorrhage
STEM	SFX-01 Treatment & Evaluation in Patients with Metastatic Breast Cancer
RECIST	Response Evaluation Criteria In Solid Tumor: Criteria used to evaluate a patient's response to the therapy used to treat their disease

Notes

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