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Full year highlights

- Interim data released from ongoing STEM Phase IIa clinical study in breast cancer
- Eleven new sites opened for STEM trial and 44 patients recruited to date
- Two new sites opened for SAS trial and 65 patients recruited to date
- Launch of Scientific and Medical Advisory Board (SMAB) with first two members: Professor Giovanni Mann (King’s College) and Professor Albena Dinkova-Kostova (University of Dundee)
- Further elucidation of SFX-01 mechanism of action in breast cancer
- Additional patents granted over SFX-01, including first patent grant in Europe for SFX-01
- Financial performance in-line with expectations:
  - Total comprehensive loss of £2.6m (2017: loss of £3.1m)
  - Net cash outflow of £0.2m (2017: outflow of £3.3m (before short-term investment movements))
  - Cash and short-term investments and cash on deposit at 31 March 2018 of £3.63m (31 March 2017: £3.86m)
- Fundraising in December 2017 raised £2.1m after expenses
Company summary

- Clinical stage drug development company with a new class of pharmaceuticals
- Based in Cheshire (UK) and listed on AIM (LSE: EVG)
- Focused on the development of well-tolerated, stable, sulforaphane-based compounds that:
  - inhibit the STAT3 pathway – a target for reducing cancer proliferation and metastases; and
  - activate the Nrf2 pathway – a target for reducing neurodegeneration
- Lead product, SFX-01, is in two Phase II trials (oncology and neurology) utilising two separate mechanistic targets with expected read-outs around the end of 2018
- Worldwide exclusive licence to an IP estate covering composition, manufacturing and a series of novel derivatives of sulforaphane, asserting a leadership position around this new class of pharmaceuticals
- Business model looks to partner post-Phase II or potentially post-Phase III (for orphan indications)
Sulforaphane modulates STAT3 and Nrf2 presenting opportunities in both oncology and neurology

Improving outcomes for patients with neurodegenerative conditions

Improving outcomes for patients becoming resistant to cancer therapies

References:
Pipeline

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<tr>
<th>Drug (MoA)</th>
<th>Indication</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
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<td>Subarachnoid Haemorrhage</td>
<td></td>
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<td>SFX-01 (STAT3)</td>
<td>Metastatic Breast Cancer (ER+)</td>
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<tr>
<td>SFX-01</td>
<td>Investigator-Initiated Clinical Studies† e.g. Triple Negative Breast Cancer, Ischaemic stroke</td>
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- Potential for different formulations to establish more than one product line based on SFX-01
- Completion of Phase I studies in healthy human volunteers means that SFX-01 is Phase II-ready for other indications†
- Pipeline further supported by a library of novel derivatives of sulforaphane (SFX-02 to SFX-42) in early preclinical development
Growth in sulforaphane publications and strong academic collaborations support the scientific fundamentals

Scientific publications on "sulforaphane" (Source: Pubmed)

New sulforaphane analogues

Prostate cancer

Ischaemic stroke

ASD

NASH

ER+ breast cancer

Triple negative breast cancer

Acute Lymphoblastic Leukemia

Chemical proteomics / MoA

Osteoporosis

Osteoarthritis

Parkinson’s Disease

Glioblastoma

New sulforaphane analogues

The University of Manchester
SFX-01 in ER+ (Estrogen-Receptor Positive) Metastatic Breast Cancer
ER+ metastatic breast cancer

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

\(^1\)American Cancer Society; \(^2\)Palbociclib and Letrozole in Advanced Breast Cancer (2016) N Engl J Med
Market landscape in ER+ metastatic breast cancer

- Incidence of ER+ metastatic breast cancer is approximately 130,000\(^1\) in US and Europe
- CDK4/6 inhibitors are now first line treatment, in combination with hormone therapy
- Pfizer (Ibrance\(^\text{®}\)/palbociclib), Novartis (Kisqali\(^\text{®}\)/ribociclib) and Eli Lilly (Versenio\(^\text{®}\)/abemaciclib) are the key players with sales forecasts of $4.4bn, $0.3bn and $0.17bn respectively in 2018\(^e\)\(^2\)
- CDK4/6 inhibitor sales forecast to reach c.$9bn by 2021\(^e\)\(^2\)
- **However, patients become resistant to CDK4/6i with hormone therapy after c. 25 months on average**
- Potential of SFX-01 after CDK4/6 inhibitor therapy: a unique mechanism of action and a more favourable side-effect profile

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

- **Aromatase inhibitors**: Anastrazole, Letrozole, Exemestane
- **ER modulators**: Tamoxifen, Fulvestrant
- **CDK4/6 inhibitors**: Palbociclib, Ribociclib, Abemaciclib
- **mTOR inhibitors**: Everolimus
- **SFX-01**
Entry point: the potential to change the standard of care in second-line therapy

First-line therapy

- Aromatase Inhibitors (AI)\(^1\)
- CDK4/6i\(^2\)

Median PFS c.15 months for AI, extended to c.25 months in combination with CDK4/6i\(^3\)

Second-line therapy

- Fulvestrant/Exemestane
- Everolimus

Median PFS 3.7-6.5 months for Fulvestrant and 3.2 months for Exemestane, extended to 7.9 months for the combination of Everolimus with Exemestane\(^4\)

- Fulvestrant/Exemestane
- SFX-01

Improved Median PFS? More favourable safety and tolerance?

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\(^1\)First-line in post-menopausal – for premenopausal, tamoxifen can also be given as 1\(^{st}\)-line therapy
\(^2\)Palbociclib is approved in 1\(^{st}\) and 2\(^{nd}\)-line settings, Ribociclib is approved in the 1\(^{st}\)-line setting, Abemaciclib is approved in the 1\(^{st}\)-line setting and also later lines as monotherapy
SFX-01 targets cancer stem cells, deactivates STAT3 and reduces metastases

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

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

- **STEM**: SFX-01 Treatment and Evaluation in patients with Metastatic breast cancer
- A European, multi-centre, Phase II trial on 60 patients evaluating SFX-01 as an adjunct to failing hormone therapy (i.e. the “salvage” setting)
- Hormone resistant patients: tamoxifen, aromatase inhibitors or fulvestrant
- Chief Investigator: Dr Sacha Howell at Manchester’s Christie NHS Foundation Trust
- Primary Endpoints: Safety and Clinical Benefit Rate (stable or responsive disease at 6 months)
- Compassionate use programme accepted first patient in June 2017
- 44 patients recruited to date and final read-out expected around end of 2018
- Interim update announced in June 2018
SFX-01 is proving to be well tolerated with no safety concerns arising

SFX-01 shows encouraging early signs of anti-tumour activity:

- Four patients had their disease stabilised (that is, having joined the trial with progressive disease their tumours stopped progressing) for the full duration of the study through to, and including, a favourable final scan result at week 24. Of these four patients, one also had a partial response which is a reduction in tumour size of at least 30% on one scan.

- In addition to the above four patients, a further two patients had their disease stabilised through to, and including, the week 18 scan but then showed disease progression at the final week 24 scan. One of these two patients also demonstrated a partial response on one scan before disease progression was recorded at the final scan.

Principal Investigator, Dr Sacha Howell of the Christie Hospital, UK, said:

“The design of the STEM study, adding the drug to endocrine therapy on which a patient’s cancer was progressing, sets a high bar for SFX-01. In light of this, these interim results are highly encouraging. Objective responses indicate activity in this setting, and disease stabilisation for 6-12+ months represents clinically meaningful prolongation of response . . .”
A clinical pathway for SFX-01 as a potential second line therapy post CDK4/6i

**Phase II**

- **SFX-01 (300mg BID) + Fulv/Exem** (20 patients)
  - 2nd line ER+ mBC post CDK4/6i
- **SFX-01 (300mg QD) + Fulv/Exem** (20 patients)
  - 2nd line ER+ mBC post CDK4/6i
- **Placebo + Fulv/Exem** (20 patients)
  - 2nd line ER+ mBC post CDK4/6i

14 months
Current SFX-01 formulation
EU

1º: Tumour size @ 18 weeks
2º: Biomarkers

**Phase IIb/III**

- **SFX-01 + Fulv/Exem** (100+ patients)
  - 2nd Line ER+ mBC post CDK4/6i
- **Placebo + Fulv/Exem** (100+ patients)
  - 2nd Line ER+ mBC post CDK4/6i

28 months
New solid dose SFX-01 formulation
US and EU

1º: PFS (progression-free survival)
2º: CBR (clinical benefit rate), OS (overall survival), biomarkers
Commercial opportunity and monetisation

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

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

- Defined by bleeding in the outer layers of the brain due to a ruptured brain aneurysm
- 40% of patients die within 30 days and for the survivors c.50% will have long-term cognitive impairment
- A Delayed Cerebral Ischaemia (DCI) occurs days after the SAH and, at that point, becomes the most important cause of mortality and poor neurological outcome
- Current standard of care, nimodipine, was first approved in 1989 and new pharmacological treatments are needed to prevent and treat DCI
SAH market landscape

- Annual incidence of 9 per 100,000\(^1\) equating to c.45,000 in the EU\(^1\) and c.30,000 in US\(^2\)
- Current standard of care, nimodipine, reduces calcium-dependent smooth muscle contraction
- Nimodipine side-effects include unusually fast or slow heart beats and systemic hypotension is a risk factor that requires monitoring
- SFX-01 is believed to be the only Nrf2-activator in the clinic for SAH and is safe and very well tolerated
- Evgen apart, thin development pipeline – benign competitive landscape

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\(^1\)Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. De Rooij et al. (2007) J Neurol Neurosurg Psychiatry,

\(^2\)Population statistics: EU 512m (www.statistica.com) and US 327m (www.census.gov)
In experimental SAH, sulforaphane upregulates Nrf2, reduces apoptosis and ameliorates motor deficits.

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

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

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

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

- **SAS**: SFX-01 After Subarachnoid Haemorrhage – a Phase II, double-blind, placebo-controlled trial on 90 patients (45 in test and placebo arm respectively)
- Administered alongside the calcium channel antagonist, nimodipine
- Primary Endpoints: improved blood flow (ultrasound) associated with the DCI, levels of drug in plasma and cerebral spinal fluid and safety
- Secondary endpoints: cognitive measures at 3 and 6 months
- Chief Investigator: Mr Diederik Bulters, Consultant Neurosurgeon, Wessex Neurological Centre in Southampton
- Read-out expected around end of calendar year 2018
- **Orphan drug designation** granted by FDA in 2016
The next clinical trial is a pivotal Phase III potentially leading to registration in the US and EU

Phase III

SFX-01 + nimodipine
175+ patients

Placebo + nimodipine
175+ patients

Futility analysis

Final Analysis

Go / no go

30 month trial
Futility analysis at mid-point
New sachet SFX-01 formulation
EU and US

1st: Cognitive measure (GOSE) @ Day 90
Commercial opportunity and monetisation

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

\(^1\)Credit Suisse Research Report, 26 Oct 2015 – Edge Therapeutics
FINANCIAL RESULTS
for the year ended 31 March 2018
Financial Highlights

- Total comprehensive loss of £2.6m (2017: £3.1m)
- Net cash outflow (before equity raise) of £2.3m (2017: £3.3m)
- Net outflow after fundraise £0.2m (2017: 3.3m)
- Cash and short term investments and cash on deposit at 31 March 2018 of £3.6m (31 March 2017: £3.9m)
- Operating expenses decreased to £3.0m (2017: £3.6m); lower clinical costs from SAS clinical hold and reduced SBP
- R&D tax credit of £0.44m (2017: £0.58m)
## Financial Summary

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<th>(£’000)</th>
<th>Y/ended 31 March 2018</th>
<th>Y/ended 31 March 2017</th>
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<td><strong>Net (decrease)/increase in cash</strong></td>
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<td><strong>Cash and deposits at period end</strong></td>
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Summary

- Evgen is building a stabilised sulforaphane platform (Sulforadex®) with multiple commercialisation routes
- Lead product, SFX-01, is in two Phase II trials (ER+ metastatic breast cancer and subarachnoid haemorrhage), with read-outs around the end of 2018
- To date, SFX-01 is well tolerated, no safety issues and encouraging interim clinical data
- Large body of preclinical data demonstrating efficacy in a broad range of cancer and neurodegenerative disease models
- Worldwide exclusive licence to an IP estate covering composition, manufacturing and a series of novel derivatives of sulforaphane, asserting a leadership position around this new class of pharmaceuticals
- Monetisation horizon from 2019 via partnering
Evgen Pharma plc

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

Yanyan Li\textsuperscript{a,b}, Tao Zhang\textsuperscript{a}, Hasan Korkaya\textsuperscript{c}, Suling Liu\textsuperscript{c}, Hsiu-Fang Lee\textsuperscript{a}, Bryan Newman\textsuperscript{a}, Yanke Yu\textsuperscript{a}, Shawn G. Clouthier\textsuperscript{c}, Steven J. Schwartz\textsuperscript{b,*,}, Max S. Wicha\textsuperscript{c,†,} and Duxin Sun\textsuperscript{a,**}

Abstract

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

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

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

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

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

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

**CONCLUSION**

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

**Sulforaphane activates the cerebral vascular Nrf2-ARE pathway and suppresses inflammation to attenuate cerebral vasospasm in rat with subarachnoid hemorrhage.**

Zhao X¹, Wen L², Dong M¹, Lu X³.

**Author information**

**Abstract**

Nrf2-ARE pathway reportedly plays a protective role in several central nervous system diseases. No study has explored the role of the Nrf2-ARE pathway in cerebral vasospasm (CVS) after subarachnoid hemorrhage (SAH). The purpose of the present study was to investigate the activation of the cerebral vascular Nrf2-ARE pathway and to determine the potential role of this pathway in the development of CVS following SAH. We investigated whether the administration of sulforaphane (SFN, a specific Nrf2 activator) modulated vascular caliber, Nrf2-ARE pathway activity, proinflammatory cytokine expression, and clinical behavior in a rat model of SAH. A two-hemorrhage protocol was used to generate an animal model of SAH in male Sprague-Dawley rats. Administration of SFN to these rats following SAH enhanced the activity of the Nrf2-ARE pathway and suppressed the release of proinflammatory cytokines.

**Vasospasm was markedly attenuated in the basilar arteries after SFN therapy. Additionally, SFN administration significantly ameliorated two behavioral functions disrupted by SAH. These results suggest that SFN has a therapeutic benefit in post-SAHI, and this may be due to elevated Nrf2-ARE pathway activity and inhibition of cerebral vascular proinflammatory cytokine expression.**
Role of the Nrf2-ARE Pathway in Early Brain Injury After Experimental Subarachnoid Hemorrhage

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

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

Key words: early brain injury; subarachnoid hemorrhage; Nrf2

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### IP Schedule (April 2018): Novel sulforaphane analogues

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# Development pipeline – Metastatic ER+ Breast Cancer

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<th>Phase II</th>
<th>Phase III</th>
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<td>SERD</td>
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<td>TORC1/2</td>
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<td>SFX-01 + Tam/Fulv/Al</td>
<td>STAT-3</td>
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## Development pipeline – NRF2

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