Efficacy of SFX-01, a sulforaphane-based drug, in experimental autoimmune encephalomyelitis

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Introduction

Oxidative stress secondary to cell-mediated inflammation plays an important role in the pathology of multiple sclerosis (MS) (1, 2). Sulforaphane, a naturally occurring isothiocyanate, has dual therapeutic potential in MS by upregulating Nrf2-mediated anti-oxidant cytoprotective mechanisms and inhibiting NF-kB-mediated inflammatory responses (3, 4). Activation of Nrf2 by sulforaphane in a reporter gene assay is an order of magnitude higher compared to dimethyl fumarate (BG-12) (Figure 1), marketed as Tecfidera®. SFX-01 is a proprietary, synthetic and stabilised form of sulforaphane, developed as a pharmaceutical product (Figure 2). First-in-man trials have documented safety in single and multiple ascending dose studies, and the product is in Phase II clinical trials for other indications.

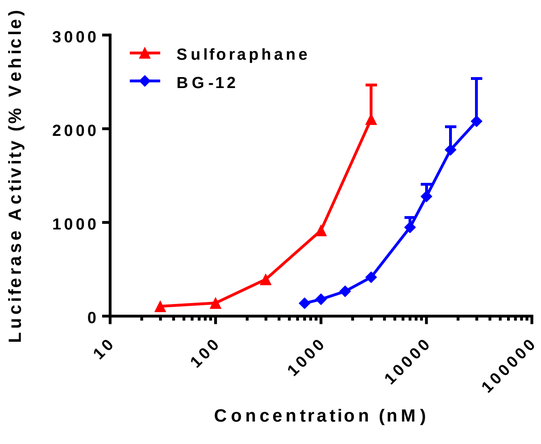

Figure 1. Potency of sulforaphane and BG-12 as inducers of an Nrf2 luciferase reporter in H4IIE rat hepatoma cells, which were treated for 6 h.

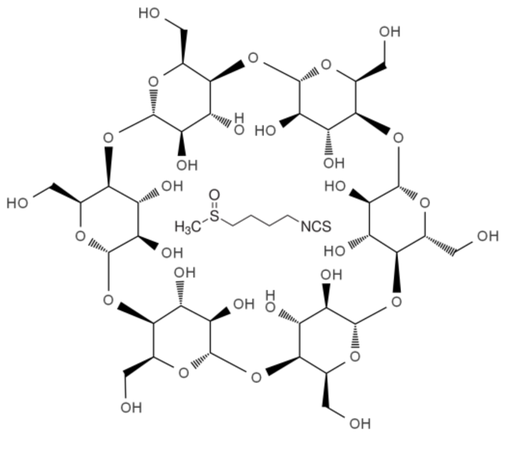

Figure 2. SFX-01 is a complex of sulforaphane and α-cyclodextrin forming a stable, solid-form, Active Pharmaceutical Ingredient (API).

Aim

Here the efficacy of SFX is tested in experimental autoimmune encephalomyelitis (EAE), a mouse model recapitulating some features of MS.

Methods

EAE was induced in 72 female SJL mice using PLP139-151 and pertussis toxin. Groups of 12 mice received vehicle, SFX-01 at 10, 50 or 300 mg/kg or BG-12 at 15mg/kg. The experiment was performed with two different dosing schedules: prophylactic (Day 0 to Day 19) and therapeutic (after recovery and before relapse, i.e. Day 19 to Day 41). Clinical scores were measured daily. At the end of the therapeutic dosing experiment, mice were perfused with phosphate-buffered saline and spinal cords were collected in 10% buffered formalin.

Results

Therapeutic dosing

With dosing started after disease induction (i.e. therapeutic dosing): (1) neither SFX-01 nor BG-12 affected relapse rate; (2) SFX-01 caused a dose-dependent reduction in EAE end score *versus* vehicle, which achieved significance at the 300 mg/kg dose (Figure 3); (3) SFX-01 300 mg/kg was superior to BG-12 using area-under-curve analysis of the last six days ($p<0.05$); (4) BG-12 did not significantly affect EAE relapse measures.

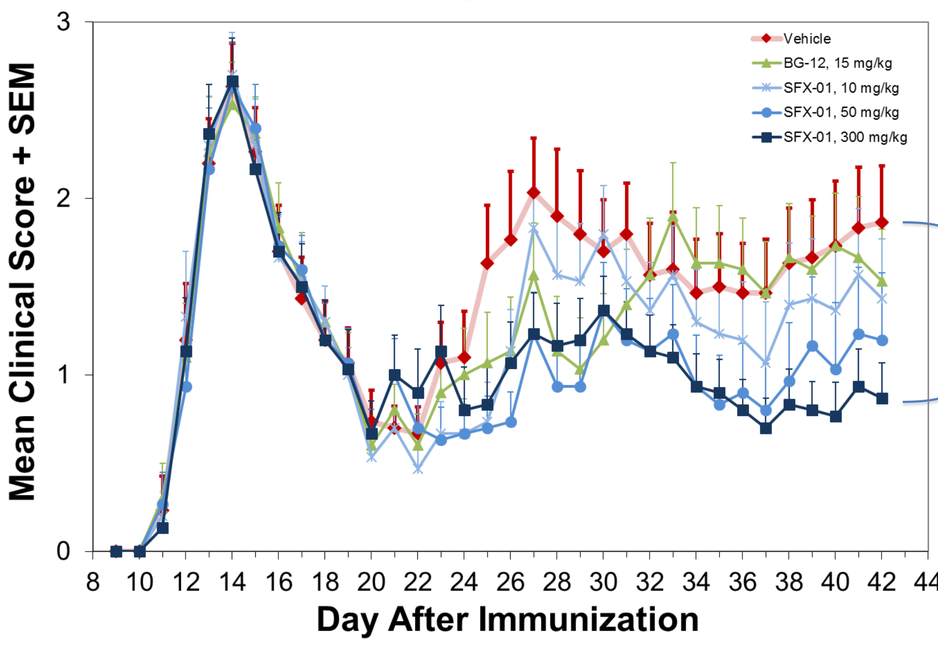

Figure 3. Therapeutic dosing

Histological examination of the lumbar, thoracic, and cervical spinal cord were consistent with the clinical findings. In SFX-01 treated animals, all histological readouts including demyelination and the number of apoptotic cells were significantly improved compared to the vehicle group (Table 1). In BG-12 treated animals, only demyelination was statistically improved.

Treatment	Inflammatory foci +/- SD	Demyelination (LFB) +/- SD	Apoptotic cells +/- SD
Vehicle	2.9 +/- 2.2	0.9 +/- 0.6	0.9 +/- 0.5
BG-12, 15 mg/kg	2.8 +/- 2.5	0.5 +/- 0.5*	1.0 +/- 1.1
SFX-01, 300 mg/kg	2.0 +/- 2.3	0.4 +/- 0.4*	0.5 +/- 0.4*

Table 1. Histological indices at day 42 after EAE induction and treatment with BG-12 or SFX-01 starting at day 19 (therapeutic dosing). Inflammatory foci with >20 cells and apoptotic nuclei were counted per section after haematoxylin and eosin staining. Demyelination was assessed after Luxol fast blue histochemistry using a customised score ranging 1-5. Three sections from each mouse were quantified with blinding to treatment and clinical readouts. * $p < 0.05$

Prophylactic dosing

When dosing was started before disease induction, SFX-01 caused a dose-dependent reduction in EAE end score which approached significance at the 300mg/kg dose (Figure 4).

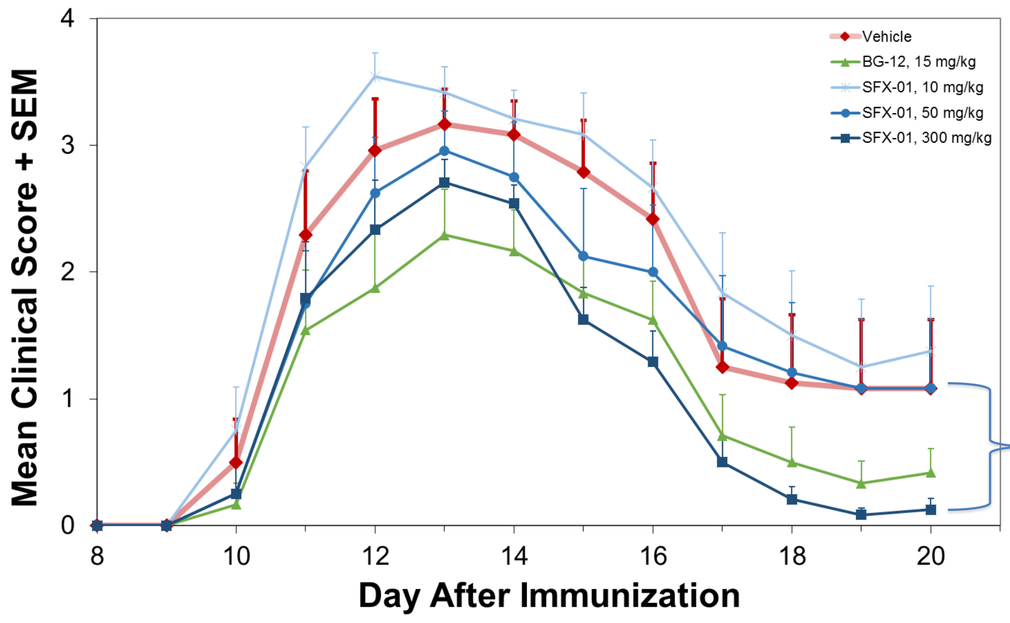

Figure 4. Prophylactic dosing

Conclusions

SFX-01 appears to be superior to BG-12 in the therapeutic EAE model. SFX-01 appears to exert maximum effects later in the course of the disease by enabling superior neurological recovery in the chronic stage after relapse. SFX-01 is a promising drug candidate in MS, and warrants further investigation.

References

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Disclosures

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