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SHORT REPORT

Patient-reported outcomes with risankizumab versus fumaric acid esters in systemic therapy-naïve patients with moderate to severe plaque psoriasis: a phase 3 clinical trial

D. Thaçi,[1,*] A.M. Soliman,[2] K. Eyerich,[3] A. Pinter,[4] M. Sebastian,[5] K. Unnebrink,[6] S. Rubant,[6] D.A. Williams,[2] P. Weisenseel[7]

[1]Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany
[2]AbbVie Inc., North Chicago, IL, USA
[3]Department of Dermatology and Allergy, Technical University of Munich, Munich, Germany
[4]University Hospital Frankfurt, Frankfurt am Main, Germany
[5]Gemeinschaftspraxis für Dermatologie, Mahlow, Germany
[6]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany
[7]Dermatologikum Hamburg, GmbH, Hamburg, Germany
*Correspondence: D. Thaçi. E-mail: Diamant.Thaci@uksh.de

Abstract

Background In a phase 3 clinical study, patients from Germany with moderate to severe psoriasis who were naïve to systemic treatment and received risankizumab had greater and more rapid disease improvements compared with those who received fumaric acid esters (FAEs).

Objective To evaluate patient-reported outcomes (PROs) in patients treated with risankizumab compared with FAEs.

Methods Adult patients were randomized 1:1 to receive either risankizumab 150 mg subcutaneous injections at weeks 0, 4 and 16 or FAEs (Fumaderm®) provided according to the prescribing label. PRO secondary endpoints assessed were Psoriasis Symptom Scale (PSS), Dermatology Life Quality Index (DLQI), 36-Item Short Form Health Survey, version 2 (SF-36v2), Patient Benefit Index (PBI), Hospital Anxiety and Depression Scale (HADS), Patient Global Assessment (PtGA) and European Quality of Life 5 Dimensions 5 Level (EQ-5D-5L). PROs were assessed at weeks 0, 16 and 24.

Results Sixty patients each were randomized to receive risankizumab or FAEs. A significant PSS improvement was observed with risankizumab vs. FAEs at weeks 16 and 24 for total and psoriasis-associated redness, itching and burning scores ($P < 0.001$). DLQI scores were significantly lower (reflecting better health-related quality of life) with risankizumab vs. FAEs, with least squares (LS) mean differences of −7.4 and −7.6 at weeks 16 and 24, respectively (both $P < 0.001$). Patients randomized to risankizumab also had larger improvements in SF-36 Physical and Mental Component Summary scores, HADS anxiety and depression scores, PtGA, and EQ-5D-5L index and visual analogue scale scores (all $P \leq 0.002$) at weeks 16 and 24 compared with FAEs. PBI was significantly higher, indicating greater benefit, with risankizumab vs. FAEs, with an LS mean difference of 1.1 and 1.3 at weeks 16 and 24, respectively (both $P < 0.001$).

Conclusions Risankizumab provides significant benefits over FAEs in improving PROs across several dimensions in patients with moderate to severe psoriasis.

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Conflicts of interest

D Thaçi has received grant/research support from AbbVie, Celgene and Novartis; has participated in a speaker's bureau for AbbVie, Amgen, Almirall, Biogen Idec, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sandoz/Hexal, Sanofi and UCB Pharma; and has served as a consultant/member of scientific board for AbbVie, Almirall, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sandoz/Hexal, Sanofi and UCB Pharma. AM Soliman, K Unnebrink, S Rubant and DA Williams are full-time employees of AbbVie and may own stock and/or stock options. K Eyerich is speaker, investigator and/or advisor for AbbVie, Almirall, Berlin Chemie, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Hexal, Galapagos, Janssen, LEO, Novartis, Sanofi and UCB Pharma. A Pinter is investigator, grant recipient, advisor/consultant and/or speaker for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, GSK, Hexal, Janssen, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer,

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Regeneron Pharmaceuticals, Roche, Sandoz Biopharmaceuticals, Schering-Plough, Tigercat Pharma and UCB Pharma. M Sebastian is investigator, grant recipient, advisor/consultant and/or speaker for AbbVie, Almirall, Boehringer Ingelheim, Celgene, Dr Reddy, Eli Lilly, Galderma, GSK, Incyte, Janssen, LEO Pharma, MSD, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals and UCB Pharma. P Weisenseel is speaker, investigator and/or advisor for AbbVie, Almirall, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dexcel, Eli Lilly, GSK, Janssen, LEO Pharma, Medac, MSD, Novartis and Pfizer.

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Introduction

Psoriasis is a chronic systemic inflammatory disease that has a major negative impact on patients' quality of life (QoL).[1-4] For patients with moderate to severe psoriasis in Germany, fumaric acid esters (FAEs) are the most frequently prescribed first-line systemic treatment with Fumaderm® the first FAE-based drug approved in Germany.[5] Clinical and observational studies have demonstrated FAEs to be beneficial in the treatment of psoriasis.[6,7] However, ≥10% of patients experience lymphopenia, and at least 14 cases of progressive multifocal leucoencephalopathy have been associated with FAEs.[6,7] Additionally, approximately 24% of patients discontinued treatment with FAEs due to adverse events (Table S1).[6]

Risankizumab (Skyrizi™) is a humanized immunoglobulin G1 monoclonal antibody to IL-23 that is approved in more than 40 countries, including the US and EU, for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy (US, EU) or phototherapy (US).[8,9] In four phase 3 trials, risankizumab demonstrated superior efficacy in patients with moderate to severe psoriasis vs. adalimumab, ustekinumab or secukinumab with comparable safety outcomes.[10-12]

In a recent phase 3 randomized controlled clinical study conducted in Germany, patients with moderate to severe psoriasis who were treated with risankizumab achieved greater and more rapid disease improvements along with a more favourable safety profile than patients treated with FAEs.[13,14] At week 24, Psoriasis Area and Severity Index (PASI) 90 was achieved by 83.3% of patients receiving risankizumab compared with 10.0% receiving FAEs.[13,14] We report on the patient-reported outcome (PRO) findings from this study.

Materials and methods

Complete materials and methods details are provided as Data S1.

Study design and patients

This was a phase 3, randomized, active-controlled and open-label study with blinded efficacy assessment conducted at 21 sites in Germany between August 2017 and July 2018 (EudraCT number 2016-003718-28, NCT03255382). Patients were randomized 1:1 to receive either risankizumab (Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany) 150 mg subcutaneous at weeks 0, 4 and 16 or FAEs (oral Fumaderm® Initial [Biogen Idec GmbH, Ismaning, Germany; 30 mg per tablet] or Fumaderm® [Biogen Idec GmbH, Ismaning, Germany; 120 mg per tablet]).

Patients 18–79 years of age with a diagnosis of chronic plaque psoriasis ≥6 months prior to receiving study drug were eligible to participate in the trial. Additional eligibility requirements included having stable moderate to severe plaque psoriasis, defined as body surface area involvement >10%, PASI score >10 and Dermatology Life Quality Index (DLQI) score >10; being naïve to and a candidate for systemic therapy; and having an inadequate response, intolerance or contraindication to topical psoriasis treatment.

Assessments

In this study, PRO secondary endpoints assessed were Psoriasis Symptom Scale (PSS), DLQI, 36-Item Short Form Health Survey, version 2 (SF-36v2), Patient Benefit Index (PBI), Hospital Anxiety and Depression Scale (HADS), Patient Global Assessment (PtGA) and European QoL 5 Dimensions 5 Level (EQ-5D-5L). PSS, SF-36v2, PBI, HADS, PtGA and EQ-5D-5L were completed by the patient at week 0, 16 and 24. DLQI was completed at screening (Day −30 to −1), and week 0, 16 and 24.

Statistical methods

Analyses were performed in the intent-to-treat population, which consists of all patients who were randomized. Demographic and baseline characteristics were summarized with descriptive statistics (mean, standard deviation for continuous endpoints, absolute and relative counts for categorical endpoints). Categorical endpoints for PSS and DLQI were analysed using a Cochran–Mantel–Haenszel test; continuous endpoints for DLQI, SF-36v2, HADS, PtGA and EQ-5D-5L were analysed using analysis of covariance; and PSS was analysed using the stratified van Elteren test. Statistical comparisons with *P* values

below a two-sided level of significance of 5% were considered 'statistically significant'. All data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

A total of 120 patients were evaluated in this study with 60 randomized to risankizumab and 60 randomized to FAEs (Table S2). Baseline characteristics were similar between the treatment groups with a mean age of approximately 42 years for both groups.

Significant improvements in PROs with risankizumab vs. FAEs

Significantly greater benefits were noted with risankizumab vs. FAEs for all PRO measures at weeks 16 and 24 ($P \leq 0.002$, Tables 1 and 2, Figs 1 and 2). These findings were consistent with the previously published efficacy results, where the percentage of patients achieving PASI 90 at weeks 16 and 24 were significantly greater for risankizumab vs. FAEs ($P < 0.001$).[13,14]

Greater improvements in PSS scores with risankizumab vs. FAEs

For PSS, a significant improvement was observed with risankizumab vs. FAEs at weeks 16 and 24 for the total and psoriasis-associated redness, itching and burning scores ($P < 0.001$, Table 1). Decreases in total and individual PSS scores with risankizumab were greater at week 24 compared with week 16. For the total PSS score, the decrease with risankizumab was from 11.0 at baseline to 2.4 and 1.5 at weeks 16 and 24, respectively. By comparison, in patients randomized to FAEs, the total PSS score decreased from a baseline value of 11.2 to 5.7 and 5.5 at weeks 16 and 24, respectively. For the total PSS score, there were 19.8% ($P = 0.001$) and 38.3% ($P < 0.001$) more patients who were randomized to risankizumab reporting PSS = 0 vs. those randomized to FAEs at weeks 16 (25.0% vs. 5.0%) and 24 (41.7% vs. 3.3%), respectively (Fig. 1).

Larger DLQI score improvements with risankizumab vs. FAEs

Significantly greater improvements in DLQI scores were also noted with risankizumab vs. FAEs from baseline values of 19.9 and 20.8, respectively, with least squares (LS) mean differences between the

Table 1 Change in PSS item scores with risankizumab vs. FAEs treatment (ITT, LOCF)

PSS item	Mean score		LS mean (SE) change from baseline		Difference between risankizumab vs. FAEs	
	Risankizumab (n = 59)	FAEs (n = 55)	Risankizumab	FAEs	LS mean difference (95% CI)	P value*
Total						
Baseline†	11.0	11.2	–	–	–	–
Week 16	2.4	5.7	−8.7 (0.51)	−5.5 (0.52)	−3.2 (−4.5, −2.0)	<0.001
Week 24	1.5‡	5.5	−9.5 (0.48)	−5.6 (0.49)	−3.9 (−5.1, −2.7)	<0.001
How severe was your pain						
Baseline†	1.8	2.1	–	–	–	–
Week 16	0.3	1.0	−1.7 (0.14)	−1.0 (0.14)	−0.6 (−1.0, −0.3)	0.101
Week 24	0.2‡	0.9	−1.7 (0.12)	−1.1 (0.12)	−0.7 (−0.9, −0.4)	0.147
How severe was the redness						
Baseline†	3.1	3.2	–	–	–	–
Week 16	0.9	1.9	−2.2 (0.14)	−1.2 (0.14)	−1.0 (−1.3, −0.6)	<0.001
Week 24	0.5‡	1.8	−2.7 (0.14)	−1.4 (0.14)	−1.3 (−1.6, −1.0)	<0.001
How severe was your itching						
Baseline†	3.3	3.2	–	–	–	–
Week 16	0.8	1.6	−2.5 (0.15)	−1.6 (0.15)	−0.9 (−1.3, −0.5)	<0.001
Week 24	0.6‡	1.6	−2.7 (0.15)	−1.7 (0.15)	−1.0 (−1.3, −0.6)	<0.001
How severe was your burning						
Baseline†	2.7	2.6	–	–	–	–
Week 16	0.4	1.2	−2.3 (0.15)	−1.6 (0.15)	−0.8 (−1.1, −0.4)	<0.001
Week 24	0.2‡	1.2	−2.5 (0.14)	−1.5 (0.15)	−1.0 (−1.4, −0.7)	<0.001

* P value calculated by stratified van Elteren test.
†Baseline values for patients with week 16 values.
‡n = 60.
CI, confidence interval; FAEs, fumaric acid esters; ITT, intent-to-treat; LOCF, last observation carried forward; LS, least squares; PSS, Psoriasis Symptom Scale; SE, standard error.

Table 2 Change in PRO scores with risankizumab vs. FAEs treatment (ITT, LOCF)

PRO	Mean score		LS mean (SE) change from baseline		Difference between risankizumab vs. FAEs	
	Risankizumab (n = 59)	FAEs (n = 55)	Risankizumab	FAEs	LS mean difference (95% CI)	P value*
Total DLQI score						
Baseline†	19.9	20.8‡	–	–	–	–
Week 16	3.3	11.0‡	−17.0 (0.94)	−9.7 (0.94)	−7.4 (−9.6, −5.1)	<0.001
Week 24	1.7§	9.5‡	−18.8 (0.87)	−11.2 (0.87)	−7.6 (−9.7, −5.5)	<0.001
SF-36v2 PCS score						
Baseline†	46.1	45.9	–	–	–	–
Week 16	53.6	49.1	7.4 (1.14)	2.9 (1.15)	4.5 (1.7, 7.2)	0.002
Week 24	54.7§	50.1	8.3 (1.08)	3.7 (1.10)	4.6 (2.0, 7.3)	<0.001
SF-36v2 MCS score						
Baseline†	37.3	37.1	–	–	–	–
Week 16	49.0	42.2	10.9 (1.47)	4.2 (1.49)	6.7 (3.1, 10.2)	<0.001
Week 24	49.8§	41.7	11.4 (1.47)	3.6 (1.49)	7.9 (4.3, 11.4)	<0.001
HADS total score anxiety						
Baseline†	8.5	8.2	–	–	–	–
Week 16	4.1	6.0	−4.3 (0.47)	−2.2 (0.48)	−2.0 (−3.2, −0.9)	<0.001
Week 24	4.2§	6.4	−4.0 (0.48)	−1.8 (0.49)	−2.3 (−3.5, −1.1)	<0.001
HADS total score depression						
Baseline†	7.3	7.0	–	–	–	–
Week 16	2.2	5.2	−4.9 (0.50)	−1.8 (0.50)	−3.1 (−4.3, −1.9)	<0.001
Week 24	2.2§	5.2	−4.8 (0.53)	−1.7 (0.54)	−3.1 (−4.4, −1.8)	<0.001
PtGA						
Baseline†	2.6	2.7‡	–	–	–	–
Week 16	0.8	1.7‡	−1.9 (0.11)	−1.0 (0.11)	−1.0 (−1.2, −0.7)	<0.001
Week 24	0.7§	1.7‡	−2.0 (0.11)	−1.0 (0.11)	−1.0 (−1.3, −0.8)	<0.001
EQ-5D-5L index score						
Baseline†	0.77¶	0.78	–	–	–	–
Week 16	0.94¶	0.86	0.17 (0.02)	0.08 (0.02)	0.09 (0.05, 0.13)	<0.001
Week 24	0.95§	0.89	0.17 (0.02)	0.11 (0.02)	0.06 (0.02, 0.10)	0.002
EQ-5D-5L VAS score						
Baseline†	56.5¶	60.9	–	–	–	–
Week 16	83.6¶	69.5	26.0 (2.28)	11.0 (2.32)	14.9 (9.4, 20.5)	<0.001
Week 24	87.7§	71.7	28.4 (2.23)	11.6 (2.29)	16.8 (11.4, 22.2)	<0.001

*P value calculated from ANOVA with prior phototherapy, baseline value and treatment in the model.
†Baseline values for patients with week 16 values.
‡n = 56.
§n = 60.
¶n = 58.
ANOVA, analysis of variance; CI, confidence interval; DLQI, Dermatology Life Quality Index; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level; FAEs, fumaric acid esters; HADS, Hospital Anxiety and Depression Scale; ITT, intent-to-treat; LOCF, last observation carried forward; LS, least squares; MCS, Mental Component Summary; PCS, Physical Component Summary; PRO, patient-reported outcome; PtGA, Patient Global Assessment; SE, standard error; SF-36v2, 36-Item Short Form Health Survey, version 2; VAS, visual analogue scale.

two treatments of −7.4 and −7.6 at weeks 16 and 24, respectively (both $P < 0.001$, Table 2). Overall, 38.3% and 56.8% more patients randomized to risankizumab vs. FAEs responded that their disease had a 'not relevant at all' or 'little' impact on PROs, including symptoms and feelings and daily activities, at weeks 16 and 24, respectively (both $P < 0.001$, Fig. 1).

Greater improvements for other PROs with risankizumab vs. FAEs

Significantly greater PRO improvements for risankizumab compared with FAEs at weeks 16 and 24 were also observed for SF-36 PCS and MCS scores, HADS anxiety and depression scores, PtGA, and EQ-5D-5L index and visual analogue scale scores (all

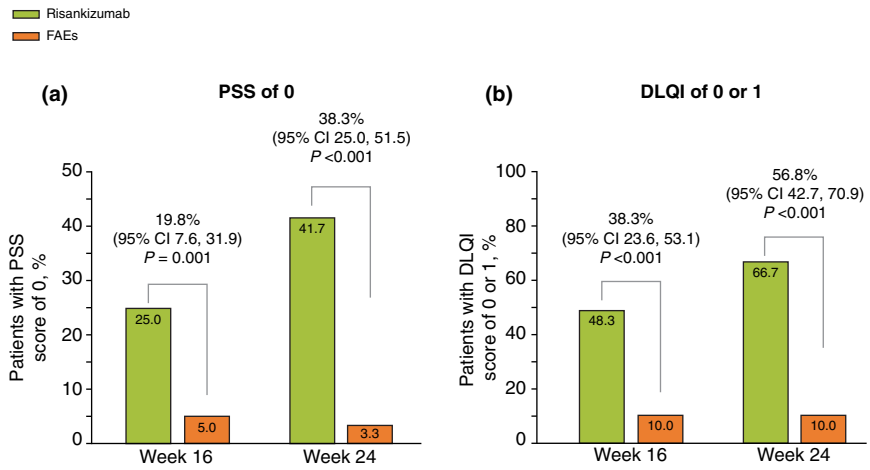

Figure 1 Proportion of patients having a minimal impact of psoriasis on their symptoms and health-related quality of life with risankizumab vs. FAEs (ITT, NRI). (a) PSS. (b) DLQI. $n = 60$ for each cohort at both time points. Calculated using the Cochran–Mantel–Haenszel test. *P* value adjusted for prior phototherapy. PSS is a four-item PRO assessing psoriasis-associated pain, redness, itching and burning in patients with moderate to severe disease with symptom severity ranging from 0 (none) to 4 (very severe). DLQI consists of 10 questions which cover six domains, including symptoms and feelings, daily activities, leisure, work and school and personal relationships, with 0 being 'not relevant at all' and 1–3 ranging from 'a little' to 'very much'. CI, confidence interval; DLQI, Dermatology Life Quality Index; FAEs, fumaric acid esters; ITT, intent-to-treat; NRI, non-responder imputation; PRO, patient-reported outcome; PSS, Psoriasis Symptom Scale.

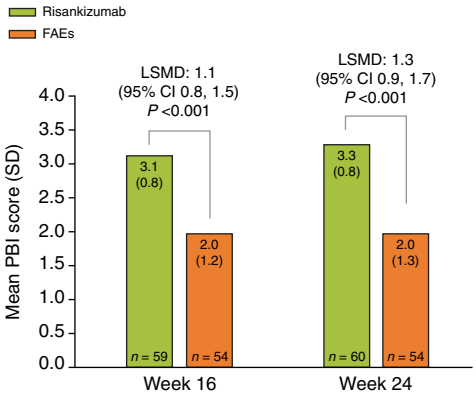

Figure 2 PBI scores with risankizumab vs. FAEs treatment (ITT, LOCF). *P* value calculated from ANCOVA with prior phototherapy, baseline value and treatment in the model. ANCOVA, analysis of covariance; CI, confidence interval; FAEs, fumaric acid esters; ITT, intent-to-treat; LOCF, last observation carried forward; LSMD, least squares mean difference; PBI, Patient Benefit Index; SD, standard deviation.

$P \leq 0.002$, Table 2). Overall, the scores for these respective PROs with risankizumab were similar or slightly better at week 24 vs. week 16 (Table 2). PBI was also significantly higher, indicating more patient-reported benefit, with risankizumab vs. FAEs, with an LS mean difference of 1.1 and 1.3 at weeks 16 and 24, respectively (both $P < 0.001$, Fig. 2).

Discussion

In this study, we demonstrated that patients receiving risankizumab reported significantly better PROs than those receiving FAEs after 16 and 24 weeks of treatment. Our findings correlate with the efficacy findings of this study which determined that significantly more patients receiving risankizumab vs. FAEs achieved PASI 90 at week 16 (76.7% vs. 11.7%, $P < 0.001$) and week 24 (83.3% vs. 10.0%, $P < 0.001$).[13,14]

This was the first extensive PRO analysis of risankizumab in patients with plaque psoriasis and confirmed earlier results from clinical studies using a limited number of PRO measurements.[10,11,15,16] In three previous phase 3 studies; UltlMMA-1, UltlMMA-2, IMMvent; 65.8–66.7% of patients with moderate to severe plaque psoriasis receiving risankizumab (150 mg at Weeks 0 and 4) achieved DLQI 0 or 1 at week 16.[10,11] PSS of 0 was obtained by 29.3–31.3% of patients at week 16 receiving risankizumab.[10] For both DLQI and PSS, the improvements observed at week 16 in the UltlMMA-1 and UltlMMA-2 studies increased with 52 weeks of treatment (every 12 weeks starting at week 16).[10] At week 52, 71–75% of patients achieved DLQI of 0 or 1, while 54–57% achieved PSS of 0 in the UltlMMA-1 and UltlMMA-2 studies, consistent with our findings with 24 weeks of treatment.[10]

Previous reports on QoL improvements with FAEs primarily focused on DLQI outcomes with results generally comparable with the findings in this study.[17-19] Decreases in DLQI score after approximately 12–16 weeks of FAEs treatment ranged from

34–50%, similar to the 47% decrease found in this current study.[17,19]

The strength of this study comes from the large number of different PRO measures used to evaluate multiple burdens experienced by patients. Also, having specific PRO topics addressed in multiple tests, such as mental health and physical functioning, provides confirmation of responses to these items. As this study evaluated patients from one country, Germany, application of the results to other countries may be limited. As PROs are influenced by patient expectations, side effects may be attributed to a given drug and can affect a patient's judgement on outcomes, despite the study being blinded.

In conclusion, risankizumab provides significantly greater improvements in a wide array of PRO parameters that address different aspects of the impact of psoriasis on a patient's well-being by 16 and 24 weeks of treatment compared with FAEs. These results provide further evidence to support the use of risankizumab as an alternative option in patients who do not adequately respond to or cannot tolerate FAEs by demonstrating a dramatic reduction in the impact of psoriasis on patients' QoL in addition to its symptomatic benefits.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Dosing schedule for FAEs.
Table S2. Baseline demographics.
Data S1. Supplemental materials and methods.