The Safety of Fenebrutinib in a Large Population of Patients With Diverse Autoimmune Conditions Supports Investigation in Multiple Sclerosis

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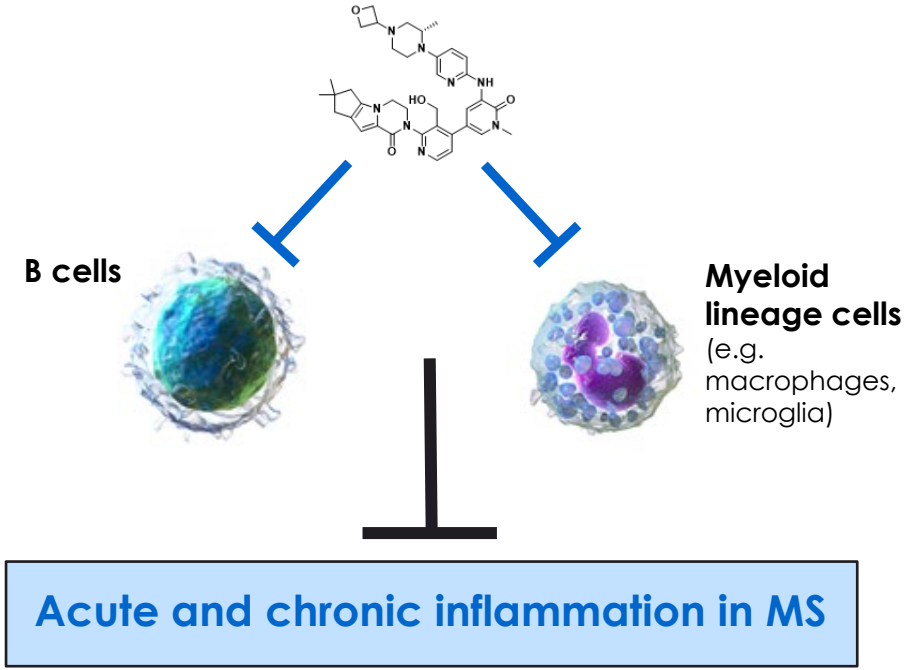
Introduction: Fenebrutinib in MS

- Fenebrutinib is a potent, highly selective oral Bruton's tyrosine kinase (BTK) inhibitor[1,a]
- The high selectivity of fenebrutinib may result in a more favorable safety profile by limiting off-target effects
- Of all currently investigated BTKis in MS, fenebrutinib has the largest clinical safety database, allowing for assessment of its potential in MS management

Fenebrutinib has a dual mechanism of action[2]



[a]See Poster P15.091 at this conference. BTK, Bruton's tyrosine kinase; MS, multiple sclerosis.

1. Crawford JJ, *et al. J Med Chem* 2018;61:2221-2245; 2. Torke S, Weber MS. *Expert Opin Investig Drugs*. 2020;29:1143-1150.

Background: Extensive clinical experience with fenebrutinib

Fenebrutinib clinical studies
Thirteen completed to date (one ongoing)[1-9]

1360 study participants[a]

365 healthy volunteers[8]

24 patients with hematologic malignancies[9]

578 patients with RA[1-3]

259 patients with SLE[4,5]

134 patients with CSU[6,7]

Exposure to 200 mg BID[b]:
>48 weeks (n=493)
>8 weeks (n=700)
>96 weeks (n=7)

Single and multiple doses tested, ranging from 0.5–600 mg (792 patients received 200 mg)

Placebo and Standard of Care (SoC) active comparators

6 Phase II trials across 3 autoimmune conditions (in combination with disease-specific SoC)

[a]Clinical database as of Phase II study database lock. [b]Across all autoimmune indications in both randomized and open-label studies. CSU, chronic spontaneous urticaria; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SoC, standard of care.

1. Chan P, et al. Pharm Res. 2020;37:25; 2. Cohen S, *et al. Arthritis Rheumatol.* 2020;72:1435–1446; 3. ClinicalTrials.gov identifier: NCT02983227; 4. ClinicalTrials.gov identifier: NCT02908100; 5. ClinicalTrials.gov identifier: NCT03407482; 6. ClinicalTrials.gov identifier: NCT03693625; 7. ClinicalTrials.gov identifier: NCT03137069; 8. Herman AE, *et al. Clin Pharmacol Ther*. 2018;103:1020–8; 9. ClinicalTrials.gov identifier: NCT01991184.

Background: Overall, fenebrutinib has been well tolerated, with mostly non-serious AEs, mild-to-moderate in nature[a]

BTKi

Risks related to class effects/MoA[b]	
Reversible liver aminotransferase elevations	Clinical trial evidence exists for a causal association
Hepatotoxicity	Not seen in clinical trials
Infections	Rates similar to those of placebo across conditions studied to date; low rates of serious infections
Effect on vaccinations	Not studied
Neutropenia/lymphopenia	Low rate across conditions studied to date
Class-related risks due to off-target effects[c]	
Bleeding events	Currently appear less relevant to fenebrutinib due to increased selectivity for BTK and based on available safety data
Cardiovascular effects (AV arrhythmia)	
Risks seen in animal studies	
Gastrointestinal effects	Translatability to humans is unknown
Vascular inflammation	
Embryo-fetal toxicity	

[a]Roche data on file; [b]May affect the efficacy of fenebrutinib, or lead to discontinuation; [c]These risks have been well characterized in ibrutinib therapy.
AE, adverse event; AV, atrioventricular; BTKi, Bruton's tyrosine kinase inhibitor; MoA, mechanism of action.

Objective and Methods: Pooled safety analysis of fenebrutinib

Objective

To analyze the large fenebrutinib safety database of prior Phase II randomized clinical trials (RCTs) and open-label extensions (OLEs) in autoimmune conditions, to allow for more confident assessment of fenebrutinib's potential in MS

A total of 792 patients from Phase II studies who were taking the highest dose of fenebrutinib (200 mg BID) with the following autoimmune conditions were analyzed

- Rheumatoid arthritis (RA; n=523)
- Systemic lupus erythematosus (SLE; n=194)
- Chronic spontaneous urticaria (CSU; n=75)

Safety assessments analyzed

- Adverse events (AEs)
- Laboratory test results
- ECGs
- Vital signs

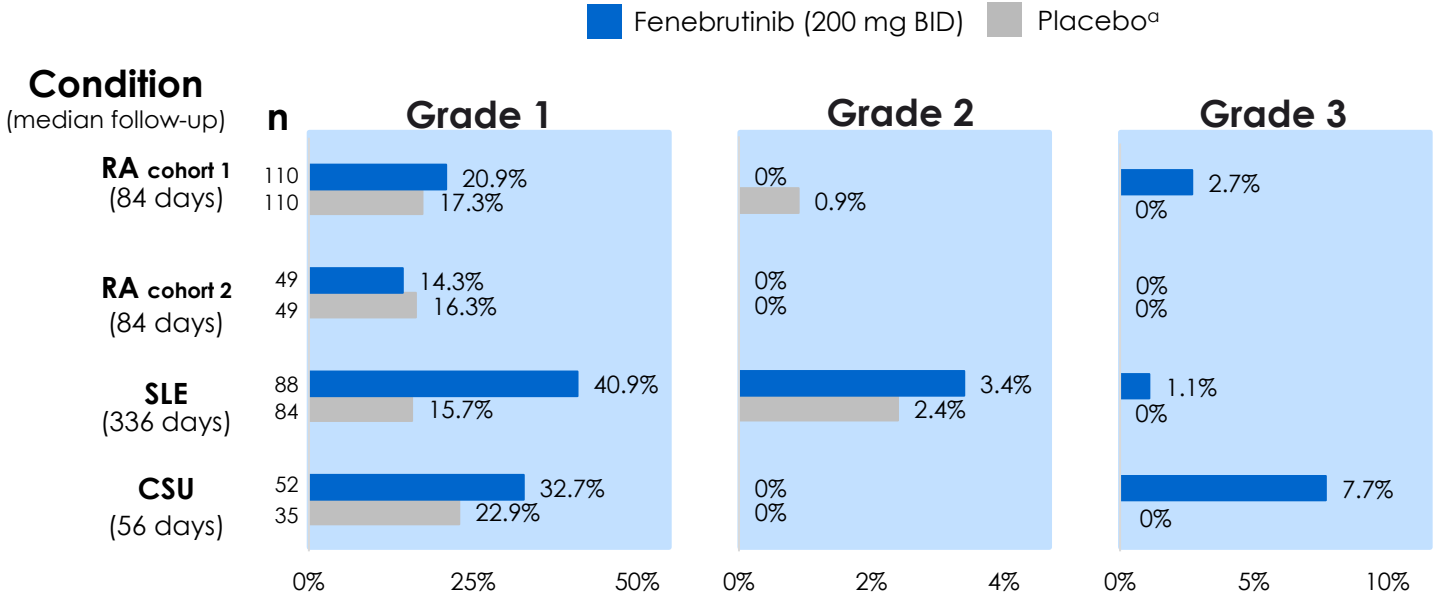
AE, adverse event; CSU, chronic spontaneous urticaria; ECG, electrocardiogram; MS, multiple sclerosis; RCT, randomized clinical trial; OLE, open label extension; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Results: AEs were mostly non-serious in patients with autoimmune conditions treated with highest dose of fenebrutinib (200 mg) in RCTs

	Fenebrutinib 200 mg BID (n=299)	Placebo[a] (n=278)
Total AEs, n	507	431
Investigator-reported events in >5% of fenebrutinib-treated patients in RCTs		
Nasopharyngitis, n (%)	18 (6.0)	13 (4.7)
Nausea, n (%)	17 (5.7)	12 (4.3)
Headache, n (%)	16 (5.4)	17 (6.1)
Patients with		
Fatal AE[b], n (%)	1 (0.3)	2 (0.7)
Serious AE, n (%)	18 (6.0)	9 (3.2)
Serious AE related to blinded fenebrutinib, n (%)	6 (2.0)	5 (1.8)
AE leading to treatment withdrawal, n (%)	32 (10.7)	13 (4.7)

[a]Placebo was standard of care for each disease; [b]The cause of death of the patient in the fenebrutinib arm was acute myocardial infarction, deemed unrelated to fenebrutinib. AE, adverse event; RCT, randomized clinical trial.

Results: Asymptomatic and reversible liver aminotransferase elevations have been the only risk causally associated with fenebrutinib to date



Percent of patients with aminotransferase elevations in RCTs[b]

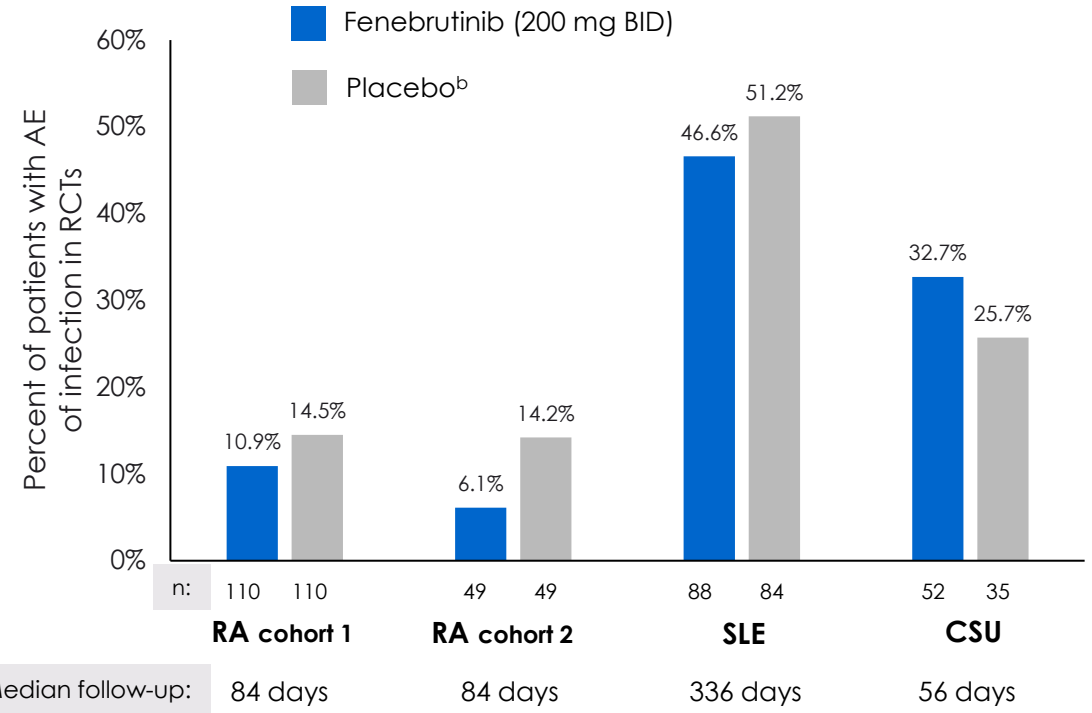
No other signs of hepatic dysfunction

No Hy's law cases

Aminotransferase levels returned to baseline/normal with treatment cessation

[a]Placebo was standard of care for each disease studied; [b]Data represent ALT or AST elevations, though in most cases ALT was higher than AST. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSU, chronic spontaneous urticaria; RA, rheumatoid arthritis; RCT, randomized clinical trials; SLE, systemic lupus erythematosus.

Results: No imbalance in infection rates in fenebrutinib arms compared to placebo, despite background immunosuppressant therapy use[a] in RA and SLE

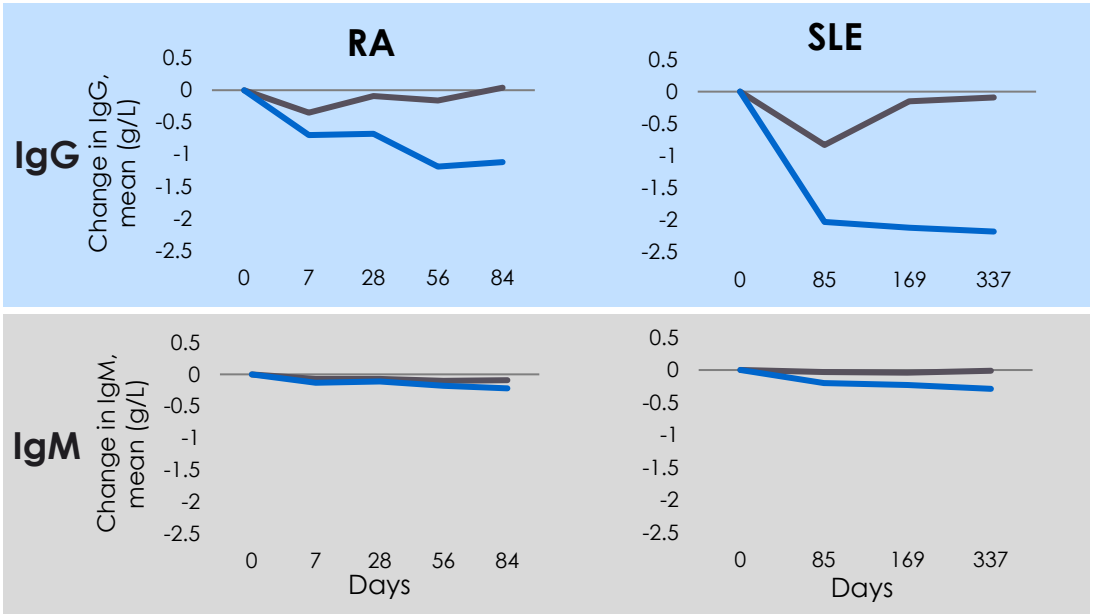


No imbalance in pattern, duration, seriousness or severity of infections in patients receiving fenebrutinib v placebo

[a]For example, methotrexate, corticosteroids. [b]Placebo was standard of care for each disease studied. [b]Six patients (2.0%) in the combined fenebrutinib arms and 5 patients (1.8%) in the combined placebo arms had serious infections. AE, adverse event; CSU, chronic spontaneous urticaria, RA, rheumatoid arthritis; RCT, randomized clinical trials; Soc, standard of care; SLE, systemic lupus erythematosus.

Results: Fenebrutinib treatment was associated with a decline in IgG and IgM v placebo, consistent with its mechanism of action

- Immunoglobulin levels remained above the lower limit of normal (LLN)[a] in nearly all the fenebrutinib-treated patients with normal baseline levels (IgG, 99.0%; IgM, 96.5%)
- Declining IgG or IgM levels were not associated with an increased risk of serious infections[b]



Fenebrutinib (200 mg BID)

Placebo[c]

Number of patients with IgG or IgM<LLN (regardless of baseline)

Condition	Treatment	IgG	IgM
RA	Fen (n=159)	1	3
	PBO (n=159)	0	1
SLE	Fen (n=88)	1	6
	PBO (n=84)	0	2
CSU	Fen (n=52)	1	1
	PBO (n=35)	0	0

[a]Normal ranges: IgG, 5.65 to17.65 g/L; IgM, 0.4 to 2.3 g/L. [b]One fen-treated patient developed serious pyelonephritis before IgM levels decreased to <LLN; no patients with IgG <LLN had serious infections. [c]Placebo was standard of care for each disease studied. CSU, chronic spontaneous urticaria; Fen, fenebrutinib; Ig, immunoglobulin; LLN, lower limit of normal; PBO, placebo; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Results: Other potential class effects appeared less relevant to fenebrutinib due to increased selectivity for BTK

Bleeding or bruising[a]

- 7.7% (n=23) in fenebrutinib arms
- 3.2% (n=9) in combined placebo[b] arms
- Bleeding events reduced with continued dosing in OLEs (5.2%)

These rates are **substantially lower** than those in reports of ibrutinib-treated patients with B cell malignancies (bleeding or bruising, 39%; major hemorrhage, 4%)[1]

Cardiovascular disease[c]

- No RCT patients had atrial fibrillations, flutters or other supraventricular tachyarrhythmias

This is **substantially lower** than what has been reported for ibrutinib[d] (4% Grade ≥3 atrial fibrillation/flutter; 1% ventricular tachyarrhythmias)[1]

Malignancy

- No imbalance in malignancies between fenebrutinib and placebo arms
- One patient developed Stage 0 cervix carcinoma (fenebrutinib, RCT) compared to zero patients receiving placebo
- One patient developed lung cancer, and 3 developed non-melanoma skin cancer in OLEs

[a]1 patient developed grade 3 purpura in the RA placebo arm; 2 patients in RA OLE study developed grade 3 vaginal hemorrhage. [b]Placebo was standard of care for each disease studied; [c]1 patient on fenebrutinib (RA) experienced ventricular extrasystole; 2 patients (0.3%) developed atrial fibrillation and 1 patient (0.1%) developed supraventricular tachycardia in OLEs. [d]Median treatment time 19.1 months. BTK, Bruton tyrosine kinase; OLE, open label extension; RCT, randomized clinical trial.

1. Imbruvica USPI. Dec. 2020. https://imbruvica.com/files/prescribing-information.pdf. Accessed March 22, 2021.

Conclusions

- Fenebrutinib's extensive safety database of prior Phase II studies includes nearly 800 patients with various autoimmune conditions, and adds to the understanding that
  - To date, fenebrutinib has been safe and well-tolerated
  - An identified risk is asymptomatic, transient liver enzyme elevations
  - Other potential class effects (infection, severe bleeding, tachyarrhthmias) appear less relevant to fenebrutinib due to its increased selectivity for BTK

Overall, fenebrutinib's safety profile supports testing in Phase III clinical trials in patients with MS, which is critical to addressing the unmet need of disease progression in MS

BTK, Bruton's tyrosine kinase; MS, multiple sclerosis.