IMC-1, a Fixed Dose Combination of Famciclovir and Celecoxib, Improves Common Symptoms Associated With Fibromyalgia in Addition to Pain: Post Hoc Analysis of a Phase 2a Trial

William Pridgen,[1] Carol Duffy,[2] Judy F. Gendreau,[3] R. Michael Gendreau[4*]

[1]Tuscaloosa Surgical Associates, P.C., LLC, Tuscaloosa, AL, USA; [2]University of Alabama, Department of Biological Sciences, Tuscaloosa, AL, USA; [3]Gendreau Consulting, LLC, Poway, CA, USA; [4]Virios Therapeutics, Alpharetta, GA, USA

INTRODUCTION

- Fibromyalgia (FM), a chronic disorder characterized by widespread pain, causes a variety of other symptoms, including fatigue, non-restorative sleep, morning stiffness, and cognitive dysfunction[1]
- It has been hypothesized that the reactivation of viral infections, such as herpes simplex virus type 1 (HSV-1), may contribute to the symptoms associated with FM and that drugs that suppress replication and/or reactivation of tissue-resident herpes virus could provide symptom relief[2]
- An oral, fixed dose combination of famciclovir and celecoxib (IMC-1) demonstrated greater tolerability and significantly greater pain reduction compared with placebo in a Phase 2a proof of concept trial (NCT01850420)[2]
- Given that FM is associated with a broad spectrum of symptoms beyond pain, it is important to understand the impact of IMC-1 on other FM-related symptoms

OBJECTIVE

- To evaluate the effects of IMC-1 compared with placebo across a range of FM symptoms assessed by the Revised Fibromyalgia Impact Questionnaire (FIQ-R), including lack of energy, stiffness, problems with sleep, problems with memory, depression, and anxiety

RESULTS

- A total of 143 patients from 12 US sites were enrolled in the study and randomized to 16 weeks of treatment with IMC-1 (n=69) or placebo (n=74)
- Baseline demographic and clinical characteristics were similar between treatment groups; most patients were Caucasian (95.8%) and female (93.7%) with a mean age of approximately 49 years
  - Patients in the placebo group had mean baseline NRS 24-hour recall scores of 7.1 compared to 6.5 for patients randomized to IMC-1 treatment; mean baseline FIQ-R 7-day recall pain scores were 6.8 in the placebo group and 6.5 in the IMC-1 group
- Study completion rates favored IMC-1, as 82.6% of patients receiving IMC-1 completed 16 weeks of treatment compared to 60.8% of patients receiving placebo (**Table 1**)
- The rates of tramadol rescue medication usage for acute pain exacerbations were significantly lower in the IMC-1 group than in the placebo group (25% vs 41%, *P*=.037)

Table 1. Patient Disposition

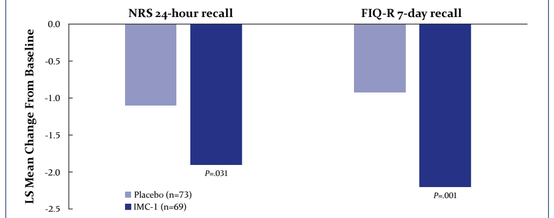
Category		Placebo	IMC-1	Total
Randomized, n		74	69	143
ITT Population,[a] n		73	69	142
Safety Population, n		73	69	142
Prematurely discontinued from study, n (%)		29 (39.2)	12 (17.4)	41 (28.7)
Completed 16 weeks of study medication, n (%)		45 (60.8)	57 (82.6)	102 (71.3)
Completed all protocol assessments, regardless of discontinuation of study drug, n (%)		62 (83.8)	62 (89.9)	124 (86.7)
Discontinuation reasons,[b] n (%)	Adverse event	12 (16.4)	4 (5.8)	16 (11.2)
	Therapeutic failure	12 (16.4)	5 (7.2)	17 (11.9)
	Non-compliance	1 (1.4)	0 (0.0)	1 (0.7)
	Withdrawal of consent	3 (4.1)	2 (2.9)	5 (3.5)
	Lost to follow-up	1 (1.4)	1 (1.4)	2 (1.4)

[a]The ITT population is one patient less than the randomized population due to the exclusion of one patient who withdrew consent after randomization but prior to taking any study drug; [b]Based on the safety population. ITT, intent to treat.

Pain Analyses

- Patients treated with IMC-1 reported significantly greater reductions in pain versus placebo, as measured by mean change from baseline to week 16 in NRS 24-hour recall scores (-1.1 vs -1.9) (**Figure 1**)
- Similarly, significant improvement versus placebo was noted in FIQ-R 7-day recall scores in patients receiving IMC-1 treatment (-0.9 vs -2.2) (**Figure 1**)

Figure 1: Mean Change from Baseline in NRS and FIQ-R Pain Recall Scores at 16 Weeks



FIQ-R, Revised Fibromyalgia Impact Questionnaire; LS, least squares; NRS, numerical rating scale.

Secondary and Exploratory Outcomes

- A significantly greater proportion of patients treated with IMC-1 versus placebo met criteria for response on the PGIC
- At week 16, IMC-1 was associated with significantly greater improvement than placebo on the FIQ-R total and all three domain scores, and PROMIS fatigue scores (**Table 2**)
- There were no statistically significant differences in change from baseline to 16 weeks in MFI scores between treatment groups

Table 2. Secondary and Exploratory Efficacy Outcomes at 16 Weeks

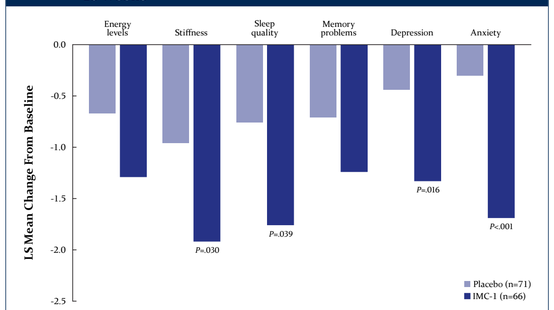
Parameter		Placebo (n=73)	IMC-1 (n=69)	Treatment difference	*P* value
PGIC responders, n (%)		14 (19.2)	23 (33.3)	-	0.040
FIQ-R total score, LS mean (SE)		-7.87 (2.3)	-17.54 (2.4)	-9.67 (3.1)	0.002
FIQ-R domains, LS mean (SE)	Functional	-5.44 (2.3)	-14.29 (2.4)	-8.85 (3.0)	0.004
	Overall impact	-1.89 (0.6)	-4.29 (0.6)	-2.4 (0.8)	0.003
	Symptom	-7.90 (2.3)	-16.77 (2.4)	-8.88 (3.1)	0.004
PROMIS fatigue, LS mean (SE)		-2.68 (0.9)	-6.65 (1.0)	-3.96 (1.2)	0.001
MFI total, LS mean (SE)		-3.69 (1.6)	-6.90 (1.5)	-3.22 (2.0)	0.107

FIQ-R, Revised Fibromyalgia Impact Questionnaire; LS, least squares; MFI, Multidimensional Fatigue Inventory; PGIC, Patient's Global Impression of Change; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error.

FIQ-R Scores: Symptom Domain

- Treatment with IMC-1 versus placebo resulted in statistically significant improvements in the FIQ-R symptom domain scores of stiffness, sleep quality, depression, and anxiety (**Figure 2**)

Figure 2. Mean Change from Baseline in FIQ-R Symptom Domain Scores at 16 Weeks



FIQ-R, Revised Fibromyalgia Impact Questionnaire; LS, least squares; NRS, numerical rating scale.

Safety

- Significantly more patients in the placebo group discontinued treatment due to adverse events than those in the IMC-1 group (16.4% vs 5.8%, *P*=.012)
- The most common treatment emergent adverse events (TEAEs) among both treatment groups were gastrointestinal disorders (35.9%), infections (24.6%), and nervous system disorders (20.4%)
- Interestingly, despite the celecoxib component of IMC-1, gastrointestinal TEAEs were reported less frequently in the IMC-1 group (29.0%) than in placebo (42.5%)
- No deaths were reported in either treatment group; serious adverse events occurred in 1 patient receiving placebo (metastatic breast cancer) and in 2 patients receiving IMC-1 (cellulitis and acute myocardial infarction [significant coronary artery disease was considered the causal factor])

CONCLUSIONS

- In this post hoc analysis of a Phase 2a trial of IMC-1 in patients with FM, patients treated with IMC-1 reported significantly greater improvement compared with placebo on FIQ-R total scores and on all FIQ-R domains
- Patients receiving IMC-1 treatment reported significantly greater improvements versus placebo in FIQ-R symptom domain scores of stiffness, sleep quality, depression, and anxiety
- Improvements in PGIC and in fatigue assessments provide additional support for the beneficial effects of IMC-1 on other FM symptoms
- These results suggest that IMC-1 may represent a promising treatment option not only for alleviating pain, but also improving other symptoms associated with FM

References

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METHODS

Study Design and Patients

- A randomized, double-blind, placebo-controlled Phase 2a trial (NCT01850420) evaluated the safety and efficacy of IMC-1 for the treatment of adults (18–70 years) with a primary diagnosis of FM
  - Patients with baseline 24-hour recall average pain intensity scores between 4 and 9 on an 11-point numerical rating scale (NRS) were eligible for study enrollment
- Participants were randomized 1:1 to receive 16 weeks of treatment with IMC-1 or matching placebo
- Minimal use of acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) was permitted for relief of minor pain, and if those agents were inadequate, tramadol could be prescribed as rescue therapy for acute exacerbations
- The primary efficacy outcome was mean change from baseline in FM pain assessed with a 24-hour recall, 11-point NRS pain scale, as well as a 7-day recall, 11-point NRS average pain score measured on the FIQ-R
- The percentage of Patient's Global Impression of Change (PGIC) responders, defined as patients who rated themselves "very much improved" or "much improved" (ie, scores of 1 or 2 on the 7-point scale) and FIQ-R total and domain scores were examined as secondary outcomes
  - Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue scores and Multidimensional Fatigue Inventory (MFI) scores were examined as exploratory outcomes
- Post hoc analysis was conducted to analyze the effects of IMC-1 versus placebo across symptom domains associated with FM using the individual symptom scores of the FIQ-R
  - The FIQ-R has 21 questions, all based on a 0-10 NRS (10 being 'worst'), and is divided into functional, overall impact, and symptom domains[3]
- Symptom domains of energy level, stiffness, sleep quality, depression, memory problems, and anxiety were assessed
- Mean changes from baseline to week 16 in NRS and FIQ-R scores were analyzed in the intent-to-treat (ITT) population, which included all randomized patients who took at least one dose of study drug
  - Data were analyzed using a mixed-effect model repeated measures (MMRM) approach with last observation carried forward (LOCF) and baseline observation carried forward (BOCF) imputation
  - Treatment was the main effect, and investigative site and baseline FIQ-R symptom scores were covariates in the MMRM model

Disclosures

William Pridgen is a founder and member of the board of directors of Virios Therapeutics. Carol Duffy has served as a consultant for Virios Therapeutics and the University of Alabama, Department of Biological Sciences and has received financial research support from Innovative Med Concepts (now Virios Therapeutics) in the form of two Sponsored Research Agreements. Judy F. Gendreau has served as a consultant for Tonix Pharmaceuticals, Dare Bioscience and Virios Therapeutics. R. Michael Gendreau has served as a consultant for Tonix Pharmaceuticals, Teva Pharmaceuticals, Swing Therapeutics, Bionomics Limited, Dare Bioscience and is an employee of Virios Therapeutics.

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