Clinically Meaningful Results With Voltaren® Arthritis Pain (Topical Diclofenac Sodium 1%), a Nonsurgical Treatment Option for Osteoarthritis of the Knee

Poster 24

Jeffrey Fudin, PharmD, DAIPM, FCCP, FASHP, FFSMB[1]; Gilbert M. Shanga, PhD, MBA[2]; Richard A. Petruschke, PharmD[2]

[1]Remitigate Therapeutics, Delmar, NY, USA; [2]GSK Consumer Healthcare, Warren, NJ, USA

Abstract

Purpose: With osteoarthritis (OA) affecting 1 in 7 adults living in the United States, it is crucial to find effective and well-tolerated ways to manage pain associated with OA.[1,2] Topical nonsteroidal anti-inflammatory drugs (NSAIDs) act locally and are strongly recommended for patients with knee osteoarthritis as a pharmacologic approach to pain management.[3] Further, it is recommended that topical NSAIDs be used prior to the use of oral NSAIDs, to minimize systemic exposure.[3] Diclofenac sodium gel (DSG) 1%, a topical NSAID, provided better pain relief than vehicle alone for patients with knee OA in 3 clinical trials.[4-6] A post hoc meta-analysis of these trials was conducted to determine the percentage of patients achieving a minimal clinically important improvement (MCII) in pain and other symptoms of OA to gain insight into the clinical impact of the benefits of DSG 1% for patients. The MCII is defined as the smallest improvement in symptoms viewed as clinically meaningful for patients.[7] Thus, the MCII represents an improvement of relevance in a clinical trial and the minimal meaningful change at an individual level.

Methods: All 3 studies pooled for this post hoc meta-analysis were conducted in US centers, and were 12-week, prospective, randomized, double-blind, multicenter, parallel-group studies with similar endpoints, comparing DSG 1% with vehicle in subjects with knee OA.[4-6] An MCII responder was defined as a patient who had an improvement of ≥20% relative to baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, function, or stiffness, or in pain on movement (POM), a definition consistent with the Osteoarthritis Research Society International (OARSI)-Outcome Measures in Rheumatology (OMERACT)-responder criteria.[8,9] The percentage of MCII responders was analyzed using the Cochran-Mantel-Haenszel test, stratified by study. Time to MCII response was analyzed using the log-rank test, stratified by study. Heterogeneity of treatment effect across studies was investigated using the Breslow-Day test.

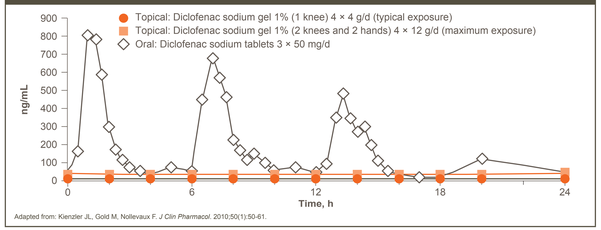
Results: The pooled analysis included 719 DSG 1%-treated patients and 705 vehicle-only-treated patients (ITT Efficacy population, N=1426). By week 1, there was a significant difference in the number of subjects reaching MCII for all endpoints (DSG 1% vs vehicle): WOMAC pain, 67.9% vs 57.2% (*P*<.0001); POM, 65.8% vs 51.6% (*P*<.0001); WOMAC function, 58.3% vs 47.8% (*P*<.0001); WOMAC stiffness, 64.5% vs 53.3% (*P*<.0001). Mean time to first MCII was shorter with DSG 1% vs vehicle for all measures: WOMAC pain, 25.5 vs 32.2 days (*P*<.0001); POM, 26.6 vs 34.9 days (*P*<.0001); WOMAC function, 30.5 vs 38.8 days (*P*<.0001); WOMAC stiffness, 28.0 vs 35.2 days (*P*=.0001). Significant differences in the percentage of patients with an MCII between groups were still evident at week 12 for all endpoints. No evidence of heterogeneity of treatment effect was found between studies, indicating the results from this post hoc meta-analysis were robust and reliable.

Conclusions: MCII signifies an improvement of relevance in a clinical trial by taking the patient's perception into account. As applied to this post hoc meta-analysis, the majority of DSG 1%-treated patients achieved clinically meaningful relief from OA pain and other symptoms within 1 week. Responses sustained over 12 weeks further suggested the clinical relevance of the meaningful patient benefits observed in the 3 original studies. Topical DSG 1%, which limits systemic NSAID exposure, was also generally well tolerated in the original studies. It provides patients with an alternative to oral NSAIDs.[4,10]

Introduction

- Osteoarthritis (OA) is the most common form of arthritis, affecting approximately 250 million people worldwide, and is a major cause of disability[9,11]
  - Oral nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce pain and improve functioning in patients with OA, but they can be associated with adverse events (AEs), including upper gastrointestinal (GI) complications (eg, bleeding and perforation), nephrotoxicity (eg, edema), hypertension, acute renal insufficiency, and congestive heart failure[12-15]
  - Topical NSAIDs reduce systemic exposure.[3] In a randomized, 3-way crossover study, systemic exposure with diclofenac sodium gel (DSG) 1% was 5- to 17-fold lower than with oral diclofenac (**Figure 1**). AE rates were low and similar with DSG 1% and oral diclofenac, but the types of treatment-related AEs differed qualitatively: AEs with DSG 1% were limited primarily to local reactions at the application site, while GI AEs were reported with oral diclofenac.[10]

Figure 1. Plasma Absorption of Diclofenac From Topical Versus Oral Administration on Day 7



Adapted from: Kienzler JL, Gold M, Nollevaux F. *J Clin Pharmacol*. 2010;50(1):50-61.

  - Due to their noninferior efficacy and favorable safety profile, topical NSAIDs may be the preferred treatment option, especially in elderly OA patients, those with comorbidities, or those at an increased risk of cardiovascular, GI, or renal side effects[4-6,16,17]
  - The 2019 American College of Rheumatology/Arthritis Foundation Guideline strongly recommends topical NSAIDs for patients with knee OA; topical NSAIDs should be considered prior to the use of oral NSAIDs[3]

- DSG 1% is a topical NSAID formulation that has already been studied for the treatment of pain in patients with OA of the knee in 3 clinical studies (**Table 1**)[4-6]:

Table 1. Primary Outcomes of Clinical Studies of DSG 1% for Patients With OA of 1 or Both Knees[4-6]

Study	Primary Endpoints
VOSG-PN-304	WOMAC pain index at week 12
	WOMAC function index at week 12
	POM - VAS at week 4
VOSG-PN-310	WOMAC pain index at week 12
	WOMAC function index at week 12
	POM - VAS at week 4
VOSG-PN-316	WOMAC pain index at week 12
	WOMAC function index at week 12
	POM - VAS at week 4

DSG, diclofenac sodium gel; OA, osteoarthritis; POM, pain on movement; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

  - Patients with OA in these 3 studies (N=514, N=420, N=492, respectively) who treated 1 or both knees with DSG 1% showed improvements in the primary endpoints: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and WOMAC function at week 12, and pain on movement (POM) at week 4, compared with patients who were treated with vehicle
- DSG 1% was generally well tolerated in the studies[4-6]:
  - Study VOSG-PN-304:
    - Most treatment-related AEs were mild to moderate (DSG 1%: 13.1%; vehicle: 2.4%), and GI AEs occurred infrequently in both arms
    - Application site reactions occurred more frequently in DSG 1%-treated patients than in vehicle-treated patients (5.4% vs 0%)
  - Study VOSG-PN-310:
    - Treatment-related AEs were infrequent (DSG 1%: 7.9%; vehicle: 7.1%), and no serious treatment-related AEs occurred with DSG 1%
    - Application site reactions occurred more frequently in DSG 1%-treated patients than in vehicle-treated patients (4.3% vs 1.7%), and <1% of patients experienced GI AEs with DSG 1%
  - Study VOSG-PN-316:
    - Treatment-related AEs were infrequent (DSG 1%: 7.7%; vehicle: 4.2%), and no treatment-related GI AEs or serious AEs occurred with DSG 1%
    - Application site reactions occurred more frequently in DSG 1%-treated patients than in vehicle-treated patients (5.8% vs 0%)
- Although the studies demonstrated statistically significant differences between the DSG 1% and vehicle treatment groups, we wanted to better understand the degree of clinical relevance of these symptomatic improvements for patients treated with DSG 1%
  - A 20% improvement in OA symptoms relative to baseline is considered the minimal clinically important improvement (MCII)[8]

Objective

- The goal of this post hoc meta-analysis was to assess the percentage of patients with OA affecting 1 or both knees who reached the criteria for MCII within 12 weeks in the pivotal studies of DSG 1%
  - This novel approach represents a more clinically relevant way to assess data from the clinical studies

Methods

- VOSG-PN-304, VOSG-PN-310, and VOSG-PN-316 were all 12-week, prospective, randomized, double-blind, multicenter, parallel-group studies that compared DSG 1% with vehicle in patients with OA in 1 or both knees[4-6]
  - Eligible patients had OA in 1 or both knees, according to American College of Rheumatology criteria, with moderate to severe pain predominating in 1 knee in the past 6 months
  - Patients underwent a ≥7-day analgesic washout period before being randomized (1:1) to DSG 1% or vehicle
- DSG 1% was applied topically in 4-gram doses, 4× daily to the symptomatic knee
  - After the baseline visit, patients were assessed at weeks 1, 4, 8, and 12
- MCII responders were defined as those patients who reached a relative improvement of ≥20% from baseline in WOMAC pain, function, and stiffness, as well as POM
  - The percentage of MCII responders was analyzed using the Cochran-Mantel-Haenszel test, stratified by study
  - Time to MCII response was analyzed using the log-rank test, stratified by study
  - Heterogeneity of treatment effect across studies was investigated using the Breslow-Day test

Results

- The pooled analysis included 719 DSG 1%-treated patients and 705 vehicle-only-treated patients in the intention-to-treat (ITT) efficacy population* (see footnote)
  - Mean (±standard deviation) age was 61.2 (±10.4) years in the DSG 1% group and 61 (±10.6) years in the vehicle group
- A significantly higher percentage of patients reached the MCII criterion with DSG 1% than with vehicle for all endpoints at all assessment intervals (**Figure 2**)
  - WOMAC pain at week 12: odds ratio (OR) 1.39 (95% confidence interval [CI] 1.10, 1.75)
  - POM at week 12: OR 1.66 (95% CI 1.33, 2.09)
  - WOMAC function at week 12: OR 1.50 (95% CI 1.21, 1.87)
  - WOMAC stiffness at week 12: OR 1.68 (95% CI 1.34, 2.11)

Figure 2. Percentage of Patients Reaching an MCII[a] for WOMAC Pain (A), POM (B), WOMAC Function (C), and WOMAC Stiffness (D)

[a]Defined as an improvement of ≥20% from baseline.
DSG, diclofenac sodium gel; MCII, minimal clinically important improvement; POM, pain on movement; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

- Time to an MCII response (**Table 2**) was significantly shorter in patients treated with DSG 1% than in those treated with vehicle across all endpoints (WOMAC pain, *P*<.0001; WOMAC function, *P*<.0001; WOMAC stiffness, *P*=.0001; POM, *P*<.0001 [**Figure 3**])
  - Mean time with DSG 1% vs vehicle was as follows: WOMAC pain, 25.5 vs 32.2 days; WOMAC function, 30.5 vs 38.8 days; WOMAC stiffness, 28.0 vs 35.2 days; and POM, 26.6 vs 34.9 days
  - 60% (percentile) of patients treated with DSG 1% had reached an MCII response for WOMAC pain and POM within 10 days of starting treatment (vs 28-29 days in those treated with vehicle)
- Significant differences in the percentage of patients with an MCII between groups were still evident at week 12 for all endpoints. No evidence of heterogeneity of treatment effect was found between studies, indicating the results from this post hoc meta-analysis were robust and reliable

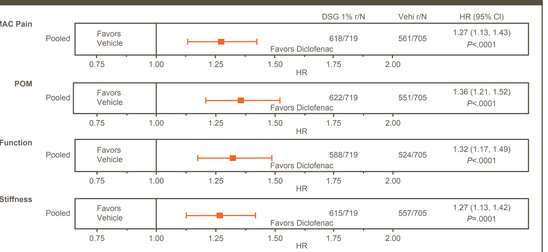
*2 patients in the DSG 1% group were excluded: 1 patient was discovered to have a prosthetic target knee, and 1 patient recalled being allergic to diclofenac after a dermal reaction to study medication.

Table 2. Median and Mean Time to MCII Response by Pooled Data – ITT Population

	Median days (95% CI)		Mean days (SE)	
	DSG 1%	Vehicle	DSG 1%	Vehicle
WOMAC Pain	9 (8,9)	10 (9,11)	25.5 (1.13)	32.2 (1.26)
POM	9 (8,9)	12 (10,28)	26.6 (1.17)	34.9 (1.32)
WOMAC Function	9 (9,10)	29 (12,29)	30.5 (1.22)	38.8 (1.36)
WOMAC Stiffness	9 (8,9)	11 (10,27)	28.0 (1.21)	35.2 (1.39)

CI, confidence interval; Diclofenac sodium gel (DSG) 1%; ITT, intention-to-treat; MCII, minimal clinically important improvement; N, total number of patients; POM, pain on movement; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 3. Time to MCII Response by Pooled Data at Week 12 – ITT Population



CI, confidence interval; DSG, diclofenac sodium gel; HR, hazard ratio; ITT, intention-to-treat; MCII, minimal clinically important improvement; N, total number of patients; POM, pain on movement; r, number of MCII responders (≥20% improvement from baseline); Vehi, vehicle; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Discussion

- In 3 randomized clinical trials of patients with OA of 1 or both knees, topical DSG 1% demonstrated better symptomatic relief than vehicle[4-6]
  - The post hoc meta-analysis of pooled data from the 3 studies demonstrated that DSG 1% improved all efficacy measures over vehicle
  - The MCII analysis was conducted to examine how statistically significant differences translate into clinically meaningful outcomes for patients
- The MCII analysis demonstrated that significantly more patients treated with DSG 1% had clinically meaningful improvements in OA symptoms than those treated with vehicle across all endpoints and every assessment interval. Please see the results section for a full representation of the percentage of patients who achieved MCII for each measure
  - This difference was evident at the first assessment visit (week 1), indicating that patients should expect to experience the onset of relief from OA symptoms within 7 days of starting treatment with DSG 1%
- A relatively high number of vehicle-treated patients achieved a response in this analysis, although this effect should be expected in a trial of a topical analgesic, based on the mode of application
  - A systematic review of topical treatments for pain found placebo vehicle response rates as high as 57% across multiple studies, presumably due to the effect of rubbing the affected area[18]

Conclusions

- MCII, defined according to the patient's perception of what constitutes an important improvement, is useful because it takes the patient's perspective into account; it provides information about the proportion of patients who achieve an improvement exceeding the level accepted as MCII
- Using the MCII to express results presents a novel and clinically relevant way of looking at data from this post hoc meta-analysis that is a useful, alternative perspective for both patients and physicians
- The majority of patients treated with DSG 1% achieved MCII responses within 1 week, and responses were sustained for up to 12 weeks
- Topical DSG 1% was also well tolerated in the 3 original studies, and may also limit systemic NSAID exposure, providing patients with a first-line alternative to oral NSAIDs[3]

Disclosures

- JF has received honoraria for consulting services from Abbott Laboratories, AcelRx Pharmaceuticals, Acutis Diagnostics, Inc., AstraZeneca, BioDelivery Sciences International, Daiichi Sankyo, Firstox Laboratories, GlaxoSmithKline (GSK), Quest Diagnostics, and Salix Pharmaceuticals
- GS is a salaried employee of GSK Consumer Healthcare
- RP is a salaried employee of GSK Consumer Healthcare
- This study was funded by GSK Consumer Healthcare

References

1. Arthritis Foundation. *Arthritis By the Numbers*. 2019;v3:4100.17.10445. https://www.arthritis.org/getmedia/e1256607-fa87-4593-aa8a-8db4f291072a/2019-abtn-final-march-2019.pdf. Accessed 8/24/20. **2.** US Bone and Joint Initiative. The Burden of Musculoskeletal Diseases in the United States (BMUS). https://www.boneandjointburden.org. Accessed 6/30/20. **3.** Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol*. 2020;72(2):220-233. **4.** Baraf HS, Gold MS, Clark MB, et al. Safety and efficacy of topical diclofenac sodium 1% gel in knee osteoarthritis: a randomized controlled trial. *Phys Sportsmed*. 2010;38(2):19-28. **5.** Barthel HR, Haselwood D, Longley S 3rd, et al. Randomized controlled trial of diclofenac sodium gel in knee osteoarthritis. *Semin Arthritis Rheum*. 2009;39(3):203-212. **6.** Data on File. GSK Consumer Health, Inc. **7.** Kvien TK, Heiberg T, Hagen KB. Minimal clinically important improvement/difference MCII/MCID) and patient acceptable symptom state (PASS): what do these concepts mean? *Ann Rheum Dis*. 2007;66(suppl 3):ii40-41. **8.** Tubach F, Ravaud P, Martin-Mola E, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: Results from a prospective multinational study. *Arthritis Care Res (Hoboken)*. 2012;64(11):1699-1707. **9.** McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22(3):363-388. **10.** Kienzler JL, Gold M, Nollevaux F. Systemic bioavailability of topical diclofenac sodium gel 1% versus oral diclofenac sodium in healthy volunteers. *J Clin Pharmacol*. 2010;50(1):50-61. **11.** Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. *J Pain Res*. 2018;11:2189-2196. **12.** Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med*. 1991;115(10):787-796. **13.** Harris RC, Zhang MZ. Cytochrome p450 metabolites in the kidney. *Compr Physiol*. 2011;1(4):1729-1758. **14.** Hermann M, Ruschitzka F. Cardiovascular risk of cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs. *Ann Med*. 2007;39(1):18-27. **15.** Hochberg MC, Dougados M. Pharmacological therapy of osteoarthritis. *Best Pract Res Clin Rheumatol*. 2001;15(4):563-583. **16.** Rannou F, Pelletier JP, Martel-Pelletier J. Efficacy and safety of topical NSAIDs in the management of osteoarthritis: evidence from real-life setting trials and surveys. *Semin Arthritis Rheum*. 2016;45(suppl 4):S18-21. **17.** Atkinson TJ, Fudin J, Pandula A, Mirza M. Medication pain management in the elderly: unique and underutilized analgesic treatment options. *Clin Ther*. 2013;35(11):1669-1689. **18.** Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017;5:CD008609.

Poster presented at PAINWeek Live Virtual Conference; September 11–13, 2020

Scan the QR code to access the poster from your computer or mobile device