Clinically Meaningful Improvements in Hand Osteoarthritis Pain With Diclofenac Sodium Gel 1%

C19

TAP TO GO BACK TO KIOSK MENU

John Howell Peniston, DO[1]; Florilene Bouisset, MSc[2]; Amy Kenneally, PharmD[3]; Roy Altman, MD[4]

[1]AMH Feasterville Family Health Care Center; Feasterville-Trevose, PA, USA; [2]GSK Consumer Healthcare; Nyon, Switzerland; [3]GSK Consumer Healthcare; Warren, NJ, USA; [4]University of California, Los Angeles; Los Angeles, CA, USA

Abstract

Background/Purpose: Topical non-steroidal anti-inflammatory drugs (NSAIDs) or capsaicin are recommended by the American College of Rheumatology for the treatment of patients with hand osteoarthritis (OA).[1] Diclofenac sodium gel (DSG) 1%, a topical NSAID, demonstrated significant improvements relative to placebo in the signs and symptoms of hand OA in a randomized clinical trial.[2] This post-hoc analysis was conducted to determine the percentage of patients in this study achieving a minimal clinically important improvement (MCII), defined as the smallest improvement in signs and symptoms of OA that is typically considered meaningful by individual patients.[3]

Methods: This study was an 8-week, prospective, randomized, double-blind, multicenter, parallel group study that compared DSG 1% with placebo in subjects with OA of the hands. MCII responders were defined as having relative improvement of ≥15% over baseline in Australian/Canadian Ostoearthritis Hand Index (AUSCAN) total, pain, function, and stiffness, and on pain intensity, based on findings defined by Bellamy et al.[4] The percentage of responders was analyzed using logistic regression with treatment and hand OA category included in the model. Time to MCII response was analyzed using the log-rank test stratified by hand OA category.

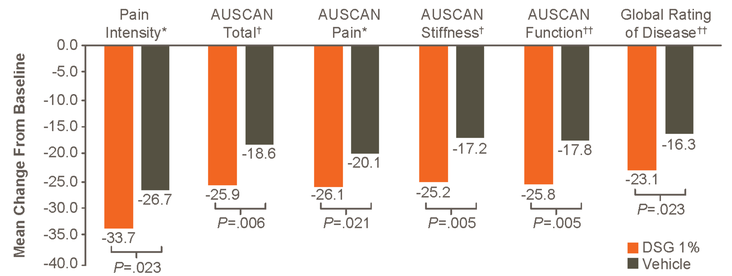
Results: This analysis included 198 patients treated with DSG 1% and 187 treated with placebo. Significant differences in the percentage of patients reaching an MCII were evident at Week 1 (DSG 1% vs placebo, odds ratio [OR; 95% confidence limits]): pain intensity, 65.2% vs 52.4%, OR 1.70 [1.12, 2.56], *P*=.012; AUSCAN total, 57.1% vs 44.4%, OR 1.66 [1.11, 2.49], *P*=.014; AUSCAN pain, 59.1% vs 48.7%, OR 1.53 [1.02, 2.30], *P*=.039; AUSCAN function, 53.5% vs 42.8%, OR 1.55 [1.03, 2.32], *P*=.034; AUSCAN stiffness, 58.1% vs 44.4%, OR 1.75 [1.17, 2.63], *P*=.007, and at both Weeks 4 and 6 (primary time points), apart from AUSCAN pain at Week 4 and AUSCAN stiffness at Week 6. For AUSCAN pain and AUSCAN stiffness, a significantly higher percentage of DSG 1% treated patients had a response at both Weeks 4 and 6 when a ≥30% relative improvement criteria was used. Mean time to first MCII response was lower with DSG 1% relative to placebo for all measures: pain intensity, 15.9 vs 24.2 days, *P*=.021; AUSCAN total, 18.6 vs 28.4 days, *P*=.001; AUSCAN pain, 18.5 vs 26.4 days, *P*=.013; AUSCAN function, 21.8 vs 30.2 days, *P*=.001; AUSCAN stiffness, 22.5 vs 29.3 days, *P*=.004. The percentage of patients with an MCII response seen at Week 1 was sustained to Week 8 within the DSG 1% group for all endpoints.

Conclusions: The MCII is a relevant measure for studies of patients with OA because it considers patient perspectives on clinical improvements. In this analysis, this criterion was applied to data from a previously published clinical trial of patients with OA of the hand for the first time. Most patients treated with DSG 1% achieved clinically meaningful relief within 1 week that was sustained for ≥8 weeks. Despite placebo response rates of 44% to 52%, a significantly higher percentage of patients had MCII responses with DSG 1%, providing evidence for the efficacy of DSG 1%.

Introduction

- Osteoarthritis (OA) is the most common form of arthritis, affecting approximately 250 million people worldwide, and is a major cause of disability[5,6]
  - Oral nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce pain and improve function in patients with OA, but they can be associated with gastrointestinal, cardiovascular, renal, and other adverse events (AEs)[7-10]
  - Topical NSAIDs provide an alternative treatment that reduces systemic exposure and has a favorable safety profile[2]
- Diclofenac sodium gel (DSG) 1% is a topical NSAID formulation that has already been shown to provide relief from symptoms of hand OA in a clinical study[2]:
  - At Week 6, patients with hand OA (N=385) who treated 1 hand with DSG 1% showed significant improvements relative to patients who were treated with vehicle in all primary outcome measures, including pain intensity Australian/Canadian Osteoarthritis Hand Index (AUSCAN) total and rating of disease. Significant improvements were also demonstrated with other AUSCAN subscores (pain, stiffness, and function) (**Figure 1**)
- The AUSCAN total score was calculated as the average of scores on 15 questions rating pain, stiffness, or function standardized to range from 0 (no pain/stiffness/difficulty) to 100 (extreme pain/stiffness/difficulty)
- DSG 1% was generally well tolerated in the study; most AEs were mild. No cardiac events, gastrointestinal bleeding, or ulcers were reported
- General disorders and administration site conditions suspected to be drug related occurred more frequently in DSG 1%-treated patients than in vehicle-treated patients (4.5% vs 2.1%)
  - All application site reactions were non-serious

Figure 1. Efficacy Outcomes in the Pivotal Study of DSG 1% for Patients With OA of the Hand[2,a]



[a]Assessed at Week 6.
*0=no pain, 100=extreme pain. †0=no pain/stiffness/difficulty, 100=extreme pain/stiffness/difficulty. ††0=very good, 100=very poor.
P-values=Difference in least-squares mean for vehicle minus that for DSG 1%.
AUSCAN, Australian/Canadian Osteoarthritis Hand Index; DSG, diclofenac sodium gel; OA, osteoarthritis.

Objectives

- While this study demonstrated statistically significant differences between the DSG 1% and vehicle treatment groups, it was not clear if these symptomatic improvements with DSG 1% were clinically meaningful for patients
  - A 15% improvement in hand OA symptoms relative to baseline is considered the minimal clinically important improvement (MCII)[4]
- The goal of the present post-hoc study was to assess the percentage of patients with OA of the hand reaching the criteria for MCII in the pivotal study of DSG 1%
  - This novel approach represents a more clinically relevant way to assess data from the clinical trial

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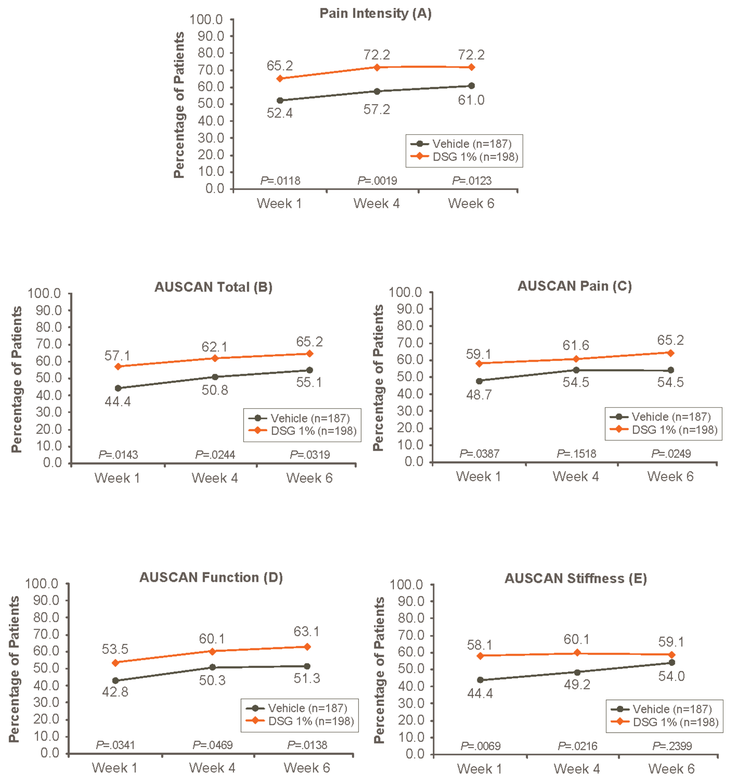
Methods

- VOSG-PN-315 was an 8-week, prospective, randomized, double-blind, multicenter, parallel-group study that compared DSG 1% with vehicle in subjects with OA of the hand[2]
  - Eligible patients had a diagnosis of OA in their dominant hand according to American College of Rheumatology criteria, with symptom onset ≥12 months before enrollment and use of an NSAID for ≥1 episode of pain
  - Patients underwent a ≥7 day analgesic washout period before being randomized (1:1) to DSG 1% or vehicle
- DSG 1% was applied topically in 2-gram doses, 4x daily for 8 weeks
  - After the baseline visit, patients were assessed for symptoms of hand OA at Weeks 1, 4, 6, and 8
- MCII responders were defined as those patients who reached a relative improvement of ≥15% from baseline in pain intensity, AUSCAN total, pain, function, and stiffness
  - Responder rates were analyzed using the logistic regression model with main effects of treatment and hand OA category
  - Depending on MCII response in relation to vehicle, responder rates based on an improvement of ≥20% (and, if appropriate, ≥30%) were also analyzed
  - Time to an MCII response was analyzed using the log-rank test stratified by hand OA category; medians and percentiles were estimated using the Kaplan-Meier method

Results

- 198 DSG 1%-treated and 187 vehicle-treated patients were available for the MCII analysis
  - Mean (standard deviation) age was 63.6 (10.2) years in the DSG 1% group and 64.7 (9.6) years in the vehicle group
- A significantly higher percentage of patients reached the ≥15% MCII criterion with DSG 1% than with vehicle for all endpoints at all assessment intervals, with the exception of AUSCAN pain at Week 4 and AUSCAN stiffness at Week 6 (**Figure 2**)
  - Pain intensity at Week 6: odds ratio (OR) 1.74 (95% confidence interval [CI] 1.13, 2.68)
  - AUSCAN total at Week 6: OR 1.57 (95% CI 1.04, 2.38)
  - AUSCAN pain at Week 6: OR 1.61 (95% CI 1.06, 2.43)
  - AUSCAN function at Week 6: OR 1.68 (95% CI 1.11, 2.53)
- When an improvement of ≥30% over baseline was used as the criterion to define an MCII for AUSCAN pain, significantly more patients in the DSG 1% group had a response at Week 4 than in the vehicle group (55.1% vs 43.3%; OR 1.58 [95% CI 1.06, 2.37; *P*=.0259]). For AUSCAN stiffness, using an improvement of ≥30% over baseline showed significantly more patients in the DSG 1% group had a response at Week 6 than in the vehicle group (54.5% vs 41.7%; OR 1.72 [95% CI 1.15, 2.58; *P*=.0089])
- Time to first MCII (≥15%) response was significantly shorter in patients treated with DSG 1% than in those treated with vehicle across all endpoints (pain intensity, *P*=.0210 (**Figure 3**); AUSCAN total, *P*=.001; AUSCAN pain, *P*=.013; AUSCAN function, *P*=.001; AUSCAN stiffness, *P*=.004)
  - 60% (percentile) of patients treated with DSG 1% had reached MCII response for pain intensity within 9 days of starting treatment (vs 15 days in those treated with vehicle)
  - 50% (median) of patients treated with DSG 1% had reached MCII response for AUSCAN total, AUSCAN pain, AUSCAN function, and AUSCAN stiffness within 9 days of starting treatment (vs 14-15 days in those treated with vehicle)
  - Mean times to reach an MCII response with DSG 1% vs vehicle were pain intensity, 15.9 vs 24.2 days; AUSCAN total, 18.6 vs 28.4 days; AUSCAN pain, 18.5 vs 26.4 days; AUSCAN function, 21.8 vs 30.2 days; and AUSCAN stiffness, 22.5 vs 29.3 days, respectively

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



[a]Defined as an improvement of ≥15% from baseline.

AUSCAN, Australian/Canadian Osteoarthritis Hand Index; DSG, diclofenac sodium gel; MCII, minimal clinically important improvement.

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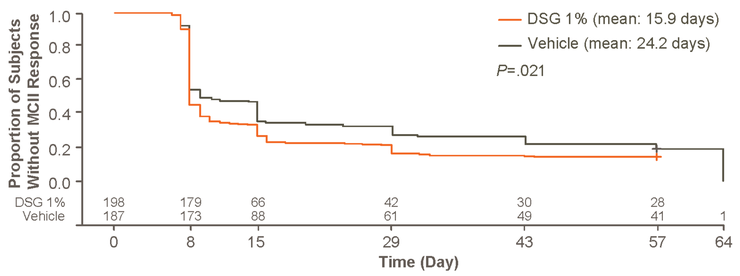
Figure 3. Time to MCII[a] for Pain Intensity[b]



[a]Defined as an improvement of ≥15% from baseline.
[b]Similar patterns were seen for all other endpoints.
DSG, diclofenac sodium gel; MCII, minimal clinically important improvement.

Discussion

- Assessments of drug efficacy are usually based on outcomes from clinical trials
  - To that end, DSG 1% demonstrated significantly better symptomatic relief compared to vehicle in a randomized trial of patients with OA of the hand[2]
  - However, statistically significant differences may still warrant examining clinically meaningful outcomes for patients
- The MCII analysis demonstrated that compared to those treated with vehicle, significantly more patients treated with DSG 1% had clinically meaningful improvements in OA symptoms across all endpoints and at almost every assessment interval
  - 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%
  - The percentage of patients with an MCII response for AUSCAN pain at Week 4 and AUSCAN stiffness at Week 6 was significantly different from vehicle only when the 30% improvement cutoff was used, suggesting that a higher MCII response criterion may be relevant to consider for AUSCAN pain and stiffness in the context of this specific study
- A relatively high number of vehicle-treated patients reached an MCII response in this analysis, although this effect should be expected in a trial of a topical analgesic
  - 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[11]
  - The differences between DSG 1% and vehicle in the present analysis indicated a pain relief benefit beyond what can be expected from just the physical effects of rubbing the joint

Conclusions

- Using the MCII to express the results is a novel and more clinically relevant way of assessing data from this clinical study that is more understandable for both patients and physicians
- The majority of patients treated with DSG 1% achieved MCII responses within 1 week, and responses were sustained throughout the 8 weeks of the study

Disclosures

- JHP has received honoraria for consulting services from Endo Pharmaceuticals Inc. and GSK
- FB is a salaried employee of GSK Consumer Healthcare
- AK is a salaried employee of GSK Consumer Healthcare
- RA has received honoraria for consulting services from GSK and Novartis Consumer Health, Inc.
- This study was funded by GSK Consumer Healthcare

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