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 ≥25% over baseline in Australian/Canadian Osteoarthritis Hand Index (AUSCAN) total, pain, function, and stiffness, and on pain intensity, based on findings 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=0.012; AUSCAN total, 57.1% vs 44.4%, OR 1.66 [1.11, 2.49], P<0.014; AUSCAN pain, 59.1% vs 48.7%, OR 1.53 [1.02, 2.30], P=0.039; AUSCAN function, 53.5% vs 42.8%, OR 1.35 [1.03, 2.32], P=0.034; AUSCAN stiffness, 58.1% vs 44.4%, OR 1.75 [1.17, 2.63], P<0.007, 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=0.005; AUSCAN total, 18.6 vs 28.4 days, P=0.004; AUSCAN pain, 26.4 vs 36.4 days, P=0.013; AUSCAN function, 21.8 vs 30.2 days, P=0.001; AUSCAN stiffness, 22.5 vs 29.3 days, P=0.004. 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 28 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.6,10
• 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 profile2

• 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, and 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

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)6
• 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

Figure 1. Efficacy Outcomes in the Pivotal Study of DSG 1% for Patients With OA of the Hand4,5

- AUSCAN Total
- AUSCAN Pain
- AUSCAN Stiffness
- AUSCAN Function
- Pain Intensity
- AUSCAN Total Ratings
- AUSCAN Pain Ratings
- AUSCAN Stiffness Ratings
- AUSCAN Function Ratings
- Global Rating of Disease

4Assessed at Week 6.
5MCII: pain, 150-extreme pain; AUSCAN, Australian/Canadian Osteoarthritis Hand Index; DSG, diclofenac sodium gel; OA, osteoarthritis.

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

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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
  - 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 1.13, 95% CI 1.06, 1.37; P=0.0259). 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 1.74, 95% CI 1.16, 2.58; P=0.0089)
  - 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=0.0210 (Figure 3); AUSCAN total, P=0.001; AUSCAN pain, P=0.013; AUSCAN function, P=0.001; AUSCAN stiffness, P=0.004)
    - 69% (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 28.4 days; AUSCAN function, 21.8 vs 30.2 days; and AUSCAN stiffness, 22.5 vs 29.3 days, respectively
Figure 3. Time to MCII* for Pain Intensity

- 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.

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.
  - 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%.

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.

References