Results from post hoc analysis of three 12-week, randomized, double-blind, parallel-group, multicenter trials

HALEON

Safety and Efficacy of Topical Diclofenac Sodium Gel for Knee Osteoarthritis in Elderly and Younger Patients

Baraf, H. S., Gloth, F. M., Barthel, H. R., Gold, M. S., & Altman, R. D. In: Drugs & aging. 2011, Vol. 28, pp. 27-40.

Voltaren

Background

- Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are highly effective and widely recommended for osteoarthritis (OA) treatment. Nevertheless, dose-related risks of gastrointestinal, cardiovascular, and hepatotoxicity effects in high-risk populations remain a serious concern
- Topical NSAIDs can be a safe choice due to their low systemic exposure, and better tolerability, thus, should be considered as a first-line pharmacologic option for the treatment of osteoarthritis

Diclofenac sodium gel 1% (DSG) is currently the only topical NSAID approved for OTC use in the United States

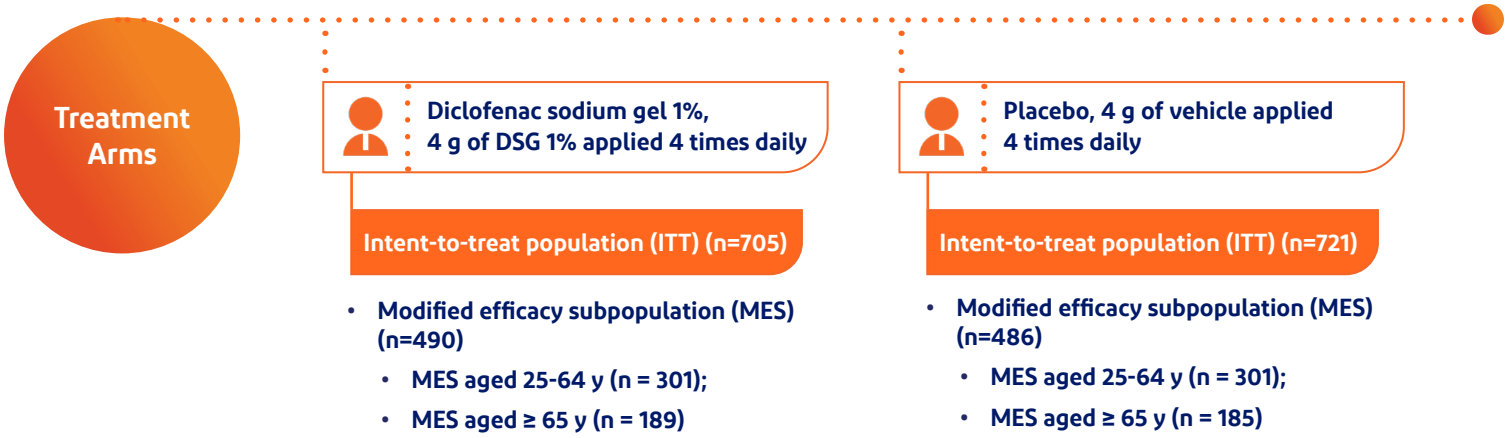
Study Objective and Methodology

To compare the safety and efficacy of topical DSG for knee OA in patients aged ≥65 years versus 25–64 years using pooled data from three clinical trials

Study Design

Three 12-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter trials comparing DSG to vehicle in adult patients with radiographically mild to moderate symptomatic knee OA were selected

A flare design was used that defined a subset of patients who experienced increased pain during the 1-week analgesic washout period (modified efficacy subpopulation [MES])



Eligibility Criteria

- Ambulatory adults aged ≥25 years with radiographically confirmed mild to moderate symptomatic knee OA, clinical diagnosis ≥6 months before screening
- Baseline pain on movement score (POM) of ≥50 mm on a 100-mm visual analog scale (VAS) and a baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain sub-scale score of ≥9 on a 20-point scale
- The POM score for the contralateral knee pain at the baseline visit after the 1-week analgesic washout period could not exceed 20 mm (for study 1 and 2) and had to increase by ≥5 mm in the more painful knee over the analgesic washout period (study 3)

Primary outcomes

- WOMAC pain, WOMAC physical function at week 12
- Global Rating of Disease (GRD) and Pain On Movement (POM) - 100-mm VAS

Secondary outcomes

- Rescue medication use and global evaluation of treatment

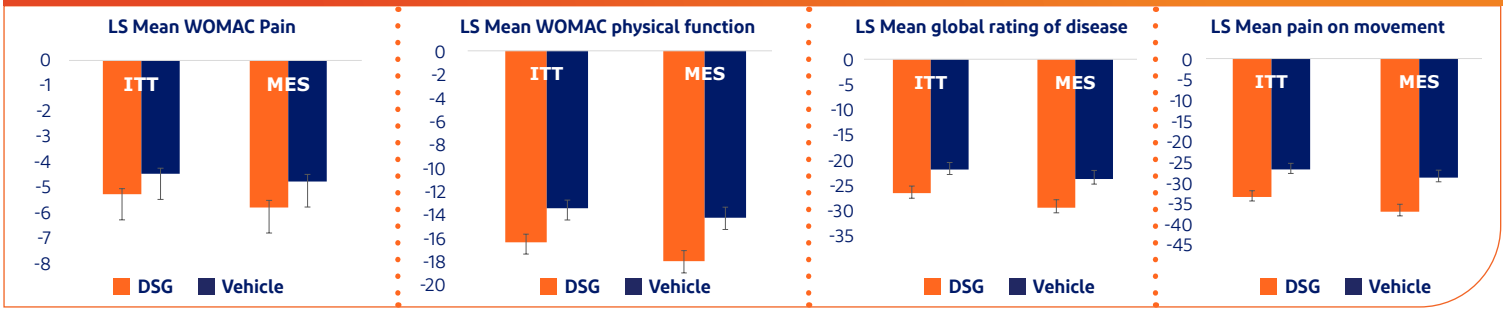
Results

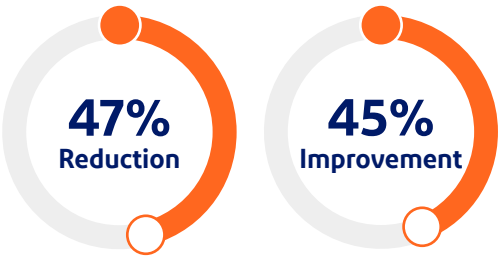
Significantly greater reductions or improvements from baseline were experienced with DSG versus vehicle in patients aged 25–64 years and aged ≥65 years

Patients aged 25–64 years

- Patients treated with DSG exhibited greater decrease in WOMAC pain index (-5.8 vs -4.7, p = 0.007), WOMAC Physical function (-17.9 vs -14.2, p = 0.002), GRD (-29.5 vs -23.8, p = 0.01) and POM (-37.3 vs -29.0, p < 0.001) in MES population
- Similar results were observed in ITT population

Change from baseline to week 12 (Patients aged 25 - 64 years)





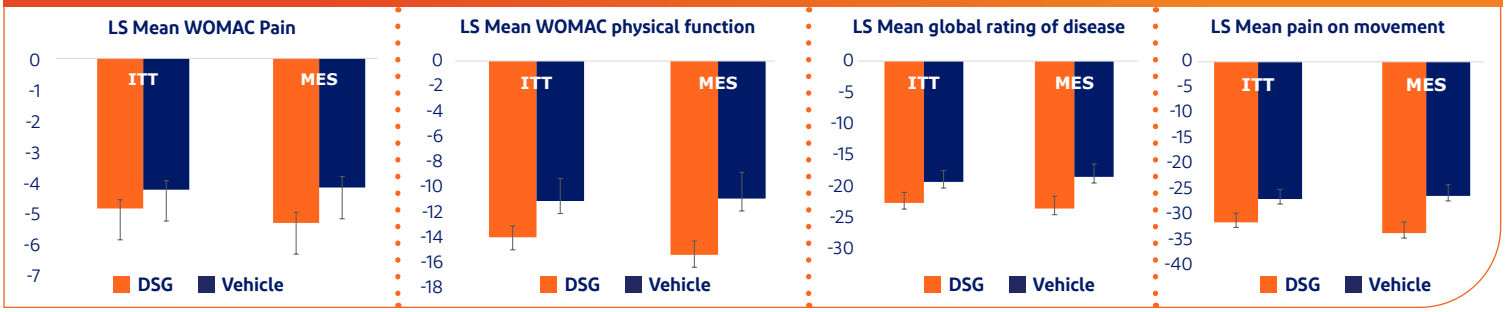
In patients aged 25–64 years, application of DSG led to around 47% improvement in pain relief and increased mobility up to 45% from baseline

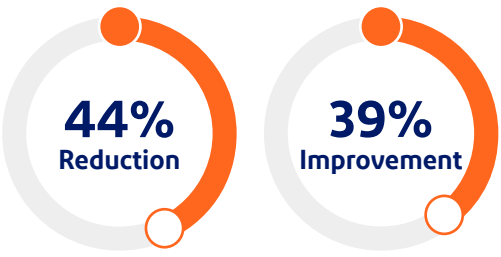
*Findings based upon MES population

Patients aged ≥65 years

- In MES population, significant superiority of DSG versus vehicle was seen in three key outcomes, WOMAC pain (-5.3 vs -4.1 [0.4], p = 0.02), physical function scales (-15.5 vs -11.0, p = 0.004) and POM (-33.7 vs -26.4, p = 0.02), but not in the GRD
- DSG exhibited greater decrease in WOMAC Physical function at week 12 in the ITT population (-14.1 vs -11.2, p = 0.02)

Change from baseline to week 12 (Patients aged ≥65 years)





Application of DSG led to 44% improvement in pain relief and increased mobility up to 39% from baseline in patients above 65 years

*Findings based upon MES population

Abbreviation: LS = least squares

ANOVA revealed no significant differences in efficacy results between patients aged 25–64 years and patients aged ≥65 years: WOMAC pain (ITT population, p = 0.69; MES, p = 0.85); WOMAC physical function (ITT, p = 0.99; MES, p = 0.70); GRD (ITT, p = 0.66; MES, p = 0.86); POM (ITT, p = 0.54; MES, p = 0.81)

The superiority of DSG versus vehicle was more pronounced in the MES than in ITT population in both age groups

Safety

- DSG was generally well-tolerated regardless of age, more than 80% of DSG-treated patients completed the study
- Application site reactions such as site dermatitis were the only treatment-related adverse events (AEs) occurring in ≥1% of patients and were more common in DSG-treated patients than in vehicle-treated patients in both younger (4.0% vs 0.7%, respectively) and older (5.8% vs 0.4%, respectively) patients
- Gastrointestinal AEs were uncommon. The overall incidence of gastrointestinal illnesses in both age groups was 0.8% in the DSG group and 0.9% in the vehicle group

Study Strengths

- The evaluation of efficacy and safety in this analysis provides a characterization of DSG relative to age, suggests that DSG would be an appropriate treatment in an aging population with knee OA
- Results of the pooled analysis that combined the MES (study 1 & 2) with the ITT population (study 3) are a reasonable representation of likely efficacy in population who respond well to oral NSAIDs but might benefit from reduced systemic NSAID exposure with a topical formulation

Study Limitations

- Duration of the studies pooled in the current analysis was only 12 weeks. Additional long-term trials of DSG and other topical NSAIDs, would provide valuable information about the long-term efficacy
- **Flare design which typically improves the efficacy of an NSAID in the studied population, may introduce bias in favor of NSAIDs** - Study has excluded patients with pain that improved or did not worsen during washout period. Excluding patients without a flare enriches the study population with patients who are more likely to respond to treatment

Conclusion

- DSG provides effective analgesia and potential tolerability benefit with low systemic exposure to adult patients with knee OA pain, regardless of age
- DSG offers clinically substantial improvement relative to baseline in measures of pain, physical function, and patient GRD that are significantly superior to vehicle over a 12-week period in adult patients with mild to moderate knee OA

Diclofenac sodium gel is an effective and generally well-tolerated treatment in elderly and younger patients for relief of mild to moderate knee OA pain