

Topical Diclofenac Reduces Joint Synovitis in Hand Osteoarthritis: A Pilot Investigation Using Fluorescent Optical Imaging

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Purpose: Synovitis, the inflammation of joint synovia, is a prominent feature of osteoarthritis (OA) manifested by enhanced synovial vascularity, endothelial leakage, and perivascular oedema. In this pilot study, we assessed the effect of topical diclofenac in hand OA (HOA) using the established semi-quantitative methods Magnetic Resonance Imaging (MRI) and Ultrasonography (US), and compared them with Fluorescent Optical Imaging (FOI), an emerging imaging modality.

Patients and Methods: Ten patients with symptomatic and diagnosed HOA used topical diclofenac for 14 days, with FOI, MRI, US, and subjective pain assessed at Baseline and after 7 (Day 8), and 14 (Day 15) days of treatment. Changes in synovitis were assessed for all 10 joints of the hand (via sum scores), and separately for the two joints most affected by synovitis. A new, fully quantitative approach for objective synovitis assessment based on the FOI images was also developed and applied.

Results: The semi-quantitative analysis of the sum scores showed a small decrease in synovitis throughout the treatment duration across the different imaging modalities. The effect of the treatment was more prominent on the two most affected joints, with a synovitis reduction vs Baseline of 21.1% and 34.2% on Day 8 and Day 15, respectively, in the FOI. The quantitative FOI pixel analysis further strengthened the evidence for this effect, with observed reduction of 17.8% and 42.4% for Days 8 and 15, respectively. A similar trend was observed for subjective pain perception, with a reduction of 7.2 and 13.3 mm on Days 8 and 15.

Conclusion: This pilot study evidenced the effect of topical diclofenac on reducing synovitis in hand OA in semi- and fully quantitative analyses, with the effect being stronger in the most affected joints. Further, supporting studies are needed to probe the accuracy of the quantitative pixel analysis of FOI images.

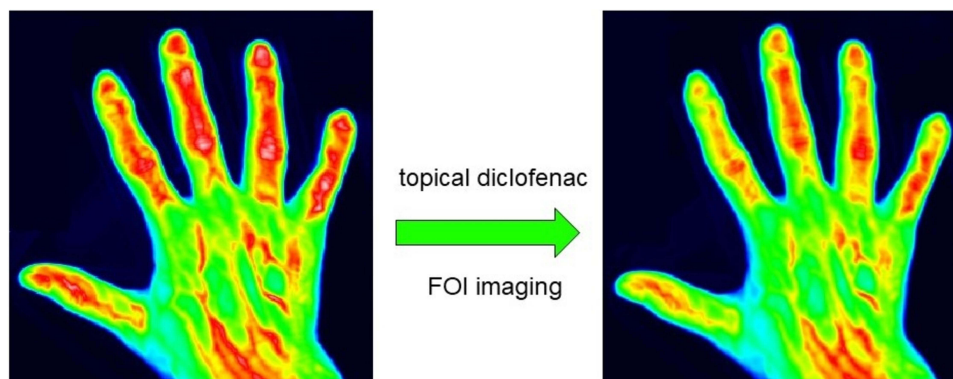
Keywords: fluorescent optical imaging, hand osteoarthritis, synovitis, topical diclofenac

Introduction

Osteoarthritis (OA) is a chronic inflammatory condition characterized by degenerative structural changes to cartilage, bones, ligaments, and synovial tissue, resulting in pain, joint stiffness, and deterioration of functional mobility.¹ The joints primarily affected by OA are in the hips, knees, hands, feet, and spine.² Hand OA (HOA), in particular, is highly prevalent after middle age and is expected to create a substantial burden on healthcare systems worldwide in view of the global increase in aging populations.³

The pathogenesis of OA is complex and attributed to a variety of factors, including aging, genetics, changes in biomechanical mechanism due to acute injuries, and chronic joint strain, among others.⁴ Evidence has shown that inflammation of the synovial tissue, also known as synovitis, is a prominent feature of OA and it could be used as an index of OA progression and associated joint stiffness and pain.^{5,6} In fact, synovitis has been linked with OA in both the early and late stages of the condition and can lead to cartilage degradation and fibrosis, among other symptoms.⁷ Thus, monitoring changes in synovial vascularity, a key feature of synovitis, could be used to assess the condition progression, as well as to benchmark the effectiveness of different treatments and regimens.

Graphical Abstract



Magnetic Resonance Imaging (MRI) and Ultrasonography (US) have both been used in research and clinical settings to track the progression of rheumatologic conditions, offering important insights into the mechanisms underlying OA.⁸ In recent years, Fluorescent Optical Imaging (FOI) has emerged as a promising imaging modality for assessing inflammation/synovitis by visualization of microvessel density, microvascular perfusion, and endothelial leakage.^{9,10} The optical contrast in this technique is provided by the fluorescent dye Indocyanine Green (administered intravenously) which binds to plasma proteins in the tissues.¹¹ FOI has been found to correlate well with the results from clinical examinations of patients at the early stages of arthritis and, under certain conditions, could be even more sensitive in detecting disease activity compared with other imaging modalities.¹² Additionally, it has been successfully applied to monitor the progress of synovial inflammation across a range of conditions such as rheumatoid and psoriatic arthritis,¹³ and is able to differentiate between inflamed and non-inflamed joints in patients with rheumatoid arthritis.^{9,10,13} It should be noted that, across all imaging modalities, the assessment of vascularity, synovitis and OA progression in general is done in a semi-quantitative manner, requiring subjective interpretation of the scans.^{8,9,13} Although the semi-quantitative method of analysis is well established and reliable, the assessment of changes in synovitis is still subject to individual assessors' interpretations of the images, which could be biased.

With regard to OA treatment, the non-steroidal anti-inflammatory drug (NSAID) diclofenac is often used to provide analgesia and improve physical function in patients with OA.¹⁴ Its topical administration has been found to be effective in improving pain, stiffness, and physical function at the same level as oral NSAIDs, with the added benefit of fewer side effects. Thus, topical diclofenac is recommended as a first-line treatment for OA, particularly for older patients with comorbidities where oral NSAID could lead to a higher likelihood of adverse events.¹⁵

This pilot study aimed to evidence the effect of topical diclofenac in HOA using FOI and compare this assessment with one performed using the established semi-quantitative modalities MRI and US.¹⁶ In addition, and considering the potential limitations of semi-quantitative assessments, we compared these results with those from a newly developed technique for fully quantitative FOI assessment, which could help minimize subjective biases in clinicians' interpretations.

Materials and Methods

Ethical Conduct of Study

The study protocol, informed consent, subject information sheet and other information that required pre-approval were reviewed and approved by the Ethics Committee of the Charité Research Organization GmbH, Berlin (study no. 130751). The study was conducted in accordance with Good Clinical Practice and the guiding principles of the Declaration of Helsinki. Written informed consent was obtained from each patient prior to performing any study procedure.

Study Population and Treatment

For this pilot study, the sample size was not based on statistical calculations, but the completion of 10 patients with HOA was considered to be sufficient. To be eligible to participate in this study, patients had to have confirmed OA in at least two hand joints, including distal or proximal interphalangeal joints (DIP & PIP), interphalangeal joint (IP), or the thumb base joint (CMC1), assessed with a Gray-Scale US (GS-US) score of ≥ 2 . Patients also had to have a screening pain score of ≥ 40 mm on a 100-mm visual analogue scale (VAS) within the last 24 hours, and a medical need for topical diclofenac. The exclusion criteria comprised: presence of concomitant inflammatory joint disease (eg gout, rheumatoid, reactive, or psoriatic arthritis); receipt of NSAID or other antiphlogistic drugs within 7 days before baseline visit or 5 half-lives (whichever was longer); receipt of any drug that might confound the interpretation of the study results as determined by the investigator; known or suspected allergy to MRI contrast medium, FOI fluorescent agent, or iodine; wear of pacemakers or other non-removable metal objects inside or on the body which would interfere with MRI scans; pregnant or nursing (lactating) women. Furthermore, the patients had to agree to refrain from taking/applying systemic or topical medications to the target hand or any other part of the body other than diclofenac gel and rescue medication.

The treatment consisted of a topical diclofenac diethylamine 1.16% gel (Voltaren Schmerzgel 1.16%). Patients were asked to use it four times a day for a total of 14 days. Treatment could have been stopped at Day 8 (7th day of treatment) if the MRI synovitis score showed a reduction of $\geq 25\%$. Patients were asked to focus application of the gel on one of the two hands (target hand) based on the level of inflammation at baseline.

Study Visits and Assessments

The study was conducted by the Charité Research Organization, GmbH, Berlin. The patients visited the study site on three different occasions: on Baseline (Day 1), Day 8, and Day 15 (7 and 14 days post the treatment start, respectively). The assessment of inflammation in 10 hand joints of the target hand (ie, the CMC1, IP, PIP I–V, and DIP I–V) was performed by the investigating Charité team on all three occasions using four imaging modalities: MRI, GS-US, Power-Doppler ultrasound (PD-US), and FOI, using standardized procedures. For MRI, the 10 joints of the target hand were evaluated semi-quantitatively for joint inflammation (synovitis). The synovitis score for a single joint could range between 0 and 3, and the sum score of all 10 joints—between 0 and 30 (higher scores indicating higher levels of synovitis). For GS- and PD-US, scanning was performed on the dorsal and palmar aspects of the target hand. The target joints were assessed semi-quantitatively, with the assessors assigning a grade between 0 and 3 for each. The sum for both aspects of the joint could range from 0 to 6. FOI findings were analyzed semi-quantitatively applying the FOI Activity Score. The synovitis score for a single joint could range between 0 and 3. For FOI, four different scores are available: scores for phases 1 to 3, which represent the time interval following the intravenous administration of the dye, and the Prima Vista Mode (PVM) score which is the composite of 360 images generated across all phases 1 to 3.¹⁰ Full methodological details can be found in.⁹ For this study, only the PVM score was analyzed. Additionally, pain over the last 24 hours was self-assessed by the patients using a 100-mm VAS at Baseline and Days 8 and 15.

FOI Quantitative Pixel Analysis

Considering the biases that can arise from subjective interpretations, we developed a fully quantitative technique to assess changes in synovitis in FOI and compare the results of this methodology to the semi-quantitative results already available.

In the composite FOI images (ie, PVM), the fluorescent dye concentration which reflects the degree of synovitis is displayed via a false-color grading: white and red corresponding to the highest dye concentrations, followed by yellow, green, and blue in descending order. Thus, the higher the number of white and red pixels, the higher the level of synovitis.

The pixel analysis was performed in Adobe Photoshop v.22.5.9. A circular area of a 100-pixel diameter was selected around each joint to be assessed. To ensure that we select the exact same area across the images collected at the three measuring occasions, the images of the selected joints collected during all visits of the same patient were initially laid on top of each other with 50% transparency and manually adjusted to overlap fully. The counting of the pixels was performed by the software using the “Measure” function of the “Measurement Record” palette.

Statistical Analysis

Descriptive statistics were calculated by visit using the observed values or change from baseline values. FOI image data were analyzed in raw scale (absolute pixel count) and percentage scale (percentage of pixels relative to Baseline). No missing data adjustments were performed. There was no formal hypothesis planned for this study and no adjustments were made for multiplicity of planned and unplanned analyses. As such, this study was conducted for hypothesis-generating purposes.

The following analysis sets were used for this study: the intention-to-treat (ITT, N=10) and “two worst joints” (N=8) wherein each subject had at least two joints with greater than zero PD-US palmar scores at baseline. The two worst joints at baseline in each qualifying subject were selected as those with the highest score with tied scores resulting in selection of the most problematic joints for pain (CMC1 > IP > PIP II > PIP III > PIP IV > PIP V > DIP II > DIP III > DIP IV > DIP V).

Results

Study Patients

Ten patients (3 males, 7 females) with HOA, aged 45–77 (mean age of 59.0 years) were included in the study. All patients enrolled had baseline hand pain ≥ 40 mm VAS and a GS-US score of ≥ 2 in at least two joints of the target hand. None of the patients showed a reduction of $\geq 25\%$ in synovitis measured by MRI at Day 8, and therefore all 10 patients continued using the product until Day 15. In general, the majority of patients had only mild synovitis at baseline. No major deviations were recorded, and no adverse events were reported throughout the duration of the study.

Imaging-Assessed Synovitis

[Supplementary Table 1](#) summarizes the time evolution of the semi-quantitative mean sum synovitis scores (and the associated standard deviations) assigned from each imaging modality, based on analyses of all joints (ad hoc, N=10) and the two most affected joints (post hoc, N=8).

For MRI, as one of the joints (CMC1) was not evaluable at Baseline for two patients, the analysis was conducted in three different ways: a) no CMC1 values for the two patients, b) complete exclusion of the two patients, and c) CMC1 Baseline values imputed with Next Value Carried Backward. Across analyses, the mean sum score of synovitis for the entire hand decreased slightly during the study, with the maximum decrease found at Day 8 compared to Baseline (reduction of 0.2 ± 0.6 , 0.4 ± 0.5 , and 0.2 ± 0.6 for each analysis approach, expressed as mean \pm standard deviation). Reductions were still present on Day 15 but to a lesser extent (reduction of 0.1 ± 0.9 , 0.3 ± 0.9 , and 0.1 ± 0.9 for each analysis approach, expressed as mean \pm standard deviation).

For both GS-US and PD-US (combining palmar and dorsal aspects), the results largely followed the MRI findings, with the largest decrease being identified on Day 8 (change of 1.4 ± 4.5 and 1.0 ± 1.8 for GS- and PD-US, respectively, expressed as mean \pm standard deviation) and a smaller decrease on Day 15 (change of 0.4 ± 2.7 and 0.4 ± 1.5 for GS- and PD-US, respectively, expressed as mean \pm standard deviation).

Similar to the other imaging modalities, FOI showed a reduction in the synovitis sum score on Day 8 (change of 0.7 ± 3.9 , expressed as mean \pm standard deviation). However, this trend continued on Day 15, with a reduction of 1.0 ± 2.8 compared to Baseline. [Figure 1](#) shows representative FOI images collected from the target hand of one patient at Baseline, Day 8, and Day 15.

Post Hoc Analyses for the Most Affected Joints

In addition to the analyses of the results for the whole hand, we conducted post-hoc analyses on the joints most affected by synovitis at Baseline. For this analysis, we included subjects having at least two joints with a GS-US (dorsal and palmar) score of ≥ 2 , and pain of at least 40 mm on the 100-mm VAS (see [Supplementary Table 1](#)).

For MRI, only a small decrease in the sum score of the two most affected joints was found on Day 8 and Day 15 relative to the Baseline (0.1 and 0.2, respectively). For GS-US, a larger reduction of approximately 0.7 for Day 8 and 0.9 for Day 15 was observed. Following a similar pattern to GS-US, PD-US showed a reduction of 1.3 and 0.9 on Day 8 and 15, respectively. For FOI, analysis of the two most affected joints followed a similar pattern to the results of the entire hand, with a reduction of 0.8 at Day 8 and a stronger reduction of 1.3 at Day 15 (corresponding to a reduction of the synovitis of 21.1% and 34.2% relative to baseline, respectively).

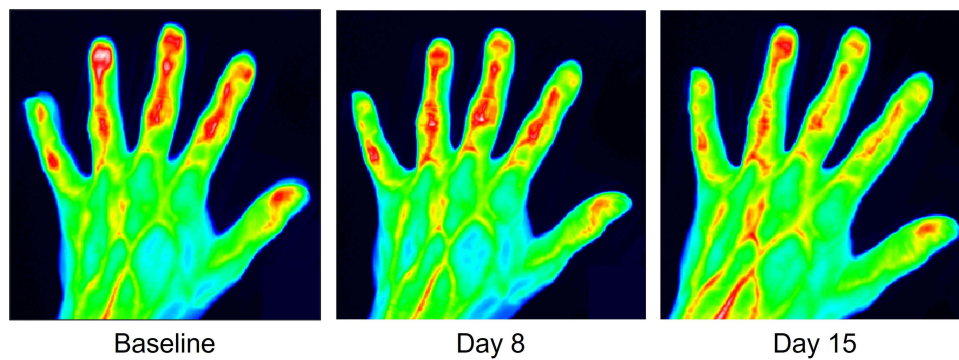


Figure 1 Representative FOI images collected from the target hand of one patient at Baseline, and after 7 (Day 8) and 14 (Day 15) days of using topical diclofenac.

FOI Quantitative Pixel Analysis

We quantified the number of white and red pixels in the FOI scans collected at Baseline and after 7 (Day 8) and 14 (Day 15) days of using topical diclofenac, focusing on the two joints most affected by synovitis, similarly to the post hoc analysis described earlier. Because the patients had only mild synovitis at baseline, the numbers of white and red pixels were combined together, indicating highest levels of synovitis. **Figure 2** shows the mean counts of white and red pixels in the individual joints of the target hands and in the two most affected joints at Baseline, Day 8, and Day 15. **Table 1**

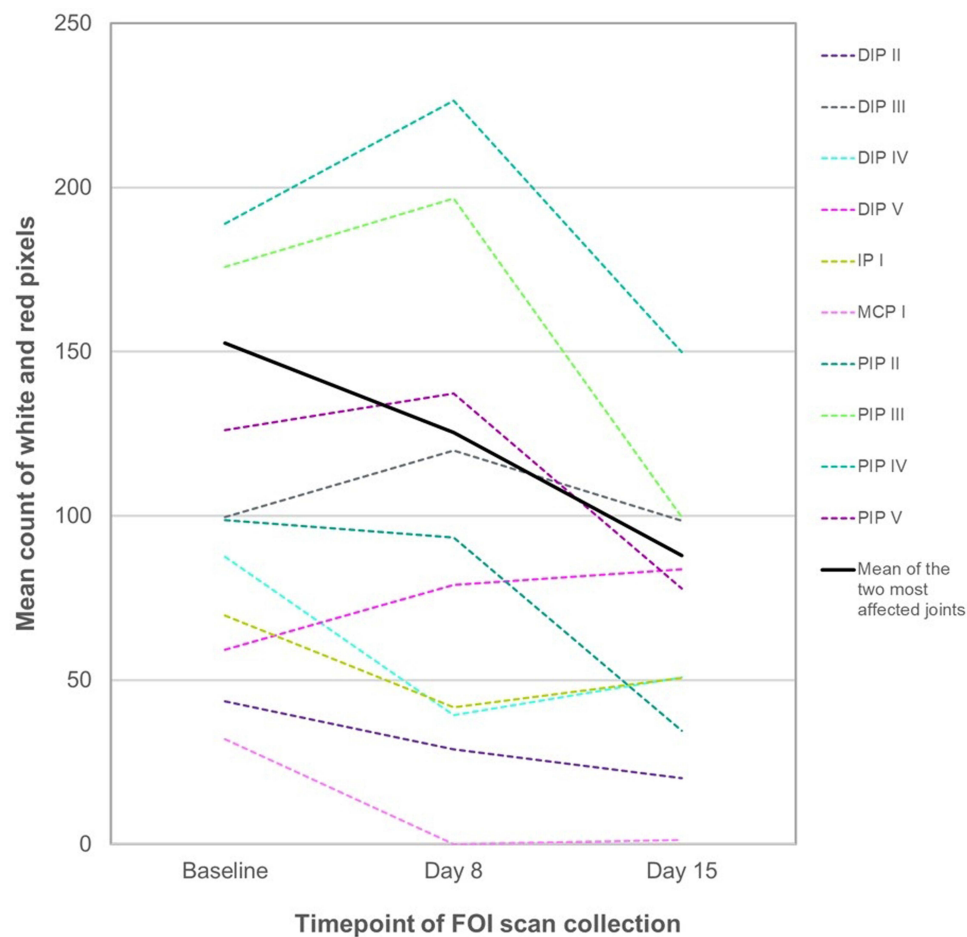


Figure 2 Quantitative pixel analysis of the Fluorescent Optical Imaging (FOI) data: mean counts of white and red pixels indicating the highest levels of synovitis in the individual joints of the target hands (dashed thin colored lines) and in the two most affected joints (solid thick black line) at Baseline and after 7 (Day 8) and 14 (Day 15) days of using topical diclofenac.

Table 1 Summary Quantitative Pixel Analysis of the Fluorescent Optical Imaging (FOI) Data: Absolute Count and Percentage Reduction of the Number of White and Red Pixels (Indicating the Highest Levels of Synovitis) in the Two Most Affected Joints, at Baseline and After 7 (Day 8) and 14 (Day 15) Days of Using Topical Diclofenac

	Number of White and Red Pixels Mean (Standard Deviation)	Percentage Change of the Number of Pixels Relative to Baseline
Baseline	152.6 (226.5)	–
Day 8	125.4 (150.4)	–17.8%
Day 15	87.9 (167.3)	–42.4%

summarizes the quantitative pixel analysis in terms of absolute pixel count and percentage reduction at the same timepoints vs Baseline. The trend of reducing the counts of white and red pixels with the duration of treatment was similar to the one observed in the FOI post hoc analysis.

Subjective Pain

Upon treatment with diclofenac, the patients reported a reduction in pain, resulting in a decrease of the mean pain score \pm standard deviation from 69.1 \pm 14.7 at Baseline to 61.9 \pm 9.2 and 55.8 \pm 18.6 on Day 8 Day 15, respectively.

Discussion

The purpose of this pilot study was to evidence the effect of topical diclofenac (Voltaren Schmerzgel 1.16%) on synovitis in patients with HOA using semi-quantitative assessment based on FOI, MRI, and US, and compare it with a fully quantitative FOI assessment of the changes in synovitis. During the 14-day treatment with topical diclofenac, the largest percent changes in the synovitis sum scores between Day 8 and Day 14 were as follows: MRI (3.7% reduction, Day 8), GS-US (7.8% reduction, Day 8), PD-US (32.3% reduction, Day 8), and FOI (19.6% reduction, Day 15). When examining the effects of diclofenac on the two most affected joints of the patients, the observed effects were more consistent, with reduction of the level of synovitis observed across all imaging modalities. Importantly, patients reported lower levels of subjective pain at both Days 8 and 15 compared with Baseline, mirroring the reduction in synovitis identified through imaging.

Although the semi-quantitative interpretation of the imaging modalities is well established and widely practiced, it nevertheless carries the risk of the interpretation being biased by the assessors' subjective views of what constitutes high levels of synovitis. To address this potential risk, we developed a fully quantitative technique for the analysis of FOI data based on the number of pixels indicating the highest levels of synovitis (ie, those colored white and red). This analysis showed a reduction in synovitis across Days 8 and 15 of topical treatment compared to Baseline, consistent with the results of the semi-quantitative analysis (Table 1, Figure 2 and Supplementary Table 1). Importantly, this reduction amounted to a 42.4% decrease in the number of white and red pixels on Day 15, demonstrating the ability of the topical diclofenac to reduce high levels of synovitis in patients with HOA. To our knowledge, this is the first time a fully quantitative approach has been used to objectively assess changes in synovitis in FOI images. Taken together with the observed decrease of the subjective pain perception over time, this pilot study showed that topical diclofenac use leads to improvements in both subjective and objective aspects of pain and inflammation in patients with HOA.

The study had several limitations. Being a pilot study, it had a relatively small sample size of 10 patients exhibiting overall only mild-to-moderate levels of synovitis at baseline. Additionally, it is possible that the lack of a placebo arm and the open-label nature of the study influenced the subjective pain perception in patients. FOI is a relatively new imaging technique, and its clinical validity is still being established.¹⁶ Applying the fully quantitative approach to larger study samples in placebo-controlled, double-blind trials and benchmarking the findings against established methodologies would be necessary to confirm its accuracy in the future.

Conclusion

This pilot study evidenced the ability of topical diclofenac to reduce the degree of synovitis, a sign of OA-induced inflammation in patients with HOA. Using a newly developed, fully quantitative analysis of FOI images, we estimated that diclofenac could reduce synovitis by up to 42.4% after two weeks of daily use.

Abbreviations

CMC1, thumb base joint; DIP, distal interphalangeal joint; FOI, fluorescence optical imaging; GS-US, Gray-Scale ultrasonography; HOA, hand osteoarthritis; IP, interphalangeal joint; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; PD-UA, Power-Doppler ultrasound; PVM, Prima Vista Mode; PIP, proximal interphalangeal joint; US, ultrasonography; VAS, visual analogue scale.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, either in the conception, study design, execution, acquisition of data, analysis and interpretation or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The clinical study was executed by Charité Research Organization GmbH, Berlin, Germany, and was funded by Novartis Consumer Health SA, a lawful predecessor of Haleon CH SARL. The pixel count analysis was performed in collaboration with Light In Motion, Prague, Czech Republic, and was funded by Haleon CH SARL. The authors were Haleon employees during this work. After completion, Konstantinos Mantantzis became an employee of Bayer Consumer Care AG. The authors report no other conflicts of interest in this work.

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