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A Systematic Review of the Efficacy and Safety of Profhilo® and Profhilo® Body

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Skin aging causes cumulative structural, physiological, and progressive skin changes, as well as wrinkles, uneven skin tone, elasticity loss, and skin thinning. We performed a systematic review of nine studies involving 278 participants to assess the efficacy and safety of the stable, *hybrid cooperative complexes of high molecular weight hyaluronic acid* (HCC-HA) and *low molecular weight hyaluronic acid* used in Profhilo® and Profhilo® Body (IBSA Farmaceutici Italia Srl, Lodi, Italy) on skin laxity, elasticity, hydration, density, wrinkle severity, and facial volume loss. We found that treatment with Profhilo® and Profhilo® Body led to a statistically significant change or a trend toward an improvement in mean viscoelasticity, elasticity, or plastoelasticity parameters (malar/submalar regions of the face, neck, inner arms, abdomen, and hands); skin hydration (malar/submalar face regions, the neck, inner arms, abdomen, and knees); skin density parameters (face, neck, inner arms, abdomen, hands, and knees); skin laxity (neck, inner arms, abdomen, knees, and hands); and Wrinkle Severity Rating Scale and Facial Volume Loss Scale scores (face). Photographic evidence showed improved skin turgor, tone, and texture, reduced nasolabial fold depth and wrinkles, and overall amelioration. Adverse events (i.e., bruising, edema, a light pinching sensation, a small bump, localized hematomas) were mild, expected, and usually resolved within 72 hours. Profhilo® and Profhilo® Body can improve skin laxity, hydration, elasticity, and density while reducing wrinkles and facial volume loss.

Key words: *Profhilo®; Profhilo® Body; hyaluronic acid; skin laxity; hybrid cooperative complexes*

Skin aging causes cumulative structural, physiological, and progressive skin layer alterations as well as changes in skin appearance (e.g., wrinkles, uneven skin tone, loss of elasticity, and skin thinning) (Ganceviciene et al., 2012). This multifaceted process involves gradual face or body remodeling through bone, soft tissue, and skin changes and comprises *intrinsic aging* (i.e., associated with genetics, cellular metabolism, hormones, and metabolic processes) and *extrinsic aging* (i.e., related to exposure to the environment, including ultraviolet [UV] radiation, smoking, pollution, chemicals, and toxins) (Ganceviciene et al., 2012; Shin et al., 2023; Swift et al., 2021).

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Antiaging approaches include cosmetic care (e.g., daily skin care, UV ray protection, noninvasive aesthetic procedures); topical agents (e.g., antioxidants, cell regulators); invasive procedures (e.g., chemical peeling, visible light devices, intense pulsed light, ablative and nonablative laser photo-rejuvenation, high-intensity focused ultrasound, radiofrequency, microneedling, microdermabrasion, injectable skin biostimulation, and rejuvenation); and systemic agents (e.g., hormone replacement therapy, antioxidants) (Ganceviciene et al., 2012; Shin et al., 2023).

Injectable fillers (e.g., poly-L-lactic acid, calcium hydroxyapatite, polycaprolactone, hyaluronic acid [HA]) induce slow and sustained neocollagenesis and extracellular matrix deposition (Guida et al., 2024). However, these synthetic fillers act through a biostimulatory mechanism, meaning that they elicit a subclinical inflammatory response involving activation of the immune system by inducing production of collagen Type I and augmenting tissue by activating fibroblasts (Kim, 2019; Loghem et al., 2015; Vleggaar, 2005). Notably, this mechanism may lead to foreign body reactions and the formation of nodules and granulomas at later time points (Kim, 2019; Loghem et al., 2015; Vleggaar, 2005).

HA-based dermal fillers are the most popular, nonpermanent, minimally-invasive injectable aesthetic treatment for correcting soft tissue facial defects (Brandt & Cazzaniga, 2008), and their global use has increased over time (Coimbra D, 2021). HA formulations that are available commercially comprise different molecular weights (i.e., 50–≤2 million kDa) (Laurino et al., 2015).

Developed using patented *nano hybrid complex* (NAHYCO®) technology, Profhilo® (IBSA Farmaceutici Italia Srl, Lodi, Italy) is an HA product used to treat the skin laxity of the face and neck that consists of hybrid cooperative complexes (HCC-HA) of 32 mg of high molecular weight HA (1,100–1,400 kDa) and 32 mg of low molecular weight HA (80–100 kDa) in an injectable concentration (64 mg/2 mL) (Cassuto et al., 2020; Laurino et al., 2015).

In contrast to biostimulatory molecules, HCC-HAs act differently and do not induce inflammatory responses. HCC-HAs use a bioremodeling mechanism, a process that reverses tissue laxity, facilitating extracellular matrix homeostasis by reestablishing elastin, collagen Types I, III, IV, and VII, and restoring the viability and metabolism of fibroblasts, keratinocytes, adipocytes, and myocytes (Humzah et al., 2024). Because of its mechanism of action and rheological properties, Profhilo® has a low viscosity that enables optimal tissue diffusion for facial bioremodeling (Cassuto et al., 2020; Laurino et al., 2015).

The commercially available kit of Profhilo® Body (IBSA Farmaceutici Italia Srl, Lodi, Italy), which is indicated for treating skin laxity of the body, includes a 3 mL syringe consisting of 32 mg/mL HCC-HA. When used in combination with Profhilo® Figura body cream and Profhilo® Figura body patch (IBSA Farmaceutici Italia Srl, Lodi, Italy). This treatment improves skin elasticity and global tissue homeostasis of the body (Sparavigna et al., 2023b).

To help healthcare practitioners fully understand the characteristics of the various products used during aesthetic procedures and select the best products for their patients, it is fundamental for aesthetic practitioners to evaluate data retrieved from both clinical studies and real-world evidence. By comparing all of the published data practitioners can better comprehend the efficacy and safety profiles of aesthetic products. Therefore, the objective of this systematic review was to evaluate the safety and efficacy of Profhilo® and Profhilo® Body for improving skin laxity, elasticity, hydration, and density of the face and body, as well as reducing the severity of wrinkles and loss of facial volume.

METHODS

Ethical Statement

This systematic literature review did not involve human participants and therefore did not require ethical approval.

Search Strategy

We conducted this review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

We performed a systematic literature search of the EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and the Cochrane Skin Specialized Register with no restriction of beginning search date through February 23, 2024. The search terms we used for each database are shown in Supplemental Digital Content Table S1 available at: http://links.lww.com/PSN/A7. We also conducted a manual search of other relevant references (including references in nonindexed journals).

Eligibility Criteria

Our inclusion criteria are shown in Table 1. We only included articles published in the English language and articles where the researchers administered Profhilo® or Profhilo® Body using a *Bio Aesthetic Points* (BAP) technique for all body areas (aside from the hands, where we included administration of the product via a cannula).

BAP Technique

The BAP technique is a method of injecting skin rejuvenation treatments into five specific points located in the treatment area. The injection points are strategically designed to maximize the spread of the product and achieve a natural and even distribution of the product across the facial area (IBSA Farmaceutici Italia srl, 2019a, 2019b). Following are the recommended injection points for the malar/submalar, neck, and upper arms/abdomen:

- **Malar/Submalar**: Inject 0.2 mL of Profhilo® using a bolus technique into the dermal/subcutaneous

TABLE 1 Eligibility Criteria

Criteria	Details
Studies	• Clinical trials, including single-arm trials and within-person trials (such as split-face trials or facial subunit studies), and case series investigating the clinical efficacy and safety of Profhilo® or Profhilo® Body that included ≥10 participants • Prospective and retrospective studies
Participants	• Participants of any age with a clinical diagnosis of skin laxity
Interventions	• Treatment with Profhilo® or Profhilo® Body and Profhilo® Figura body cream and Profhilo® Figura body patch • Profhilo® or Profhilo® Body administered according to the manufacturer's instructions provided in the product leaflets • Use of the Bio Aesthetic Point technique according to the manufacturer's instructions provided in the product leaflets for the face, neck, or any body part, aside from the hands where the product may be administered using a cannula (technique not described in the manufacturer's instructions provided in the product leaflets)
Primary outcomes	• Efficacy outcomes, including skin hydration, elasticity determined through torsiometric parameters, density/firmness/roughness determined through profilometric parameters, TEWL, pore count/volume, and melanin level • Efficacy outcomes assessed with WSRS, FVLS, and/or Beagley-Gibson Scale scores; skin laxity scores assessed with IBSA Neck Laxity Scale and/or IBSA Upper Inner Arm Laxity Scale; investigator- or participant-assessed GAIS scores; self-assessment questionnaire scores; and two- or three-dimensional photographic documentation
Secondary outcomes	• Frequency of adverse events, serious adverse events, and tolerability as determined by expected adverse events and serious adverse events described in the product leaflets, unexpected adverse events and serious adverse events not described in the product leaflets, and early- and late-onset adverse events and serious adverse events • Tolerability evaluated by participants and investigators, as well as by a VAS scale

Note. FVLS = Facial Volume Loss Scale; GAIS = Global Aesthetic Improvement Scale; HA = hyaluronic acid; TEWL = transepidermal water loss; VAS = visual analog scale; WSRS, Wrinkle Severity Rating Scale.

levels at each of the following five points. Massage gently at the injection points.

- ***Zygomatic protuberance:*** At least 2 cm away from the external corner of the eye.
- ***Nasal bas***e: Intersection between a line drawn from the nostril to the tragus and a perpendicular line from the pupil midline.
- ***Tragus***: At least 1 cm in front of the lower margin of the tragus.
- ***Chin***: Intersection between a vertical line in the center of the chin, a perpendicular line one third from the top of the vertical line, and 1.5 cm toward the oral commissure.
- ***Mandibular angle***: 1 cm above the mandibular angle (IBSA Farmaceutici Italia srl, 2019b).
- **Neck**: Inject 0.2 mL of Profhilo® using a bolus technique into the dermal/ subcutaneous levels at each of the following 10 points. Massage gently at the injection points.
- ***Hyoid bone***: Midway between the chin edge and hyoid bone.
- ***Thyroid cartilage***: Midway between the Adam's apple and thyroid cartilage.
- ***Trachea***: Midway between the hyoid cartilage and the manubrium.
- ***Sternal notch***: Apex of the manubrium.
- ***Sternocleidomastoid muscle* (SCM)**: 0.5 cm from the medial edge of the right and left SCM, under the mandibular angle.
- ***SCM***: 0.5 cm from the medial edge of the right and left SCM, at a level that is horizontal to the thyroid cartilage.
- ***SCM***: 0.5 cm from the medial edge of the right and left SCM, at a level that is horizontal to the trachea (Sparavigna et al., 2022a).
- **Upper arms/abdomen**: Inject 0.3 mL of Profhilo® Body using a bolus technique into the deep dermal/ subcutaneous levels at each of the following 10 points. Massage gently at the injection points.
  - Identify 10 points on three horizontal levels (three on the first, four on the second, and three on the third) where there are no large vessels or nerve branches (IBSA Farmaceutici Italia srl, 2019a).

The advantages of administering the product using a BAP technique include fewer injection points, a reduced likelihood for adverse events, and fewer treatment sessions (Beatini et al., 2016). The product manufacturer recommends two treatment sessions of Profhilo® (IBSA Farmaceutici Italia srl, 2019a) or Profhilo® Body (IBSA Farmaceutici Italia srl, 2019b), 30 days apart, followed by maintenance injections every two months, if desired.

Study Selection and Data Extraction

We compiled the references into EndNote™ 20 (Clarivate, Philadelphia, PA, USA), and removed any duplicates. Two reviewers checked the titles or abstracts to confirm whether they met the eligibility criteria for this

analysis. If insufficient information was provided in the abstract, we assessed the full-text article. We extracted efficacy, safety data, study design, and participant characteristics from the full-text articles and placed the data into tables using Microsoft® Excel® for Microsoft 365 MSO, Version 2403 (Microsoft Corporation, Redmond, WA, USA). For figures that did not provide exact data, we extracted the values from plots using WebPlotDigitizer (Automeris LLC, Austin, TX, USA).

Data Synthesis

We performed a descriptive comparison of efficacy and safety outcomes from the individual studies. Using Comprehensive Meta-Analysis Version 4 (Biostat Inc., Englewood, NJ, USA), we conducted a meta-analysis of the rate of adverse events for six studies that quantitatively reported this information (Beatini et al., 2016; Laurino et al., 2015; Sparavigna et al., 2022a, 2022b, 2023c; Sparavigna & Tenconi, 2016). We used a random-effects model for the meta-analysis which assumes that the studies in the analysis are a random sample from a pool of potential studies.

RESULTS

Study Design and Participant Characteristics

We identified 38 articles from four databases and 7 articles by manual searching. We screened 30 records for eligibility and included nine articles in the review (Figure 1; Table 2). Of the nine included articles, eight were single-center studies (Laurino et al., 2015; Sparavigna et al., 2022a, 2022b, 2023b, 2023c, 2023d, 2022c; Sparavigna & Tenconi, 2016) and one was a retrospective analysis (Beatini et al., 2016) (Table 2). Only one of the studies included men (Sparavigna et al., 2023c); however, the researchers did not specify the number of men included in the study. One study included Chinese women (Sparavigna et al., 2023d). Six studies included less than 30 participants (Beatini et al., 2016; Laurino et al., 2015; Sparavigna et al., 2022a, 2022b, 2023d, 2022c), and three studies included more than 30 participants (Sparavigna et al., 2023b, 2023c; Sparavigna & Tenconi, 2016). Across the studies, the mean age range of the participants was 30–73 years. The treated body areas represented in the studies included the malar/submalar area (Beatini et al., 2016; Laurino et al., 2015), the

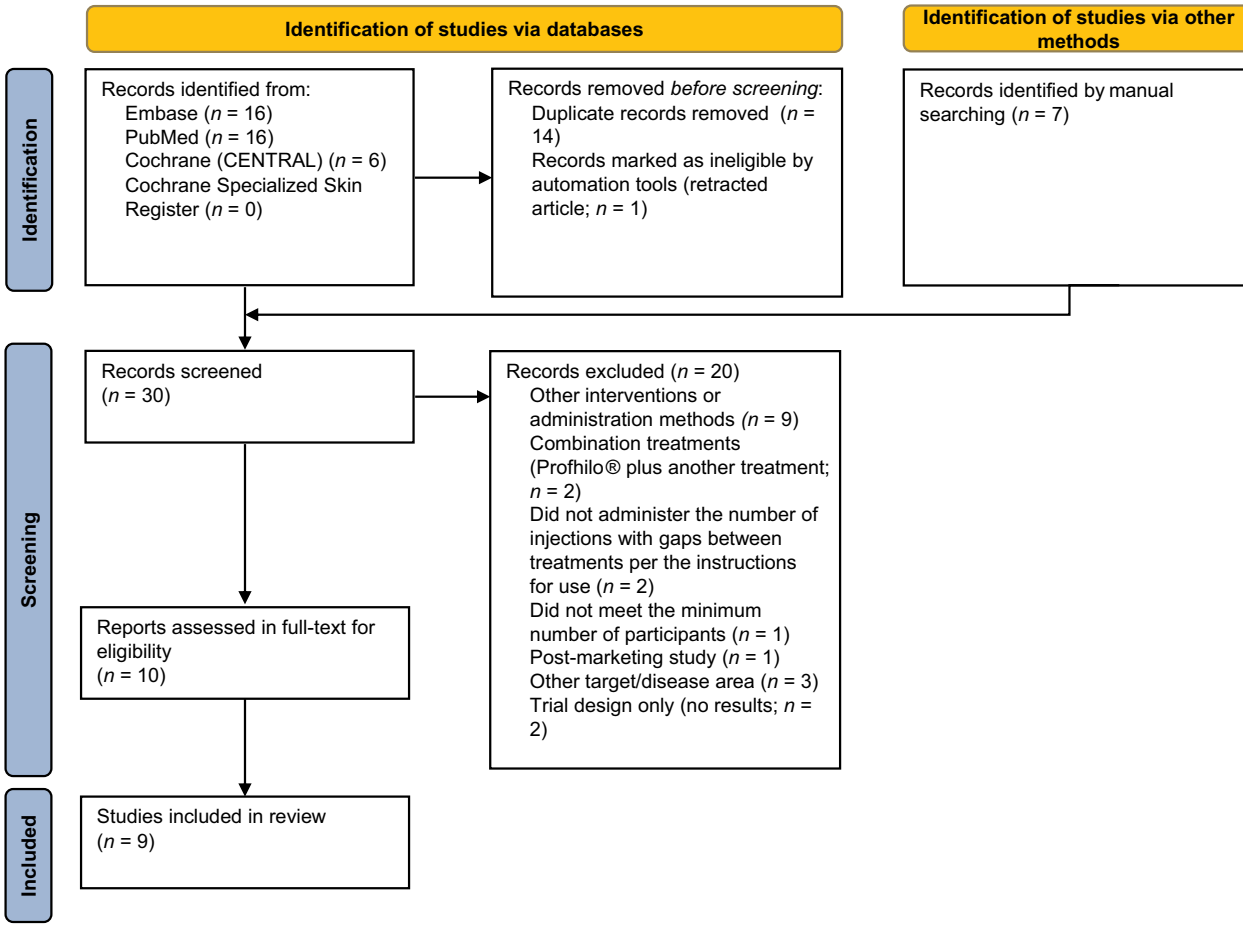

FIGURE 1. Flowchart of the systematic literature review. © 2020 Page et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited..

TABLE 2 Study Design and Participant Characteristics

Publication	Study design	Inclusion criteria	*N*[a]	Age range, years (mean)	Product	Treated body areas	Total number of injections	Follow-up visits	Outcome measures
Beatini et al. (2016)	Retrospective evaluation	• Women 35–65 years	15	39–65 (53)	Profhilo®	Malar/ submalar	2	Week 4, 8	• Viscoelasticity (Uv/Ue) • Percentage skin hydration • Photographic documentation • Patient satisfaction survey • Safety
Laurino et al. (2015)	Single-center, retrospective, observational study	• Moderate facial photoaging • VAS score between 4 and <7	11	48–67 (56)	Profhilo®	Malar/ submalar	2	Week 4, 12	• Hydration • Elasticity • Transepidermal water loss • Stromal density and vascular tone • Photographic documentation • Safety • Physician-evaluated features of the injection procedure • Physician satisfaction • Participant satisfaction
Sparavigna et al. (2022a)	Single-center clinical trial	• Women 40–65 years • IBSA Neck Laxity Scale score, 3–4	23	41–65 (54)	Profhilo®	Neck	2	Week 4, 16	• Photographic documentation • IBSA Photographic Scale for the Assessment of Upper Inner Arm Laxity • Superficial hydration • Deep hydration • Plastoelasticity • Skin density • Safety • Participant satisfaction survey

(*continues*)

TABLE 2 Study Design and Participant Characteristics (*Continued*)

Publication	Study design	Inclusion criteria	*N*[a]	Age range, years (mean)	Product	Treated body areas	Total number of injections	Follow-up visits	Outcome measures
Sparavigna and Tenconi (2016)	Single-center, prospective clinical trial	• Women 30–60 years • 55% of participants had a prior facial aesthetic procedure	60[b]	38–60 (53)	Profhilo®	Face	2	Week 4, 8, 12, 16	• WSRS • FVLS • Beagley and Gibson Scale • Self-evaluation questionnaire • Optical colorimetry • Superficial hydration • Deep hydration • Plastoelasticity • Viscoelasticity • Immediate elastic recovery • Profilometry • Photographic documentation • Safety
Sparavigna et al. (2023d)	Single-center, pilot study	• Chinese women 30–60 years living in Italy	28 (neck = 18; face = 10)	38–60 (51)	Profhilo®	Face, neck	2	Week 4, 8[c]	• WSRS • FVLS • IBSA Photographic Scale for the Assessment of Upper Inner Arm Laxity • Superficial hydration • Deep hydration • Facial skin color changes • Photographic documentation • Safety

(*continues*)

TABLE 2 Study Design and Participant Characteristics (*Continued*)

Publication	Study design	Inclusion criteria	*N*[a]	Age range, years (mean)	Product	Treated body areas	Total number of injections	Follow-up visits	Outcome measures
Sparavigna et al. (2022b)	Single-center clinical trial	• Adult women with at least initial signs of aging	23	50–73 (63)	Profhilo®	Face	7 (2 and then 5 injections every 2 months)	Week 4, 1 year	• WSRS • FVLS • Photographic documentation • Safety
Sparavigna et al. (2022c)	Single-center study	• Individuals 45–60 years with abdominal and upper arm roughness • IBSA Photographic Scale for the Assessment of Upper Inner Arm Laxity Grade, 3–4, and desire to restore laxity and reduce roughness	22	47 to 65[d]	Profhilo® Body	Upper arm, Abdomen	2	Week 4, 16	• Photographic documentation • IBSA Photographic Scale for the Assessment of Upper Inner Arm Laxity • Visual score for abdominal skin laxity • Superficial hydration • Deep hydration • Plastoelasticity • Self-assessment questionnaires
Sparavigna et al. (2023b)	Single-center study	• Women with mild/moderate skin roughness and laxity of the upper arms, abdomen, or knees, 35–65 years • IBSA Photographic Scale for the Assessment of Upper Inner Arm Laxity, Grade 3–4	50	35–65[d]	Profhilo® Body	Inner arm, abdomen, and knees	2	Week 4, 16	• IBSA Photographic Scale for the Upper Inner Arm Laxity • Visual score for abdominal skin roughness and laxity • Photographic documentation • Deep hydration • Skin density • Self-assessment questionnaire • Safety

(*continues*)

TABLE 2 Study Design and Participant Characteristics (*Continued*)

Publication	Study design	Inclusion criteria	*N*[a]	Age range, years (mean)	Product	Treated body areas	Total number of injections	Follow-up visits	Outcome measures
Sparavigna et al. (2023c)	Single-center study	• Individuals 18–65 years requesting hand rejuvenation	46	38–65[d]	Profhilo® Body	Hands	2	Week 4, 16	• Roughness and laxity grade • Photograph documentation • Resistance to pinching • Skin density • Plastoelasticity • Deep hydration • Self-assessment questionnaire • Safety

Note. DTM = Dermal Torque Meter; FVLS = Facial Volume Loss Scale; Ue = immediate extensibility; Uv = viscoelasticity; VAS = visual analog scale; WSRS = Wrinkle Severity Rating Scale.

[a]Excludes participants who enrolled in a study but did not complete the study. The number of participants reflects the number of participants included in the efficacy and safety analysis.

[b]Four participants did not have a follow-up at Week 16 but were still included in the analysis.

[c]Three participants were also evaluated at Week 12 for the face, and no participants were evaluated at Week 16 due to the COVID-19 pandemic.

[d]Mean age was not stated.

face and/or neck (Sparavigna et al., 2022a, 2022b, 2023d; Sparavigna & Tenconi, 2016), the inner arms and abdomen with/without knees (Sparavigna et al., 2023b, 2022c), and the hands (Sparavigna et al., 2023c).

Efficacy Outcomes Assessed with Instruments

Elasticity

As described in Supplemental Digital Content Table S2, available at: http://links.lww.com/PSN/A7, Beatini et al. (2016) used a MicroCAMERA (Dermotricos SRL, Coccaglio, Italy) to assess skin elasticity. Laurino et al. (2015) used *Young's Modulus*, which is a measure of the skin's resistance to elastic elongation. In four studies, the researchers used a Dermal Torque Meter (DTM; Dia-Stron Ltd, Andover, UK) to assess *plastoelasticity* (i.e., elastic recovery, residual deformation) (Sparavigna et al., 2022a, 2023c, 2022c; Sparavigna & Tenconi, 2016). Plastoelasticity is defined by the torsion angle at *maximum extensibility* (Uf) and *immediate elastic recovery* (Ur) (Sparavigna et al., 2014). *Skin elasticity* is the Ur/Uf ratio, Uv is *viscoelasticity*, and *elastic recovery* is Ur/Ue, where Ue is *immediate extensibility*.

- **Malar/Submalar Area.** Beatini et al. (2016) found a statistically significant improvement in mean viscoelasticity (i.e., Uv/Ue ratio) of the malar and submalar areas at Week 4 (right: $p = .019$, left: $p = .41$) and Week 8 (right: $p = .0029$, left: $p = .47$) compared with baseline. Laurino et al. (2015) found a statistically significant improvement in mean elasticity of the malar and submalar areas at Week 4 (right/left: $p < .01$) and Week 12 (right/left: $p < .01$) compared with baseline.
- **Face/Neck.** Sparavigna et al. (2022a) found there was a trend toward improvement of all plastoelasticity parameters of the neck after treatment compared with baseline, and this was statistically significant for Ur at Week 16 ($p < .05$). Sparavigna and Tenconi (2016) found a statistically significant improvement in Uf and Uv of the face at Week 16 ($p < .05$) compared with baseline.
- **Inner arms/Abdomen.** Sparavigna et al. (2022c) found a statistically significant improvement in Uf at Week 4 ($p < .05$) and Ur of the inner arms at Week 4 ($p < .05$) and Week 16 ($p < .05$) compared with baseline. Furthermore, the researchers found there was a statistically significant improvement in Ur of the abdomen at Week 16 ($p < .05$) compared with baseline.
- **Hands.** Sparavigna et al. (2023c) found that all plastoelasticity parameters for the hands were improved at Week 16 compared with baseline. This change was significant for Ue ($p < .05$), Uv ($p < .05$), and Ur ($p < .05$).

Skin Hydration

As shown in Supplemental Digital Content Table S2, available at: http://links.lww.com/PSN/A7, the results from all studies where the researchers measured skin hydration showed an increase in skin hydration post-treatment.

- **Malar/Submalar.** Beatini et al. (2016) found a statistically significant improvement in mean percentage of skin hydration of the malar/submalar areas (Week 4, right: $p < .001$, left: $p < .0001$; Week 8, Right: $p < .0001$, Left: $p < .00001$) compared with baseline. Laurino et al. (2015) found a statistically significant improvement in mean skin hydration of the malar/submalar areas at Week 4 (right/left: $p < .01$) and Week 12 (right/left: $p < .01$).
- **Face/Neck.** Sparavigna et al. (2022a) found a statistically significant improvement in mean superficial skin hydration of the neck at Week 16 ($p < .05$), a statistically significant improvement in mean deep (0.5 mm) skin hydration at Week 4 ($p < .05$), and a statistically significant improvement in mean deep (1.5 mm) skin hydration at Week 16 ($p < .05$) compared with baseline. Sparavigna and Tenconi (2016) found a statistically significant improvement in mean superficial skin hydration of the face at Week 4 ($p < .05$), Week 12 ($p < .05$), and Week 16 ($p < .05$) compared with baseline.
- **Inner Arms/Abdomen/Knees.** Sparavigna et al. (2022c) found a statistically significant improvement in mean superficial skin hydration of the inner arms and abdomen at Week 4 ($p < .05$) and Week 16 ($p < .05$), a statistically significant improvement in mean deep (0.5 mm) skin hydration of the inner arms at Week 4 ($p < .05$), and a statistically significant improvement in mean deep (1.5 mm) skin hydration of the inner arms at Week 4 ($p < .05$) and of the abdomen at Week 4 ($p < .05$) and Week 16 ($p < .05$) compared with baseline. Sparavigna et al. (2023b) found a statistically significant improvement in mean deep (0.5 mm) skin hydration of the inner arms and abdomen at Week 4 ($p < .05$) and Week 16 ($p < .05$) and a statistically significant improvement in mean deep (0.5 mm) skin hydration of the knees at Week 4 ($p < .05$) and additionally found a statistically significant improvement in mean deep (1.5 mm) skin hydration of the inner arms at Week 16 ($p < .05$) compared with baseline.

Skin Density

Skin density parameters include average roughness (Ra), total height (Rt), and maximum total depth (Rv). In five studies (Sparavigna et al., 2022a, 2023b, 2023c, 2022c;

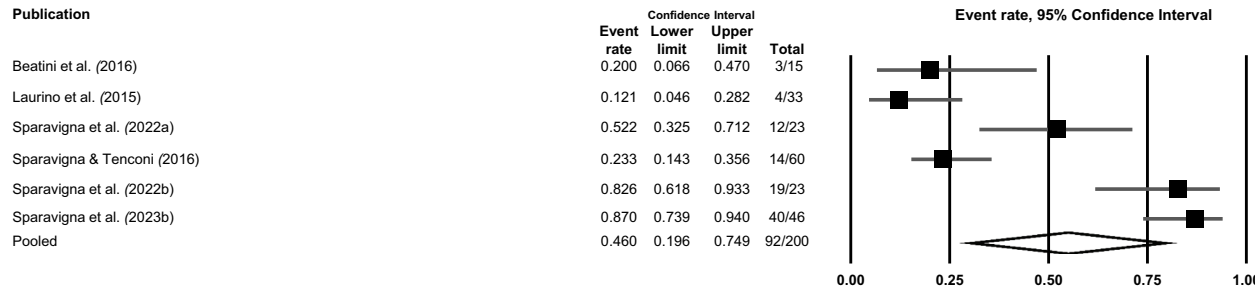

FIGURE 2. Meta-analysis of adverse events. Mean effect size = 0.460; 95% confidence interval: 0.196–0.749.

Sparavigna & Tenconi, 2016), the researchers measured these parameters using PRIMOS, a three-dimensional skin measurement system (GF Messtechnik GmbH, Berlin, Germany).

- **Face/Neck.** Sparavigna et al. (2022a) found a statistically significant improvement at Week 4 ($p < .05$) and Week 16 ($p < .05$) in Ra, Rt (Week 4: $p < .05$; Week 16: $p < .05$), and Rv (Week 4: $p < .05$; Week 16: $p < .05$) of the neck compared with baseline. Sparavigna & Tenconi (2016) found a statistically significant improvement at Week 16 in Ra ($p < .05$), Rt ($p < .05$), and Rv ($p < .05$) of the face compared with baseline.
- **Inner Arms/Abdomen/Knees.** Sparavigna et al. (2022c) found a statistically significant improvement at Week 4 ($p < .05$) and Week 16 ($p < .05$) in Ra of the inner arms and a statistically significant improvement at Week 16 ($p < .05$) in Rt of the inner arms compared with baseline. Sparavigna et al. (2023b) found a statistically significant improvement at Week 4 ($p < .05$) and Week 16 ($p < .05$) in Ra of the inner arms and abdomen (Week 4: $p < .05$; Week 16: $p < .05$), and a statistically significant improvement at Week 16 ($p < .05$) in Ra of the knees compared with baseline. Sparavigna et al. (2023b) additionally found a statistically significant improvement at Week 4 ($p < .05$) and Week 16 ($p < .05$) in Rv of the inner arms and a statistically significant improvement at Week 16 ($p < .05$) in Rv of the abdomen compared with baseline.
- **Hands.** Sparavigna et al. (2023c) found a statistically significant improvement at Week 16 ($p < .05$) in Ra of the hands and a statistically significant improvement at Week 4 ($p < .05$) in Rv of the hands compared with baseline.

Transepidermal Water Loss

Laurino et al. (2015) measured transepidermal water loss and found a statistically significant improvement at Week 4 ($p < .01$) and Week 12 ($p < .01$) in the malar and submalar regions compared with baseline.

Pore Count/Volume and Melanin Level

Although we had planned to include quantitative outcomes of pore count and volume and melanin levels, none of the studies included in the systematic review assessed these.

Efficacy Outcomes Assessed with Clinical Evaluation Methods

Skin Laxity

As shown in Supplemental Digital Content Table S3, available at: http://links.lww.com/PSN/A7, the results of the systematic review showed that treatment of the neck (Sparavigna et al., 2022a), face (Sparavigna et al., 2023d), inner arms and abdomen (with or without knees; Sparavigna et al., 2023b, 2022c), and hands (Sparavigna et al., 2023c) with Profhilo® or Profhilo® Body led to a statistically significant decrease or a trend toward a decrease in mean skin laxity for at least one follow-up timepoint compared with baseline scores.

Wrinkle Severity Rating Scale, Facial Volume Loss Scale, and Beagley-Gibson Scale

Treatment of the face with Profhilo® resulted in a trend toward a decrease or a statistically significant decrease in mean Wrinkle Severity Rating Scale (WSRS; Day et al., 2004) and mean Facial Volume Loss Scale (FVLS; Lorenc et al., 2012) scores for at least one follow-up timepoint compared with baseline. Sparavigna & Tenconi (2016) investigated skin laxity of the face before and after treatment with Profhilo® using the Beagley-Gibson Scale (Beagley & Gibson, 1980) and also found a statistically significant decrease in mean visual scores for all follow-up timepoints compared with baseline.

Photographs

In seven of the nine studies included in the systematic review (Beatini et al., 2016; Laurino et al., 2015; Sparavigna et al., 2022a, 2023b, 2023d, 2022c; Sparavigna & Tenconi, 2016), the researchers provided photographic

evidence and described improved skin turgor, decreased skin wrinkles, brighter skin, reduced nasolabial fold depth, improved texture, better pigmentation/skin tone, and overall amelioration following treatment with Profhilo® or Profhilo® Body.

Safety Outcomes

As shown in Supplemental Digital Content Table S4, available at: http://links.lww.com/PSN/A7, all of the researchers of the studies included in the systematic review reported safety outcomes involving adverse events at the injection site that included bruising, which occurred in 13%–88% of the study participants, edema, which occurred in 7%–8% of the participants, a light pinching sensation during the injections, which occurred in 2% of the participants, small bumps, which occurred in 17% of the participants, and localized hematomas, which occurred in 12% of the total injections. All of the adverse events were mild, expected, and discussed in the Profhilo® and Profhilo® Body package inserts (IBSA Farmaceutici Italia srl, 2019a; IBSA Farmaceutici Italia srl, 2019b). These reactions were transient (usually lasting approximately 72 hours). None of the researchers reported any serious adverse events or serious adverse device events.

We conducted a meta-analysis of the adverse event rate reported by the researchers of six of the included studies (Beatini et al., 2016; Laurino et al., 2015; Sparavigna et al., 2022a, 2022b, 2023c; Sparavigna & Tenconi, 2016) using a random effects model. As shown in Figure 2, the mean effect size was 0.460 with a 95% confidence interval of 0.196–0.749, meaning that the mean event rate of mild adverse events occurring during or after treatment was 46% (95% CI, 20%–75%).

Patient Satisfaction Levels

As shown in Supplemental Digital Content Table S4, available at: http://links.lww.com/PSN/A7, the researchers of seven studies included in the systematic review (Beatini et al., 2016; Laurino et al., 2015; Sparavigna et al., 2022a, 2023b, 2023c, 2022c; Sparavigna & Tenconi, 2016) reported patient satisfaction levels or self-evaluation of the efficacy of the treatment that they ascertained using nonvalidated, self-assessment questionnaires.

Beatini et al. (2016) reported that 60% of the participants ($n = 9$) were "satisfied" after treatment of their malar and submalar areas with Profhilo®. Laurino et al. (2015) reported that 87.9% of the participants ($n = 29$) were "very satisfied" (87.9%; $n = 29$) after treatment of their malar and submalar areas with Profhilo®. In three studies (Sparavigna et al., 2022a, 2023b, 2022c), 64%–94% of the participants reported improved skin roughness, laxity, suppleness, smoothness, and hydration after treatment with Profhilo®. In four studies (Sparavigna et al., 2022a, 2023b, 2022c; Sparavigna & Tenconi, 2016), 64%–94% of the participants reported a remodeled or more defined silhouette, and in three studies (Sparavigna et al., 2022a, 2022c; Sparavigna & Tenconi, 2016), 64%–96% of the participants reported a lifting effect after treatment with Profhilo® or Profhilo® Body.

DISCUSSION

In this systematic review, we evaluated the efficacy and safety of Profhilo® and Profhilo® Body. We found that the techniques used by the researchers to measure skin plastoelasticity varied across the studies. According to Takema et al. (1994), plastoelasticity measurements decrease with an individual's facial age and increase with their forearm age. This difference may be due to sunlight exposure, which would result in an increase in the plastoelasticity parameters of the face, neck, and hands (i.e., regions usually exposed to the sun) and a decrease in parameters of the inner arms and abdomen. Sparavigna et al. (2022a) found an increase in plastoelasticity parameters after treatment of the neck and Sparavigna et al. (2023c) found an increase in plastoelasticity parameters post-treatment of the hands. However, Sparavigna and Tenconi (2016) found a decrease in plastoelasticity parameters after treatment of the face and Sparavigna et al. (2022c) found a decrease in plastoelasticity parameters after treatment of the inner arms and abdomen.

Treatment with Profhilo® or Profhilo® Body also led to a statistically significant change or a trend toward improvement in mean skin hydration (malar/submalar, face/neck, inner arms, abdomen, knees); skin density parameters (face/neck, inner arms, abdomen, hands, knees); skin laxity (neck, inner arms, abdomen, knees, hands); and WSRS and FVLS scores. Photographic documentation showed improved skin turgor, texture, tone, and brightness, as well as reduced nasolabial fold depth and wrinkles, and overall amelioration in the areas treated.

Sparavigna et al. (2023b) emphasized the importance of maximizing treatment efficacy when using Profhilo® Body as a treatment for skin laxity by selecting patients with clear signs of skin laxity and roughness, with or without limited ptosis of muscle and adipose tissue.

A limitation of this systematic review is that the researchers of the included articles primarily investigated the effects of Profhilo® and Profhilo® Body in White women. Notably, in a pilot study that included Chinese women, Sparavigna et al. (2023d) found a positive effect of Profhilo® after the first round of treatment across the efficacy endpoints. Additionally, in a comparative analysis of three studies that included 87 White women and 28 Chinese women, Sparavigna et al. (2023a) found that the Chinese women had a faster treatment response and a greater reduction in wrinkle severity of the face, facial volume loss, and skin laxity of the neck than the White

women. The researchers hypothesized that genetic and molecular skin tissue differences combined with muscle and bone anthropometric variations may result in more favorable outcomes following treatment of the face and neck with Profhilo® in Chinese patients.

The efficacy of Profhilo® and Profhilo® Body in improving skin hydration, firmness, and roughness is also supported by *in vitro* findings, which improve understanding of the mechanism of action for HCC-HA. In a study using a three-dimensional skin model to evaluate the interaction between keratinocytes and dermal fibroblast cells in the presence of HCC-HA, Stellavato et al. (2016) found that production of different types of collagen (i.e., Types I, III, IV, VII) and elastin increased in the presence of HCC-HA compared with untreated cells, high molecular weight HA alone, and low molecular weight HA alone. This is likely because of the long-lasting release and concurrent action of H-HA and L-HA components on keratinocytes and fibroblast metabolism and vitality, which supports the concept that HA-based injections in the dermis counteract physiological aging signs and create a bioremodeling effect. This *bioremodeling action* of HCC-HA (i.e., the process that reverses tissue laxity, facilitating extracellular matrix homeostasis and restoring the viability and metabolism of fibroblasts, keratinocytes, adipocytes and myocytes) also explains the long-lasting efficacy of these products compared with other products that are primarily composed of linear HA, vitamins, amino acids, collagen, and nucleotides that act through a biorevitalization mechanism. *Biorevitalization* is the process that restores the loss of skin nourishment by providing vital components that are physiologically present in human cells and are fundamental for the viability of fibroblasts and the homeostasis of the extracellular matrix (collagen Type I, mainly). Although patients' perception of the beneficial effects of biorevitalizing products is immediate, the efficacy of these products is usually short-term (i.e., < 6 months).

In addition to efficacy, safety is an important feature of the injectable products used in aesthetic procedures. The results of this systematic review showed that injection site adverse events (e.g., bruising, edema, a light pinching sensation, a small bump, localized hematomas) after injection with Profhilo® and Profhilo® Body were mild, expected, and usually resolved within a few days after treatment. These effects can be relieved by applying ice to the treated area. Our meta-analysis of six studies (Beatini et al., 2016; Laurino et al., 2015; Sparavigna et al., 2022a, 2022b, 2023c; Sparavigna & Tenconi, 2016) showed that the mean event rate of adverse events occurring during injection and after treatment was 46%.

An analysis of 3-year post-marketing surveillance findings on Profhilo® showed that the product was safe and well-tolerated by greater than 40,000 participants. Minor adverse events may have been underreported in that study due to the voluntary nature of reporting adverse events by the specialists who carried out the treatment. Likewise, some participants who experienced mild symptoms may not have reported them to their physician. The adverse events reported in that analysis included early-onset injection site reactions (e.g., swelling, edema, redness, ecchymosis, erythema) and late-onset local reactions (e.g., swelling, nodules), all of which resolved without complications. The researchers found there were more quality complaints ($n = 18$) than safety incidents ($n = 12$) over three years. Considering the global product sales, this is a small number. As well, some quality issues (e.g., medical device component breakage), could have arisen as a result of incorrect device handling (Cassuto et al., 2020).

Limitations of this review include the fact that all of the included studies were single-center studies. Six studies included less than 30 participants (Beatini et al., 2016; Laurino et al., 2015; Sparavigna et al., 2022a, 2022b, 2023d, 2022c), and only one study included men (Sparavigna et al., 2023c). The techniques used to assess efficacy outcomes also varied across the studies.

Despite these limitations, to our knowledge, this is the first systematic review of studies on Profhilo® and Profhilo® Body. Future research should focus on the effectiveness of these products in participants of different ethnicities and genders and should include a large sample size, comparator arm, randomized design, homogeneity of techniques or instruments used for efficacy assessment, the use of validated questionnaires to evaluate patient satisfaction, and longer follow-up timepoints.

CONCLUSIONS

Overall, this systematic review has highlighted that treatment with Profhilo® and Profhilo® Body can improve skin laxity, hydration, elasticity, and density while reducing wrinkles and facial volume loss. Adverse events occurring after treatment are mild and resolve quickly.

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