

Development of a satisfaction survey to investigate pre- and post- treatment of the neck using hybrid cooperative complexes of hyaluronans in a cohort of Japanese patients

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Abstract. *Objective:* demand for aesthetic treatments to improve the appearance of the neck are increasing worldwide. This real-world data (RWD) collection assesses the effectiveness of a hyaluronic acid based dermal filler Profhilo[®], created using NAHYCO[®] Hybrid Technology, on neck skin laxity, firmness, tone, and texture in a group of Japanese women. *Methods:* patients received two treatments, one at baseline and the second at Day 30. Photographs of the neck were clinically evaluated at baseline, Day 30, and Day 90, using the IBSA neck skin laxity scale. Before treatment at Day 30, and at the follow-up visit at Day 90, doctors and patients answered three survey questions to assess clinical improvements and patient satisfaction related to skin laxity, firmness, and texture. Patients were also asked to record their pain level using the visual analogue scale after each treatment. *Results:* fourteen female patients, with a median age of 58 years (range: 53–75 years) and a baseline mean skin laxity score of 3, demonstrated significant improvements in mean skin laxity across evaluation timepoints ($P < 0.0001$). All patients, except one, had results that were improved or much improved following the clinical survey. Many patient's answers were the same or better than the clinical evaluation and reported low pain levels following injections. *Conclusion:* Profhilo[®] was an effective treatment for improving neck skin laxity, firmness, tone, and texture in a real-world patient satisfaction survey of Japanese patients of varying ages and baseline skin laxity and wrinkle severity.

Key words: hybrid cooperative complexes, hyaluronic acid, real-world data, patient-reported outcomes, aesthetic treatment

Introduction

Neck imperfections and wrinkles are a popular target of aesthetic rejuvenation treatments. Some of the most common reported aesthetic concerns are horizontal neck wrinkles, sagging skin, blunting of the cervicomental angle caused by increased skin laxity, and platysmal bands¹. The demand for aesthetic treatments to improve the appearance of the neck, and other areas such as the face and upper arms, is increasing worldwide².

Age-related changes to the neck are a combination of biological and genetic factors, along with environmental factors such as ultraviolet (UV) light exposure, diets, psychological stress, pollution, and skincare³⁻⁵. These genetic and environmental factors differ across ethnic groups and countries worldwide, and can impact the onset of age-related changes, baseline wrinkle severity, and the efficacy of aesthetic treatments^{4,6-8}. Differences in facial structures and dermal thickness between ethnicities can also cause variations in the onset and determine the severity of wrinkles, skin

firmness, and skin laxity⁸. Asian skin has a thicker dermis and larger melanosomes than Caucasian skin, leading to less or delayed folds and wrinkles, and more protection from UV radiation^{8,9}. Understanding these differences and their underlying mechanisms can improve treatment approaches across different populations and ethnicities^{8,10-12}.

Beside genetic differences, the increasing daily use of new technologies, such as cell phones, tablets or laptops, is also contributing to a premature aging of the neck area, especially for younger generations. This phenomenon, called Tech Neck, causes pain and premature aging, involving increasing skin laxity, wrinkling and sagging along the neck¹³. A recent study demonstrated that topical anti-aging treatments can be effective to counteract the Tech Neck mechanism in a cohort of Chinese women¹³. However, different strategies to tackle this increasing phenomenon are needed.

Hyaluronic acid (HA)-based dermal fillers are one of the most popular non-invasive facial and neck restoration approaches, with good efficacy and safety profiles across ethnicities in clinical trials and observational case studies on the neck^{6,11,12,14-17}. HA hydrogels can be formulated at different concentrations, molecular weights, and degrees of cross-linking, and these differences have a direct effect on their application and efficacy across different indications^{18,19}.

NAHYCO[®] Hybrid Technology is an innovative thermal process used in the synthesis of the HA based

product Profhilo[®] (IBSA Farmaceutici Italia S.r.l.) in absence of chemical reagents, which is a stable mix of low and high molecular weight HAs called hybrid cooperative complexes (HCCs). HCCs exhibit a lower G prime (G') and a higher Tan Delta that remains unaffected over time^{19,20}. This allows Profhilo[®] to spread easily within the dermal tissues while still maintaining its cohesive properties¹⁹. The high spreadability of HCCs were effectively demonstrated using a 3D camera system (Quantificare 3D, LifeViz Mini system) 15 minutes after the injection of Profhilo[®] in the neck. As depicted in Figure 1, Profhilo[®] can cover the entire neck area using the BioAesthetic Point (BAP) technique, which requires only 10 intradermal injections.

HCCs can facilitate extracellular matrix homeostasis thanks to a bioremodeling mechanism, improving the viability and metabolism of different cell types involved in the maintenance of youthful skin such as keratinocytes, fibroblasts, and adipocytes^{19,21}. Hence Profhilo[®] may also have several applications based on the regenerative aesthetic concepts, such as the amelioration of dermatological conditions and improving the appearance of acne scars^{19,22}. On the other hand, other molecules like poly-lactic acid (PLLA) or calcium hydroxylapatite (CaHa) currently used in aesthetic medicine to achieve skin rejuvenation, cannot actually fulfil the needs of regenerative approaches as they act through a biostimulation mechanism, a process that leads to tissue augmentation through fibroblast activation and neocollagenesis induction through

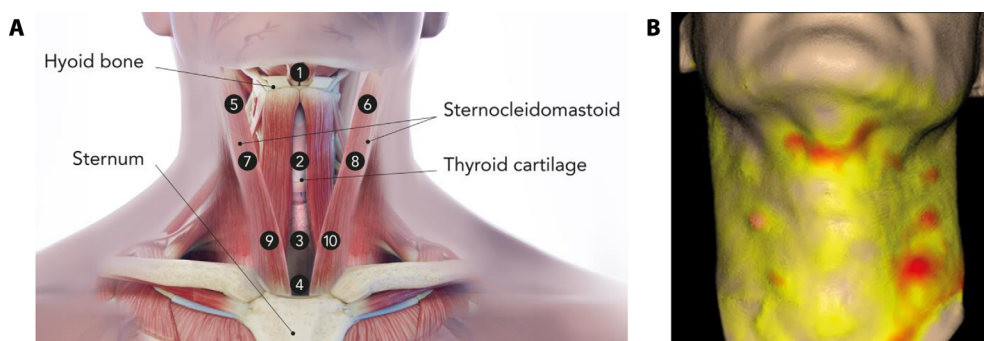


Figure 1. Profhilo[®] neck injection technique. A) Profhilo[®] BAP injection technique; B) Profhilo[®] product spreadability 15 minutes after injection was assessed using a 3D camera system (Quantificare). Yellow and red areas represent product diffusion (red areas indicate product maximum distribution).

a subclinical inflammatory response²¹. Molecules like polydeoxyribonucleotides (PDRNs) and exosomes are also widely used in rejuvenating approaches; however, they show several limitations due to the lack of standardization, as well as few or none clinical studies demonstrating their efficacy and safety²¹.

Controlled clinical trials often may not reflect true outcomes in the wider population, therefore continued data collection is necessary to assess the impact of a product or medicine in the real-world²³. Real-world data (RWD) can be defined as data collected routinely that does not form part of a randomised-controlled trial, and is used to generate real-world evidence (RWE)²³. The US Food and Drug administration describes RWE as “the clinical evidence on the usage and potential benefits or risks of a medical product derived from the analysis of RWD”²⁴. Types of RWD can include: registries, observational case or cohort studies, and patient surveys²³. The insights generated from RWE can improve decision-making, treatment outcomes, and patient safety, especially across populations not originally included in clinical trials²³. In terms of aesthetic treatments, RWD can provide information across a more diverse set of facial and skin characteristics across populations.

This survey uses RWD to evaluate treatment efficacy, clinical and patient satisfaction following the treatment with Prophilos[®] on the neck in Japanese patients.

Methods

RWD collection

This real-world patient satisfaction survey collected data from four doctors across four sites in Japan. Each patient received 2 mL of Prophilos[®] into the neck using a 29 G needle at ten BAP points (Figure 1A). At each site, 0.2 mL of Prophilos[®] was injected using a bolus technique into the dermis, at which a light massage was applied. Prophilos[®] then was able to progressively spread through the interstitial spaces of the entire neck area (Figure 1B). This technique also ensures that the injection point does not touch vital structures within the neck.

The patients received two treatments: one at baseline, and the second at Day 30. The final follow-up visit was performed at Day 90.

Patients

This real-world survey included patients based on the daily clinical routine of healthcare practitioners willing to perform the surveys.

Treated patients also agreed to avoid direct exposure to ultraviolet light without appropriate protection for the entire duration of the evaluation and to not change their daily care routine. Body mass index (BMI) has also been evaluated and patients with noticeable differences ($BMI \pm 2$) were excluded from the survey. Exclusion criteria included pregnancy, breastfeeding, having autoimmune or inflammatory diseases, chronic or skin-related pathologies, drug administration, and heavy smokers. Treated patients were also required to not have performed any other treatment or surgical procedure in the target treatment area within six months prior the survey.

All patients were required to sign an informed consent agreement and data protection form.

Photographic documentation

Before each treatment with Prophilos[®], a photograph of the patient was taken for clinical assessment. Patients were asked to remove all make-up and jewellery, and photographs were taken at 50cm from the patient's neck. Close up images of the neck were then created in post-production. Pictures were then uploaded in the surveys collection form by healthcare professionals.

Efficacy Evaluation

Clinical evaluation

The skin on the neck was rated using the IBSA neck skin laxity scale by healthcare professionals, with 1 describing no laxity and 5 very severe laxity²⁵. The mean score and standard deviation at each timepoint were calculated. Statistical significance was determined

using one-way ANOVA, corrected for multiple comparisons using Tukey's multiple comparison test, with GraphPad Prism v10.2.1.

Survey evaluation

After the treatment at Day 30 and at the follow-up visit at Day 90, healthcare professionals and patients were required to answer three survey questions to assess and record clinical improvements and patient satisfaction (Table 1).

After each injection, the patients were also asked to record their pain level using the visual analogue scale (VAS), with 1 being the least and 10 being the most pain.

Results

Baseline demographics

This real-world patient satisfaction survey included 14 female patients, with a median age of 58 years (range: 53–75 years; Table 2). The 75-year-old patient would have been excluded in a clinical trial setting due to her age and skin laxity score of 5. Notably, the age range of patients usually enrolled for clinical studies with Prohilo® are 35–65 years-old and show skin laxity scores between 2 and 4^{6,11-12}. The mean neck skin laxity score at baseline was 3.00 (Figure 2).

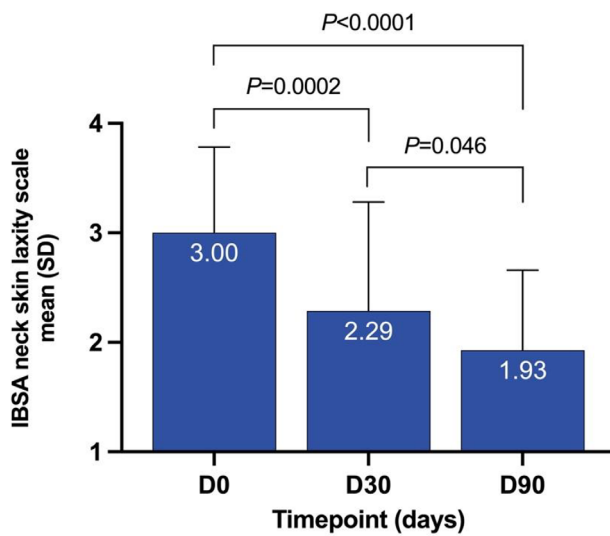
Table 1. Healthcare professional and patient survey questions at Day 30 and Day 90.

Questions		Possible answers
1	How much improvement was there in reducing skin laxity?	Worse
2	How much improvement was there in augmenting skin firmness and tone?	No change
3	How much improvement was there in the skin texture?	Improved
		Much improved
		Very much improved

Table 2. IBSA neck skin laxity scale at Baseline, Day 30, and Day 90, and the level of improvement recorded by the doctor's survey for: reducing skin laxity, augmenting skin firmness and tone, and skin texture at Day 30 and Day 90.

Patient data		IBSA neck skin laxity scale grade			Reducing skin laxity		Skin firmness		Skin texture	
Patient	Age	Baseline	Day 30	Day 90	Day 30	Day 90	Day 30	Day 90	Day 30	Day 90
J0101	61	3	2	2	MI	MI	MI	MI	I	I
J0102	62	3	2	2	I	MI	I	I	I	I
J0103	61	3	2	1	MI	MI	MI	MI	I	I
J0104	55	2	1	1	I	I	I	I	I	I
J0105	54	2	1	1	I	I	I	I	I	I
J0201	62	4	3	2	I	MI	NC	I	I	I
J0202	54	3	2	2	MI	MI	I	I	I	MI
J0301	53	2	2	2	NC	I	NC	NC	NC	I
J0302*	75	5	5	4	I	I	NC	I	I	I
J0303	65	3	3	2	I	I	NC	I	I	I
J0304	58	3	2	2	I	I	I	I	I	I
J0305	58	3	2	2	I	I	I	I	I	I
J0401	66	3	3	2	NC	I	NC	I	NC	I
J0402	56	3	2	2	I	I	I	I	I	I

*Patient would not be eligible for a clinical trial due to their age and baseline skin laxity score.
I, improved; MI, much improved; NC, no change.



D, day; SD, standard deviation.

Figure 2. Mean (SD) IBSA neck skin laxity scale score at Baseline, Day 30, and Day 90. Adjusted P-values for multiple comparisons.

Clinical evaluation

The mean skin laxity score decreased across evaluation timepoints to 2.29 at Day 30 and 1.93 at Day 90 ($P<0.0001$; Figure 2). These changes were statistically significant when comparing the mean at each timepoint were between baseline and Day 90 ($P<0.0001$), and baseline and Day 30 ($P=0.0002$; Figure 2). Patient data, IBSA neck skin laxity scores, and the doctor's answers to survey questions are presented in Table 2. All patients had either improved or much improved by Day 90 for the skin laxity, firmness and/or tone and texture except for one patient (7.1%) that did not demonstrate any change in skin firmness by Day 90 (question 2).

Nine patients (64.3%) had results that were either improved or much improved for skin laxity, firmness and tone, including the 75-year-old patient that would have been excluded in a clinical trial setting.

A selection of patient photographs is presented in Figure 3. All four patients showed improvements in the IBSA neck skin laxity scale and a reduction in neck horizontal lines. Moreover, they also showed an amelioration of skin laxity and improvement of skin firmness, tone, and texture.

Patient evaluation

The patients' VAS for pain and patient satisfaction survey answers are presented in Table 3. All VAS scores were ≤ 4 , meaning that the treatment was well tolerated. All patients reported that they had improved or greatly improved by Day 90 across each criterion, except for two patients (14.3%) that did not demonstrate any change in skin firmness by Day 90 (question 2). Most patients had a satisfaction rating that was the same or better than the doctor's evaluation, with three patients (21.4%), eight patients (57.1%), and six patients (42.9%) scoring higher than the clinical evaluation for questions 1, 2, and 3, respectively.

All the 14 patients enrolled are willing to repeat or recommend the treatment.

Discussion

This is the first real-world patient satisfaction survey evaluating the use of Profhilo[®], a HA-based product formulated with thermally stabilized HCCs, for improving the laxity and appearance of the neck in Japanese patients. The mean IBSA neck skin laxity score significantly decreased across clinical evaluation timepoints, and most patients demonstrated a clinical improvement for skin laxity, skin firmness, tone, and texture. The IBSA neck skin laxity scale is a validated and effective tool to assess the skin laxity of the neck region²⁵. The scale was developed from the creation of 5 morphed images that represented different degrees of neck skin laxity, and was tested against 50 images with six trained clinicians²⁵.

These RWD are similar to previously published results for the treatment of the neck in both Caucasian and Asian populations^{6,11,12}. A pilot study in 28 Chinese women who received Profhilo[®] twice, four weeks apart, and were assessed eight weeks after the first injection, demonstrated an amelioration in the neck, and a good tolerability to the injections¹². Treatment was also beneficial in the Caucasian (Italian) population, but Chinese patients responded to Profhilo[®] more rapidly and effectively¹¹. Biological variation in dermal thickness, skin hydration, melanin, and collagen levels may be indicative of different skin aging outcomes between the

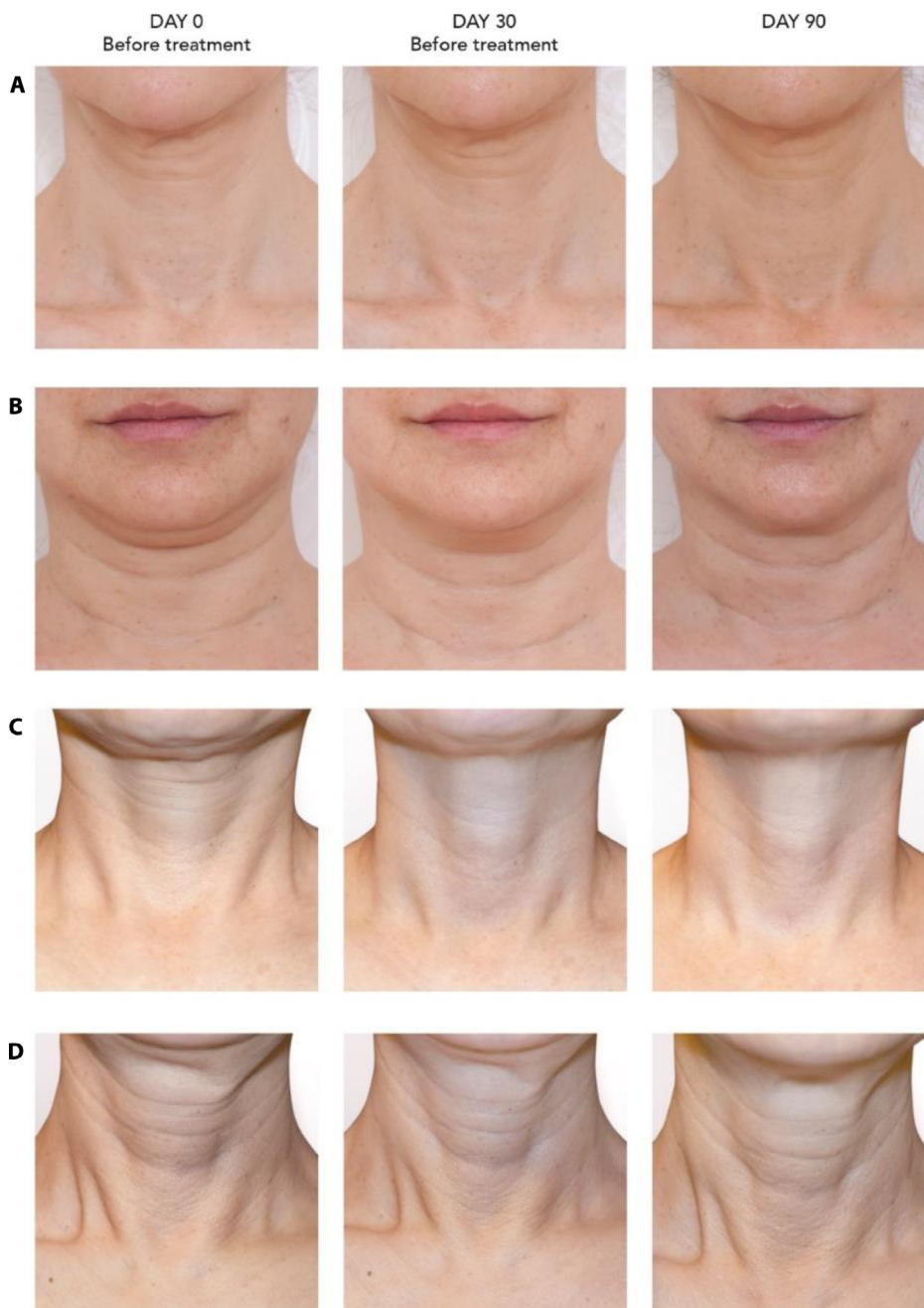


Figure 3. Representative images of four patients at Baseline, Day 30, and Day 90. Patients A) 61 years-old; B) 62 years-old; C) 65 years-old; D) 58 years-old underwent 2 Profhilo® treatment, 30 days apart, and achieved a 1-grade improvement in the IBSA neck skin laxity score.

two groups^{4,8,11}. Asian skin is often thicker, more hydrated, with higher levels of collagen and melanin that can be protective against photoaging⁸. A study comparing age-matched and sun-exposed Asian women

to Caucasian-French women found that wrinkle onset was delayed by 10 years in Asian women²⁶.

Beside the known biological factors, several environmental and cultural factors such as a negative view

Table 3. Patient reported data. VAS for pain after each procedure at Baseline and Day 30, and the level of improvement for: reducing skin laxity, augmenting skin firmness and tone, and skin texture at Day 30 and Day 90.

Patient data		VAS at each procedure		Reducing skin laxity		Skin firmness		Skin texture		Recommended treatment?
Patient	Age	First	Second	Day 30	Day 90	Day 30	Day 90	Day 30	Day 90	
J0101	61	1	3	MI	MI	MI	MI	MI	MI	Yes
J0102	62	2	2	I	I	I	MI	I	MI	Yes
J0103	61	2	2	MI	MI	MI	MI	MI	MI	Yes
J0104	55	1	1	MI	MI	MI	MI	MI	I	Yes
J0105	54	2	2	MI	MI	I	MI	I	I	Yes
J0201	62	4	2	I	MI	I	MI	I	MI	Yes
J0202	54	2	2	I	MI	NC	MI	NC	MI	Yes
J0301	53	3	2	NC	I	NC	NC	NC	I	Yes
J0302*	75	1	3	I	I	I	I	I	I	Yes
J0303	65	2	4	I	I	I	I	I	I	Yes
J0304	58	3	3	NC	I	NC	NC	NC	I	Yes
J0305	58	3	2	I	I	I	I	I	I	Yes
J0401	66	4	3	I	I	I	I	NC	MI	Yes
J0402	56	3	4	I	NC	I	I	I	I	Yes

*Patient would not be eligible for a clinical trial due to their age and baseline skin laxity score.

I, improved; MI, much improved; NC, no change; VAS, visual analogue scale.

of tanning, a diet richer in certain antioxidants and essential fatty acids that are beneficial for the skin, and lower rates of smoking, may be contributing to the delayed onset of skin ageing in Asian populations^{8,27-30}. Collecting RWD from different populations and ethnicities is therefore vital in increasing our understanding of population-based skin changes, and the effects that the treatment with HCCs may have across different ethnicities and with different baseline skin laxity and wrinkle severities.

The patient survey results demonstrated a higher level of satisfaction for treatment outcomes compared to the clinical data, and low pain levels following treatment with Profhilo[®] using the BAP neck injection technique. This is consistent with world post-marketing data reporting good tolerability following the use of Profhilo[®] and a previous clinical study demonstrating concordant results between instrumental, clinical, and patient evaluation for the improvement of horizontal neck wrinkles in 25 female patients^{6,31}. Skin ageing and the success of aesthetic treatments have a

strong psychosocial impact and are closely related to the patient's quality of life, further highlighting the importance of collecting patient data alongside clinical assessments to assess outcomes and tolerability³². In this context, it is also crucial to select and identify the correct patients to be treated, avoiding to select both patients with low skin laxity (score = 1) and very high skin laxity (score = 5). Indeed, the first category of patients will not require any treatment, while the second one will more likely benefit of different treatments, such as a surgical procedure. Older patients may also benefit from combined approaches with different products and treatments aimed to increase the efficacy on skin laxity and quality. One example is provided by a clinical experience published in 2021³³. The technique used in this clinical experience, named Amarna technique[®] by the authors, required a first phase with Profhilo[®], followed by a second treatment phase with a low-degree cross-linked gels, Viscoderm[®] Hydrobooster. This approach effectively combines the bioremodeling action of Profhilo[®] together with the hydration and stretching

activity achieved by the Viscoderm® Hydrobooster in the dynamic areas of the neck.

This patient satisfaction survey adds to growing RWE for the effective and well-tolerated use of Profhilo® for treating the neck across different ages, ethnicities, and populations. The limitations of this survey are the lack of male patients, and the small sample size. Further RWD collection is required in Japan to increase patient numbers, along with the investigation of other clinical outcomes, such as the severity of horizontal neck lines. A validated and standardised scale to assess horizontal neck lines, called the IBSA neck line scale, is now also available for future studies³⁴. This tool should be used alongside the IBSA neck skin laxity scale in future studies to better assess neck wrinkle severity together with skin laxity. A standardised questionnaire to assess clinical improvement and patient satisfaction would also improve clinical and patient reporting across studies. Indeed, the patient's quality of life and satisfaction are also major aspects to take into consideration in the development of new effective and respectful treatments³⁵.

In conclusion, Profhilo® was an effective and well-tolerated treatment for improving neck skin laxity, firmness, tone, and texture in a real-world analysis of Japanese patients consisting of varying ages and baseline skin laxity and wrinkle severity.

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