

PN HPT™ and Striae Albae-Exploratory Interim Analysis of a Randomised Prospective Study

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ABSTRACT

Introduction: The outcomes of striae albae remodelling are currently disappointing. Replenishing the fibroblast pool of nucleotide precursors through passive exposure to Polynucleotides Highly Purified Technology (PN HPT™) facilitates the dermal production of new fibres. The manuscript reports on the outcomes of a prospective study with an intradermal PN HPT™-based medical device.

Methods: Intra-subject-controlled randomised real-world study to evaluate the efficacy and safety of a medical device containing 20 mg/mL of PN HPT™ (functional ingredient) intradermal gel as therapy for moderate-to-severe striae albae. Based on a preliminary sample size assessment, the study estimated the need to enrol at least 65 mature albae from 18-to-55-year-old male and female subjects seeking ambulatory treatment (mean age: 34.1 ± 10.65). Up to eight symmetrical striae albae in the target areas (breast, abdomen, buttocks, thighs) per enrolled subject underwent randomisation into the two parallel "PN HPT™ intradermal infiltration" active group and "no-treatment striae albae" intra-subject control group. Actively treated striae albae underwent a four-session intradermal therapy cycle with the PN HPT™ device. Comparative efficacy assessments, performed at the two final evaluation visits by independent evaluators:

Width of actively treated and untreated control striae albae (digital calliper). Global Aesthetic Improvement Scale (GAIS) outcomes (by investigators and subjects, respectively; assessments on digital photographic documentation). Width and wrinkling of actively treated and control striae albae (quantitative Antera 3D CS skin imaging technology).

Results: The digital-calliper-assessed width for the exploratory sample of the 44 actively treated striae albae (29 control striae) decreased, on average, from 4.6 ± 2.31 at the V1 baseline visit to 2.7 ± 1.42 at V5 (first follow-up visit) one month after the last PN HPT™ intradermal infiltration at V4 (-40.8% vs. baseline, $p < 0.01$). In a subset of 17 striae (7 subjects), the mean digital-calliper-assessed width was still a significant 2.0 ± 0.94 at the final V6 follow-up visit, six months after V1 and three months after V4 (-54.5% vs control striae albae at V6, $p < 0.05$). At the V5 assessment, three months after V1 and one month and a half after V4, investigators and treated subjects reported average GAIS scores of 3.8 ± 0.51 (median, 4.0) and 4.0 ± 0.66 (median, 4.0) out of 5.0 as GAIS maximum score for both. The occasional mild local pain and irritation at the injection site, expected and known in the previous PN HPT™ literature, were of no clinical significance and rapidly transitory.

Discussion: PN HPT™ are an innovative option with a solid rationale for treating mature striae albae. The efficacy outcomes of PN HPT™ dermal infiltrations appear noteworthy, with excellent safety and ease of use, confirming the previous results. However, waiting for complete results and confirmation by other controlled studies is prudent.

Keywords

Antera 3D CS, GAIS, PN HPT™, Polynucleotides Highly Purified Technology, Stretch marks, Striae albae, Striae distensae.

Introduction

Striae distensae are frequent on the abdomen, thighs, buttocks, and breasts in girls, while the upper arms, the lumbosacral region, and the outer thighs are the elective regions in males. Often called stretch marks in the vernacular and appearing as indented streaks from dermal scarring when mature, striae distensae are common causes of morbidity, psychological distress, and loss of self-esteem and self-confidence [1]. In a recent prospective observational study, striae distensae have sometimes caused burning and itching; much more frequently, they severely impact the psychosocial quality of life and everyday interpersonal relations, especially in subjects like adolescents who often experience high anxiety due to peer judgments [2]. In primigravidae and pregnancies associated with much weight gain, the emotional and psychosocial distress of striae gravidarum is often severe, compounding the emotional stress of pregnancy up to requiring psychological support and adjustment strategies [3].

Early-phase inflammatory striae distensae appear pink to violaceous, often slightly raised and itchy (“striae rubrae”) with markedly inflammatory microscopic features. These early lesions then chronically morph into the lightly or not pigmented finely wrinkled dermal depressions known as striae albae [1,4,5]. At the microscope, the markers of those final atrophic stages of stretch mark scarring are epidermal and dermal atrophy, blunting of rete ridges with sparse dermal vessels, and densely packed, thin and horizontal collagen bundles like mature atrophic scars and oriented according to mechanical forces [1,5,6]. Unsurprisingly, the several attempts at treating the modestly inflammatory, scar-like striae albae have usually led to disappointing outcomes, and the medical need for innovative treatment strategies is pressing.

The manuscript reports the outcomes of a real-world study investigating the efficacy and safety of a Class-III CE-mark medical device for the intradermal treatment of mature striae albae. The analysed data regard 73 well-individualised moderate-to-severe striae albae from twenty-four 18-to-55-year-old ambulatory subjects of either gender. The real-world conditions without rigid inclusion and exclusion criteria and the highly selected patient samples are the clues that support the investigation’s value.

The study rationale was to verify the short-term safety and soundness of Polynucleotides Highly Purified Technology (PN HPT™) as an effective therapeutic strategy for mature striae albae. PN HPT™ are a mixture of DNA polynucleotides of different lengths extracted from male salmon trout gonads thanks to advanced purification and high-temperature sterilisation procedures that ensure high

safety [7-9]. The investigated PN HPT™-based medical device is available in Italy and other countries with the Plinest brand.

Materials and Methods

Experimental design

Multicenter, prospective, intra-subject-controlled study with short-term and medium-term efficacy evaluations in 18-to-55-year-old ambulatory male and female subjects of Caucasian ethnicity and I-IV Fitzpatrick skin phototypes seeking therapy for moderate-to-severe mature striae albae. The limited exclusion criteria aimed to mirror the everyday clinical practice of aesthetic medicine specialists and dermatologists who choose to use the intradermal PN HPT™ option. Exclusion criteria included pregnant or lactating women, heavy smokers (more than 15 cigarettes per day), drug or alcohol abusers, and subjects with severe concomitant diseases or exposed to radiotherapy or energy-based treatments (laser, radiotherapy) in target areas or who had received systemic retinoid or corticosteroid therapies or revitalising treatments, including platelet-rich plasma, during the previous six months.

After full disclosure of foreseeable benefits and risks of the proposed procedure with written acceptance by signed informed consent and advice to avoid exposure to natural or artificial ultraviolet-ray sources, all subjects underwent a four-session intradermal treatment cycle with a Class-III CE-mark medical device containing 20 mg/mL of PN HPT™ as a functional ingredient (brand name: PLINEST, Mastelli S.r.l., Sanremo, Italy). PN HPT™ are formulated as a fluid gel in 2-mL prefilled disposable syringes with 30G/13 mm needles. The target areas for the actively treated and control striae albae, symmetrical in each subject as far as possible (see below), were the breast, abdomen, buttocks, and thighs, with the treatment of no more than four striae albae areas per subject (four other symmetrical striae albae kept as untreated controls).

Linear dimensions of target striae albae, quantitatively and reproducibly assessed with a digital calliper to minimise assessment bias amongst investigators: at least 3 cm long and no more than 1 cm wide at the widest point with a minimum width of 3 mm. Other information collected about target striae albae is the subject’s age at detection, previous treatments (if any), and aetiology (if known). The symmetrical, untreated striae albae acting as intra-subject controls were selected in the same target areas, although at a distance of at least 5 cm and with similar characteristics to the actively treated striae albae. At baseline, the selected mature stretch marks were randomised with the WinPepi software into the two groups — 44 striae albae undergoing PN HPT™ treatment and 29 untreated intra-subject controls — and numbered (Figure 1) to allow easy identification by independent evaluators during treatment and follow-up (Figures 2 and 3). Independent evaluators also established the baseline quantitative and score parameters.



Figure 1: Preliminary procedures before the randomisation: identification of candidate striae albae — no less than 3 cm long and no more than 1 cm wide at the widest point — and numbering. Thanks to the courtesy of Dr. Carmen De Luca, published with the author’s and patient’s permission.



Figure 2: Digital-caliper assessment of selected striae albae randomised to PN HPT™ treatment: PRIMA=before (baseline, V1); DOPO= after (first follow-up visit, V5). Thanks to the courtesy of Dr. Laura Maioli, published with the author’s and patient’s permission.

The office-based study respected the Helsinki Declaration and Good Clinical Practice principles with the study protocol and study materials preliminarily peer-reviewed for ethical problems.

Planned Treatment Plan and Injection Procedures

Structured on a four-session cycle of Plinest injections in the dermis of target striae albae at intervals of 14 to 21 days:

V1 session [immediately after baseline evaluation]

V2 session [14 ± 7 days after baseline]

V3 session [14 ± 7 more days after V2]

V4 session [14 ± 7 more days after V3]

Intradermal infiltrations were performed by either the micro-wheal

or linear technique (possibly both) according to the investigator’s evaluation, with a total dose administered in a single session of no more than two 2-mL prefilled syringes per subject.

Figure 3: Digital-caliper assessment of selected striae albae left untreated



as intra-subject controls: PRIMA=before (baseline, V1); DOPO= after (first follow-up visit, V5). Thanks to the courtesy of Dr. Laura Maioli, published with the author’s and patient’s permission.

Planned Assessment Procedures and Techniques (Independent Evaluator)

V1 session [baseline evaluation immediately before the first injection]:

- Demographics and clinical presentation of target striae albae; adopted infiltration technique (micro-wheals or linear).
- Quantitative digital-caliper assessment of the mean width of selected striae albae (actively treated and untreated controls), followed by tabulation as nominal parameters — “None”, “Mild” (width 1-3 mm), “Moderately severe” (width more than 3 mm, less than 6 mm), “Severe” (width 6 mm or more).
- Photographic documentation of selected striae (digital camera, actively treated and untreated controls) and qualitative evaluation of clinical evolution by investigators and treated subjects with the Global Aesthetic Improvement Scale (GAIS)—“Exceptional improvement” (>75% vs baseline), “Very improved” (51-75% vs baseline), “Improved” (26-50% vs baseline), “Unaltered or minimally improved” (0-25% vs baseline), “Worsened”.
- Width and wrinkling of selected striae albae, quantitative assessment (Antera 3D CS skin imaging technology, actively treated and untreated controls).
- V5 session [three months after the baseline session (V1) and one month and a half after the last treatment session (V4) ± seven days]:
- Quantitative digital-calliper assessment of the mean width of actively treated striae albae and untreated controls; tabulation as nominal parameters (see V1 session for details).
- Photographic documentation of actively treated striae and untreated controls; GAIS assessment of clinical evolution (investigator and treated subjects—see V1 session for details).

- Antera 3D CS quantitative width and wrinkling assessment of selected striae albae.
- Side effects, if any (see “Safety assessment” paragraph for details).
- V6 session [six months after the baseline session (V1) and three months after the last treatment session (V4) ± seven days; assessment in a cohort subset of 17 subjects out of 44 (38.6%)];
- Quantitative digital-caliper assessment of the mean width of actively treated striae albae and untreated controls; tabulation as nominal parameters (see V1 session for details).
- Photographic documentation of actively treated striae and untreated controls; GAIS assessment of clinical evolution (investigator and treated subjects—see V1 session for details).
- Antera 3D CS quantitative width and wrinkling assessment of selected striae albae.
- Side effects, if any (see “Safety assessment” paragraph for details).

The camera-equipped Antera 3D CS optical imaging device (Miravex Limited, Dublin, Ireland), already validated for the qualitative and quantitative analysis of skin texture and wrinkles, allows the tri-dimensional measurements and basal vs end-of-treatment quantitative and graphical comparisons of skin roughness, pores, wrinkles, and stretch marks [10,11].

Safety assessments

Structured safety interviews by the investigators, planned at V5 and V6 sessions, to investigate in depth the clinical presentation and severity of any known side effect (oedema, erythema, injection-site pain, bruising, dyschromia, local heat sensation, injection-site induration, other side effects) or unknown adverse events or emergent risk. Moreover, the investigators questioned the subjects about safety problems at each treatment session.

Spontaneous reporting by phone or email: strongly recommended throughout the study.

Pre-study sample size estimation

A statistically adequate sample size was estimated at a minimum of 65 striae albae using the G*Power statistical program version 3.14 based on the worst-case hypothesis and the assumption of a 90% power of avoiding false-negative type II errors ($\beta=0.10$) [12]. The parameters entered in the sample size estimation were the baseline mean width of fifteen candidate striae albae (digital-caliper assessed according to protocol) and a conservative 65% improvement at follow-up. Under these assumptions, the power to detect a significant difference (digital calliper-assessed width) in an estimated treatment cohort of at least 65 striae albae would have been greater than 0.87. For further caution, the investigators enrolled and randomised even more striae albae than the preliminary statistically adequate estimate.

Statistical analysis

Software: Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA), version 13.0 [13]. Tabulation of descriptive data will be as means ± standard errors of the mean (SEM). Although variances appear homogeneous as confirmed

by Levene’s test on the two baseline groups of actively treated and control striae albae), the relatively low estimated number of mature stretch marks to enrol suggested a prudent non-parametric approach even for continuous parameters like the digital-calliper-assessed width of actively treated and control mature stretch marks. The non-parametric statistical tool used was the Mann-Whitney test for two categorical independent groups [13]. For the semi-quantitative ordinal outcomes (GAIS scores), nominal parameters (“None”, “Mild”, “Moderately severe”, and “Severe”) were tabulated as frequency contingency tables and compared with the chi-square and Fisher’s exact test. All significance thresholds (two-sided tests) will be set at p-values less than 0.05.

Results

The mean age of the cohort 24 subjects (twenty women and four men) was 34.1 ± 10.65 years old (median 33.5 years old, range, 20-51). The body framework was standard for Caucasian subjects (mean weight 68.1 ± 12.32 kg, mean height 166.9 ± 9.09 cm), with fourteen Fitzpatrick phototype-2 subjects, nine with Fitzpatrick phototype-3, and one Fitzpatrick phototype-4. Table 1 illustrates when the fourteen cohort subjects first detected their mature striae albae; Table 2 shows the reasonably balanced topographical distribution of the 44 intradermally treated striae albae and 29 untreated controls. At the first short-term V5 follow-up visit three months after the V1 baseline session, the mean digital-calliper-assessed width for the whole treated striae albae group decreased significantly by 40.8% compared with baseline (Figure 4), with individual per cent improvements in the striae albae selection ranging between 3.6% for the least responsive up to 80.3% for the most responsive mature stretch mark. By comparison, the mean width change for the control striae albae (−1.4%) was of no clinical significance. At the V5 assessment, investigators and actively treated subjects reported average GAIS scores of 3.8 ± 0.51 (median, 4.0) and 4.0 ± 0.66 (median, 4.0) out of a GAIS maximum score for both of 5.0. The occasional, mild, known side effects at the injection site — local pain, oedema, ecchymosis, and erythema — were of no clinical significance and resolved rapidly.

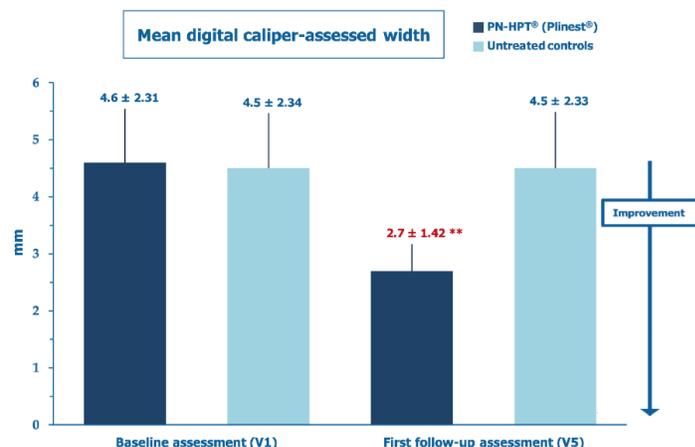


Figure 4: Changes in the mean striae albae width three months after the V1 baseline visit and one month and a half after the last V4 treatment session (means ± standard errors of the mean). ** p < 0.01 vs. baseline.

Table 1: Age at which the 24 cohort subjects first detected their mature striae distensae.

Age of striae albae detection	Number of subjects
Adolescence (12-16 years old)	10
Young adulthood (≥ 17 years old)	6
Pregnancy	1
Infancy	1
Unknown	6

Table 2: Distribution of the 44 treated mature striae albae and 29 untreated control striae.

Striae albae area	PN HPT™ treated subjects	Untreated subjects
Abdomen	16	9
Buttocks	13	9
Thighs	10	6
Breasts	3	1
Other/unknown sites	2	4

Figure 5 illustrates the mean digital-calliper-assessed widths of treated and control striae albae in a subset of 17 subjects at the second follow-up visit, six months after baseline, still showing a significant 54.5% decrease vs baseline with no significant difference vs V5.

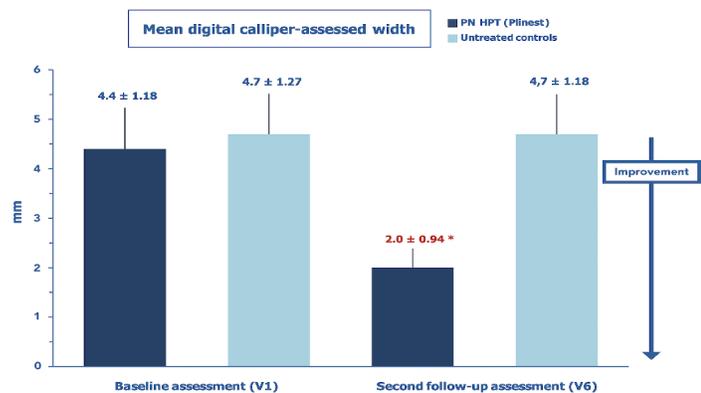


Figure 5: Changes in the mean striae albae width in a cohort subset of 17 subjects six months after the V1 baseline visit and three months after the last V5 treatment session (means \pm standard errors of the mean).

* $p < 0.05$ vs. baseline.

Discussion

Endocrine influences like hypercortisolism or local or systemic corticosteroid therapy, family history, and genetic disorders such as the Marfan syndrome are known risk factors, but mechanical stretching, e.g., by muscle hypertrophy in bodybuilders, is the leading pathophysiologic mechanism. The striae tend to parallel the relaxed tension lines, suggesting that the skin's failure to elongate under low-intensity forces is the ultimate determinant. Dermal brittleness and loss of fibrillin, fibronectin, collagen, and elastic disruption in the extracellular matrix are the final-stage outcomes [1,4,6]. Over the years, the emphasis on subjective well-being has led to increasingly looking for effective treatments for striae albae [4,5]. The nature of stretch marks, perceived as an actual disease by subjects like adolescents because of their frequently severe psychosocial impact, further reinforces the case for effective therapies.

No one can deny therapeutic advances, yet no strategy fulfilling expectations has emerged. Research in PubMed/Medline, Scopus, and Google Scholar reveals a wealth of conflicting-outcome studies with topical treatments like tretinoin and energy-based devices radiofrequency, intense pulsed-light or infrared phototherapy and CO₂, Er:YAG (Erbium-doped Yttrium Aluminum Garnet), diode, Q-switched Nd:YAG (pulsed Neodymium-doped Yttrium Aluminum Garnet), pulse dye and excimer lasers [1,4,5]. Also inconclusive are the studies with platelet-rich plasma, chemical peels with glycolic and trichloroacetic acids or L-ascorbic acid, aluminium oxide microdermabrasion, micro-needling, carboxytherapy, and galvanopuncture [1,4,5]. Moreover, many studies with topical tretinoin and laser devices targeting the oxyhaemoglobin chromophore confirm that outcomes with early inflammatory striae rubrae are, on average, more gratifying than those observed with atrophic striae albae. Benefits on mature striae albae are also poor over time with the ablative fractional 10,600-nm CO₂ laser, long considered the gold standard for treating striae albae. The rule also proved true for recent devices like the 1,064-nm Nd: YAG laser [14].

Most of those treatment strategies aim to stimulate the production of new collagen, reduce inflammation, and increase pigmentation [4,5]. PN HPT™ have similar properties, exploited to promote the healing of chronic wounds and other indications in dermatology, orthopaedics, and gynaecology [7-9,15-18]. In dermatology, PN HPT™ indications have long explored depressed scars and striae distensae, including striae albae [19-21]. Some small studies also investigated the striae albae indication [22]. After intradermal injection, PN HPT™ rapidly hydrate the skin, increasing volumes and helping relieve skin depressions due to dermal scarring [7-9]. The highly hydrophilic PN HPT™ polymers reorganise in tissues into a three-dimensional gel that persistently binds water. This passive mechanism is the basis of the short-term skin voluminising effect [7-9]. Over the longer term and always passively, PN HPT™ facilitate the production of new collagen and elastin fibres immersed in a new dermal matrix by passively replenishing the pool of genetic information precursors [7-9]. Electron-rich PN HPT™ also act as free radical scavengers [23,24].

As ingredients of a medical device, PN HPT™ must have no active pharmacologic action and only act as potent yet passive fibroblast activators. The PN HPT™ passive action develops by replenishing the fibroblast pool of nitrogen bases, nucleosides, and nucleotide precursors [7]. The long-term outcome is supporting and promoting the dermal fibroblast viability and production of dermal fibres and matrix. The PN HPT™ impact on collagen production is more potent than hyaluronic acid [7]. A recent paper on gingival dermal fibroblasts confirms the enhanced collagen production associated with PN HPT™ [25]. The investigations targeted at safety show that PN HPT™ lack all toxicological liabilities at the clinically administered doses [26].

The study outcomes, albeit limited in the medium term (six months), support the concept that drove the study design—PN HPT™

deserving consideration as a viable treatment strategy for mature striae albae. The caliper-assessed width of the nineteen untreated control striae showed no change over the ten to thirteen weeks until the first follow-up V5 assessment. Conversely, the mean width of the twenty-six PN HPT™-treated striae albae decreased by about 42%. Interestingly, the second medium-term follow-up assessment session, four months after the last PN HPT™ treatment session, confirmed the short-term benefits are stable over time with no tendency to regression—the width of monitored mature striae albae still more than halved compared with baseline and reduced by 54.5% compared with controls at the same time.

The illustrated favourable outcomes appear solid and reliable thanks to the lack of assessment bias allowed by the digital calliper—even more if performed by independent evaluators. It also contrasts with the results reported in the mature striae albae literature, often biased because study outcomes are subjective and qualitative and, even when quantitative, liable to imprecision [1,4,5]. Some sensations by investigators suggest that abdominal striae albae might show especially favourable outcomes, but it is too early for reliable considerations.

Thanks to the lack of significant side effects other than a few local episodes of mild irritation and pain at the injection site, the GAIS assessment gave similarly encouraging and rapidly attained results, with a mean GAIS score of 4.0 out of 5.0 for treated subjects at V5. The study confirms the high PN HPT™ safety consistently demonstrated in the extensive PN HPT™ literature [8,9]. When available after the whole five-to-seven-month follow-up, the Antera 3D CS optical imaging device assessments will allow even more accurate quantitative estimates with minimum subjective bias. Unfortunately, the validated Antera 3D CS outcomes currently available at V5 and V6 are still too few to be of value and will be part of a more extensive report in the future. When available, the complete midterm GAIS assessments of the clinical evolution of actively treated striae albae and untreated controls by investigators and treated subjects will also provide a more detailed and nuanced picture of the longer-term PN HPT™ potential in the challenging mature striae albae indication. The complete analysis of all outcomes will help to answer the crucial question of all striae albae treatments how long does the benefit persist? When, on average, should a new PN HPT™ intradermal treatment cycle be planned, if any is required, to maintain the benefits rapidly attained with the first treatment cycle?

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