Global Scientific and Academic Research Journal of Dentistry and Oral Medicine
ISSN: 2584-2382 (Online)
Frequency: Monthly
Published By GSAR Publishers
Journal Homepage Link- https://gsarpublishers.com/journal-gsarjdom-home/

Evaluation of the Therapeutic Potential of Bioestimulator in Areas of Repetitive Movement: A literature review and case report

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Article History
Received: 25- 11- 2025
Accepted: 01- 12- 2025
Published: 03- 12- 2025

Vol – 2 Issue – 12

PP: 01-07

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Abstract

Poly-L-lactic acid (PLLA) is a collagen biostimulant widely used in facial aesthetics. However, there is little evidence for its use in areas of high muscle movement, such as the forehead, which may be an area at higher risk for adverse events. The objective of this study was to conduct a literature review and evaluate the therapeutic potential of PLLA (Angelis®) in areas of repetitive movement, under a hyperdilution protocol and in combination with botulinum toxin. A narrative review of PLLA and its correlation with tissue response was performed, complemented by a clinical case report. A 48-year-old female patient underwent combined application of botulinum toxin and hyperdiluted Angelis® PLLA in the forehead. Clinical follow-up was performed at 5 and 90 days post-procedure. The protocol resulted in immediate, stable reconstitution, with no signs of clumping or precipitation, allowing for safe application immediately after preparation. At 90 days, significant improvement in firmness, texture and dermal thickness was observed, with no adverse events. The optimized micromorphology of Angelis® PLLA and the hyperdilution technique reduce tissue polymer density and promote homogeneous dispersion, minimizing the localized inflammatory response. The combination with botulinum toxin created an environment of reduced muscle tension, enhancing the orderly deposition of collagen and promoting safe rejuvenation in dynamic areas. Thus, Angelis® PLLA demonstrated no side effects and efficacy in areas of repetitive movement, supporting its immediate use after reconstitution and confirming its potential as a next-generation biostimulator. This formulation represents a significant advancement in aesthetic practice, expanding the clinical indications for PLLA with a lower risk of complications.

Keywords: Poly-L-Lactic Acid; Collagen Biostimulators; Botulinum Toxin; Forehead.

INTRODUCTION

The growing interest and investment in facial rejuvenation, coupled with advances in understanding the aging process, has led to collagen biostimulators, such as Poly-L-Lactic Acid (PLLA), gaining market prominence (Signori et al., 2024; Bravo et al., 2024).

PLLA is a synthetic, biocompatible, biodegradable, and biologically inert polymer that has attracted attention in aesthetics as a filler and for stimulating the formation of type I collagen (Oh et al., 2023; Ao et al., 2024; Bernardo et al., 2024; Signori et al., 2024; Zhang et al., 2025).

When injected into the skin with a carrier solution, it acts by immediately increasing volume at the injection site, rapidly biodegrading as the carrier solution is absorbed into the tissue. The remaining particles are degraded into lactic acid, resulting in increased collagen synthesis by fibroblasts and gradually increasing dermal thickness. This occurs due to immune cells recognizing the dermal material as a foreign body, thus subclinical inflammatory reactions to foreign bodies can cause induced collagen synthesis (Oh et al., 2023; Bernardo et al., 2024).

Historically, PLLA has been a challenging material in terms of handling and safety. Initially approved in Europe in the 1990s, and after a few years also in the United States, as a filler treatment for people with the human immunodeficiency virus (HIV) who presented with lipoatrophy. Over the years, its use has been approved for other purposes, such as aesthetics in healthy patients (Signori et al., 2024).

Evidence suggests that two factors are crucial to the safety of PLLA: handling and injection technique (depth of application and dilution) and the intrinsic physicochemical characteristics of the microparticle size and shape (Fitzgerald et al., 2014; Alessio et al., 2014). The hyperdilution technique, using large volumes of diluent, revolutionized the use of PLLA, transforming it from a primary volumizing agent to a pure biostimulatory agent with a lower risk of accumulation. This dilution allows application to more superficial planes and areas of high muscle mobility, such as

the forehead (frontal region) and the perioral region, which were previously contraindicated (Alessio et al., 2014).

Innovative PLLA research focuses on optimizing particle microstructure to enhance the safety of hyperdilution. While traditional PLLA presents irregular particles in the shape of "flakes" and a size of 45−63 µm (Sedush et al., 2023), new generation formulations, such as Angelis® (Pharmaesthetics/PRP Science Co), present superior morphological characteristics: average micron of 30.4 µm and spherical shape (Angelis PLLA, 2025).

Furthermore, PLLA or other biostimulants can be combined with other treatments, such as botulinum toxin, dermal fillers, and energy-based devices like laser therapy and radiofrequency. These combinations are often used to achieve improved aesthetic results, but there is little evidence regarding the efficacy and safety of these combinations (Tam et al., 2025).

In this context, seeking to provide new evidence, this article evaluated the synergistic impact of optimized characteristics (lower micron size and sphericity) of PLLA combined with botulinum toxin treatment on improving the safety profile, justifying its potential use in areas of repetitive motion under the hyperdilution protocol.

LITERATURE REVIEW

Mechanism of action and tissue response

PLLA emerged as an injectable filler in the 1950s, developed by French chemists, and has since spread to several European countries. Currently, several brands use it for facial rejuvenation, effectively and safely, such as Sculptra (France), Derma Veil (America), AestheFill (South Korea), Rebron (China), and EVOPLLA (China) (Ao et al., 2024).

Chemically, polylactic acid (PLA) is a poly-α-hydroxy acid derived from lactic acid, existing as two stereoisomers, L-LA and D-LA, whose polymerization generates homopolymers, Poly-(L-lactide) (PLLA) and Poly-(D-lactide). In this context, PLLA is the main polymer of the PLA series used in aesthetics, with freeze-dried microparticles, being absorbable and non-toxic. The immediate filling effect of PLLA disappears approximately one week after application due to solvent absorption. However, residual microparticles are encapsulated by macrophages activated by subclinical inflammation of the foreign body, remaining present and associated with lymphocytes for up to three months. Thus, PLLA degrades into lactic acid and is subsequently metabolized into carbon dioxide and water or used in glucose synthesis, in irreversible reactions. In the first six months, as inflammation decreases, a gradual proliferation of type I collagen occurs, which can persist for two years or more (Ao et al., 2024)

The high efficacy is due to the composition and mechanism of action, which promote neocollagenesis. The particles have an average size of 52 µm, resulting in a lower degradation rate when injected into tissues, which favors the neocollagenesis process for a longer period (Signori et al., 2024). Thus, PLLA is recognized by immune cells as a foreign body, generating a controlled cellular inflammatory response. In this process, monocytes differentiate into macrophages and giant cells, which recruit fibroblasts and increase TGF-β1 and TIMP1 levels, promoting the deposition of type I and III collagen. This stimulation of neocollagenesis results in increased skin firmness, thickness, and elasticity (Signori et al., 2024).

In the first week after injection, PLLA is encapsulated by tissue containing monocytes, lymphocytes, and mast cells. From the second week onward, the inflammatory response decreases and collagen synthesis intensifies. Over the following six months, collagen production progressively increases, with a reduction in macrophages and fibroblasts and a return of inflammation to baseline levels. Between 6 and 24 months, there is a significant accumulation of type I collagen and the presence of type III collagen, while PLLA gradually degrades into lactic acid, being completely metabolized during this period (Ouyang et al., 2025).

The filler is relatively safe, with injection-related adverse events typically mild to moderate, such as local reactions, swelling, bruising, and nodules. Complications, although rare, include granuloma or tissue formation (Ao et al., 2024; Bravo et al., 2024).

The influence of particle micromorphology

There have been numerous technological advances and innovations in facial PLLA injections, with one focus being the optimization and reduction of particle size. This increases biocompatibility and degradation rates, reducing the incidence of side effects. This occurs because smaller particles are distributed more evenly throughout the tissues, reducing the risk of nodule formation. This increases adhesion and allows for greater control and precision of distribution. Because of this, innovations in this area are growing daily (Ouyang et al., 2025).

It is known that during the initial stage of PLLA injection, protein adsorption occurs on the microspheres, followed by macrophage recruitment and a mild inflammatory response, which induces fibroblast proliferation and collagen synthesis. This promotes dermal thickening and gradually improves wrinkles and depressions. In order to achieve fast and long-lasting filling, innovations are developed, such as associating cross-linked collagen hydrogel composites with PLLA microspheres, aiming to overcome limitations of Sculptra®, such as intense inflammation and slow collagen regeneration (Zhao et al., 2025).

The microparticles act as a scaffold, promoting a controlled foreign body reaction, where monocytes differentiate into macrophages and, subsequently, into foreign body giant cells that encapsulate the polymer. This process is followed by fibroplasia and deposition of new collagen, primarily type I (Vleggaar, 2005; Sedush et al., 2023).

Nodule formation occurs when there is a dysregulated inflammatory reaction, often due to the excessive accumulation of material (particle clusters) that the immune system cannot process or disperse homogeneously (Vleggaar, Fitzgerald, 2021).

The method for reconstitution of PLLA particles is constantly reviewed and improved, which impacts the number of protocols and the heterogeneity of the studies analyzed. Reconstitution instructions have evolved significantly as manufacturer recommendations are updated, reflecting the period and technical context of each investigation (Signori et al., 2024).

Thus, polymeric materials engineering demonstrates that the tissue inflammatory response is impacted by microparticle morphology,

especially size and shape. Regarding the former, there is a consensus in the literature that microparticles with a diameter greater than 25–30 μm are large enough to resist rapid phagocytosis by macrophages, ensuring tissue permanence and prolonged stimulation (Laeschke, 2004). Traditional PLLA uses larger particles (45–63 μm), which can lead to a more localized and intense inflammatory response if not dispersed properly. PLLA Angelis®, at 30.4 μm (manufacturer's data), is within the ideal range for stimulation, but with a micron closer to the minimum threshold for phagocytosis resistance, potentially favoring more efficient initial dispersion (Angelis, 2025). Regarding the variable related to shape (sphericity), comparative morphological analysis studies indicate that particles with a spherical and homogeneous shape present greater circularity, resulting in a smoother surface interaction with the tissue. Irregular or "flaky" particles (as described for traditional PLLA) have edges that increase surface roughness and create points of hydrodynamic tension during reconstitution, which favors agglomeration (Moran et al., 2024). The spherical shape of Angelis® is a differential that reduces particle-particle friction, promoting a more stable suspension and minimizing the chance of microaggregate formation, which are the precursors of nodules (Moran et al., 2024; Sedush et al., 2023).

Suspension stability and risk of agglomeration

For use, reconstitution of lyophilized PLLA is the main step of the protocol. Traditional PLLA requires a prolonged hydration period of 24 to 72 hours to achieve homogeneity and completely dissolve irregular flakes. Insufficient or immediate reconstitution is a proven risk factor for nodule formation (Alessio et al., 2014). Advances are being made precisely to overcome this and explore the safety of immediate use (Palm et al., 2021).

The suspension reconstituted with 8 mL of water for injections, after vigorous manual shaking for one minute, presents the same characteristics of homogeneity, particle size distribution, and sodium content at 0, 24, and 72 hours. This finding is essential because it indicates that Angelis® PLLA can be used immediately after resuspension. This makes the protocol viable due to the optimized morphology of the microparticle, which resists agglomeration even under immediate use (Bravo; Carvalho, 2021; Baumann et al., 2020).

The recommendation for reconstitution 72 hours before use, with lidocaine added to the vial at the time of treatment, was because it was believed that early reconstitution would better hydrate the particles. This impacts the logistics of consultations and scheduling (Vasconcelos-Berg et al., 2024).

Hyperdilution as a safety factor in dynamic areas

Areas of constant movement, such as the forehead and perioral region, require the implant to integrate into the tissue invisibly, without mechanical resistance to muscle contraction. Placing a filler or biostimulant material in superficial areas or areas with a high particle concentration can lead to the visibility or palpation of nodules with facial expressions (Alessio et al., 2014).

Hyperdilution involves increasing the diluent volume well beyond that recommended for volumetric filling (e.g., diluting 10 mL, 12 mL, or more for a 150 mg vial of lyophilized PLLA), resulting in a suspension with very low viscosity. This low rheology allows the suspension to spread evenly over a large area, minimizing particle density per tissue volume (Soarez et al., 2024).

It is known that safety in dynamic areas is directly proportional to the uniformity of distribution (Park; Kim, 2023). Although the 2014 European consensus discouraged the use of PLLA in these regions (Alessio et al., 2014), more recent evidence, using the hyperdilution technique to treat perioral and neck sagging and rhytids, has shown high efficacy and safety, with an absence of persistent nodules (Evangelista et al., 2024).

When the increased incidence of non-inflammatory subcutaneous nodules was observed due to the PLLA-to-liquid ratio, a larger-volume reconstitution approach began to be recommended for facial use, depending on each region. Therefore, uniformly distributed hyperdiluted PLLA applications have proven to be a viable and more effective option (Vasconcelos-Berg et al., 2024).

In this context, Angelis® PLLA (Pharmaceutics, Pinhais, Brazil) is a type I collagen biostimulator that is minimally invasive and 100% absorbable by the body (Pharmaesthetics, 2025). Table 1 shows a comparison between Traditional PLLA (Sculptra®) and New Generation PLLA (Angelis®).

Table 1 - Morphological Comparison between Traditional PLLA (Sculptra®) and New Generation PLLA (Angelis®).

Features	Traditional PLLA (Sculptra®)	New Generation of PLLA (Angelis®)	Implications for mobile area	Reference
Micronization	45 to 63 μm	30.4 μm (Mean)	Smaller micron size favors greater suspension stability and more uniform tissue dispersion.	Sedush et al., 2023; Pharrmaesthetics, 2025
Format	Irregular, flakes	Spherical, homogeneous	Spherical shape reduces friction and interaction between particles, decreasing the propensity for agglomeration.	Moran et al., 2024; Pharrmaesthetics, 2025

Stability	Classic: Requires 24-72h of hydration. Recent studies: Immediate use.	Immediate use (0h)	Eliminates the risk of clumping due to insufficient hydration.	Alessio et al., 2014; Palm et al., 2021; Pharrmaesthetics, 2025

CASE REPORT

This is a clinical case report that followed the Case Reports (CARE) checklist.

A 48-year-old female patient, phototype III, presented to the clinic with a chief complaint of sagging skin in the forehead and the presence of static rhytids (Figures 1 and 2), also known as horizontal lines, that did not respond satisfactorily to botulinum toxin alone. The patient had no relevant comorbidities or history of autoimmune diseases.

Figure 1 - Frontal region before treatment.

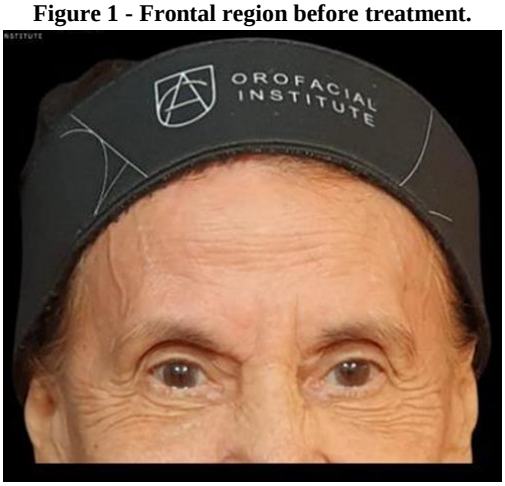
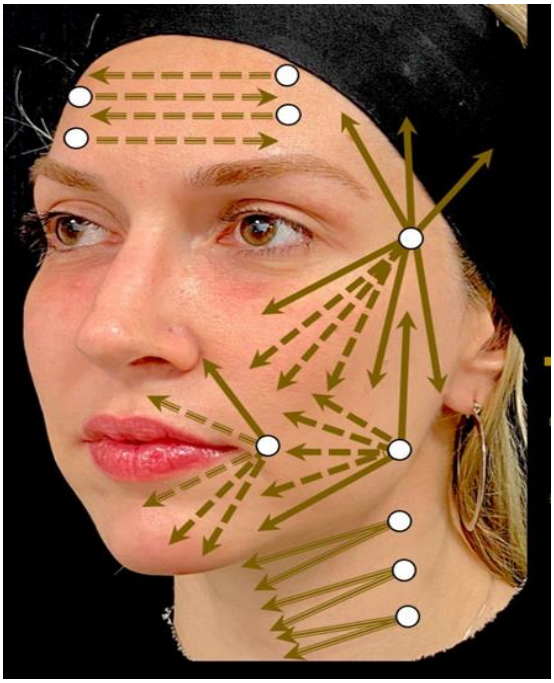


Figure 2 - Facial region before treatment highlighting the presence of wrinkles.

The therapeutic plan established a two-phase approach, performed in the same session, with the goal of optimizing neocollagenesis in an environment of minimal muscle tension. The planning can be seen in the following figure 3.

Figure 3 - Planning for the protocol.



Initially, muscle immobilization with botulinum toxin administration was used to neutralize frontalis muscle activity and reduce dynamic rhytids, paving the way for biostimulation. Subsequently, dermal biostimulation (PLLA, Angelis®) was performed, injecting next-generation PLLA using a hyperdilution protocol to treat sagging and residual static rhytids, aiming to improve dermal quality. Angelis® PLLA (150 mg) was reconstituted immediately prior to injection using a total volume of 12 mL (10 mL of sterile water for injection and 2 mL of articaine with vasoconstrictor), which constitutes hyperdilution. The vial was vigorously shaken manually for one minute, according to the immediate use protocol (Figure 4).

Figure 4- Reconstruction protocol flowchart for neck, frontal and perilabial regions.

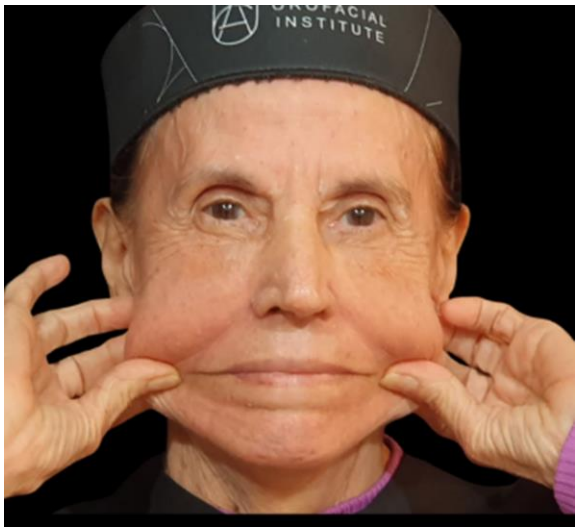
Twenty-five units of BoNT were initially administered. Subsequently, the PLLA was injected with a 22G x 50 mm microcannula into the dermal-subcutaneous plane of the forehead using linear retroinjection. The injection volume per route was strictly limited (maximum 0.1 mL) to ensure uniformity, with a

total volume of 1 mL of the suspension (≈12.5 mg of PLLA) distributed over the forehead.

The patient was followed up 5 (Figure 5) and 90 (Figure 6) days after the procedure. Muscle paralysis caused by BoNT was clinically evident within 14 days.

Figure 5 - Frontal region after treatment.

Figure 6 - Facial region after treatment.



After 90 days, the patient demonstrated substantial improvement in the firmness and texture of her forehead skin, with a significant reduction in residual static rhytids. The intervention surpassed previous results obtained with botulinum toxin alone. No local complications were recorded, such as prolonged edema, persistent erythema, or, crucially, the formation of subcutaneous papules or nodules.

DISCUSSION

The application of PLLA to the forehead (frontal region) aims to improve skin quality and superficial sagging, rather than deep volumization, with high efficacy and safety in reducing volume loss and increasing elasticity (Ouyang et al., 2025; Zhang et al., 2025). Angelis®, when hyperdiluted, is transformed into a low-concentration scaffold. In this context, the risk of complications is dominated by the morphology of the agglomerated particles. This case report shows encouraging results from the combination of botulinum toxin and poly-L-lactic acid (PLLA), indicating synergy in the management of sagging and static facial rhytids, especially in areas of high muscle mobility, the focus of this study, which had a positive outcome regarding efficacy and safety.

Reconstruction, handling, and application are essential to avoid adverse events. The literature indicates that a longer hydration time reduces the risk of nodule formation, however, evidence from recent years, in vitro and in vivo, shows that immediate reconstitution is safe and effective, however there is almost nothing in the literature (Vasconcelos et al., 2024). Recent evidence reinforces the effectiveness and safety of collagen biostimulators, as PLLA, in facial rejuvenation. A systematic review showed thar the effects of PLLA were sustained for up to 25 months with mild adverse effects, such as pain and edema at the injection site (Ferreira et al., 2025).

A systematic review investigated the efficacy, durability, and adverse events of PLLA treatment for aesthetic indications, indicating increased dermal thickness, significant improvements in the severity of facial lipoatrophy, and clinical aesthetic scores after PLLA treatment, which is superior to injectable human collagen (Signori et al., 2024).

By applying botulinum toxin, an environment with less muscle contraction is created, favoring the uniform deposition of collagen induced by the biostimulator, enhancing the dermal rejuvenation effects. In the reported case, a progressive increase in dermal thickness and firmness was noticeable, with clinical results evident starting eight weeks after application.

Thus, the choice of PLLA Angelis® in a hyperdilution protocol (12 mL) aimed to reduce particle density and promote uniform dispersion, minimizing the risk of subclinical nodules and optimizing collagen stimulation in areas of reduced skin thickness, such as the forehead. These findings are supported by the literature, which reinforces that hyperdilution increases the safety of PLLA in dynamic areas, maintaining its biostimulatory efficacy and reducing late inflammatory reactions (Baumann et al., 2023; Bravo, Carvalho, 2021). Furthermore, it is in line with evidence that immediate reconstitution maintains the product's physicochemical properties, such as viscosity, particle size, and pH, equivalent to those of previously reconstituted preparations (Baumann et al., 2023).

Recent studies indicate that immediate reconstitution of PLLA does not alter its physicochemical properties or compromise its safety profile, with parameters such as viscosity, pH, excipient concentration, and particle size remaining stable for up to 72 hours after reconstitution (Bauamann et al., Vasconcelos-Berg et al., 2024).

The present clinical case demonstrated a significant clinical improvement in the texture and firmness of the skin in the frontal region after 90 days. The combined protocol provides a more lasting correction of static rhytids without adverse events, which is consistent with previous reports of adverse effects of hyperdiluted PLLA (Vasconcelos-Berg et al., 2024). It is noteworthy that the absence of events such as persistent erythema, prolonged edema, or nodule formation reinforces the importance of the linear retroinjection technique and controlled volume per path, which are determining factors for uniform polymer deposition.

The clinical findings of the report indicate that the described protocol shows promise for the treatment of sagging and static wrinkles in areas of constant movement, as it combines temporary functional immobilization with sustained dermal stimulation. However, because this is a single case report, the results should be interpreted with caution. Clinical studies with larger sample sizes and longer follow-up are needed to validate the efficacy and safety of this combined approach. Furthermore, this case report supports the premise that the safety and efficacy of PLLA can be extended to dynamic regions through the combination of quality materials and an improved technique.

The advantage the PLLA used on this study lies in the reduced residual risk of agglomeration, as its spherical and more stable particles enhance the safety of the hyperdilution technique. Unlike this new material, traditional PLLA, even when subjected to long periods of hydration, its irregular/flocculent shape carries an intrinsic risk of microaggregates, which, if injected superficially in areas of high facial movement, can become noticeable. The PLLA minimizes this risk through its spherical and more stable particles, enhancing the safety of the hyperdilution technique (Camatta; Barroso, 2022).

The use of hyperdiluted PLLA in previously restricted areas, such as the neck and perioral region, is already supported by clinical evidence, provided the dilution volume is high (above 1:2 or 1:3) and the injection plane is superficial subcutaneous/dermal-subcutaneous (Evangelista et al., 2024). Evidence on new PLLA formulations with porous microspheres, which also aim to reduce agglomeration and accelerate degradation, has demonstrated a faster onset of action and a substantially lower incidence of microaggregates in histological analyses (Cao et al., 2025). Although Angelis® PLLA is a solid microsphere, its optimization for sphericity and reduced micron size aligns with the same trend of minimizing the risk of nodules. This improvement in the physical-chemical profile, when combined with the hyperdilution technique, provides a double safety effect, essential for use in areas of repetitive movement, such as the frontal and perilabial regions.

This study adds further evidence to the literature on the use of PLLA Angelis®, demonstrating the safety of the procedure, which reduces product loss/waste and increases efficacy, without affecting adverse event rates. Therefore, this study aims to reinforce the safety of the immediate reconstitution protocol and the clinical success of the combined techniques.

CONCLUSION

This study demonstrates that the new-generation Angelis® PLLA, with its optimized micromorphology, represents a significant advancement in the field of collagen biostimulants. It provided greater suspension stability and demonstrated immediate usability after reconstitution, reducing the intrinsic risk of particle agglomeration.

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