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FEATURE ARTICLE

New Hyaluronic Acid Product That Could be a Game-Changer...
Introducing PROFHILO®

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Introducing PROFHILO® Non-BDDE Hyaluronic Acid (HA) Hybrid Complexes For Bio-Remodelling



The buzz in the United Kingdom started at the beginning of this year as practitioners hopped across the channel to IMCAS in Paris to see what was new in Europe. The excitement continued at ACE in the UK this April, so by the time the official UK launch of PROFHILO® came at the Facial Aesthetic Conference and Exhibition (FACE) 2016 in June, there were packed out workshops, with standing-room only, as UK practitioners clamoured to see, hear and learn more about this latest hyaluronic acid (HA) based product.

You'd be forgiven for switching off at this point –

"...Yeah, yeah, heard it all before, it's another HA!"

– but please don't, because PROFHILO, and the technological innovation behind it, makes it **anything but**, just another hyaluronic acid injectable product to hit the marketplace. I urge you to keep reading!

PROFHILO is manufactured and commercialised by Swiss pharmaceutical parent company Institut Biochimique SA (IBSA) through their Italian subsidiary IBSA Farmaceutici Italia and distributed into the UK marketplace by HA-Derma Ltd. (Other HA based products in their range include Viscoderm® and Aliaxin®).

IBSA is somewhat new to the aesthetic marketplace, but brings with it much experience gained in manufacturing products for the dermatology field, with much expertise in wound healing and tissue regeneration. IBSA also distinguishes itself from other pharmaceutical companies in the aesthetic marketplace by controlling the entire product life cycle, from the bio-fermentation of the raw HA material through to the finished product in pre-filled syringes ready for use.

I was fortunate enough to visit the Italian factory near Naples where the raw material is made, speak to the

scientists who pioneered the formula and the leading practitioners at the front line of clinical practice and trials of this new innovation. In this article I hope to explain to you why I think this is the most interesting development in hyaluronic acid based products for a decade!

What is PROFHILO®?

Well let's first just deal with the 'F' word - 'Filler' - there I said it!

We use the term 'filler' all too often when discussing cosmetic injectable products, whether saying 'dermal filler' or 'soft tissue filler' to describe a variety of products that are used as implantable materials, added primarily to the face and hands, through injection.

Yet, as time and 'line chasing' has moved on, so products have become less about filling per say and more about revolumising, recontouring and reshaping the structures.

It's true to say that many temporary and semi-permanent injectable products still achieve this new goal by actually filling and creating implanted material within the tissue, but there is a move towards developing solutions that stimulate the natural tissue and encourage neocollagenesis, long after the original product has been degraded by the body. Such products do not neatly fit into the category of 'filler', so 'tissue stimulators', 'skinboosters', 'bio-rejuvenators' and 'bio-revitalisers' have evolved into more recent terms used in aesthetics.

This is the broad category that PROFHILO sits within, not with the fillers.

It may be based on hyaluronic acid technology but it is not a filler, it is a bio-remodelling product which uses their proprietary HydroLift® Action.

"It's important to understand that PROFHILO is NOT a volumising dermal filler..."

The manufacturers assert that it requires fewer injection points, treatment is quick, requires fewer top-up sessions than other bio-stimulators, has reduced adverse effects and limited pain or side effects associated with HA delivery, and results are sustained for longer.

The product flows and distributes itself, integrating within the tissue, rather than existing in lumps, blobs or lines where it is placed. This characteristic also means that there is no need for a local anaesthetic ingredient, such as lidocaine, as there is no resistance within the tissue when injected, so the patient feels no pain.

IBSA Farmaceutici Italia President, Giorgio Pisani is quoted as saying that their HydroLift® Action; "...supports the concept of 'curing wrinkles' compared with the typically cosmetic 'wrinkle filling' concept".

Therefore, it's important to get the 'filler' word out of your head when considering and treating patients

with this product. You will need to emphasise to patients that PROFHILO is not a filler, but a remodelling and stimulatory product which will slowly evolve their own tissue, without creating immediate volumisation or augmentation where it is placed.

"It's important to understand that PROFHILO is NOT a volumising dermal filler. It is also not mesotherapy. It sits between skinboosters and fillers as a SuperSkinBooster in that it offers fantastic hydration but ALSO triggers collagen and elastin production, resulting in bio-remodelling of the skin", said Dr. Ravi Jain, UK KOL for PROFHILO.

Founding scientist for the product, Professor Chiara Schiraldi agrees; *"It is not a filler, it has a lower filling activity compared to other fillers, but because it is very active at biorevitalisation, the cells are themselves producing all the extracellular matrix to produce a better quality and more elastic dermis, which is filling or volumising naturally".*

Therefore, any long term 'filling' effect is not caused by a fibrotic effect, or a foreign body reaction, as seen with PLLA (Sculptra®), but via stimulation of different collagen types within the tissue.

So, it's not a filler, but what else makes PROFHILO innovative?

The characteristics that make PROFHILO such a novel and revolutionary product are multi-faceted.

It is a BDDE-free, thermally-linked product and it provides a slow and long-lasting release of both high and low molecular weight HA, which all goes a long way to distinguish it from other HA injectable products in the aesthetician's armamentarium. The stable, cooperative,

hybrid nature of PROFHILO is a first, never seen before in an injectable product and could be marked out as a true innovation.

BDDE (1,4-butanediol diglycidyl ether), is usually employed in the cross-linking process of HA product manufacture to give the resulting gel more longevity once implanted than non-cross linked HA, making a longer-lasting result for the patient.

PROFHILO is BDDE free, with the manufacturers having perfected a way of stabilising the HA thermally. Thus, it can provide the much needed longevity and no chemical modifications are needed.

PROFHILO contains both high (HMW) and low molecular weight (LMW) HA which generates a dual action, incorporating hydration and tissue stimulation from the LMW, referred to as the HYDRO effect, alongside dermal scaffold support from the HMW, referred to as the LIFT effect. All in the company market this as the HydroLift® Action.

The product is presented as a high concentration of hyaluronic acid with 32mg of HMW HA (1100 - 1400 kDa) and 32mg of LMW HA (80 - 100 kDa), combined as a thermally stabilised unit of 64mg in a 2ml pre-filled syringe to be injected with a 29G needle, (two supplied per pack). The cost price is £125 + VAT. The product is available direct from HA-Derma Ltd or from NeoPharma UK, Cosmedic Pharmacy, Church Pharmacy and Med-fx who all run various offers.

Production



IBSA obtain the raw hyaluronic acid that they use in all their product portfolio, including PROFHILO, through their partner company Altergon Italia, who have a manufacturing facility based in Morra de Sanctis in the Province of Avellino, just east of Naples in Italy.



At their state-of-the-art factory, which is AIFA (Italian Medicines Agency) and FDA authorised, they can produce the exact specifications of sodium hyaluronate used within the IBSA range. The facility produces around 150kgs of both pharmaceutical and cosmetic grade HA per year.

Production of the raw hyaluronic acid starts with 1ml of frozen bacteria – *Streptococcus equi*. This is rapidly grown in a liquid medium, creating a fermenting 'broth'. As fermentation progresses the bacteria produces a capsule of hyaluronic acid around itself.

Once this occurs the fermentation is stopped and the broth is cooled from 37°C to 10°C. It is at this point that the patented purification and filtration process begins to separate the HA away from the now spent bacteria. Filtration is done with the aid of diatomaceous earth and the mixture is further purified to remove any remaining residues and impurities using activated carbon.

The purified solution of sodium hyaluronate is then neutralised with hydrochloric acid, and then finally, ethanol is added at supersonic speeds to produce incredibly small crystals of HA, which can then be dried by vacuum, and turned into kilos of raw sodium hyaluronate (HANa) powder.

This raw HA then goes on to form the foundation of all the IBSA HA injectable products via ongoing

proprietary production methods at their other manufacturing facility in Northern Italy where the compilation of the pre-filled PROFHILO syringes is completed.

The 'recipe' for the raw HA can be modified by Altergon to produce each of the specific requirements for compounding the final IBSA products.

Having visited inside the factory myself, where I was required to put on (unflattering) sterile attire, I was both incredibly impressed and fascinated to see such a high-end production environment. There is great reassurance in seeing first-hand the expert production methods and product traceability standards in place.

The Science

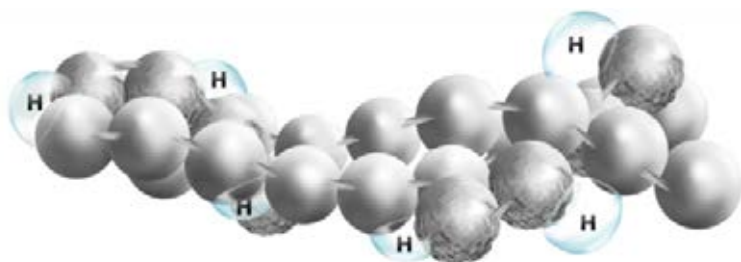
The 'mother and father' of the scientific innovation that underpins the NAHYCO® technology implemented in PROFHILO, named after Sodium (NA) HYaluronate COmplex, are Professor Chiara Schiraldi and Professor Mario De Rosa from the 2nd University of Naples - Bioteknet. It is in their laboratories

that the discovery of the hybrid formulation was made during in-vitro studies.

PROFHILO is made of entangled high and low molecular weight hyaluronic acid chains without any chemical bridge.

This stabilised hybrid complex is created by combining the two types of HA, and firstly breaking the weak hydrogen bonds that HMW HA tend to form between themselves, a process of thermally cooling the mixture of HMW and LMW HA is then employed, which causes the formation of new bonds to hydrogen between the long chains of the HMW HA and short chains of the LMW HA.

The resulting hybrid and co-operative complex gives a slow and long lasting delivery of the LMW and HMW HAs and this stimulates the fibroblasts and keratinocytes in the dermis to regenerate. It has high cohesivity, so resists breaking up into smaller particles within the tissues, but spreads naturally and smoothly with ease into the interstitial tissue. It also has a low extrusion force, making it easy to inject.



Even though the product uses both low and high molecule weight HA, the components do not demonstrate the same properties within the complex as when LMW and HMW HAs are used independently. This is a key factor to the success of this product.

LMW HA is scientifically known to have the best potential for interacting with HA receptors in the body (CD44 interaction), but has the disadvantage of being pro-inflammatory. HMW HA has anti-inflammatory properties.

The low molecular weight HA is released slowly from the network which means that the inflammatory reaction on the cells (the activation of the TGF- β expression) is reduced as there is a gradual delivery of the LMW HA, rather than a rapid shock and initiation of the inflammatory cascade.

As well as this, there is also lower inflammation apparent in the use of PROFHILO than is noted when using products which contain HMW HA alone, which themselves are anti-inflammatory.

Similarly, the PROFHILO hybrid complex has been shown to effectively 'protect' the HMW HA, augmenting its resistance to hyaluronidase, and producing a prolonged action. This means that there is a reduction in the degradation of the HMW HA within PROFHILO by eight times that of the degradation seen with HMW HA on its own.

The pure nature of the HA in PROFHILO, without the use of cross-linking agents such as BDDE, also eliminates adverse effects known to be linked to this chemical addition.

PROFHILO engages with the body's receptors to cause the collagen stimulation, a much more natural reaction than a foreign body reaction.

It has a much higher activation of types I and III collagen in the fibroblasts than HMW and LMW HA on their own, plus type IV and VIII in keratinocytes. It also produces a higher activation of elastin synthesis in the fibroblasts and keratinocytes compared to independent application of HMW and LMW HA.

The Proof

By this summer, IBSA had 150 individual cases registered as part of professional clinical trials for PROFHILO. To date, study results and approximately 10 months of active practitioner use, and more than 50,000 syringes used in Italy alone, have shown improvements in all parameters of skin assessment. The manufacturers expect this to have a long-lasting effect for patients.

A study which used a combined method based on fluorescence lifetime imaging (FLI) and high-frequency ultrasound to quantify the presence of filler products in the subcutaneous tissue of mice found that PROFHILO proved to have a greater stability (producing longer durations) than a low cross-linked HA filler.

To date four studies on PROFHILO have been completed: two clinical evaluations and two in vitro studies.

There are currently two ongoing, both of which are looking at future applications for PROFHILO to reveal the effect it has in the subcutaneous fat layer and to look at adipose stem cell action in vitro.

'Watch this space', I think we can safely say, as the scientists look at just how many applications and effects these hybrid complexes can have.

One published study by Antonella D'Agostino et al, from 2015, entitled '*In vitro analysis of the effects on wound healing of high- and low-molecular weight chains of hyaluronan and their hybrid H-HA/L-HA complexes*', aimed to compare the activity of HMW and LMW HA against PROFHILO (hybrid complexes) for its potential application for tissue regeneration. The study looked at stability (i.e. hyaluronidases digestion), their ability to promote wound healing of human keratinocytes in vitro and for their effect on cellular biomarker expression trends.

The research showed that PROFHILO performed better than LMW HA and HMW HA alone. It demonstrated a greater resistance to hyaluronidase compared to HMW HA, a low inflammatory response in treated samples compared to cells treated

with LMW HA and a lower viscosity than LMW HA and HMW HA alone.

Another study, in submission for peer-reviewed publication looked at the remodelling of dermal components in vitro, again comparing PROFHILO with LMW and HMW HA alone. The data gathered from this found that there was increased elastin expression in fibroblasts, with PROFHILO compared to HMW HA and LMW HA. It also showed increased activation of COLI and COLIII synthesis in fibroblasts and increased COLIV and COLVIII expression in keratinocytes compared to HMW HA and LMW HA.

Further data is now being published looking at in vivo cases and active in-practice experiences with the product.

A pilot study of 64 female patients (aged 38-60) by Dr. A Sparavigna, also pending peer-reviewed journal publication, showed the results from subjects treated with PROFHILO twice, with a one-month interval between treatments, using the BAP technique (explained below).

Data showed that there was a volume improvement of at least one degree (using the Facial Volume Loss Scale) two months after the second treatment in 70% of the subjects. The results were confirmed using the Canfield Vectra digital imaging system which showed that one month after the second treatment there was a significant improvement in 73% of the subjects. 90% of patients reported an improvement in at least one skin parameter (roughness, tightening, texture, brightness and hydration) so satisfaction was high.

Another prospective study of 30 patients (aged 40- 68) by Dr. Moisés Rodríguez Abascal and Dr. Miguel Saldaña Fernández in Spain, published in the European Aesthetic Plastic Surgery Journal, looked at evaluating the short and long term efficacy and results of treatment, patient satisfaction and possible complications from PROFHILO treatment.

Each patient was treated with 2ml of PROFHILO, and photographs were compared with control and those at 30 and 60 days post the first treatment. Patients also completed satisfaction surveys. Of the 30, only 3 had mild bruising and

2 complained of some pain during the injections. Patient satisfaction and clinical evaluation was high. The authors felt that bio-remodelling with PROFHILO has a low complication rate, is well tolerated, with a high patient satisfaction level and with a notable improvement in all the skin parameters evaluated – wrinkles, texture and appearance of the skin.

Treatment Protocols

Full training in the use of PROFHILO is provided by HA-Derma Ltd in the UK.

When developing and testing the product, after the in-vitro studies, IBSA worked with a team of Italian physicians and came up with the BAP technique – Bio Aesthetic Points as the optimum method for delivery of the product.

The BAP technique identifies 5 injection sites on each side of the face, away from major vessels, nerves etc. and in such a way as to maximise the 'spreadability' of the product through diffuse regions of the cheek and jawline.

At each of these points a bolus of 0.2ml of PROFHILO can be injected, slowly and smoothly, due to the low viscosity of the product, at the deep dermal layer. Thus 1ml of product is injected into each side of the face.

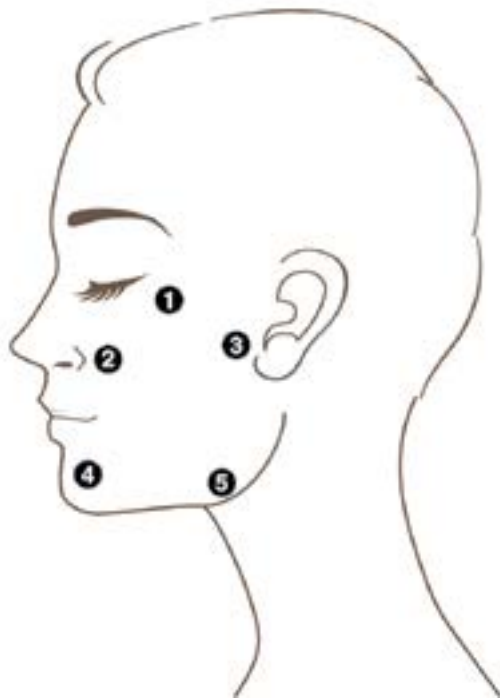
This technique is aimed at improving age related atrophy in the cheek and jaw regions, which will consequently have an effect on other structures and improve the general elasticity of the facial skin and improve superficial wrinkling across the whole area.

IBSA note that treatment is intended to be performed across two separate sessions, spaced one month apart. If required, with higher levels of ageing

diagnosed in the patient, a further treatment can be performed two months after the second session. This treatment cycle can then be repeated twice per year for optimum results for the patient.

Some examples of treatment protocols were demonstrated during a workshop at the recent FACE conference by Dr. Ravi Jain and Dr. Hema Sundaram.

"Whenever I see anything in the centre of the face, such as a deep naso-labial fold, I always look at the frame of the face for the cause, and how I can address that to correct the centre. It's important to also think in 3D and look at the projection of the face"; said Dr. Hema Sundaram.



"I think of it (PROFHILO) as a weight-less volumisation. It's not bulking up the tissue, but it's giving us the improvement that we're looking for when we inject into these volume depleted areas, and there is a very dramatic improvement in tissue quality. It combines the benefits of volumetry and skin boosters."

Dr. Sundaram demonstrated the use of PROFHILO injected with a cannula into the subcutaneous plane of the preauricular submalar region, on each side of the patient's face, a 69 year old female, in order to give a lateral pull to the face.

Dr. Jain also demonstrated two

different techniques on the same patient; 1ml of PROFHILO following the BAP Technique using a 29G needle and the remaining 1ml on the other side of the face using the fanning technique placed by cannula.

The use of PROFHILO is now being actively studied by a number of UK and European practitioners within their own practices with applications in the forehead, periocular region, submalar area and the neck, as both a stand-alone product and within combination protocols where structure is created using cross-linked HA filler products, such as IBSA's own Aliaxin® range, with PROFHILO used to assist with long-term remodelling of the tissues.

Dr. Ravi Jain showed at the same workshop, that when treating hands, the practitioner can place 2ml of PROFHILO in one large bolus in the centre of the upper hand (without complaint from the patient).

As the audience drew breath watching the quantity of product go in to one single place, he then showed how the product instantly flows across the upper hand region to integrate evenly with only minimal massage. I think many were prepared to applaud at that point.

A typical syringe of 2ml of PROFHILO can be charged at approximately £250+, average £350, depending on your business model. A treatment programme of two syringes, with one month apart is IBSA's protocol.

Before and After Photographs

We are now able to see a multitude of before and after photography which not only shows and gives credibility to all the in vitro studies discussed, but which also highlight the many applications and indications that PROFHILO is now being tested in by practitioners actively using the product in their clinical practice across Europe.

PROFHILO®





Figure 3 (A) Before treatment, and (B) 1 month after second treatment

Courtesy of Dr. Annalisa Beatini



Courtesy of Dr. Moisés Rodríguez Abascal



Before (Left) and After (Right) PROFHILO treatment for skin laxity in the arms.
Courtesy of Gabriel Ghinea RGN, E-Cliniq



Before (Left) and After (Right) of neck treatment with PROFHILO after 2 months.
Courtesy of Professor Daniel Cassuto & Dr Irfan Mian

Conclusion

I hope that this article has encouraged you to think past the moniker of 'just another filler' when considering PROFHILO, as I think you can agree it's certainly much more than that!

Some practitioners have remarked on PROFHILO being like the "icing on the cake", as a complementary product which can also be used with other, more traditional HA filler ranges to compliment an overall skin rejuvenation result, dependent on the needs of the patient.

But, as a stand-alone bio-remodelling product, the way that the hybrid complexes of HA behave, compared to LMW and HMW HA is something of a true innovation, and one which is still very embryonic.

We probably won't know the true outcomes, longevity and applications of PROFHILO for a few years to come as more long-term study data is evaluated.

It certainly appears to have the effect of 'jump-starting' the body's own rejuvenation processes by the way in which both collagen and elastin biosynthesis is boosted by the hybrid

complexes, as in vitro studies have proven extensively. This is in strong agreement with the practitioner's and patient's feeling of remarkably improved hydration, texture and elasticity, with a "natural look".

It's true also to say that the fact that the product is BDDE-free is very exciting and is something of a bonus on top of the actual product performance. As we are noting that more and more patients tend to look for more natural, pure, chemical-free solutions to all their skincare and anti-ageing options these days, this is a USP. This makes it perhaps much easier to 'sell' as a rejuvenation concept to the more health savvy and ingredient conscious client who you may consult at your clinic.

As mentioned, this product is both new and showing exciting, never seen before results and applications. I look forward to seeing how clinical data evolves with PROFHILO and I fully expect it to be on academic agendas for aesthetic conferences in the coming few years.

It was a privilege to be invited to visit the manufacturing facility in Italy and to meet the pioneering team behind PROFHILO. I would like to thank IBSA Farmaceutici Italia and HA-Derma Ltd for the opportunity.

Lorna Jackson, BSc.



Lorna has been Editor of Consulting Room, the UK's largest aesthetic information website since 2003. She has become an industry commentator on a number of different areas related to the aesthetic industry, collating and evaluating statistics, plus researching, investigating and writing feature articles, blogs, newsletters and reports for Consulting Room and various consumer and trade publications, including Cosmetic News, Journal of Aesthetic Nursing, Body Language, PMFA News, Aesthetic Medicine and Aesthetic Dentistry Today. Lorna has also been asked to present at various industry events, including Smart Ideas, FACE and the CCR Expo. She was awarded Journalist of the Year at the MyFaceMyBody Awards 2014.

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