Summary of Clinical Studies

Subject Device

amalian SF 24 advanced

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II List of Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BDDE	1,4-Butanediol diglycidyl ether
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (The Federal Institute for Drugs and Medical Devices in Germany)
CER	Clinical Evaluation Report
FDA	Food and Drug Administration (US)
FWCS	Fitzpatrick Wrinkle Classification System
GACD	Society of aesthetic surgery Germany e.V.
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GHTF	Global Harmonisation Task Force
HA	Hyaluronic Acid
ICH	International Conference on Harmonisation
IRR	Injection related reactions
KTR	Korean Testing & Research Institute
MEDDEV	Medical Devices Directives
NLF	Naso-Labial-Folds
PMA	Premarket approval
PMCF	Post-Market Clinical Follow-Up
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SRS	Severity Rating Scale
UADE	Unanticipated Adverse Device Effects
WSRS	Wrinkle Severity Rating Scale method

1 Overview

The manufacturer conducted a controlled premarket clinical trial as well as a systematic literature review in accordance with MEDDEV 2.7.1 during the premarket clinical evaluation of the device amalian Dermal Implant. The clinical trial and clinical evaluation established the safety and effectiveness of the device, whereby a Conformité Européenne (CE) was obtained. After marketing authorisation the manufacturer continued to conduct annual clinical evaluation and post -market clinical follow-up. The post-approval studies for the amalian® dermal implant: amalian SF 24 advanced have been conducted since 2013. Table 1 shows an overview of the clinical studies conducted with the amalian® SF 24 advanced.

Table 1.Overview of conducted clinical studies with the amalian® Dermal Implant

Time Frame	Number of Patients	Drop-out with no data	Study sites	Number of injectors	Status	Endpoints in Focus	So far reported AR/ SAEs
2013 - 2017	114	10	7 sites in Germany	9	Prospective -Study still ongoing at one site.	Safety and effectiveness for intended use	None
General Safety outcome			Only expected injection related reactions such as swelling, haematoma, redness and pain. Mild to moderate in severity and resolved usually in less than a week without intervention.				
General effectiveness out come			Significant improvement ($p < 0.01$) for at least 6 months. Responders: 100%, 96% and 85% at months, 0.5, 3 and 6, respectively.				

1.1 Adequacy of data

Data gathered from the clinical investigations with the medical device at hand, is statistically adequate and sufficient for the assessment of the safety and effectiveness of the device. All clinical investigations were conducted in accordance with EN ISO 14155, Parts 1 and 2, Clinical investigations of Medical Devices for Human subjects. All clinical studies were planned and conducted in compliance with the rules of the Declaration of Helsinki adopted by the World Medical Association, in accordance with International standards and European guidance documents specifically the EN ISO 14155:2011 [Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2011)]. The manufacturer, S&V Technologies GmbH, sponsored the clinical investigations appointing independent medical staff: principle investigators, investigators and study nurses. A monitor, obligated to maintain confidentiality and objectivity, regularly conducted both onsite and remote monitoring of the clinical investigations including all documents.

2 Introduction

A first clinical evaluation for the amalian dermal implant was conducted in 2009. Re-evaluation according to the MDD 93/42/EC Annex I and Annex X and the MEDDEV 2.7/ 1 rev. 3 and 4 is carried out annually (last evaluation date 01.12.2017). The clinical data from equivalent devices (covering an estimated number of patients n > 500) and the clinical data from manufacturers own clinical studies conducted at 7 different sites in Germany,

investigating long and short term safety and effectiveness. This summary presents results from manufacturers own clinical data concerning the amalian® Dermal Implant: amalian SF 24 advanced.

2.1 Clinical need and expected benefit

Hyaluronic acid based dermal implants provide an effective and non-invasive alternative to surgical procedures for correction of facial contour defects and viscoaugmentation due to their enormous ability to bind water, biocompatibility and easiness of implantation[1]. Surgical procedures require significant time for recovery and expose the patient to the inherent risks of general anaesthesia. In some cases, surgical intervention may even intensify the apparent loss of volume[2]. Moreover, surgical alternatives to correcting facial defects are permanent and pose additional risks, as they are difficult to reverse. HA based dermal fillers on the other hand, can easily be removed by injecting commercially available hyaluronidase; even in the same session as the treatment. For the past two years HA dermal fillers are the second most common non-surgical procedure for correction of volume loss and facial defects (ASAPS, 2014), as they are biocompatible, non-immunogenic, easy to distribute and store and require no allergy testing[3].

3 Preclinical Overview

The results show that the products are non-toxic, non-sensitizing, non-irritant, non-mutagenic and non-genotoxic. Details are presented in a separate document: *Biocompatibility Summary Report*

4 Material and Methods

4.1 Material description in summary

The amalian® dermal implant is a clear, sterile, viscoelastic class III medical device made of sodium hyaluronate: the salt form of hyaluronic acid (HA), which is a naturally occurring polydisaccharide, i.e. a biomacromolecule[4]. Hyaluronic acid is ubiquitous in the healthy human body: i.e. in the skin, connective tissues, synovial tissues, synovial fluid and in the vitreous humor. Therefore, HA is considered most tolerable as a dermal implant[5]. The HA in fillers have structural properties similar to those of native tissue, excellent biocompatibility, and good tissue integration, especially if they stem from a natural source and are non-animal based. Furthermore, uniquely among other filler substances HA can be reversed using hyaluronidase. Sodium hyaluronate in this medical device is obtained from a natural and non-animal source. It contains BDDE (1,4-butanediol diglycidyl ether) cross-linked molecules to slow down degradation. The medical device is a temporary enzymatically degradable “dermal filler“. The degradation of HA (depolymerisation) of HA primarily involves two mechanisms: enzymatic degradation and free radical degradation[6]. Enzymatic degradation can be slowed down when the HA in device is cross-linked and can be induced when hyaluronidase is injected.

4.2 Study Population

Patients above the age of 18 who passed the inclusion-exclusion criteria and were considered eligible for treatment after first anamnesis were to be included in the study. All patients had to carefully read the patient brochure and sign the informed consent form before study begin. All patients were also informed of all known risks and of post treatment care.

Patients were excluded if the patient was pregnant or lactating, was hypersensitive to hyaluronic acid or to local anaesthetics, had a predisposition to increased scarring, suffers from one or more chronic systemic debilitating diseases including diabetes mellitus (insulin-dependent or non-insulin-dependent), had an autoimmune diseases or a malignant tumour diagnosed within the last 5 years, is HIV-positive, has hepatitis A, B or C, regularly takes an immunosuppressive, has a blood disorder or takes/ has taken anticoagulants before or during the study, has facial injuries or dermal infections, has had a flu within 3 weeks pre-treatment or suffers attacks of inflammatory skin diseases. Furthermore, the treatment was not carried out if the patient had hyaluronic acid injected into the intended injection area within the last 6 months or a permanent dermal filler injected into the intended injection area at all.

4.3 Outcome measures and method of assessment

Effectiveness and Efficacy

Effectiveness of device is assessed in: improvement of wrinkle/volume loss and duration of the achieved correction.

- Investigator Assessment of wrinkle and fold severity using the 5-point MERZ Aesthetics Scales™ over the period of 12 Months.
- Responder Rates Percentage of treated patients with at least +1 scale point [Merz Aesthetics Scales™] above base line value directly after treatment and at each follow up visit.

Secondary:

- Patient and physician satisfaction with treatment outcome on a 5 Point Global Aesthetics Improvement Scale (GAIS).

Safety

Safety of the device is assessed in: the type and severity of adverse reactions as well as the duration and resolution of the reaction.

- Investigator Assessment of adverse reactions (side effects) using a 5 point severity scale (0=none to 4 = very strong).
- Safety of the device in relation to injection related reactions as well as device related relations; immediate or delayed, short term or prolonged.

Ooccurrence of any SAEs or AR were to be immediately reported.

Table 2. Methods of assessment for primary and secondary outcome measures.

Effectiveness	
Correction	Merz Aesthetics Scales™[7,8,9,10,11,12] (0 to 4) from no wrinkles to severe wrinkles/sagging/folds. For Lip Fullness Scale is reversed (4 to 0) from full to very thin. [Guidance booklet delivered to each investigator]
Longevity	Duration of sustainability of achieved correction in comparison to baseline values [Merz Aesthetics Scales™] and degree of maintained correction at each follow-up visit. Correction considered still maintained when. MERZ value is at least +1 scale point above base line value.
Responder Rates	Percentage of treated patients with at least +1 scale point [Merz Aesthetics Scales™] above base line value at each follow up visit. Product effectivity still high at responder rates ≥ 70%.
Patient and Physician satisfaction	Global Aesthetics Improvement Scale (GAIS) defining subjective assessment of worsening. Unchanged, Improved, Highly improved and very Highly Improved as: -1, 0, 1, 2 and 3, respectively.
Safety	
Severity	A four point scale (1-4) from slight to very sever judged according to physicians assessment
Duration	In days from onset of event.
Onset of event for late reaction assessment	After X days post treatment
General AE/ SAE Reports	Free physician commentary
Assessment Period	
Short Term	Directly after treatment; safety follow up at least up to 3 months
Long Term	Directly after treatment (V1); 2-3 Weeks after treatment (V2); 3 months after treatment (V3); 6 months after treatment (V 4) and 12 months after treatment (V 5).

4.4 Statistical analysis

The change in correction value (Merz Aesthetics Scales™) from baseline value to month 12, including scores directly after treatment at day 0 (V1) and at each visit 2-3 weeks after treatment, 3 months after treatment and 6 months after treatment was analysed using the mean values. To evaluate the significance of continuous outcomes a paired t-tests were used. Statistical tests were two-sided, and P values < 0.01 were considered statistically significant. A clinically meaningful treatment effect and the primary outcome variable for this study were defined as an improvement (reduction) of one point or more on the severity scale of Merz Aesthetics Scales™. Based on this outcome, a further assessment was conducted to determine the percentage of patients with a meaningful treatment effect at month 6; as responders.

Additional analysis of GAIS was conducted using mean values as well as descriptive statistics to determine distribution of possible side effects and injection related reactions as well as their severity and duration.

5 Summary of Results

5.1 Study population

A total of 114 patients were enrolled at 7 different sites in Germany. From the enrolled patients 104 completed treatment and set follow-up per. For long-term data a further 3 more were lost to drop-out before the end of the follow-up period (12 – 13 months).

5.2 Treatment

Treatment was conducted according to the manufacturer's instruction for use for the intended use of the device.

5.3 Effectiveness

The initial mean aesthetic scale (2.70) was reduced to 1.22 directly after treatment and remained improved after 2-3 weeks, 3, 6 and 12 months after treatment at: 1.17, 1.38, 1.66 and 2.28, respectively (Figure 1).

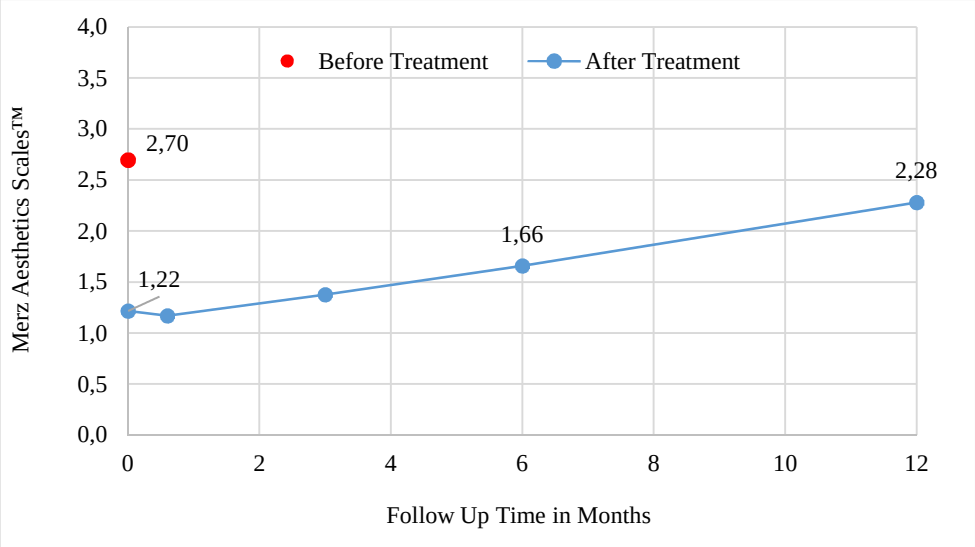

Figure 1. Achieved correction after treatment with amalian® SF24 advanced over 12 months

The change in mean aesthetic scale from the mode of 3 at baseline (severe) for each of the follow up visit is shown in (Figure 2). At month 6 severity was reduced by 1.04 scale points, which was a significant improvement compared to baseline (P value < 0.00001). The results prove an improvement of at least 1 aesthetics scale point after 6 months. Improvement directly after treatment was also statistically significant with responder rates of 100%. Responders remained at 100% beyond 2-3 weeks and remained high at 96% and 85% at months 3 and 6, respectively.

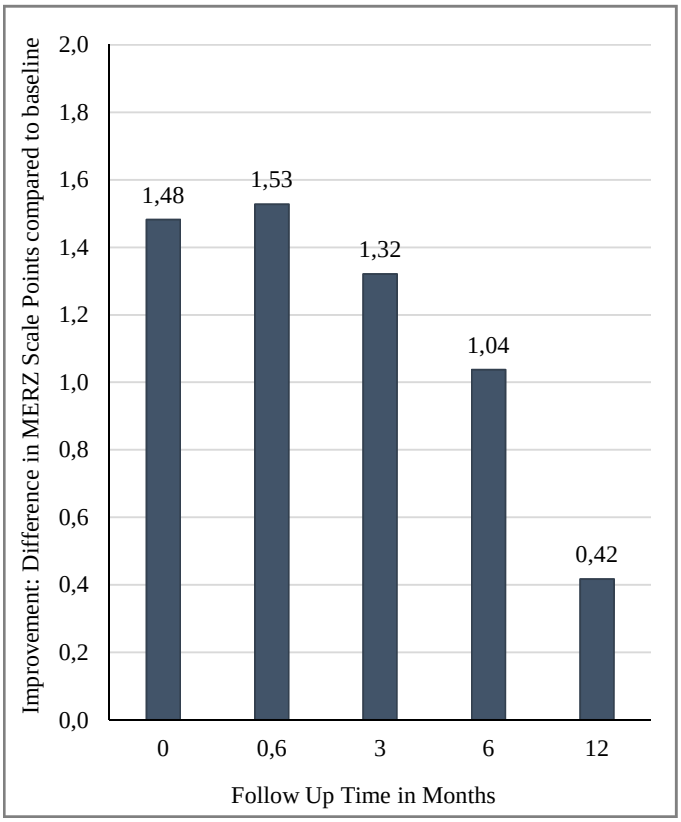

Figure 2. Achieved improvement– Difference to baseline value

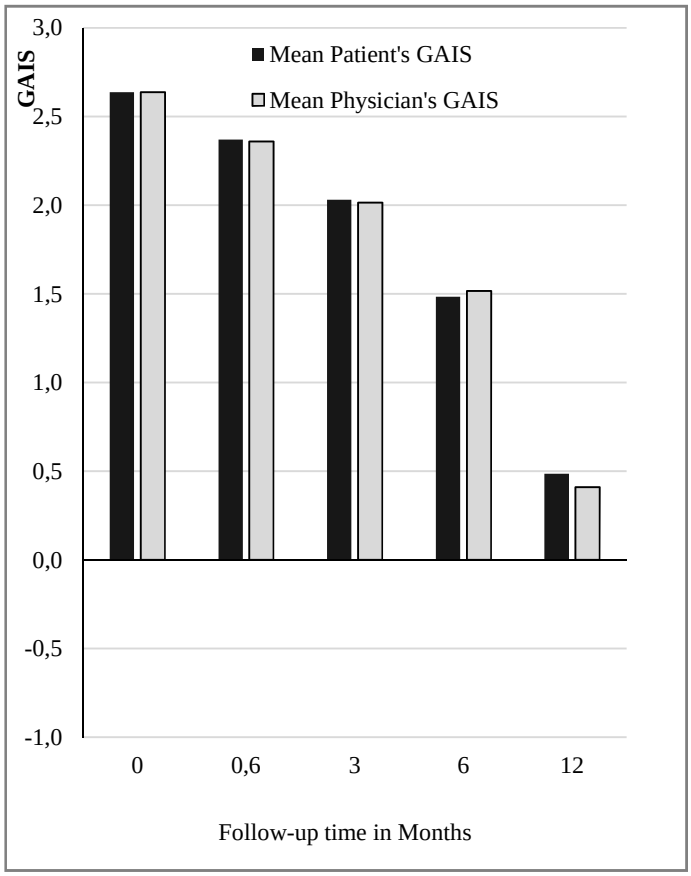

Figure 3. Patient and physician satisfaction with treatment

Results measuring patient and physician satisfaction according to the Global Aesthetic Improvement Scale also showed a high level of patient and physician satisfaction with the treatment outcome. Both patient and physician perceived the appearance of corrected area as highly improved or very highly improved with GAIS levels at 2.6, 2.4 and 2.0 at directly after treatment, 2-3 weeks after treatment and 3 months after treatment, respectively. The GAIS levels at month 6 show that both patient and physician viewed the outcome as more than improved at 1.5. The GAIS levels remained above 0.4 even throughout month12 (Figure 3).

Safety

Mainly injection related reactions were reported: swelling, redness, hematoma and pain with an occurrence rate of 4.04%, 2.19%, 2.19%, and 1.35%, respectively. The mean severity of these reactions was less than 1.5 (slight – below moderate), with a mean duration of not more than 3 days. Injection related reactions resulted therefore with slight swelling (mean intensity on a scale of 1-5 from slight to strong: 1.3), haematoma (1.5), redness (1.2) and pain (1.5) lasting for 1.8, 2.0, 5.2 and 2.8 days, respectively. Table 3 shows data for the severity and duration of expected injection related reactions. Isolated cases (only 1 patient) of itching and discolouration was reported and attributed to sensitivity toward topical anaesthetic cream.

Table 3. Occurrence, severity and duration of expected injection related reactions (n=101).

	swelling		redness		hematoma		pain	
	Severity	Duration	Severity	Duration	Severity	Duration	Severity	Duration
MEAN	1.25	1.73	1.15	2.00	1.46	5.15	1.50	2.78
MIN	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
MAX	3.00	7.00	3.00	7.00	3.00	14.00	3.00	7.00
MODE	1.00	1.00	1.00	1.00	1.00	5.00	1.00	2.00
% of occurrences	**4.04**		**2.19**		**2.19**		**1.35**	

There were no product related adverse reactions such as lumps, nodules, dislocation or granulomas. No SAE occurred. No reactions lasted longer than a week with the exception of one patient with haematoma, which was visible for 14 days but without pain or swelling. More than half of the patients (58%) exhibited no reactions at all.

6 Conclusion

The results prove the effectiveness and safety of amalian® SF 24 advanced, with no SAEs or product related adverse reactions. Safety data shows only expected injection related reactions, which are concomitant to such treatments and also backed up by the annual clinical evaluation and literature clinical data of equivalent devices. These reactions were slight to less than moderate in severity and resolved in less than a week without any intervention. Reactions, which lasted a week, or only in a single case 2, were all haematoma related. Furthermore, more than half of the patients treated experienced no reactions at all.

In addition to its strong lifting properties, even at small amounts of 1ml, both patients and physicians report a positive experience with very highly improved aesthetic outcomes and proven longevity. The device efficacy has is proven with significant improvement of the aesthetics scale points, which lasted for at least 6 months. Clinical results not only convey highly favourable results in terms of correction and user satisfaction but also in terms of safety and minimal down-time after treatment. These results are strongly supported by the literature search results 2015 -2016 as well as the clinical evaluation of the amalian dermal implant, which includes data of over 500 patients (equv. device) and PMS results from 120 365 units marketed between 2015 – 2016.

As required by the “Essential Requirements” according to Annex I of the EC-Directive 93/42/EEC (General Requirements): safety data of the amalian® SF 24 advanced gathered through clinical studies, as well as safety data demonstrated by the literature search 2015 - 2016 for equivalent devices, confirms that the device, when used under the conditions and for the purposes intended, does not compromise the clinical condition or safety of patients, or the safety and health of users.

7 References

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