

Statistical Summary Review of PMA P020023

Background

Restylane is a medical device that has been used on the European market for facial tissue augmentation since September 1996. It is a clear, transparent, viscous and sterile gel, supplied in a single use disposable glass syringe. Restylane consists of non-animal, stabilized Hyaluronic Acid (NASHA) at a concentration of 20mg/ml, suspended in a physiological buffer pH 7. Each syringe contains 0.4 or 0.7 ml gel. The contents of the syringe are sterile.

Restylane is intended to be used for facial tissue augmentation. It is indicated for subcutaneous contour deformities, such as nasolabial folds. Restylane acts by adding volume to the tissue, thereby restoring the skin contours to the desired level of correction.

Two clinical studies have been performed in order to evaluate the safety and effectiveness of Restylane for the treatment of facial wrinkles and folds, a pivotal randomized study performed in the U.S. and supporting data of a study performed in Sweden.

Pivotal Study

The pivotal study was a randomized, double-blind, multicenter clinical study on Restylane vs. Zyplast indicated for nasolabial folds, performed in the U.S. under IDE G990258. 138 patients were treated in 6 centers. For each patient, one of the nasolabial folds was randomly assigned to be corrected with Restylane and the opposite side was treated with the comparator product Zyplast. In other words, each subject served as his or her own control, allowing for comparison for the outcome between the colateral sides. Dosing was as required to achieve optimal cosmetic result. Treatments were administered by a non-blinded treating investigator and a blinded evaluating investigator performed the effectiveness assessments. The response of the initial treatment was evaluated after two weeks and in case of non-optimal cosmetic result a touch-up treatment could be performed. The touch-up procedure was repeated every two weeks until the response was optimal.

Sample Size

A total of 138 patients were randomized, given the treatment and subsequently obtained an optimal cosmetic result. Only 137 subjects were properly randomized. 4 subjects withdrew and 26 had major protocol deviations resulting in only 108 subjects (78.3%) being evaluated for effectiveness (per-protocol population). Consequently, 134 subjects completed the study up until the 6-month visit. In summary, 138 were included in the safety analysis and 134 in the effectiveness analysis (intent-to-treat population).

Safety

Adverse events are descriptively summarized in Table 5 (page 129, Vol 5).

Effectiveness

The clinical effectiveness assessments were performed at:

?? The treatment visit (pre-treatment assessment)

?? When an optimal cosmetic result was obtained (baseline)

?? At the follow-up visits: 2, 4, and 6 months post baseline

The sponsor used two scales in measuring effectiveness: the Severity Rating Scale (5 grades) and the Global Aesthetic Improvement (5 grades). The primary endpoint was the evaluation of Restylane as compared with Zyplast regarding differences in the Severity Rating Scale (validated in a separate study) assessed by the Evaluating Investigator, six months after completed treatment.

The secondary endpoints were:

- ?? to evaluate safety (adverse events)
- ?? to evaluate severity of wrinkles at other time points, 2 and 4 months, by the evaluating investigator.
- ?? to evaluate severity of wrinkles at 2, 4, and 6 months by the subjects
- ?? to evaluate the Global Aesthetic Improvement as judged by the Evaluating Investigator and subject
- ?? to evaluate the number of sessions for each treatment group to achieve optimal cosmetic result
- ?? to assess the effect of masking

Supporting Data

A second non-randomized, open, multi-center study performed in Sweden was presented as supporting clinical data. The second study evaluated 112 patients in 3 centers with indication of using Restylane to treat nasolabial folds, glabellar lines, oral commissures, facial scars, etc. In this case the patients were followed for 6 months (26 weeks) after receiving treatment. The protocol was later amended to include also a week 52 evaluation. Out of the 112 patients, 11 withdraw from the study. Only 20 patients had the week 52 evaluation.

This memorandum discusses only the pivotal study since the supporting study presented only descriptive statistics and no statistical inference methods were used.

Reviewer's comments

1 Longitudinal Analysis

The sponsor claims that the primary endpoint is effectiveness at 6 months. The lack of longitudinal analysis will prevent us from analyzing trends and interactions, but this is not very troublesome if our main interest is the outcome at 6 months. The graphs in Appendix 24 can be helpful in evaluating trends. They present the mean change in SRS scores assessed by both the evaluating investigators and the subjects at each time point up to 9 months (ITT population). In addition, the mean treatment difference within subjects has also been displayed at each time point up to 9 months. Note, however, that at 9 months the sample had only 34 patients.

2. Open Label Extension of the Study

The study started with 134 patients and 100 were re-treated at 6 months. Consequently, the sponsor cannot claim that Restylane lasts more than Zyplast based on the Open Label Study. Since 100 patients needed re-treatment at 6 months, one would say that for 74.6% of the patients, neither Restylane nor Zyplast lasted more than 6 months.

Only (25%) patients were considered for evaluation of effectiveness beyond 6 months. As the sponsor states in the submission, it is hard to determine whether the fact that those 34 patients did not need re-treatment after 6 months was related to clinic effectiveness or to product effectiveness.

The 34 patients that were not re-treated constitute a “biased sample” and it is very difficult to draw any conclusions of superiority based on this sample alone. Among those 34 patients, 21 had better results with Restylane than Zyplast and 11 patients had better results with Zyplast than Restylane. However, if we consider all patients in the study, the numbers are as follows:

100 out of 134: Neither product lasted beyond 6 months – 74.6%

21 out of 134: Restylane was better than Zyplast at 9 months – 15.7%

13 out of 134: Restylane and Zyplast were equivalent at 9 months – 9.7%

All statistical analyses performed beyond 6 months for effectiveness disregarded the 100 patients who were re-treated at 6 months, the majority of the initial sample and consequently any conclusions beyond 6 months are questionable. In addition, most investigators that found Restylane appeared to be better than Zyplast in the Open Label phase of the study were in the same center.

3 Superiority of the Product by lasting more than 6 months

The sponsor claims that the effect of Restylane was sustained over nine months but the 9-month time point was calculated with only 34 subjects. For the remaining 100 subjects the effect of both treatments was gone by 6 months and consequently re-treatment was necessary.

4 Superiority of the Product by presenting a better SRS score assessed by the evaluating investigator

The sponsor used the following difference for the “evaluation on the SRS scale”:

$$D = (Pre_{Res} - Month6_{Res}) - (Pre_{Zyp} - Month6_{Zyp}) =$$

$$D = (\text{treatment result at 6 months for Restylane}) - (\text{treatment result at 6 months Zyplast})$$

If $D > 0$? Restylane is superior to Zyplast

If $D = 0$? Restylane is equal to Zyplast

If $D < 0$? Zyplast is superior to Restylane

According to the evaluating investigator’s assessment, for the ITT population (137 subjects) Restylane was superior to Zyplast in 78 cases (56.9%), Restylane was equal to Zyplast in 46 cases (33.6%) and Zyplast was superior to Restylane in 13 subjects (9.5%). For the PP population, the results were similar (total of 108 subjects; in 64 cases Restylane was superior (59.3%), in 34 cases the products were equivalent (31.5%), and in 10 cases Zyplast was superior (9.3%)).

McNemar’s test was performed only on the discrepant cases (subjects with $D=0$ were not included in the test) and statistical significance was shown. For the ITT population, there were 91 discrepant cases, 78 of them showing superiority of Restylane. Considering only the discrepant cases, as McNemar’s test does, the lower 1-tailed 95% Binomial confidence limit to

the proportion of cases in which Restylane is superior to Zyplast is 79%, and a null hypothesis of equivalence (50%) would be rejected.

However, please note that this test does not take into account the number of patients in which there was no discrepancy. The results would be the same whether there were 5 patients or 10,000 patients for whom Zyplast was equivalent to Restylane. In this case, there were 46 patients (33.6%) for whom Zyplast and Restylane were equivalent.

The clinical reviewers, together with the statistician, should think about this issue. In my opinion, when the patient chooses one treatment over the other based on the effectiveness, the patients wants to know what is the chance that the chosen treatment will be superior in his or her case. The fact that for 33.6% of patients, the treatments were equivalent, should be taken into account when the clinical reviewers consider the proposed claim of Restylane's superiority.

5 Superiority of the Product by presenting a higher mean SRS score assessed by the evaluating investigator

Data indicates that, although patients treated with Restylane show lower mean values in the SRS scale for all follow-up time points post treatment, the mean difference between Restylane and Zyplast was always less than 1 point, the minimal clinically significant difference. However, for each individual patient for whom Restylane was better than Zyplast, the difference was at least 1 point in the SRS scale. The mean difference was less than one point because for 42.9% of the patients Zyplast was equivalent or better than Restylane.

6 ITT and PP populations

Considering the ITT (intent-to treat) population for evaluating treatment effectiveness: The sponsor provided results based on the ITT population (137 subjects) and on the PP (per-protocol) population (108 subjects). The PP population excluded 25 major protocol violators and 4 withdrawals, resulting in a total of 108 subjects.

The results were similar but the clinical reviewers should agree that the ITT is the correct population to be considered. The PP population supported the results from the ITT population.

7 Treatment of Missing Values

Withdrawn patients: The sponsor explains that if the subject was withdrawn during the study, the pre-treatment Severity Rating Scale was used for all subsequent endpoints and consequently Restylane was considered equivalent to Zyplast with respect to the primary endpoint. That implies that the withdrawn patient was not included in the McNemar's test, since only discrepancies were considered. That may provide a biased estimate if the subjects that were not considered presented superior results in the Zyplast side of the nose.

Missing values: a missing value on the other effectiveness variables was handled according to the "last observation carried forward" method, which is objectionable in this case because treatment effects tend to decrease over time. This method could bias the results, but the bias could be attenuated by the fact that both treatments were applied in the

same subject (different sides of the nose) and both treatments should experience the same missing values and consequently, similar bias.

8 Assessment of Masking

Masking was not very good and as a consequence, the results may be substantially biased since the evaluation of the endpoints depends heavily on the (subjective) opinion elicited by the evaluating investigator and the subject.

Statistical tests were performed to assess the effect of masking for both the evaluating investigator and the subject.

?? The hypothesis that the evaluating investigator did not know which treatment was used in each side of the nose (probability of correct guessing was 50%) was rejected at all time points for the ITT population:

~~///~~ at baseline the chance of a correct guess was 64.2%

~~///~~ at 2 months the chance of a correct guess was 66.4%

~~///~~ at 6 months the chance of a correct guess was 70.1%

This fact is particularly troublesome since the primary endpoint is composed by a subjective evaluation performed by the evaluating investigator, and the results could be heavily biased by the lack of masking.

?? The hypothesis that the subject did not know which treatment was used in each side of the nose (probability of correct guessing was 50%) was also rejected at all time points for the ITT population. Like the investigator's guess, the subject's guess was correct in about two thirds of the cases.

This fact is also troublesome with the potential of biasing the results for the secondary endpoints.

The clinical reviewers should take the potential for bias into account when evaluating the effectiveness of this device particularly when considering Restylane's claim of superiority.

9 Homogeneity among centers

6 centers participated in the study. In all centers, the proportion of cases in which Restylane was superior to Zyplast at 6 months was larger than the proportion in which Zyplast was superior to Restylane, for both the evaluating investigators and the subjects (ITT and PP populations). However, for the ITT population, centers 3, 4, and 6 had a larger proportion of cases in which the treatments were equivalent. For the PP population, this happened for centers 3 and 4. This fact should be taken into account by the clinical reviewers when considering the claim of Restylane's superiority.

10 Validation of the Wrinkle Severity Rating Scale:

The sponsor carried out a study based on 30 photographs in order to validate the wrinkle severity scale. The proportion of agreement between test and re-test values and also between investigators was about 70%. This may constitute a satisfactory percentage of agreement: the sponsor calls it "an excellent agreement". However, it is far from perfect and indicates a considerable degree of subjectivity and lack of precision of the evaluation procedures: only in 70% of the cases an evaluator would give a wrinkle the same score

when evaluating it at two occasions. The clinical reviewers should take this fact into account when considering the claim of superiority proposed by the sponsor.

11. Safety: Mean duration of maximum intensity of Local Symptoms

Data indicates that the mean duration of swelling, pain, tenderness, and itching were statistically higher for Restylane than for Zyplast after the initial treatment. However, the time difference was less than a day. The clinical reviewer should assess the clinical significance of such finding that although statistically significant if not likely to be clinically significant.

After the touch-up sessions, Restylane did not show statistically significant longer duration for any of the symptoms.

Conclusion

A conclusion that Restylane is superior to Zyplast is problematic for the following reasons:

- ~~the~~ subjective nature of the evaluations and the imperfect validation of the Severity Rating Scale
- ~~the~~ lack of an effective masking procedure
- ~~the~~ lack of homogeneity among the centers (some centers had a considerable percentage of patients for whom the results provided by both treatments were equivalent)
- ~~the~~ overall percentage of patients for whom the treatments were equivalent (33.6%) and for which Zyplast was better (9.5%). In total, the overall percentage of patients for which Zyplast was equivalent or better was 42.9%.
- ~~the~~ imputation of missing data

In addition, it is difficult to conclude that Restylane lasts longer than 6 months because only 34 patients were not retreated at 6 months.