

 GALDERMA	<small>Title</small> SAP 43TW1628, Restylane Perlane Lidocaine vs. Restylane Perlane	<small>Doc id</small> MA-34458
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Statistical Analysis Plan

Clinical Trial Number: 43TW1628

**A randomized, multi-center, subject-blinded and evaluator-blinded study
comparing the pain and the safety profile associated with correction of
moderate to severe nasolabial folds using Restylane® Perlane Lidocaine
compared to Restylane® Perlane**

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<i>10.2.2 Related Adverse Events</i>	<i>35</i>
<i>10.2.3 Unrelated Adverse Events</i>	<i>40</i>

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1 Study Information

1.1 Introduction

1.1.1 Study design

This is a randomized, subject-blinded and evaluator-blinded study comparing the pain and the safety profile associated with correction of moderate to severe nasolabial folds (NLFs) using Restylane® Perlane Lidocaine (Perlane-Lido) compared to Restylane® Perlane (Perlane).

The study will be conducted at approximately 3 sites located in Taiwan and subjects aged 20 or older of Chinese origin will be enrolled. Each subject will be involved in the study for up to 31 days, including the screening period.

For more information regarding the study, please refer to the Clinical Study Protocol (CSP), MA-34273.

1.1.2 Number of subjects and randomization

The aim is to include 70 subjects treated with Perlane-Lido in one NLF and Perlane in the opposite NLF, as randomly assigned to one of the following treatment sequences:

- Perlane-Lido in the subject's right NLF followed by Perlane in the subject's left NLF.
- Perlane in the subject's right NLF followed by Perlane-Lido in the subject's left NLF.

Treatment will always start in the subject's right NLF.

1.2 Study Objectives

1.2.1 Primary objective

The primary objective is to evaluate the pain associated with injections of Perlane-Lido compared to Perlane for correction of moderate to severe NLFs.

1.2.2 Secondary objective

The secondary objective is to evaluate the dermal filler effectiveness of Perlane-Lido compared to Perlane for correction of moderate to severe NLFs.

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1.2.3 Safety objective

The safety objective is to evaluate the safety of Perlane-Lido and Perlane throughout the study.

1.3 Pain Assessments

1.3.1 Visual Analog Scale (VAS)

The VAS is a subjective scale used to measure pain intensity (Figure 1). The subject shall be instructed to put a vertical mark (|), approximating the pain experienced during the procedure, on a 100 mm horizontal line labeled 'No pain' at the left end and 'The worst pain you can imagine' at the right end. The VAS score is obtained by measuring the distance from the left end ('No pain') to the subject's VAS mark with a standard ruler.

Figure 1: Visual Analog Scale (VAS)

No pain ————— The worst pain you can imagine

Subjects will evaluate injection site pain for each side of the face at the time of injection (before massaging) and at 15, 30, 45, and 60 minutes post-treatment by completing a VAS.



1.4 Dermal Filler Effectiveness Assessments





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A horizontal bar chart showing the distribution of 1000 samples across 10 categories. The categories are represented by vertical bars on the left, each with a black segment at the top and a white segment below. The length of the black segment corresponds to the value of the sample for that category. The categories are ordered from highest to lowest value.

Category	Value
1	980
2	950
3	900
4	850
5	800
6	750
7	700
8	650
9	600
10	550

A large black rectangular redaction box covers the majority of the page content, starting below the header and ending above the footer. It is positioned in the center of the page.

10. **What is the primary purpose of the *Journal of Clinical Endocrinology and Metabolism*?**

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1.4.3 *Photography*

Digital photographs, taken of each subject pre-treatment at baseline, will be used [REDACTED]

1.5 Endpoints

1.5.1 *Primary endpoint*

- (i) Proportion of subjects that have a within-subject difference in VAS score (Perlane – Perlane-Lido) of at least 10 mm at injection.

1.5.2 *Secondary endpoints*

- (ii) Proportion of subjects that have a within-subject difference in VAS score (Perlane – Perlane-Lido) of at least 10 mm at 15, 30, 45, and 60 minutes after injection.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

1.6 Safety Assessments

The methods for collecting the safety data are described in Section 9 of the CSP and include assessments of pre-defined, expected post-treatment events collected in the subject diary, Adverse Events (AEs), and device deficiency.

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The subject will be instructed by the Investigator to record symptoms [REDACTED]

[REDACTED]

Each subject will be questioned about AEs at each clinical visit following the screening visit. A two-point scale ('Yes' or 'No') will be used to assess causality of AEs, serious as well as non-serious. The investigator shall be asked to indicate a response to each of the following questions in the electronic case report form (eCRF):

- *"Do you consider that there is a reasonable possibility that the event may have been caused by the study product?"* and
- *"Do you consider that there is a reasonable possibility that the event may have been caused by the study product injection procedure?"*

If any of these questions are answered with a 'Yes', the AE will be considered related.

Each AE will also be assessed for causal relationship and seriousness by the Sponsor, in order to fulfill regulatory requirements. In case of a disagreement, the AE will be considered 'Related'.

Digital photographs, taken at baseline and day 15 follow-up visit, will be used to document AEs in the treated area. If necessary, additional photo should be taken when AEs have occurred. No covering make-up should be used in the photographs.

Any device deficiencies discovered in relation to treatment at baseline and day 15 follow-up visit will be recorded.

1.7 Safety Endpoints

Safety endpoints include:

- (i) Incidence, intensity, duration and onset of related AEs collected throughout the study.
- (ii) Incidence, intensity, and number of days with pre-defined, expected post-treatment events collected using a subject diary for 14 days after treatment.

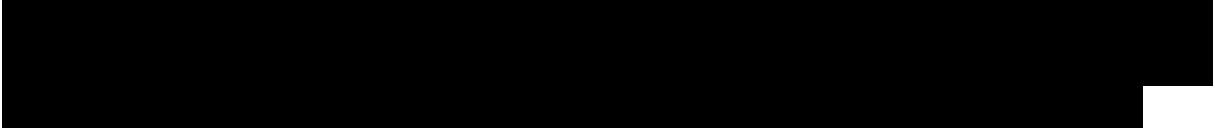
Number of days is defined as the total number of days with any observed event (to any intensity level) in a subject's diary.

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2 Statistical Methods

2.1 General Methods

All statistical analyses, including summary tables and data listings, will be performed using the SAS® system (version 9). Confidence intervals will be two-sided and constructed at the 95% confidence level.




2.2 Analysis Populations

The following populations will be defined:

- Safety
- Full Analysis Set (FAS)
- Per Protocol (PP)





The FAS population is the primary population for all effectiveness analyses. All safety analyses will be based on the Safety population. If there are any CSP deviations considered to have substantial impact on the primary effectiveness outcome at time of injection, a PP population excluding those subjects will be defined.



2.3 Study Subjects

2.3.1 Subject disposition

The disposition of subjects (Table 4-1) will be presented by site, and in total, including number and percentage of subjects that were screened, enrolled and withdrawn.

The number of withdrawn subjects will also be accounted for by visit, as well as number of completed subjects (Figure 2).

Screening failures, if applicable, will be listed by subject screening number, and reason for screening failure (Table 4-2).

2.3.2 Analysis populations

2.3.3 Protocol deviations

Definition of protocol deviations that will exclude subjects from the PP population are defined (but not limited to) in Table 2-1 below.

Table 2-1: Protocol deviations excluding subjects from the PP population

	■	
	■	
	■	
	■	
	■	
	■	
	■	

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2.3.4 Demographics and baseline characteristics

[REDACTED]

2.3.5 Medical history, and concomitant medication and procedures/treatments

All summaries will be based on the FAS population. Medical history will be coded according to medical dictionary for regulatory activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

Medical history/concurrent disease

[REDACTED] subjects reporting facial dermatological procedures or surgeries performed [REDACTED] will be presented.

[REDACTED] subjects reporting relevant medical history/concurrent diseases and prior facial dermatological procedures performed [REDACTED] will be summarized by [REDACTED]

[REDACTED]

Concomitant medication and procedures/treatments

[REDACTED] subjects reporting concomitant medication will be summarized in total (Table 6-1)

[REDACTED]

Concomitant medication taken due to an AE will be summarized [REDACTED]

[REDACTED]

[REDACTED]

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2.3.6 *Extent of exposure*

[REDACTED]

[REDACTED]

[REDACTED]

2.4 Primary and Secondary Analyses

2.4.1 *Data sets analyzed*

All variables will be analyzed using the FAS population. The primary analysis will also be repeated using the PP population. If it is deemed necessary, other analyses will be repeated using the PP population.

2.4.2 *Handling of missing data*

As the study design is intra-individual, in which the outcome of both treatments to be compared is available on each subject, it is expected that when a data is missing, it will be missing for both NLFs in most of the cases. A majority of the deviations from the protocol can be expected to affect both NLFs and evaluations of the same subject the same way.

[REDACTED]

All other endpoints will be analyzed on available data, i.e. no imputations will be done.

(i) Sensitivity analysis

[REDACTED]

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2.4.3 Primary analysis

The proportion of subjects that have a within-subject difference in VAS (Perlane minus Perlane-Lido) of at least 10 mm at the time of injection will be calculated together with a two-sided 95% confidence interval. The objective is to show that the confidence interval lies above 50% based on the FAS analysis set. To assess the robustness of the results, the same analysis will be re-run using the PP analysis set (Table 8-1).

The calculation of this proportion utilizes the split-face design of the study since it is based on within-subject difference in pain. The limit of 50% is chosen in order to show that the majority of subjects have at least 10 mm less pain when treated with Perlane-Lido as compared to Perlane.

2.4.4 Secondary analysis

The proportion of subjects that have a within-subject difference in VAS of at least 10 mm at post injection time points (15, 30, 45 and 60 minutes after injection) will be calculated together with a two-sided 95% confidence interval (Table 9-1). The mean VAS by treatment (Table 9-2 and Graph 9-1) and the mean within-subject difference in VAS (Table 9-3) will be calculated at each time point (at injection and 15, 30, 45 and 60 minutes after injection) and presented using descriptive statistics for continuous endpoints.

2.5 Safety Analysis

All safety variables will be summarized descriptively based on the safety population.

2.5.1 Predefined, expected post-treatment events

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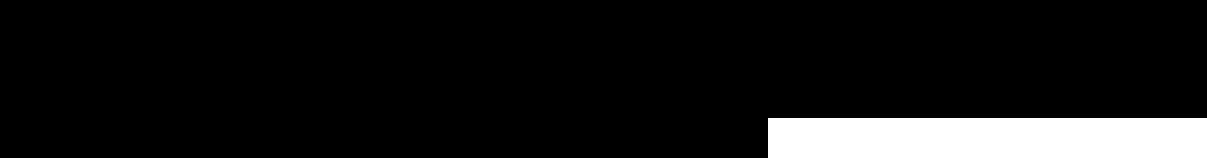
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2.5.2 *Adverse events*

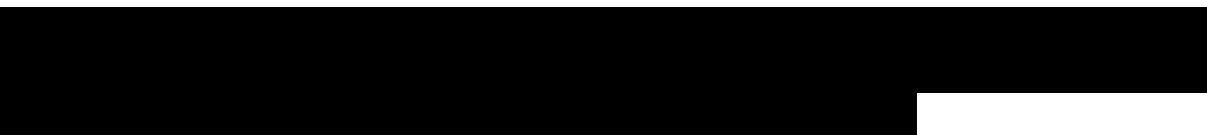
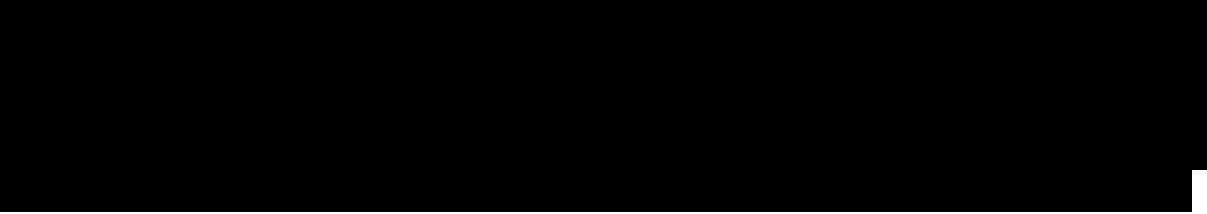
All AEs will be summarized and listed by SOC and PT assigned using MedDRA.



All AEs will be included in the data listings. Any serious Adverse Events and/or AEs that led to withdrawal will be listed separately.

2.6 **Interim Analysis**

No interim analysis is planned.



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2.8 Changes in the Analysis Planned in the Protocol

3 Reference List

1 Brandt F, Bank D, Cross SL, Weiss R. A lidocaine-containing formulation of large-gel particle hyaluronic acid alleviates pain. *Dermatol Surg*. 2010 Nov; 36 Suppl 3:1876-85.

2 Weiss R, Bank R, Brandt F. Randomized, Double-Blind, Split-Face Study of Small-Gel-Particle Hyaluronic Acid with and without Lidocaine During Correction of Nasolabial Folds, *Dermatol Surg* 2010;36:750–759.

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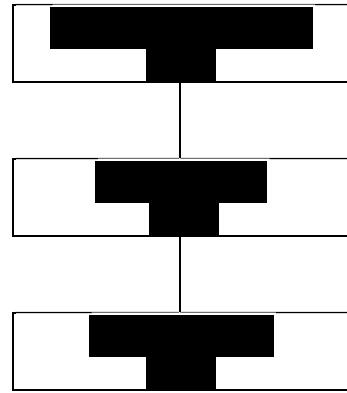
4 Appendix A1: Study Subjects

Figure 1. The effect of the number of hidden neurons on the performance of the neural network.

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5 Appendix A2: Demographics and Baseline Characteristics

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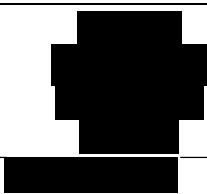
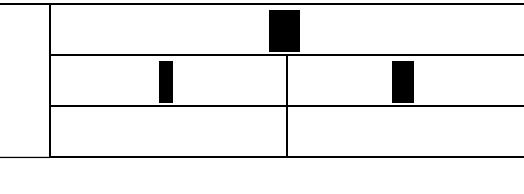
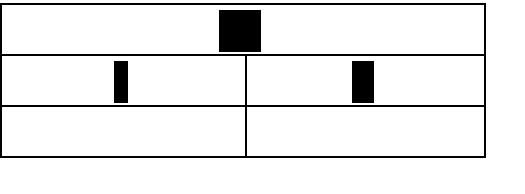
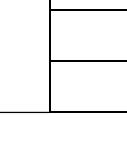
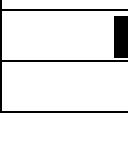
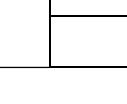
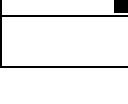
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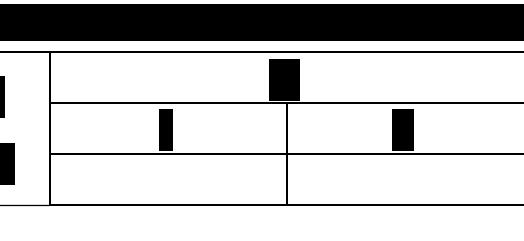
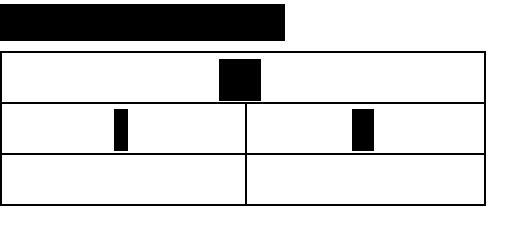
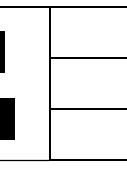
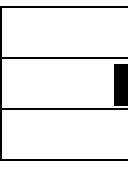
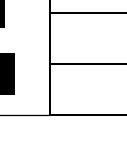
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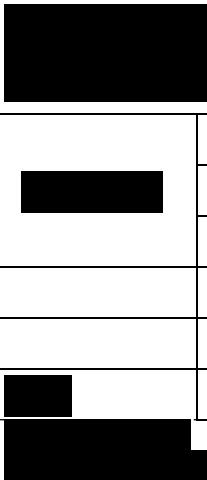
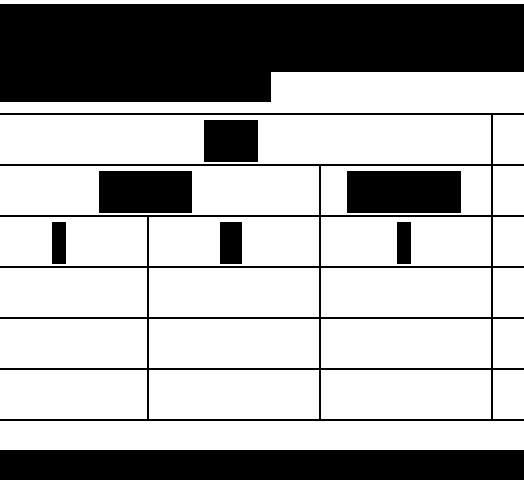
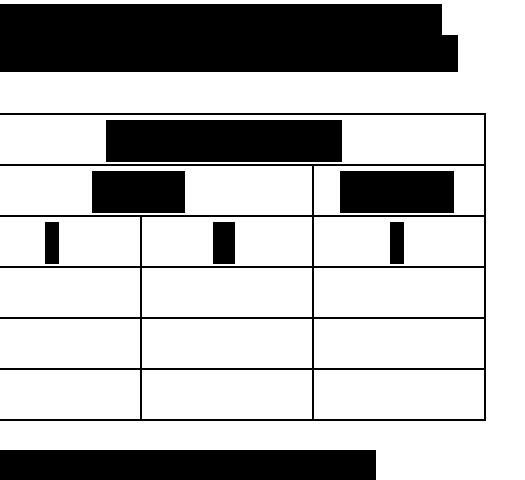
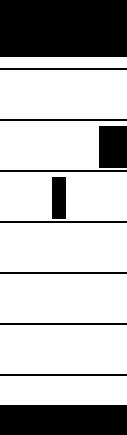
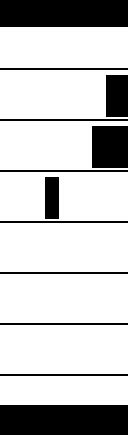
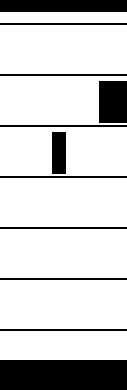
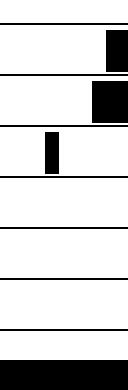
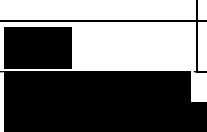
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6 Appendix A3: Concomitant Medication and Procedures/Treatments

Figure 1. The effect of the number of hidden neurons on the performance of the neural network.

[REDACTED]

A diagram consisting of several black geometric shapes on a white background. On the left, there is a large T-shaped block. In the center, there is a 2x2 grid of smaller black L-shaped blocks. At the bottom, there is a large L-shaped block.

[REDACTED]



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7 Appendix A4: Treatment Procedure

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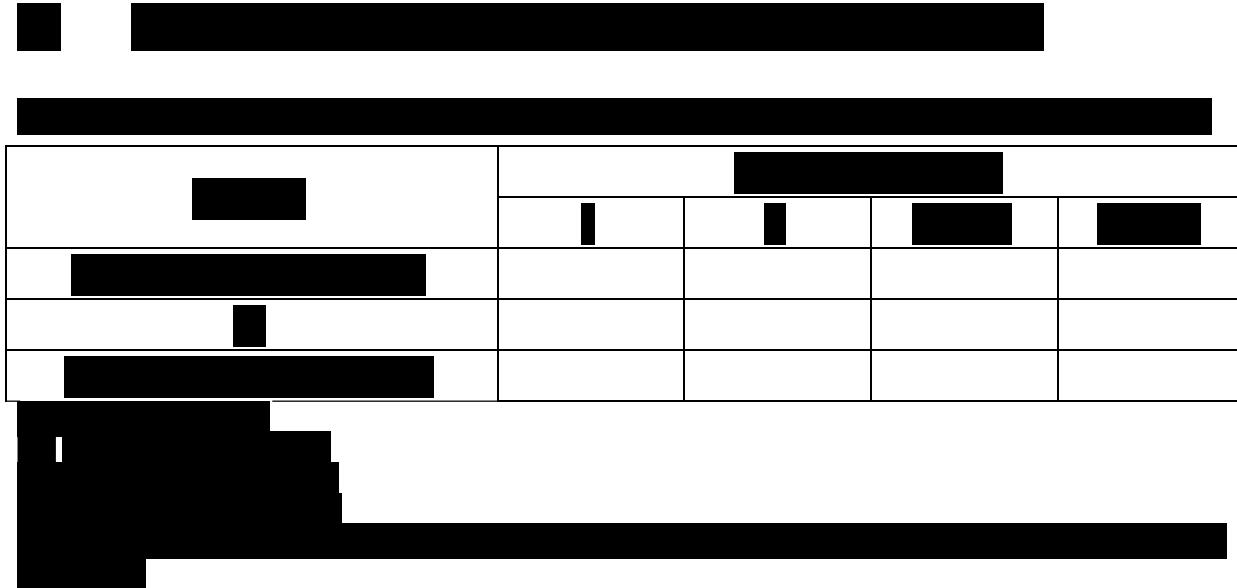
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9 Appendix A6: Secondary Analyses

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[REDACTED] [REDACTED]

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[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



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A 10x10 grid of black bars. The first two columns are solid black. The third column has a black bar at row 1 and a shorter black bar at row 2. The fourth column has a black bar at row 1 and a shorter black bar at row 3. The fifth column has a black bar at row 1 and a shorter black bar at row 4. The sixth column has a black bar at row 1 and a shorter black bar at row 5. The seventh column has a black bar at row 1 and a shorter black bar at row 6. The eighth column has a black bar at row 1 and a shorter black bar at row 7. The ninth column has a black bar at row 1 and a shorter black bar at row 8. The tenth column has a black bar at row 1 and a shorter black bar at row 9. The bottom row has a solid black bar from column 1 to column 2, and a solid black bar from column 9 to column 10.



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10 Appendix A7: Safety Evaluation

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A 10x10 grid of black and white squares. The first two columns are black. Columns 3-4 are white. Columns 5-6 are black. Columns 7-8 are white. Columns 9-10 are black. The last row is solid black.

[REDACTED]



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10 of 10

[REDACTED]

A horizontal bar chart with 10 bars. The first 9 bars are black and of varying lengths, decreasing from left to right. The 10th bar is light purple and is the same length as the 8th bar. The bars are set against a grid of light gray lines.



Title

SAP 43TW1628, Restylane Perlane Lidocaine vs. Restylane Perlane

Doc id

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A 6x10 grid of black and white squares. The first two rows are mostly black, with the second row containing several white squares. The third row has a single black square. The fourth row has two black squares. The fifth row has one black square. The sixth row has one black square. The last row is mostly black, with a single white square.





The image consists of a grid of black rectangles on a white background. In the top half, there are several large, horizontal rectangles of varying widths. In the bottom half, there are smaller, more scattered rectangles. Some rectangles overlap, and some are positioned on top of each other. The overall effect is abstract and geometric.





Black box for the first part of the proof of Theorem 1.

For more information, contact the Office of the Vice President for Research and Economic Development at 515-294-6450 or research@iastate.edu.



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