GALDERMA	Title **SAP 43TW1628, Restylane Perlane Lidocaine vs. Restylane Perlane**	Doc id **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

Effective

Version: 1.0

Effective date: 2017-09-07 12:43
Effective
Version: 1.0

Table of Contents

1 Study Information 4
1.1 Introduction 4
1.1.1 Study design 4
1.1.2 Number of subjects and randomization 4
1.2 Study Objectives 4
1.2.1 Primary objective 4
1.2.2 Secondary objective 4
1.2.3 Safety objective 5
1.3 Pain Assessments 5
1.3.1 Visual Analog Scale (VAS) 5
1.3.2 Treatment Preference Question 5
1.4 Dermal Filler Effectiveness Assessments 5
1.4.1 [redacted]
[redacted]
1.4.3 Photography 7
1.5 Endpoints 7
1.5.1 Primary endpoint 7
1.5.2 Secondary endpoints 7
1.6 Safety Assessments 7
1.7 Safety Endpoints 8
2 Statistical Methods 9
2.1 General Methods 9
2.2 Analysis Populations 9
2.3 Study Subjects 10
2.3.1 Subject disposition 10
2.3.2 Analysis populations 10
2.3.3 Protocol deviations 10
2.3.4 Demographics and baseline characteristics 11
2.3.5 Medical history, and concomitant medication and procedures/treatments 11
2.3.6 Extent of exposure 12
2.4 Primary and Secondary Analyses 12
2.4.1 Data sets analyzed 12

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

2.4.2 Handling of missing data *12*

2.4.3 Primary analysis *13*

2.4.4 Secondary analysis *13*

2.5 Safety Analysis 13

2.5.1 Predefined, expected post-treatment events *13*

2.5.2 Adverse events *14*

2.6 Interim Analysis 14

2.7 Determination of Sample Size 14

2.8 Changes in the Analysis Planned in the Protocol 15

3 Reference List 15

4 Appendix A1: Study Subjects 16

4.1 Disposition of Subjects 16

4.2 Analysis Populations 17

4.3 Withdrawals 17

4.4 Protocol Deviations 17

5 Appendix A2: Demographics and Baseline Characteristics 18

5.1 Demographics 18

5.2 Medical History 19

6 Appendix A3: Concomitant Medication and Procedures/Treatments 21

6.1 Concomitant Medication 21

6.2 Concomitant Procedures/Treatments 23

7 Appendix A4: Treatment Procedure 24

8 Appendix A5: Primary Analysis 27

8.1 Within-Subject Difference in VAS Scores at Time of Injection 27

9 Appendix A6: Secondary Analyses 28

9.1 Visual Analogue Scale (VAS) 28

9.2 Treatment Preference Question 29

[redacted]

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10 Appendix A7: Safety Evaluation 32

10.1 Pre-defined, expected post-treatment events 32

10.2 Adverse Events 34

10.2.1 Summary of all reported Adverse Events 34

10.2.2 Related Adverse Events 35

10.2.3 Unrelated Adverse Events 40

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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.

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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.

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1.4 Dermal Filler Effectiveness Assessments

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Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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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]

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.

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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.

[redacted]

2.2 Analysis Populations

The following populations will be defined:

- Safety [redacted]
- Full Analysis Set (FAS) [redacted]
- Per Protocol (PP) [redacted]

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.

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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

[redacted]

2.3.3 Protocol deviations

[redacted]

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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Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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]

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]

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

2.3.6 Extent of exposure

[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]

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

[redacted]

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.

[redacted]

[redacted]

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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Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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2.5.2 Adverse events

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

[redacted]

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.

[redacted]

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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.

Effective date: 2017-09-07 12:43

Effective

Version: 1.0

4 Appendix A1: Study Subjects

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Effective date: 2017-09-07 12:43

Effective

Version: 1.0

5 Appendix A2: Demographics and Baseline Characteristics

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Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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Effective date: 2017-09-07 12:43

Effective

Version: 1.0

6 Appendix A3: Concomitant Medication and Procedures/Treatments

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Version: 1.0

7 Appendix A4: Treatment Procedure

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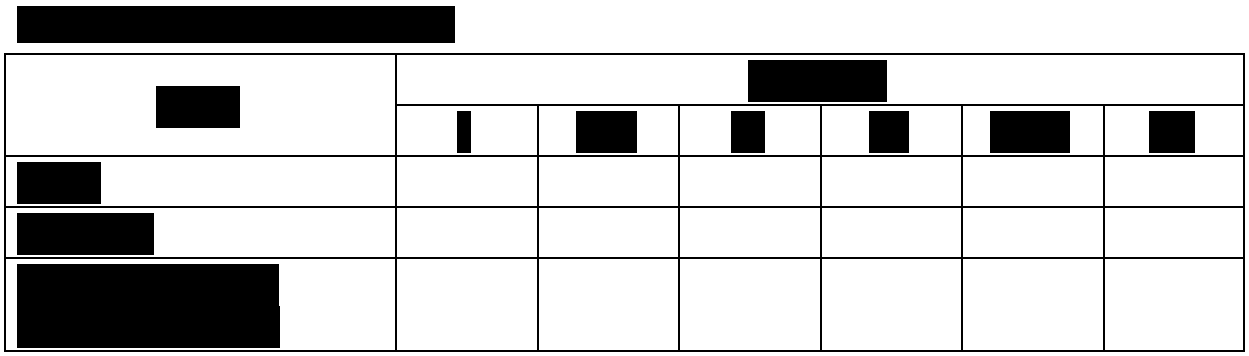

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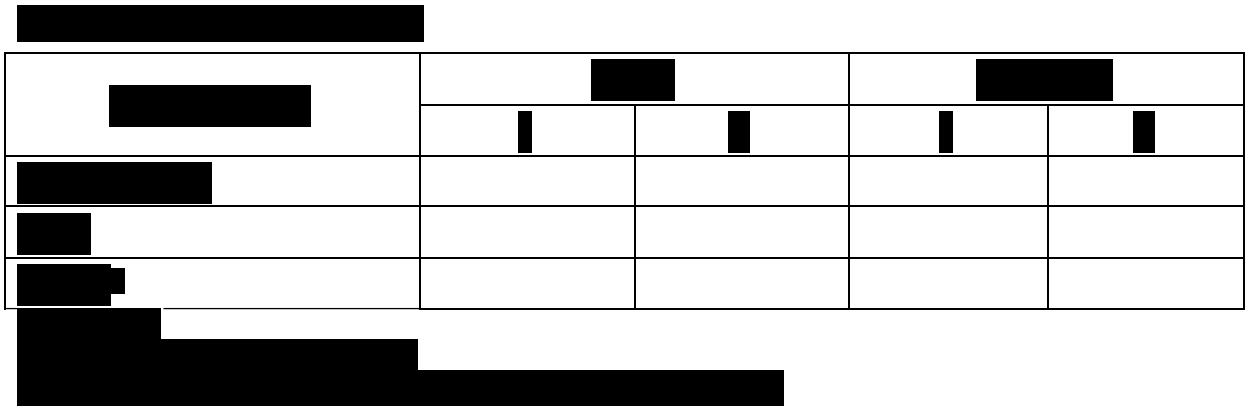

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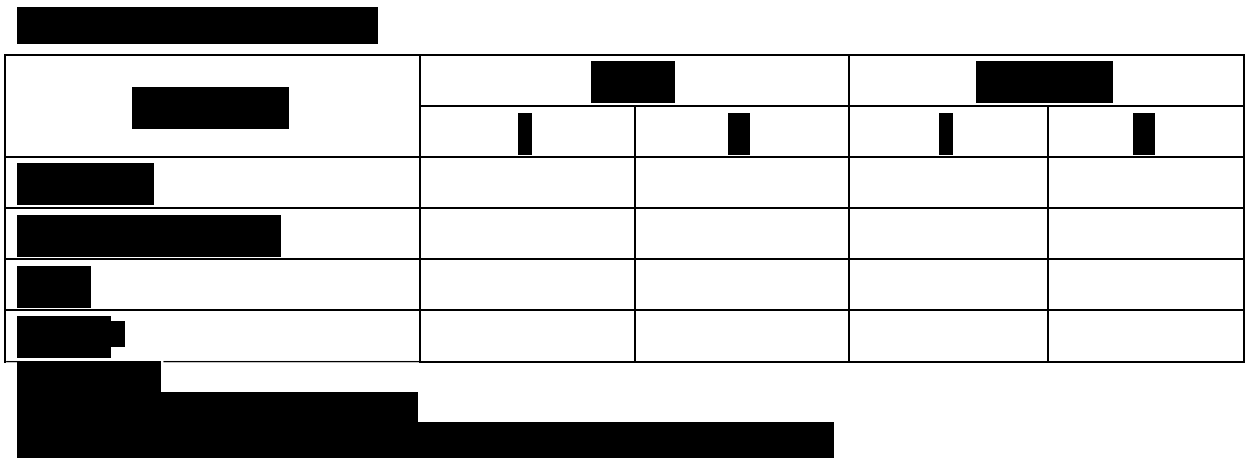

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8 Appendix A5: Primary Analysis

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Effective date: 2017-09-07 12:43

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Version: 1.0

9 Appendix A6: Secondary Analyses

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10 Appendix A7: Safety Evaluation

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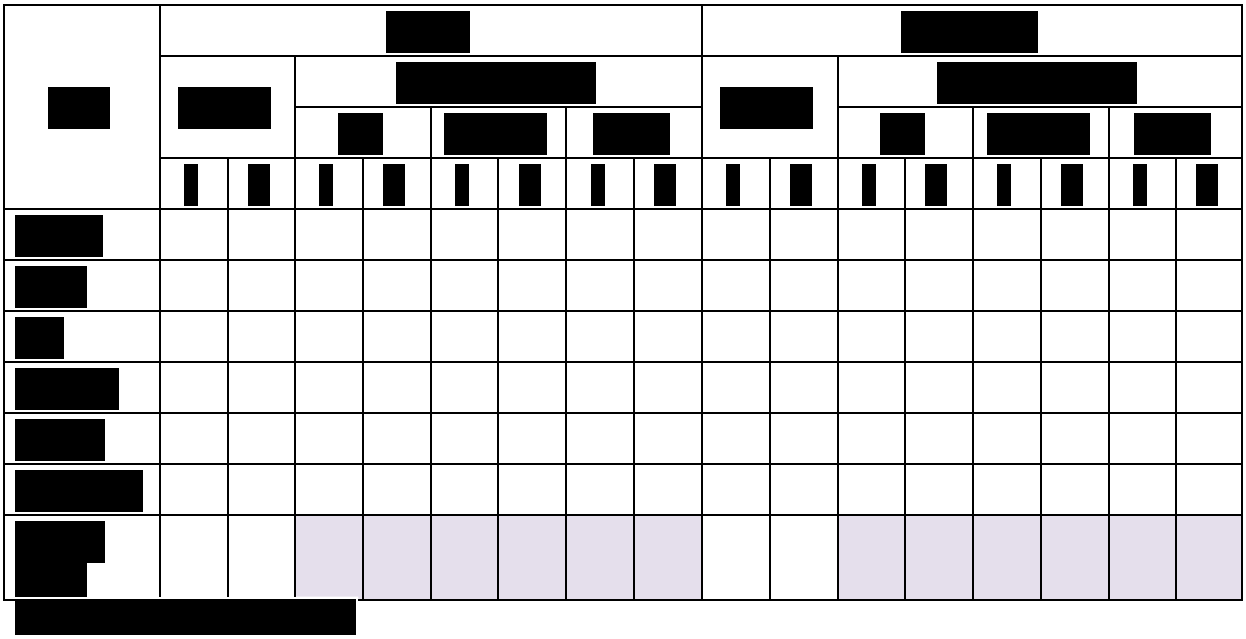

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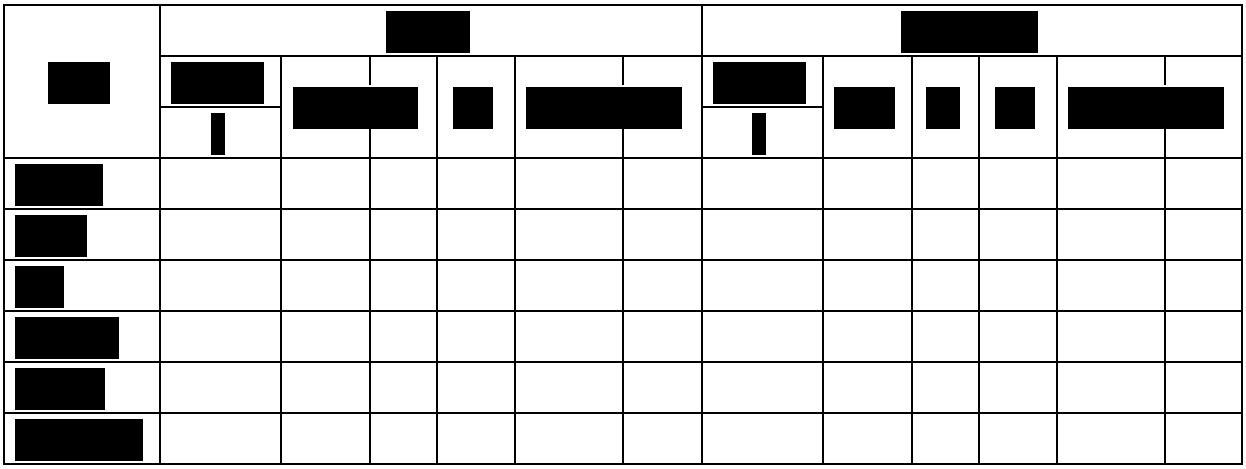

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Effective date: 2017-09-07 12:43

Effective

Version: 1.0

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