STATISTICAL ANALYSIS PLAN

Date: 19-Feb-2020

A randomized, controlled, double-blinded, within-subject (split-face), multicenter, prospective clinical study to compare the level of pain using the dermal filler RHA® formulated with two different anesthetics in the treatment of perioral rhytids

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Confidentiality Statement
The information contained in this document is provided in confidence. It is understood that this information will not be disclosed to others without prior agreement with the Sponsor.

SAP APPROVAL SIGNATURE PAGE

The following individuals approve this version of the [redacted] Statistical Analysis Plan.

Sponsor – TEOXANE SA:

[redacted] Clinical Program Manager DATE

Clinical Research Organization - [redacted]

[redacted] DATE

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1. INTRODUCTION

This statistical analysis plan (SAP) gives a comprehensive and detailed description of statistical techniques to be used for [redacted]. The purpose of this SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches for the analysis of study data prior to database lock. This SAP provides additional details concerning the statistical analyses outlined in the protocol. Whenever differences exist in descriptions or explanations provided in the protocol and SAP, the SAP prevails.

1.1 Background

Hyaluronic acid (HA) is a long-chain, repeated dimer, N-acetyl glucosamine and D-glucuronic acid polymer and is a major component of the extracellular matrix. HA is widely present in all animal species and does not differ from one species to another. Due to this extended compatibility, non-human HA can be used in humans without unacceptable adverse effects. Due to its natural viscoelastic and hydrogel properties, HA is widely used as matrix in tissue regeneration and particularly in dermal defect reconstruction.

RHA® [redacted] and RHA® [redacted] dermal fillers are devices containing colorless, biodegradable, sterile, biocompatible, crosslinked HA of non-animal origin (i.e., bacterial fermentation using *Streptococcus zooepidemicus*). Crosslinking is performed using 1,4-butanediol diglycidyl ether (BDDE) to form a gel. RHA® [redacted] product contains 0.3% w/w of lidocaine hydrochloride, and RHA® [redacted] contains 0.3% w/w of [redacted] hydrochloride. Both lidocaine and [redacted] are drug substances widely used for their anesthetic properties (i.e., they block the origin and transmission of nervous influx at the point of injection by stabilizing the neuronal membrane).

1.2 Rationale for Study

[redacted]

1.3 Hypothesis

The anesthetic effect of RHA® [redacted] with [redacted] will be non-inferior to RHA® [redacted] with lidocaine in terms of injection site pain felt by the subject during injection into the upper perioral rhytids assessed immediately after injection of each upper quadrant using a 100 mm Visual Analog Scale (VAS).

1.4 Primary Objective

The study objective is to demonstrate the non-inferiority of RHA® [redacted] with [redacted] versus the control (RHA® [redacted] with lidocaine) in terms of reducing pain during device injection into the upper perioral rhytids. Injection pain during injection will be based on the 100 mm Visual Analog Scale (VAS), as assessed by subjects immediately after injection of each upper perioral quadrant.

2. OVERVIEW OF STUDY DESIGN

2.1 Study Design

This is a randomized, controlled, double-blinded, within-subject (split-face), multicenter, prospective study to investigate whether RHA® [redacted] with [redacted] is non-inferior to RHA® [redacted] with lidocaine in terms of injection site pain felt by the subject during injection.

At screening, the Treating Investigator (TI) will evaluate subjects' perioral rhytid severity (using the Perioral Rhytid Severity Rating Scale; PR-SRS) to confirm eligibility and to establish a pre-treatment score for assessing aesthetic improvement.

At Visit 1, RHA® [redacted] with [redacted] will be administered in a random sequence (first or second injection) and side of the mouth and RHA® [redacted] with lidocaine will be administered to the other side. Study subjects and the TI injecting study devices will be blinded.

[redacted]

Immediately <u>after</u> injection of an upper perioral quadrant, subjects will rate injection site pain experienced **during injection** using a 100 mm Visual Analog Scale (VAS). Injection site pain in each side of the mouth will also be assessed at 15, 30, 45 and 60 minutes after the upper quadrant was injected.

[redacted]

Safety evaluation will consist of AE assessments, [redacted] a 30-day CTR diary, and a follow-up call performed by the study site at 72 hours after injection.

Subjects will attend Visit 2 (30 days post-injection) during which efficacy and safety assessments will be conducted. Subjects who present with an unresolved clinically significant device related AE at Visit 2 will receive the optional follow-up phone call no later than 30 days after Visit 2. If the clinically significant AE remains unresolved, the Investigator will request that the subject attend the optional in-clinic follow-up visit (i.e., Visit 3) within 5 working days. Follow-up of the clinically significant AE will continue until the AE is resolved or the TI determines that additional follow-up is not necessary.

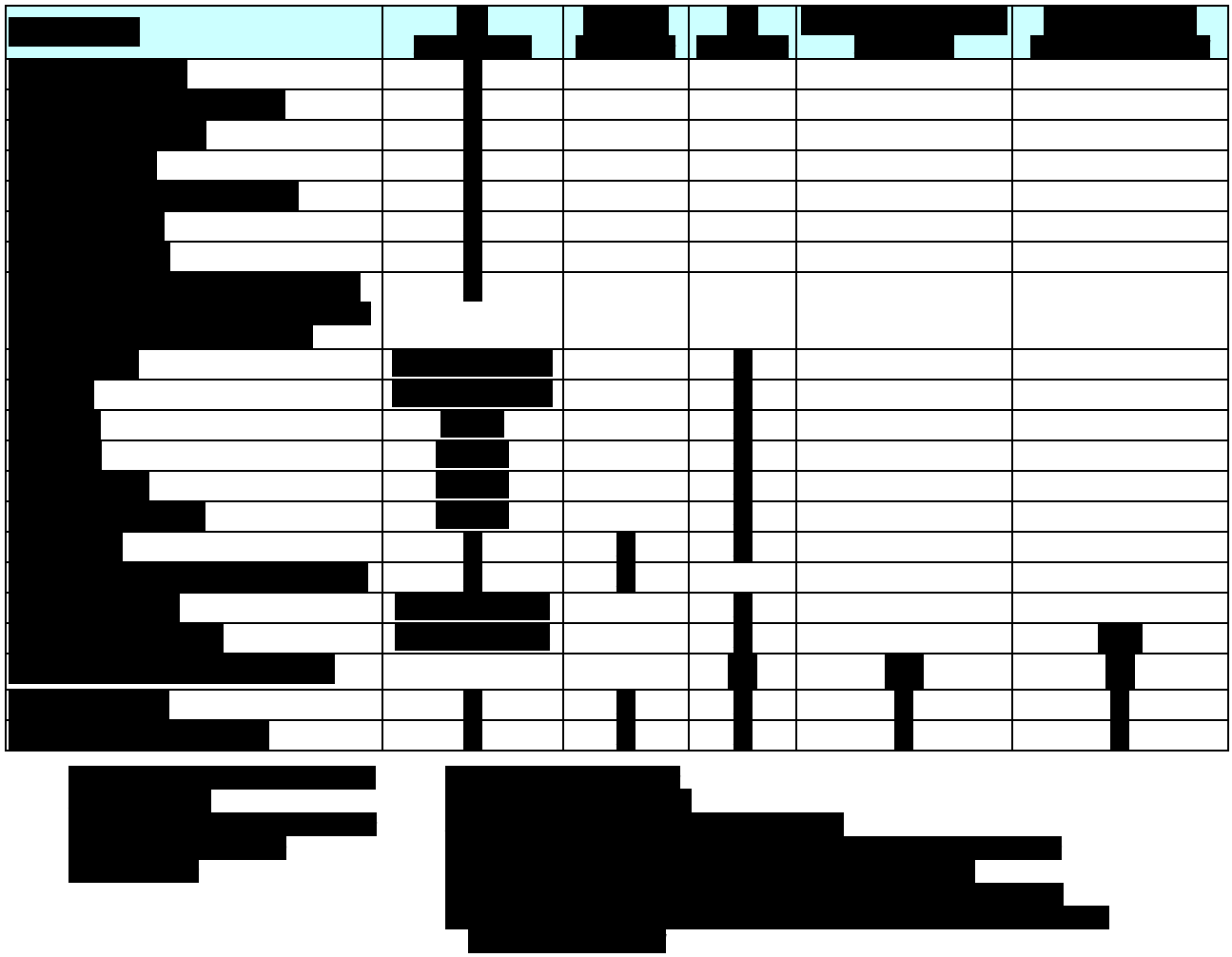
[redacted]

2.2 Study Design Rationale

2.2.1 Study Population

Maximum 30 subjects will be enrolled and receive study treatment. The study population includes female and male subjects who are ≥22 years old. [redacted] See Study Protocol Section 5 for a full description of the inclusion and exclusion criteria.

TABLE 1. STUDY SUMMARY TABLE



3. TREATMENT ALLOCATION, RANDOMIZATION AND BLINDING

Upon qualifying for treatment, subjects will be randomized for the side of mouth and the order of injection of study devices (i.e., left or right / 1st or 2nd order). If needed to improve cosmetic results, the lower perioral quadrant of a side will be injected only after both upper perioral quadrants have been injected.

[redacted]

4. DEVICE APPLICATION

4.1 Injection of Study Devices

[redacted]

4.1.3 Injection Sequence

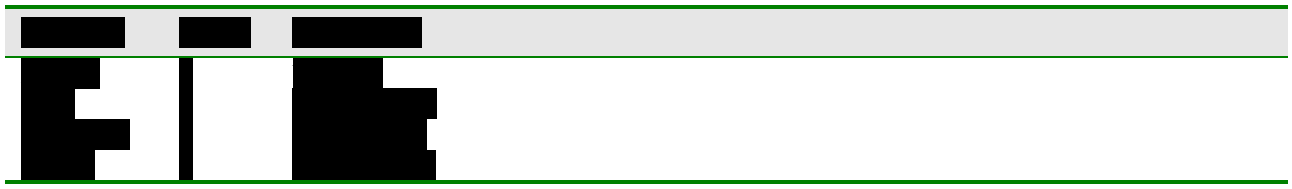
Upon qualifying for treatment, subjects will be randomized for the side of mouth and the order of injection (i.e., left or right / 1st or 2nd order). Both upper perioral rhytids will be injected prior to injection of either lower perioral rhytid. [redacted]

[redacted]

5. STUDY EVALUATIONS

5.1 Effectiveness Variables

[redacted]



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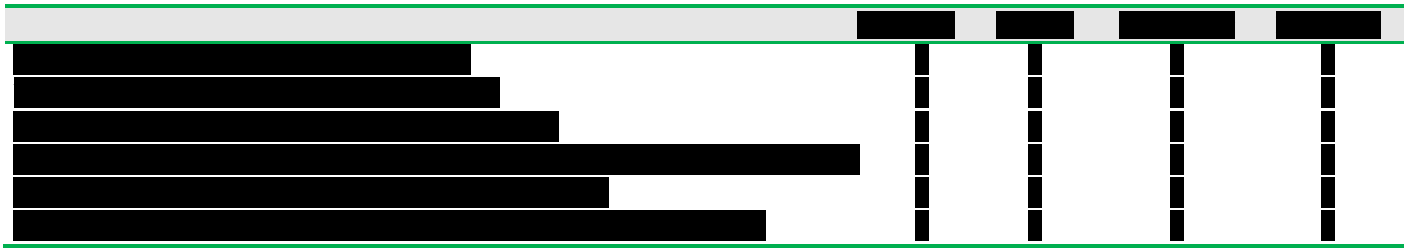

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5.2 Safety

Safety will be evaluated through a 30-day patient Common Treatment Response (CTR) diary that captures post-injection signs/symptoms and AE reporting based on phone follow-ups and clinic visits. [redacted].

5.2.1 30-Day Patient Common Treatment Response Diary

The subject will receive a diary booklet and instructions for recording his/her observations of the CTRs of the study treatments for the first 30 days after treatment.

The subject diary will capture the following CTRs that typically occur following the injection of a dermal filler; specifically, redness, pain, tenderness, firmness, swelling, lumps/bumps, bruising, itching, discoloration, and "other". Subjects will record the presence and the severity of each observed sign/symptom as: none, mild, moderate, or severe.

[redacted]

5.2.4 Adverse Events

The Investigator will assess AEs and record details of seriousness, severity, duration, and action taken with the study device, and relationship to the study device. AEs will be reported from the time of consent until the final visit, or to 30 days following the last treatment.

6. STATISTICAL METHODS

6.1 Primary Endpoint

The primary endpoint will be the injection site pain felt during injection of the upper perioral quadrants assessed by the subject immediately following injection with RHA® [redacted] with [redacted] compared to the injection site pain felt during injection of the contralateral upper perioral quadrant assessed immediately following injection with RHA® [redacted] with lidocaine.

The effectiveness of RHA® [redacted] with [redacted] will be demonstrated if the injection site pain during injection of the upper perioral quadrant assessed by subjects immediately following injection with RHA® [redacted] with [redacted] is statistically non-inferior to the injection site pain felt during injection of the contralateral upper perioral quadrant assessed by subjects immediately following injection with RHA® [redacted] with lidocaine.

The primary endpoint will use a paired design and will be analyzed using hypothesis test.

For achieving non-inferiority, the observed p value must be ≤0.05, taking account of the non-inferiority margin (i.e., 10mm difference in Pain VAS between the two treatment groups).

In case of non-inferiority, for achieving superiority of RHA® [redacted] with [redacted] over RHA® [redacted] with lidocaine in terms of reducing pain, the observed p-value must be ≤0.05.

[redacted]

6.4 Analysis Populations

Three subject analysis populations are defined: Intent-to-Treat (ITT) Population, Per Protocol (PP) Population, and Safety (SAFT) Population. All analysis populations will be defined and determined prior to database closure and unblinding for the final analysis.

6.4.1 Intent-to-Treat (ITT) Population

[redacted]

[redacted]

6.4.2 Per Protocol (PP) Population

[redacted]

6.4.3 Safety (SAFT) Population

[redacted]

6.6 General Considerations

Data will be listed by treatment group and subject number. The safety and efficacy data will be summarized by treatment allocation. Descriptive statistics will consist of mean, standard deviation, minimum and maximum for continuous variables, and frequency and percent for discrete variables.

This SAP will be finalized and approved by the study Sponsor prior to the last subject's last visit. All programs for data output and analyses will be written in SAS version 9.4 or higher (SAS Institute, Inc., Cary, NC).

[redacted]

6.7 Effectiveness Analysis

6.7.1 Primary Endpoint

Effectiveness of RHA® [redacted] with [redacted] versus control will first be analyzed in a non-inferiority statistical model using the pain felt by the subject during injection. If non-inferiority is achieved, pain felt by the subject during injection will be tested for superiority (i.e., to confirm if RHA® [redacted] is superior to RHA® [redacted] for reducing pain).

[redacted] Wilcoxon signed-rank test

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6.7.2 Secondary Endpoints

[redacted] Wilcoxon signed-rank test

6.8 Safety Analysis

The SAFT Population will be used to summarize the safety of the study devices and will consist of all treated subjects. The primary safety analysis is the calculation of the incidence of CTRs and adverse events in the study period. Point estimates for all CTRs, AEs and SAEs will be presented and two-sided exact 95% confidence intervals will be calculated for the overall incidence of AEs and SAEs. Tables will be generated which summarize AEs by investigator assessments of both relationship to treatment and severity.

6.8.1 Adverse Events (AEs)

Safety outcomes will be incidence rate of AEs, including UADEs, types of AEs and their relationship to study treatment. Severity and relationship to study treatment will be assessed and recorded.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. These events, irrespective of relationship to study medication, will be summarized by MedDRA system organ class (SOC) and MedDRA preferred term (PT). The number of subjects reporting an AE, the number of AEs, and percentages of subjects in each category will be summarized. AEs by severity and relationship to study will be summarized in a similar way. Serious AEs will be summarized separately. Specifically, the following AE incidence tables will be provided:

- All and possibly* related AEs sorted by SOC
- All and possibly* related AEs sorted by decreasing frequency
- SAEs: All and possibly* related SAEs sorted by seriousness criterion
- SAEs: All and possibly* related SAEs sorted by SOC
- UADEs: All UADEs sorted by SOC
- Death: All and possibly* related deaths sorted by SOC

** definitely probably, possibly*

Incidence rates with two-sided exact 95% confidence intervals will be calculated for the overall incidence of AEs and SAEs

Statistical analysis will also be performed to evaluate the potential impact of the injection technique on the safety data.

APPENDIX A: SUMMARY OF STATISTICAL TESTS

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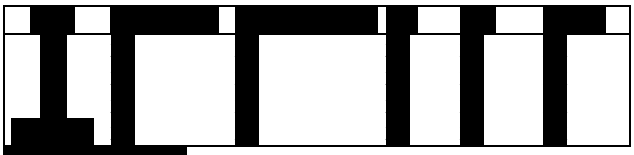

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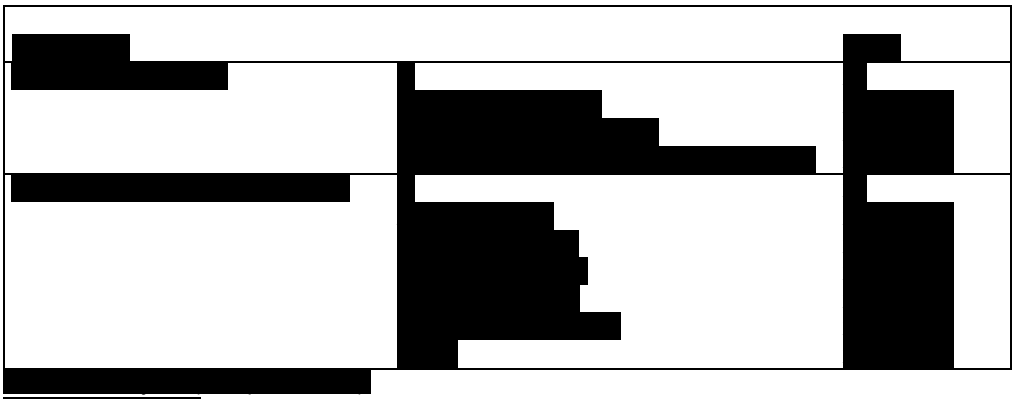

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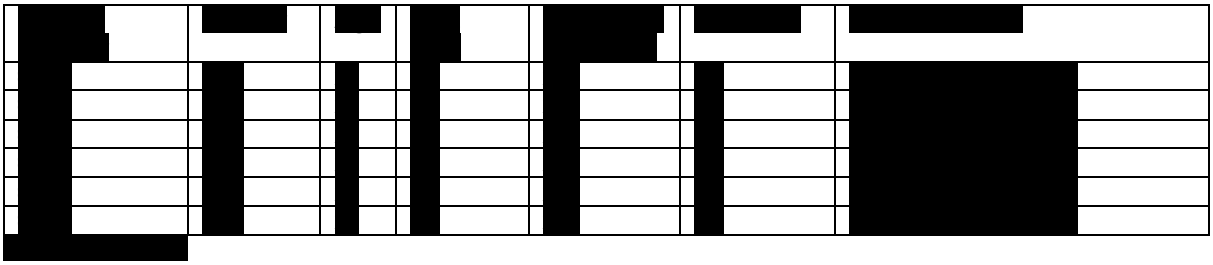

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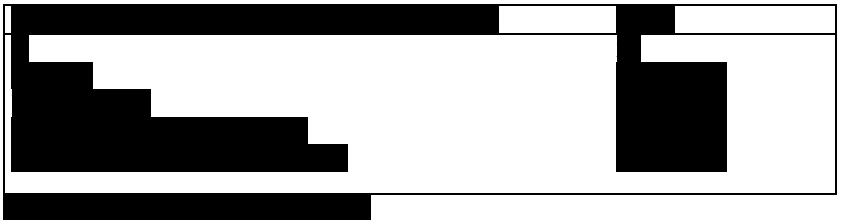

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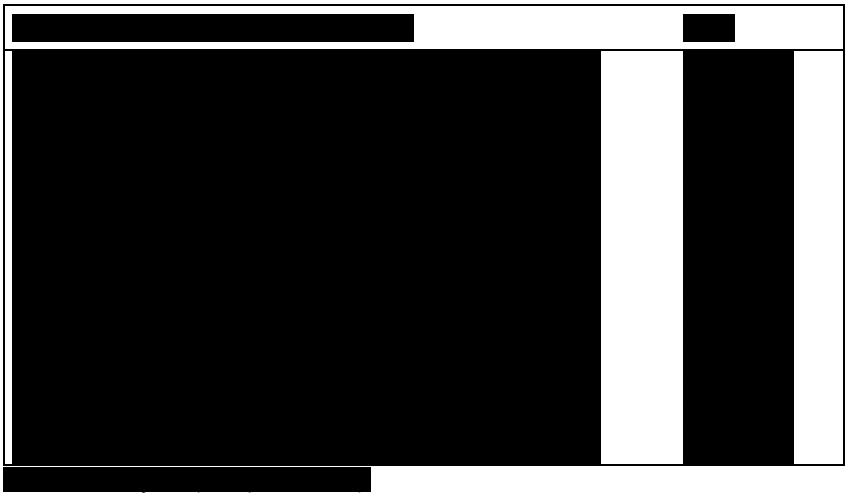

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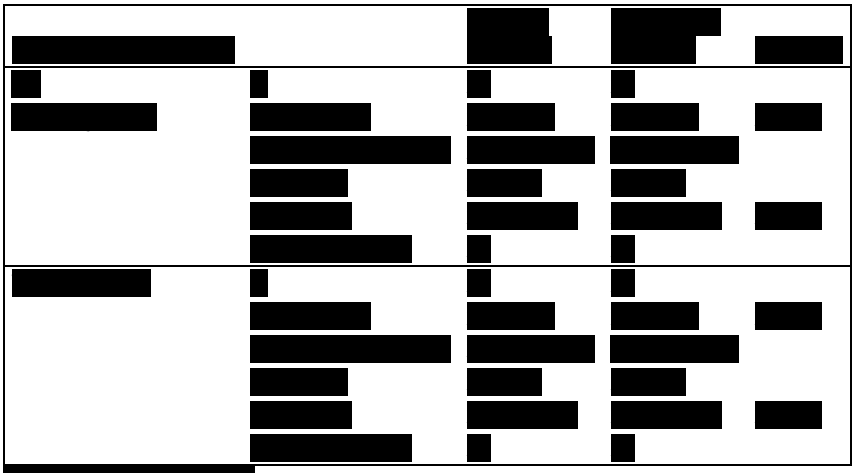

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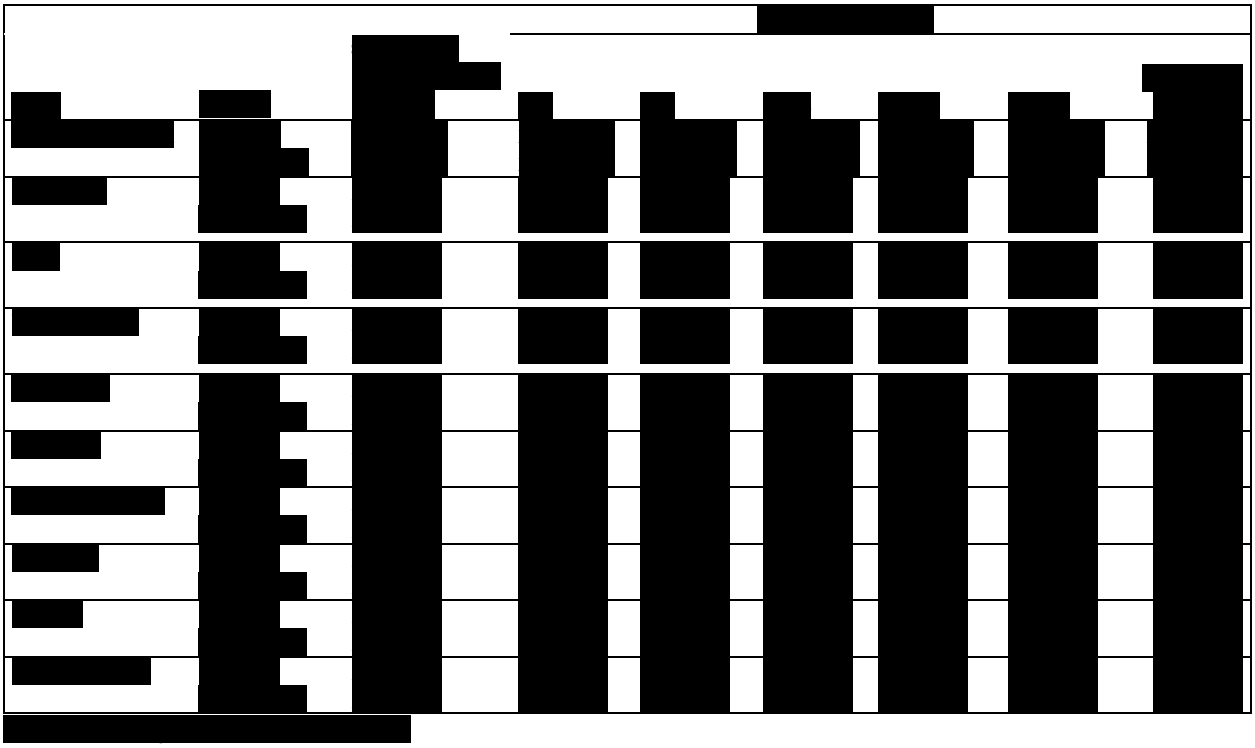

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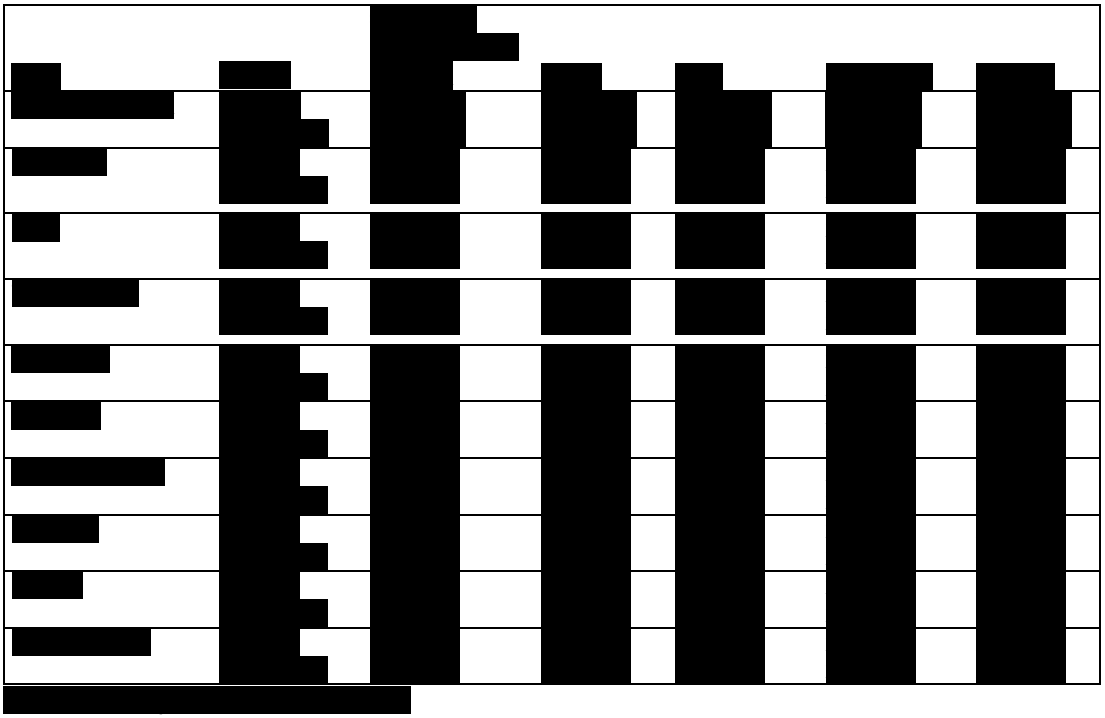

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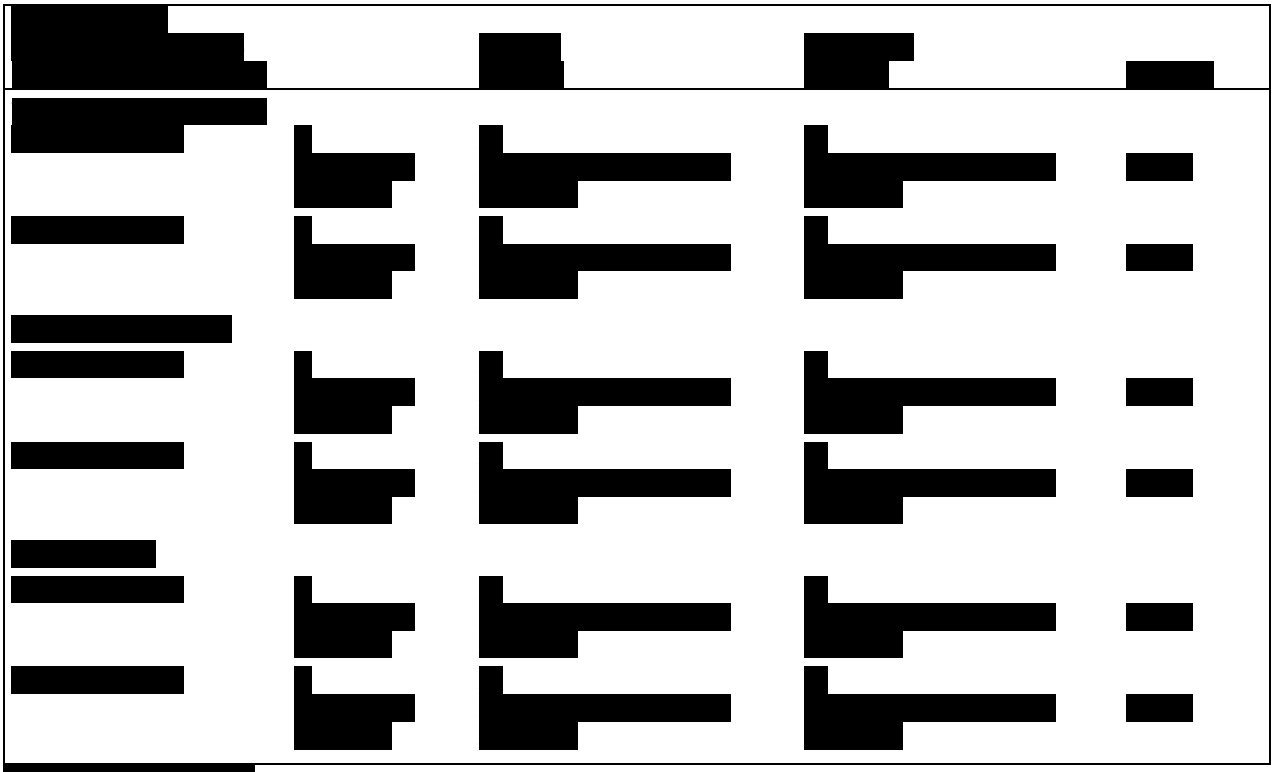

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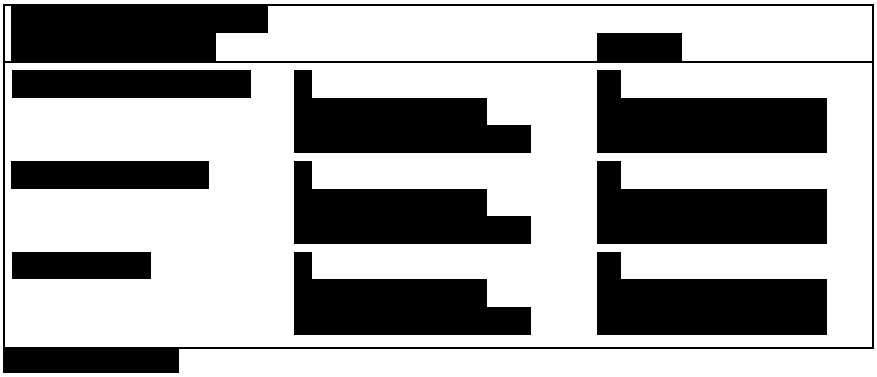

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