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® 4 formulated with two different anesthetics in the treatment of nasolabial folds

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Clinical Research Organization

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 study [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® 4 and RHA® 4-[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® 4 product contains 0.3% w/w of lidocaine hydrochloride, and RHA® 4-[redacted] contains 0.3% w/w of [redacted]. 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® 4-[redacted] with mepivacaine will be non-inferior to RHA® 4 with lidocaine in terms of injection site pain felt by the subject during injection assessed immediately after injection of each side using a 100 mm Visual Analog Scale (VAS).

1.4 Primary Objective

The study objective is to demonstrate the non-inferiority of RHA® 4-[redacted] with [redacted] versus the control (RHA® 4 with lidocaine) in terms of reducing pain during device injection into the NLFs. Injection pain during injection will be based on the 100 mm Visual Analog Scale (VAS), as assessed by subjects immediately after injection of each side.

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® 4-[redacted] with [redacted] is non-inferior to RHA® 4 with lidocaine in terms of injection site pain felt by the subject during injection.

At screening, the Treating Investigator (TI) will evaluate subjects' NLF severity (using the Wrinkle Severity Rating Scale; WSRS) to confirm eligibility and to establish a pre-treatment score for assessing aesthetic improvement.

At Visit 1, RHA® 4-[redacted] with [redacted] will be administered in a random sequence (first or second injection) and side of the face and RHA® 4 with lidocaine will be administered to the other side. Study subjects and the TI injecting study devices will be blinded.

Immediately after injection of each NLF (see Protocol Section 7.2.5), 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 face will also be assessed at 15, 30, 45 and 60 minutes post-injection.

[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.

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 Section **Erreur ! Source du renvoi introuvable.** for a full description of the inclusion and exclusion criteria.

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3. TREATMENT ALLOCATION, RANDOMIZATION AND BLINDING

Upon qualifying for treatment, subjects will be randomized for the side of the face and the order of injection of study devices (i.e., left or right / 1st or 2nd order).

Subjects will be considered "enrolled" at the time of consent, and will be considered "enrolled and randomized" at the time of randomization. The required sample size is based on "enrolled and randomized" subjects. If an enrolled subject withdraws from the study prior to being randomized, he/she may be replaced.

This is a double-blinded study in which subjects and TIs will be blinded to treatment allocation.

4. DEVICE APPLICATION

4.1 Injection of Study Devices

At Visit 1, each enrolled and randomized subject will receive injections of RHA® 4-[redacted] with [redacted] into the NLF of the left or right side of the face, and injections of the control device (i.e., RHA® 4 with lidocaine) into the contralateral NLF, to optimal correction.

[redacted]

4.1.2 Injection Sequence

Upon qualifying for treatment, subjects will be randomized for the side of face and the order of injection (i.e., left or right / 1st or 2nd order).

5. STUDY EVALUATIONS

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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. Safety assessments will also include visual assessment tests.

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]

5.2.3 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 during injection into one NLF assessed by the subject immediately following injection with RHA® 4- with compared to the injection site pain felt during injection into the contralateral NLF assessed immediately following injection with RHA® 4 with lidocaine.

The effectiveness of RHA® 4- with will be demonstrated if the injection site pain during injection assessed by the subject immediately following injection with RHA® 4- with is statistically non-inferior to the injection site pain felt during injection of the contralateral NLF assessed by the subject immediately following injection with RHA® 4 with lidocaine.

The primary endpoint will use the PP population, 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® 4- with over RHA® 4 with lidocaine in terms of reducing pain, the observed p value must be ≤0.05.

6.2 Secondary Endpoints

The following secondary effectiveness endpoints will be explored:

6.3 Safety Endpoints

[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]

6.4.2 Per Protocol (PP) Population

[redacted]

6.4.3 Safety (SAFT) Population

[redacted]

[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®4-[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® 4-[redacted] is superior to RHA® 4 for reducing pain).

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Wilcoxon signed-rank test

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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.

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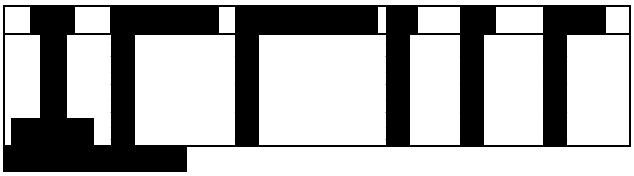

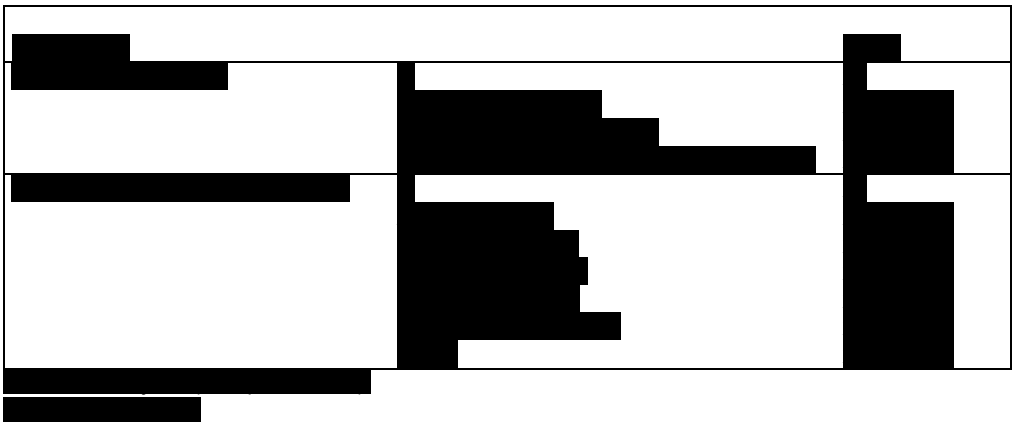

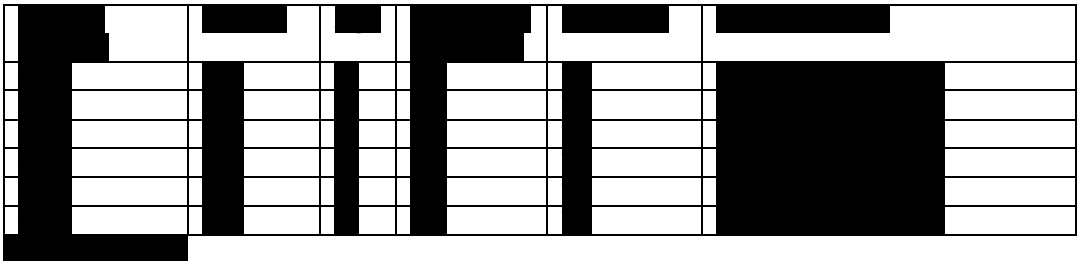

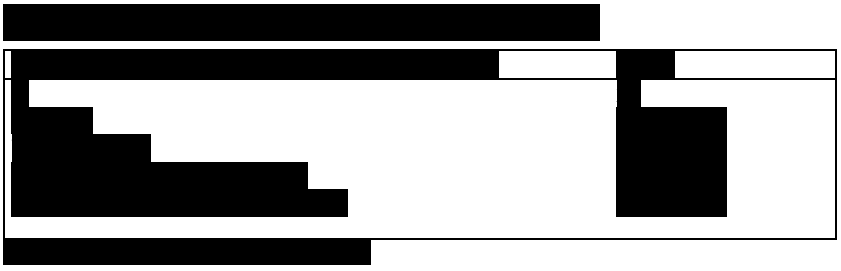

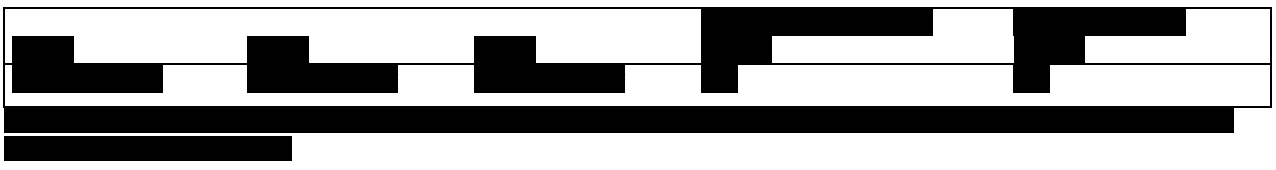

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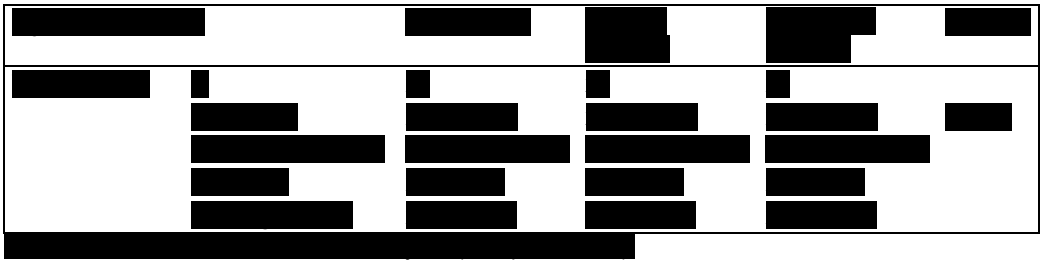

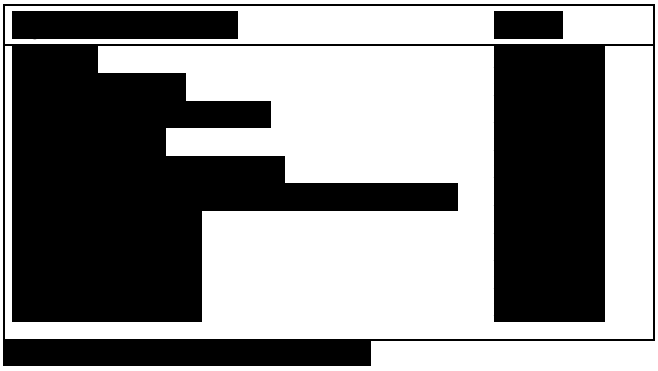

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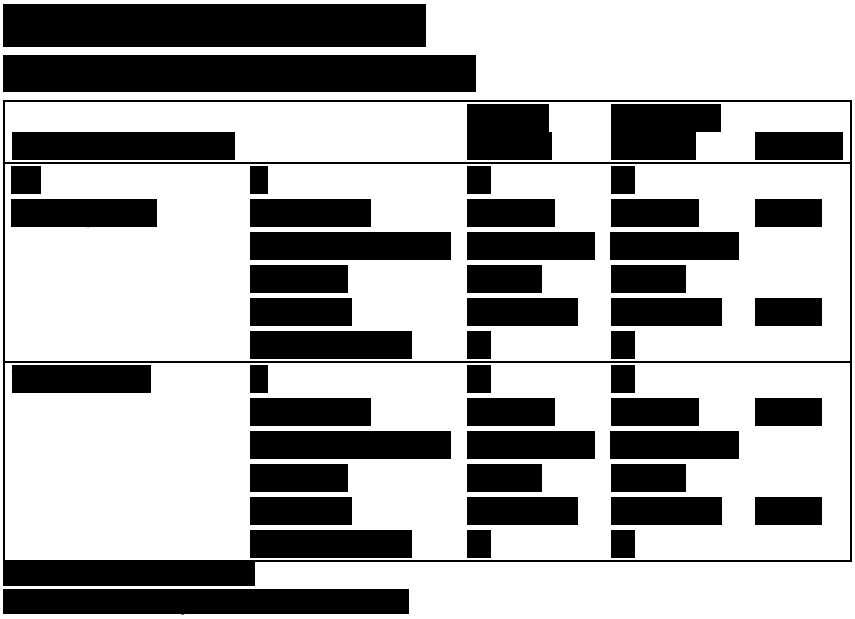

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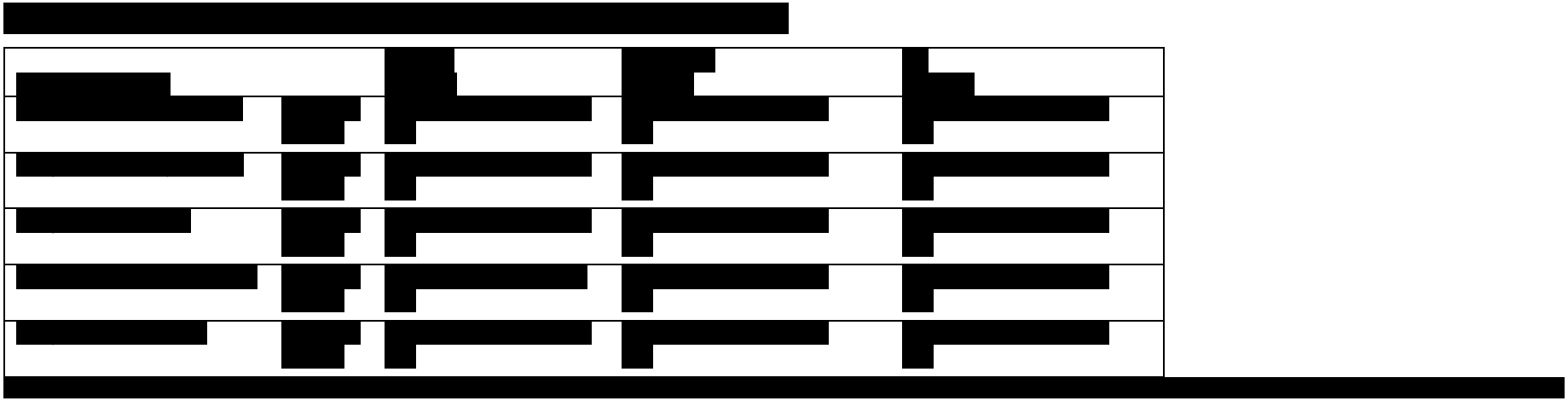

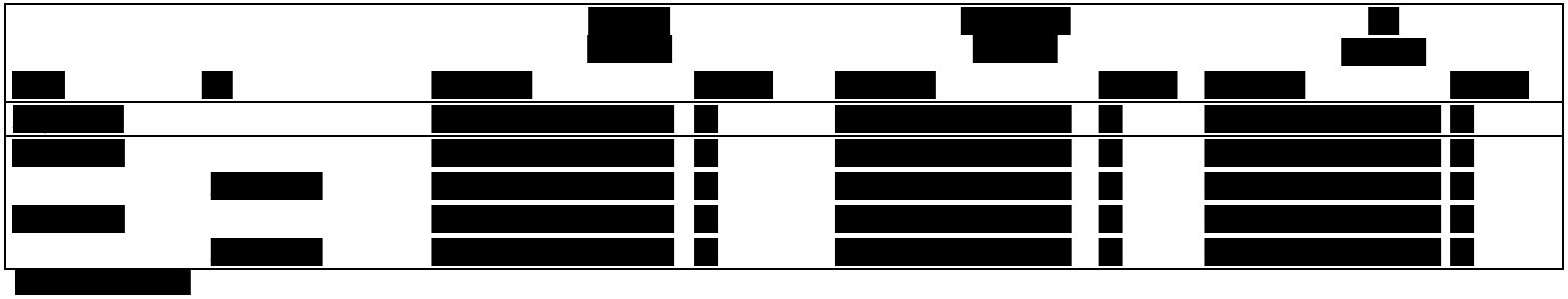

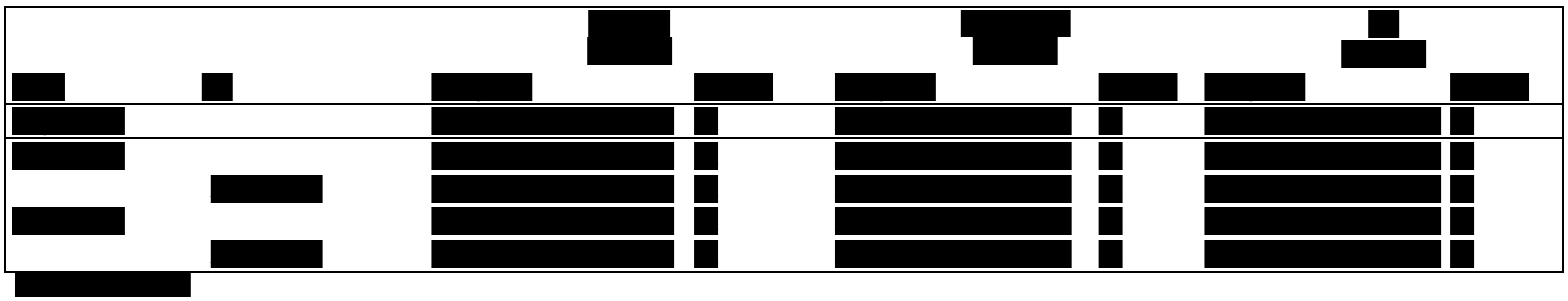

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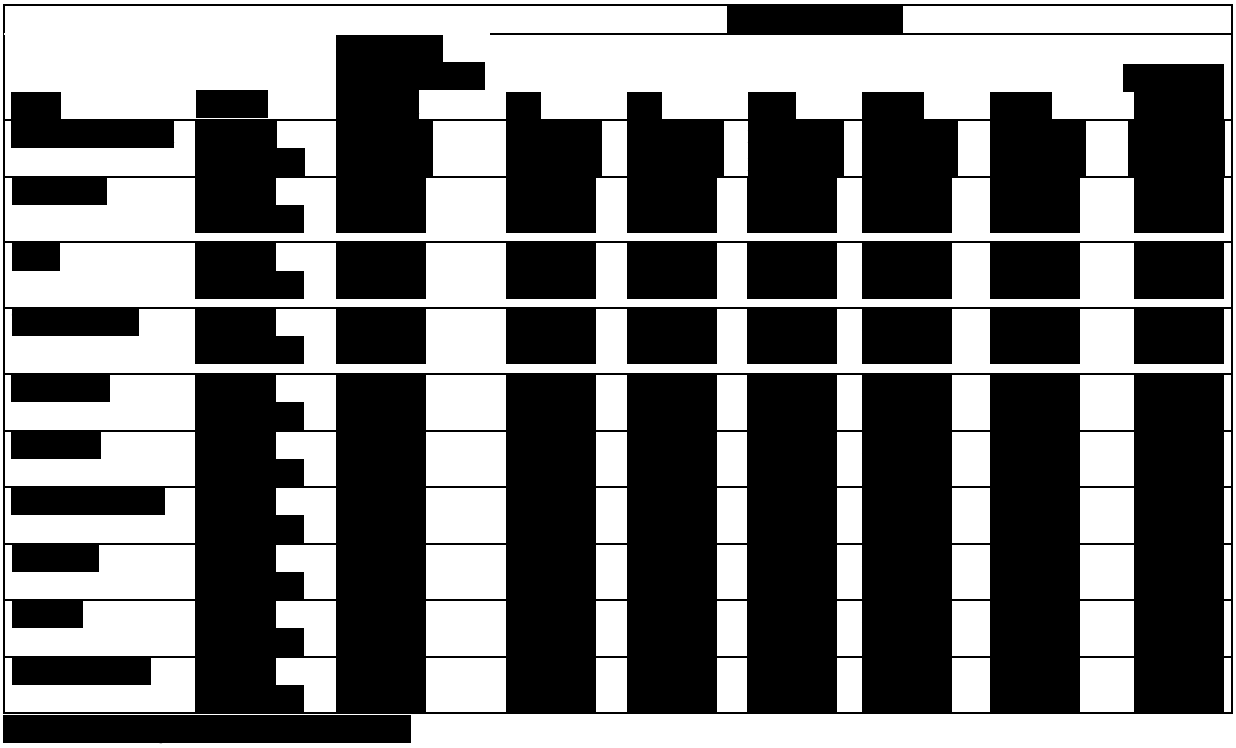

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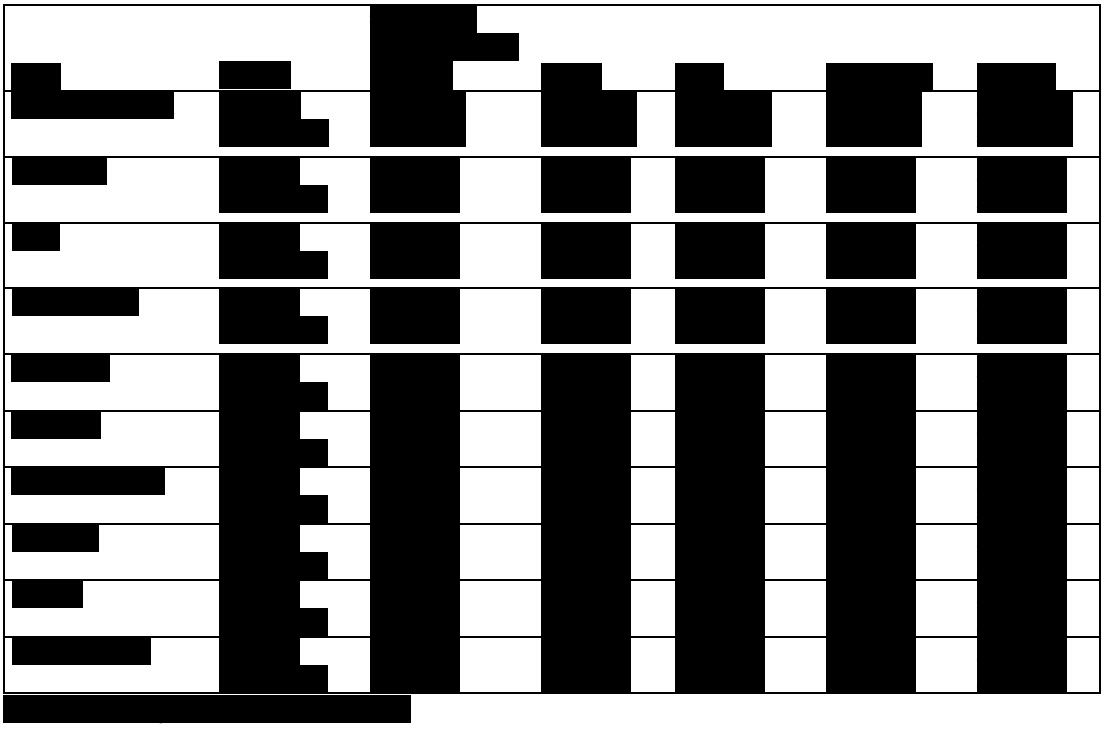

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