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Title: LIPS: A Prospective, Open-label Study to Evaluate the Effectiveness of Juvéderm® VOLIFT™ with Lidocaine for Lip Augmentation

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Statistical Analysis Plan for Interventional Studies

Sponsor Name: Allergan

Protocol Number: CMO-MA-FAS-0512
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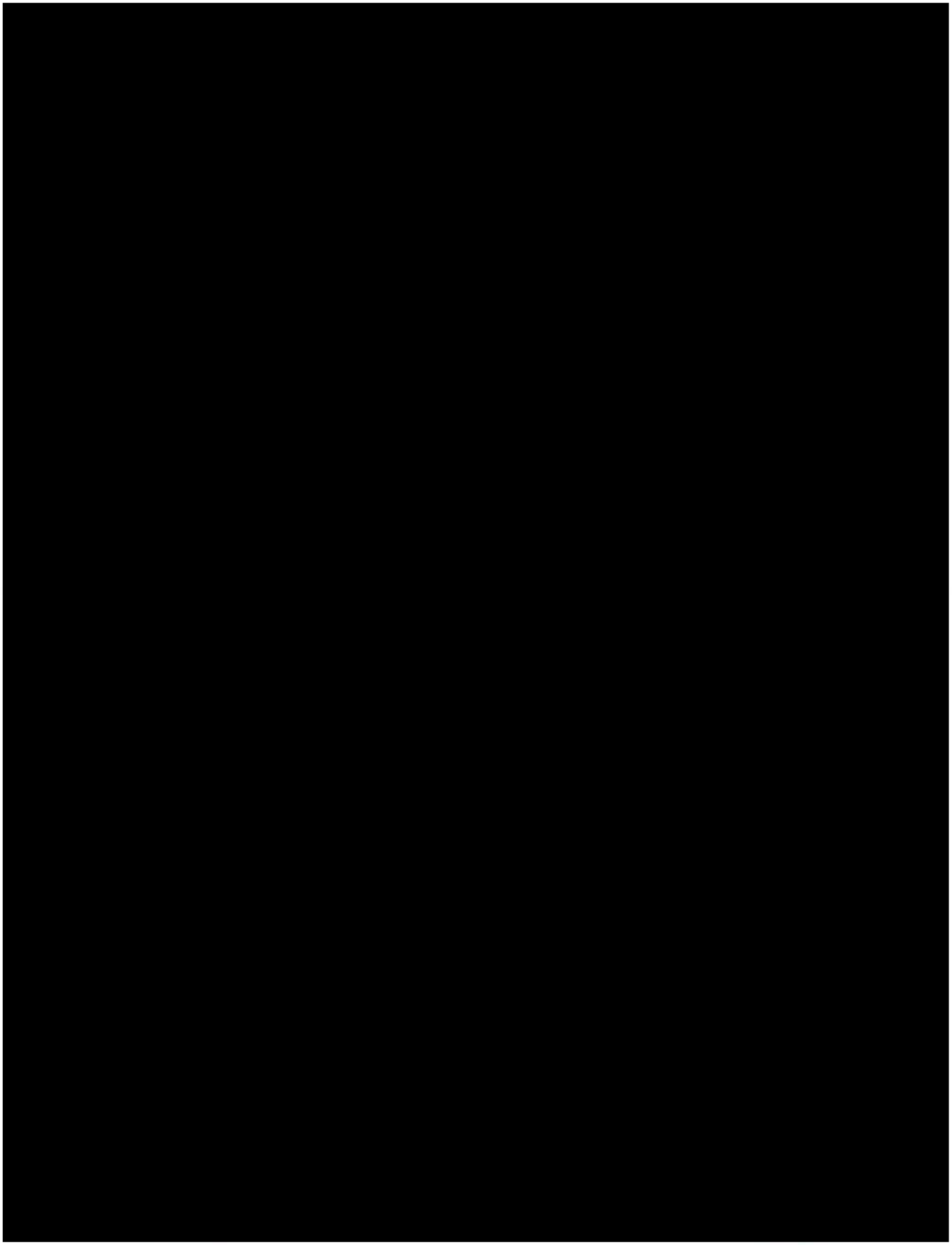
Authors: [redacted] Principal Biostatistician

[redacted]

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	09-May-2019	Catriona Murray	Initial Release Version
2.0	27-Nov-2019	Catriona Murray	Updates for Protocol Version 3 and other minor clarifications



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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
CTMS	Clinical Trial Management System
DFU	Directions for Use
eCRF	Electronic Case Report Form
ES	Evaluable Set
FAS	Full Analysis Set
GAIS	Global Aesthetic Improvement Scale
HA	Hyaluronic Acid
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISR	Injection Site Reaction
LFS2	Lip Fullness Scale
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of Observations
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OCSS	Oral Commissures Severity Scale
PD	Protocol Deviation
pdf	Portable Document Format
POLSS	Perioral Lines Severity Scale
PPS	Per Protocol Set
PT	Preferred Term
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Analysis Set
TEAE	Treatment-emergent Adverse Event

Abbreviation	Description
TFLs	Tables, Figures and Listings
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

The primary analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study. An interim analysis will be performed when all patients complete their 6 months visit (or discontinue early).

3. Study Objectives

3.1. Primary Objective

To evaluate the effectiveness of Juvéderm® VOLIFT™ with Lidocaine for lip augmentation.

3.2. Secondary Objective(s)

To quantify the Investigators' and subject's assessment of aesthetic improvement of their lips.

3.3. Brief Description

This is a prospective, open-label, multi-center, interventional, medical device, post-marketing study evaluating the effectiveness of Juvéderm® VOLIFT™ with Lidocaine for lip augmentation. Subjects will attend up to 7 visits: Screening, Initial Treatment, Day 14 (touch-up, if required), Day 30, Month 3, Month 6, and Month 12 (study exit; see Figure 1). 60 subjects will be enrolled.

Eligible subjects will undergo treatment with Juvéderm® VOLIFT™ with Lidocaine administered via injection for enhancement as per the current directions for use (DFU) [redacted]

[redacted]

[redacted]

Figure 1 Overall Study Design

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.4. Subject Selection

60 subjects will be treated in this study. Subjects who "drop out" after receiving treatment on Day 1 will not be replaced.

3.4.1. Inclusion Criteria

The following are requirements for entry into the study.

1. Male or female, 18 years of age or older.

2. Signed the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form prior to any study-related procedures being performed.

3. Accept the obligation not to receive any other facial procedures or treatments anywhere in the lower face (below the orbital rim), neck, and oral cavity at any time during the study that are not related to the study.

[redacted]

5. Women of childbearing potential must have a negative urine pregnancy test before each injectable treatment and practice a reliable method of contraception throughout the study.

6. Ability to follow study instructions and likely to complete all required visits and assessments, as assessed by the Investigator.

3.4.2. Exclusion Criteria

[redacted]

2. Has lip tattoos or is planning lip tattoos during the course of the study, piercings, facial hair, or scars that would interfere with visualization of the lips and perioral area.

3. Has dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities.

4. Has undergone oral surgery (e.g., tooth extraction, orthodontia, or implantation) within 6 weeks before

enrollment or is planning to undergo any of these procedures during the study.

5. Has ever undergone facial plastic surgery or received permanent facial implants (e.g., polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck, or is planning to be implanted with any of these products during the study.

6. Has undergone semi-permanent dermal filler treatment (e.g., hyaluronic acid, calcium hydroxylapatite, poly-L-lactic acid) in the lower face (below the orbital rim) within 24 months before enrollment or is planning to undergo such treatment during the study.

7. Has undergone mesotherapy or cosmetic resurfacing (laser, photo-modulation, intense pulsed light, radiofrequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures) anywhere in the face or neck, or Botulinum toxin injections in the lower face (below the orbital rim) within 6 months before enrollment or is planning to undergo any of these procedures during the study.

8. Has used any lip plumping products within 10 days before enrollment or is planning to use such products during the study (study treatment may be delayed as necessary to accommodate this 10-day washout period).

9. Has begun using any over-the-counter or prescription, oral or topical, anti-wrinkle products for the lips or around the mouth within 90 days before enrollment or is planning to begin using such products during the study (subjects who have been on a regimen of such products for at least 90 days are eligible for the study if they intend to continue their regimen throughout the study).

10. Is on an ongoing regimen of anti-coagulation therapy (e.g., warfarin) or non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, ibuprofen) or other substances known to increase coagulation time (e.g., herbal supplements with garlic or gingko) within 10 days of undergoing study device treatment (study treatment may be delayed as necessary to accommodate this 10-day washout period).

11. Is on a concurrent regimen of lidocaine or structurally related local anesthetics (e.g., bupivacaine.)

12. Has a history of anaphylaxis, atopy, or allergy to lidocaine, hyaluronic acid (HA) products, or Streptococcal protein, or is planning to undergo desensitization therapy during the study.

13. Has an active inflammation, infection, cancerous or precancerous lesion, or unhealed wound in the mouth area.

14. Has porphyria.

15. Has epilepsy.

16. Has impaired cardiac conduction, severely impaired hepatic function, or severe renal dysfunction.

17. Has any uncontrolled disease.

18. Females who are pregnant, nursing, or planning a pregnancy.

19. Current enrollment in an investigational drug or device study, participation in such a study within 6 weeks before enrollment, or be planning to participate in another investigation during the course of this study.

20. Is an employee (or immediate relative of an employee) of the Investigator, Allergan, or a representative of Allergan.

[redacted]

3.5. Determination of Sample Size

It is expected that the responder rate for this study is approximately 80% based on the results of a pivotal study of a similar investigational product Juvéderm Volbella XC. (See Geronemus *et al.*, 2018, unpublished manuscript). The margin of error (associated with 95% CI) for estimating an 80% expected responder rate is 10%, which is desirable to attain by having a sample size of 60 subjects for the study. Subjects' dropout rate is expected to be negligibly small at Day 30 post-treatment when the primary efficacy assessment is collected, thus 60 subjects will be recruited into the study.

3.6. Treatment Assignment & Blinding

This is an open-label, single-arm study. Thus, blinding and randomization methods will not be implemented.

3.7. Administration of Study Medication

The Investigator will determine the appropriate volume of Juvéderm® VOLIFT™ with Lidocaine to be injected to augment the lips (e.g., add fullness). It is anticipated that the volume of Juvéderm® VOLIFT™ with Lidocaine to be injected for lip augmentation will not exceed 3.0mL total per subject.

3.8. Study Procedures and Flowchart

3.8.1. Washout of Prohibited Medications/Treatments

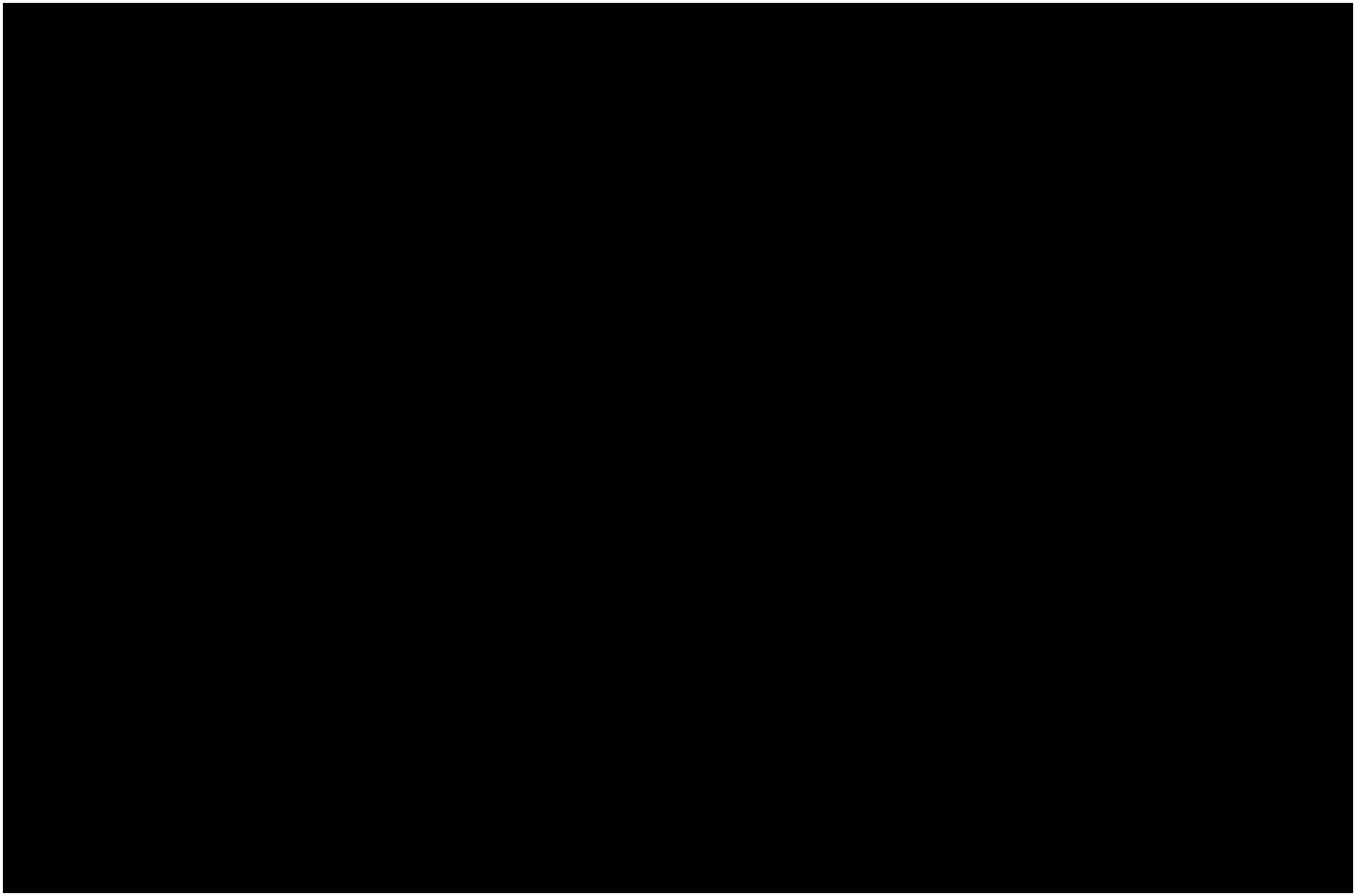
If washout of any medications is required, the subject must provide written informed consent before the washout can commence. Table 1 lists the medications/treatments that are prohibited during the study and the length of time that must pass between the medication/treatment and treatment in the study.

Study treatment may be delayed as necessary to accommodate the washout period. If treatment is delayed beyond the 14-day screening period (see Table 2: Schedule of Visits and Procedures), screening procedures are to be repeated as necessary to confirm participation eligibility. The inclusion/exclusion criteria must be reassessed and the subject eligibility confirmed prior to study treatment.

3.8.2. Unscheduled Visits

Each time the subject returns to the study center, the investigator (or designee) will solicit and record information about injection site reactions (ISRs), adverse events (AEs), and concomitant medications/procedures. An interim or unscheduled visit may replace a scheduled visit if it occurs within the acceptable visit window for a scheduled visit or if the scheduled visit was missed. All applicable procedures should be performed.

3.8.3. Flowchart



[redacted]

[redacted]

[redacted]

[redacted]

4. Endpoints

4.1. Primary Efficacy Endpoint

The primary endpoint will be the responder rate for lip fullness on the LFS2, which is defined as the proportion of subjects who show ≥ 1-point improvement on the LFS2 compared to baseline assessment, at Day 30 after last treatment received.

4.2. Secondary Efficacy Endpoints

4.2.1. Oral Commissures Severity Scale (OCSS)

Change from baseline in OCSS will be determined at each post-treatment visit.

4.2.2. FACE-Q™ – Satisfaction with Lips Questionnaire

Subject's assessment of satisfaction with treatment of their lips as measured by the change from baseline in the FACE-Q™ Satisfaction with Lips questionnaire at all post-treatment visits.

4.2.3. Global Aesthetic Improvement Scales (GAIS)

- Investigator's assessment of global facial aesthetic improvement as measured by the 5-point GAIS at post-treatment visits beginning at Day 30 after last treatment received.
- Subject assessment of global facial aesthetic improvement as measured by the 5-point GAIS at post-treatment visits beginning at Day 30 after last treatment received.

4.2.4. Natural Look and Feel/Product Smoothness/Dynamic Lip Lines

- Subject's assessment of natural look and feel of their lips as measured by the 5-point Likert scale at post-treatment visits beginning at Day 30 after last treatment received.
- Investigator's assessment of product smoothness as measured by the 5-point Likert scale at post-treatment visits beginning at Day 30 after last treatment received.
- Investigator assessment of dynamic lip lines upon animation at post-treatment visits beginning at Day 30 after last treatment received

5. Analysis Sets

The primary analysis set to be used for the analysis of the efficacy data will be the Evaluable Set (ES).

5.1. Screened Set

The Screened Set will include all subjects entered into the study (See Section 6.2 for definition of 'entered'). Unless specified otherwise, this set will be used for subject listings and for summaries of subject disposition.

5.2. Full Analysis Set

The Full Analysis Set (FAS) will include all subjects who were consented and enrolled into this study (See Section 6.2 for definition of 'enrolled'). The FAS will be used to summarize major protocol deviations (PDs) and for all efficacy data listings.

5.3. Safety Analysis Set

The Safety Analysis Set (SS) is identically defined to the FAS. The SS will be used for all analyses of safety endpoints.

5.4. Evaluable Set

The ES will include all subjects in the FAS who have had at least a baseline and a Day 30 (Visit 3) post-treatment efficacy assessment. The ES will be used for all analyses of efficacy endpoints. This will be the primary analysis set for analysis of the primary endpoint.

5.5. Per Protocol Set

The Per Protocol Set (PPS) will include all subjects in the ES who had not had any major protocol deviations. The PPS will be used to corroborate the results from the ES for the primary endpoint. Criteria for exclusion from the PPS will include the following important PDs:

- Use of a prohibited medication.
- Use of prohibited concomitant procedures.
- Violation of key inclusion or exclusion criteria.
- Violation of follow-up, or significant deviation from defined visit windows.

Subjects will be assigned to the PPS by Allergan by reviewing PDs as detailed in Section 5.6.

5.6. Protocol Deviations

PDs will be captured in the clinical trial management system (CTMS). These will be reviewed by Allergan throughout the study to determine whether each PD is major or minor with respect to inclusion in the PPS. All PDs will be listed for the Screened Set and major PDs will be summarized by deviation type using summary statistics for categorical data for the FAS.

6. General Aspects for Statistical Analysis

6.1. General Methods

- All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA).
- Unless otherwise specified, summaries will be presented for each gender and overall.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using n and percentage of subjects.
- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.

6.2. Key Definitions

A subject is considered 'entered' into the study after the subject has signed the Informed Consent Form (ICF) and a subject number has been assigned.

A subject is considered 'enrolled' after confirmation of participation eligibility and treatment with the investigational product Juvéderm® VOLIFT™ with Lidocaine has occurred during the study.

Study treatment is defined as initial or touch-up treatment with Juvéderm® VOLIFT™ with Lidocaine.

Baseline is defined as the latest assessment prior to any study treatments for each subject.

Study day will be calculated as (date of event or assessment)-(date of first filler treatment)+1 if the event or assessment was on or after the date of the first filler treatment, and as (date of event or assessment)-(date of first filler treatment) if the event or assessment was before the date of the first filler treatment. The day of first filler treatment is Study Day 1 (Visit 1). If a touch-up treatment is administered, Visits 3, 4, and 5 will be 14 days +/- 3 days later than the visit label and window, e.g. the study day for an assessment at Visit 3 (Day 30) could be 44 +/- 10, rather than 30 +/- 7.

End of study is the last clinical visit an enrolled subject has in this study. For subjects who complete this study, the end of study visit will be their Visit 5; for subjects who drop out early, they will be asked to come back for the last clinical visit for end of study data collection.

6.3. Missing Data

No imputation of missing data will be made for any of the outcome variables.

For the purpose of assigning treatment-emergent AEs (TEAEs), prior and concomitant medications, and prior and concomitant procedures, the followings rules will be applied for partial or missing start dates:

- If the day is missing, the first day of the given month will be used unless the month and year are the same as the month and year of enrollment, in which case the date of enrollment will be used.
- If the day and month are missing, the 1st of January will be used unless the year is the same as the year of enrollment, in which case the date of enrollment will be used.

- If the whole date is missing, the date of enrollment will be used.

Imputed dates will not be displayed in data listings.

Other dates will not be imputed.

6.4. Visit Windows

Not applicable.

6.5. Pooling of Centers

Not applicable.

6.6. Subgroups

As males and females may have differing expectations/perceptions of aesthetic improvement, all data will be analyzed by gender separately.

In addition, all baseline and efficacy tables will be presented for the following subgroups:

- Age group - 18 to 29 years, 30 to 45 years, and 46 years upwards.
- Baseline LFS2 score.
- Fitzpatrick skin phototype - I/II, III/IV, and V/VI.
- Investigational site.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

The number of subjects entered and the number and percentage of subjects enrolled, completed and discontinued, together with the reasons for discontinuation will be summarized for the Screened Set. Disposition details and inclusion and exclusion criteria not met will be listed for the Screened Set.

The number and percentage of subjects included in, and reasons for exclusion from, each of the analysis sets will be presented for the Screened Set. Exclusions from analysis sets will be listed for the Screened Set.

No formal statistical testing will be carried out on these data.

7.2. Demographic and Other Baseline Characteristics

Subject demographic and baseline characteristic data will be collected at the screening visit. These data include age at informed consent, gender, childbearing potential, and Fitzpatrick skin phototype. The subject's Fitzpatrick skin phototype will be determined at the screening visit using the parameters listed in Table 3.

Table 3 Fitzpatrick Skin Phototype

Skin type	Typical Features	Tanning ability
I	Pale white skin, blue/green eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

Age at informed consent will be summarized using summary statistics for continuous data. Gender, childbearing potential, and Fitzpatrick skin phototype will be summarized using descriptive statistics for categorical data. Demographic and baseline characteristics will be listed for the Screened Set and summarized for the SS, ES and PPS.

No formal statistical testing will be carried out on these data.

7.3. Medical History and Concomitant Diseases

Medical history will be obtained from each subject at the screening visit, and include pertinent surgical history and a detailed history of prior aesthetic procedures with start and stop dates, if applicable, as well as any discontinuations due to intolerability or toxicity.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher.

Medical history data will be summarized using summary statistics for categorical data for the SS, sorting alphabetically by system organ class (SOC) and preferred term (PT) within SOC.

Medical history data will be listed for the Screened Set, sorting by subject number, date of onset, and date resolved (placing missing and partial dates first), then alphabetically by SOC and PT within SOC.

7.4. Other Baseline Characteristics

A urine pregnancy test will be performed by urine dipstick for women of childbearing potential at the screening visit and prior to administration of any study treatment (Day 1 and Day 14, if applicable and at retreatment at Month 12). These data will be listed for women of childbearing potential in the Screened Set.

The POLSS at rest will be assessed at the screening visit and prior to administration of any study treatment at Day 1. The POLSS will be listed for the Screened Set.

No formal statistical testing will be carried out on these data.

7.5. Medication

All medications or treatments (including prescription medications, dietary supplements, over-the-counter medications, and oral herbal preparations) received by the subject within 30 days before the initial treatment visit and throughout the study, and any medications or treatments received more than 30 days before screening considered pertinent to the study in the investigator's judgment, will be recorded on the prior and concomitant medications page of the electronic case report form (eCRF).

The latest version of the World Health Organization (WHO) Drug Dictionary will be used to classify prior and concomitant medications and therapies by therapeutic class and preferred name.

Prior and concomitant medications/therapies will be summarized separately using descriptive statistics for categorical data for the SS. The summary tables will show the frequency and percentage of subjects with at least 1 usage of medication/therapy by therapeutic class and preferred name, sorting by decreasing overall frequency of therapeutic class then alphabetical within therapeutic class by preferred name. Percentages will be calculated using the number of subjects in the SS as the denominator.

All prior and concomitant medications/therapies will be listed together for the Screened Set, including medication/treatment name, dose, and frequency, and sorting by subject number, start date, and stop date (placing missing and partial dates first), then alphabetically by therapeutic class and preferred name within therapeutic class. The listing will flag medications/therapies defined as prior and medications/therapies defined as concomitant.

7.5.1. Prior Medication

Prior medication/therapy is defined as those started and stopped by enrolled subjects before the date of first study treatment.

Partial or missing medication start dates will be handled as per Section 6.3.

7.5.2. Concomitant Medication

Concomitant medication/therapy is defined as those taken on or after the date of first treatment.

Partial or missing medication start dates will be handled as per Section 6.3.

7.5.3. Procedures

All procedures received by the subject within 30 days before the initial treatment visit and throughout the study, and any procedure received more than 30 days before screening if considered pertinent to the study in the investigator's judgment, will be recorded on the concomitant procedures page of the eCRF.

All prior and concomitant procedures will be listed together for the Screened Set, including date of and reason for the procedure. The listing will flag procedures as prior or concomitant, where a prior procedure took place before the date of first study treatment, and a concomitant procedure took place on or after the date of first treatment. Partial or missing dates will be handled as per Section 6.3.

8. Efficacy

Unless stated otherwise, all efficacy analyses will compare post-treatment assessment values to the subject's corresponding baseline assessment value. All efficacy tables will be presented for the subgroups defined in Section 6.6, separately by gender.

8.1. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is the responder rate for lip fullness on the LFS2, which is defined as the proportion of subjects who show ≥ 1-point improvement on the LFS2 compared to baseline assessment, at Day 30 after last treatment received.

The LFS2 is an Investigator assessment of overall lip fullness measured by a 5-point scale (see Table 4: Lip Fullness Scale 2 (LFS2)). The investigator will use the LFPS2 to perform a live assessment of the subject at the visits specified in Table 2, Schedule of Visits and Procedures. Improvement will be calculated as post-treatment LFS2 score – baseline LFS2 score.

The LFS2 score at baseline and at Visits 3, 4, 5, and 6 as well as the improvement from baseline at all post-treatment visits and the responder rate for lip fullness on the LFS2 at Day 30 will be summarized using summary statistics for categorical data for the ES, and also for the PPS as a supportive analysis. LFS2 grades, scores and improvements from baseline will be listed for the FAS.

Table 4 Lip Fullness Scale 2 (LFS2)

Grade	Description	Score
Very Marked	Very significant red lip show, lower lip pout, and upper lip pout	4
Marked	Significant red lip show and lower lip pout	3
Moderate	Moderate red lip show with slight lower lip pout	2
Mild	Some red lip show; no lower lip pout	1
Minimal	Flat or nearly flat contour, minimal red lip show	0

Photographic images will be collected to capture the subject status at the time of the live assessments. Facial photographs will be captured prior to study treatments and immediately after. Additional images will be captured at the Day 30, Month 3, Month 6, Month 12 and any subsequent visits. Images will be used by the investigator and subject for the facial assessments. 3D photographs will also be taken for each subject to aid in facial assessments and measure the volume change in the lips. Photograph collection details will be listed only for the FAS.

8.2. Secondary Efficacy Endpoint(s) and Analyses

8.2.1. Oral Commissures Severity Scale (OCSS)

Change from baseline in OCSS will be determined at each post-treatment visit. The OCSS is an investigator assessment measured on a 4-point scale (see Table 5: Oral Commissure Severity Scale (OCSS)). The Investigator will use the OCSS to perform a live assessment of the subject at the visits specified in Table 2, Schedule of Visits and Procedures. Change from baseline in OCSS will be calculated as post-treatment OCSS score – baseline OCSS score.

The OCSS score at baseline and at Visits 3, 4, 5, and 6 as well as the change from baseline scores at all post-treatment visits will be summarized using summary statistics for categorical data for the ES. OCSS grades, scores and changes from baseline will be listed for the FAS.

Table 5 Oral Commissure Severity Scale (OCSS)

Grade	Description	Score
Severe	Very deep and/or long wrinkle or crease; frown at rest	3
Moderate	Moderately deep and/or long wrinkle or crease; downturned corners	2
Mild	Shallow, just perceptible wrinkle or crease; horizontal or slightly downturned corners	1
None	No wrinkle or fold; slight upturned corners	0

Photographic images will be collected to capture the subject status at the time of the live assessments as detailed in Section 8.1.

8.2.2. FACE-Q™ – Satisfaction with Lips Questionnaire

Subject's assessment of satisfaction with treatment of their lips as measured by the change from baseline in the FACE-Q™ Satisfaction with Lips questionnaire at all post-treatment visits. The subject will assess satisfaction using the 10 items on the Satisfaction with Lips questionnaire of the FACE-Q™ (see Protocol Appendix 5). The responses to the items will be combined to create a Rasch transformed scale score that ranges from 0 to 100. Change from baseline in FACE-Q™ scale score will be calculated as post-treatment FACE-Q™ scale score – baseline FACE-Q™ scale score.

The overall scale score at baseline and at Visits 3, 4, 5, and 6 as well as the change from baseline scores at all post-treatment visits will be summarized using summary statistics for continuous data for the ES. FACE-Q™ responses, scale scores and changes from baseline will be listed for the FAS.

8.2.3. Global Aesthetic Improvement Scales (GAIS)

The Investigator's and the subject's assessments of global facial aesthetic improvement as measured by the 5-point GAIS at post-treatment visits beginning at Day 30 after last treatment received (see Protocol Appendix 6) will be summarized using summary statistics for categorical data for the ES. GAIS responses will be listed for the FAS.

8.2.4. Natural Look and Feel/Product Smoothness/Dynamic Lip Lines

Subject's assessment of natural look and feel of their lips as measured by the 5-point Likert scale at post-treatment visits beginning at Day 30 after last treatment received (see Protocol Appendix 7) will be summarized using summary statistics for categorical data for the ES.

Investigator's assessment of product smoothness as measured by the 5-point Likert scale at post-treatment visits beginning at Day 30 after last treatment received (see Protocol Appendix 8) will be summarized using summary statistics for categorical data for the ES.

Investigator assessment of dynamic lip lines upon animation on a 4-point scale at post-treatment visits beginning at Day 30 after last treatment received (see Protocol Appendix 10) will be summarized using summary statistics for categorical data for the ES.

All assessments will be listed for the FAS.

9. Safety

The analysis set used for safety analyses will be the SS. Safety will be assessed on the basis of AE reports and the ISR 30-day diary.

9.1. Extent of Exposure

Subject study product exposure will be summarized using descriptive statistics, separately for each treatment visit and overall for the SS, ES, and PPS. At Visit 1, gauge of cannula used and local anesthetic administered will be summarized using descriptive statistics for categorical data, and total volume administered for this treatment (in mL) will be summarized using descriptive statistics for continuous data. At Visit 2, the number and percentage of subjects receiving touch-up treatment will be presented, and for those subjects, gauge of cannula used and local anesthetic administered will be summarized using descriptive statistics for categorical data, and total volume administered for this treatment (in mL) will be summarized using descriptive statistics for continuous data. At Visit 6, the number and percentage of subjects receiving optional retreatment will be presented, and for those subjects, gauge of cannula used and local anesthetic administered will be summarized using descriptive statistics for categorical data, and total volume administered for this treatment (in mL) will be summarized using descriptive statistics for continuous data. Overall, the total volume administered to each subject (in mL) will be summarized using descriptive statistics for continuous data.

The total volume administered to each subject (in mL) will also be summarized using descriptive statistics for continuous data by presence or absence of an AE for the SS.

Scatter plots of total volume administered to each subject (in mL) vs. FACE-Q score by visit will be presented for the SS with the Pearson correlation coefficient calculated for each visit, separately for each gender and overall.

Treatment administered or reason not completed, date of injection, gauge of cannula used, number of filler syringes used, injection technique(s) used during administration, total volume administered (in mL), and local anesthetic administered will be listed for each subject visit for the SS.

9.2. Treatment Compliance

Not applicable.

9.3. Adverse Events

Throughout the course of the study (from the date of informed consent), all AEs will be monitored and recorded in source documents and on the AE eCRF. All AEs related to study treatments or procedures will be followed until resolved or stabilized based on the Investigator's clinical judgement.

AEs will be coded using MedDRA version 21.0 or higher, and presented by SOC and PT.

AEs will be defined as treatment-emergent if they start after the first treatment. AEs with missing or partial dates will be handled according to Section 6.3 with respect to assigning treatment-emergence. As a conservative approach, AEs are considered treatment-emergent unless there is clear indication that the event occurred before the first treatment in the study. In general, only TEAEs will be included in the summary tables, but all AEs will be included in the listings.

Treatment-related AEs are defined as AEs with a relationship to the study treatment of possible, probably or causal. Procedure-related AEs are defined as AEs with a relationship to the study procedure of

possible, probably or causal. Missing relatedness will not be imputed for the summarization of treatment-related or procedure-related events.

AEs increasing in severity will not be recorded as separate AEs. Missing severity will not be imputed when summarizing events by maximum severity.

At each level of summarization, summaries will include the number of subjects and the number of events. Events increasing in severity will only be counted once. For summaries by SOC and PT, a subject will be counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT, and maximum severity (mild, moderate, severe), a subject will be counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, subjects will only contribute once to each PT and once to each SOC level. Summaries by SOC, PT, and maximum relationship (not related, unlikely, possible, probable, causal relationship) will be handled similarly to the summaries by maximum severity. Summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following tables will be produced:

- An overall summary of the number and percentage of subjects reporting TEAEs, treatment-related TEAEs, procedure-related TEAEs, serious TEAEs, serious treatment-related TEAEs, serious procedure-related TEAEs, and TEAEs leading to study discontinuation.
- TEAEs overall and by SOC and PT
- Study-treatment-related TEAEs overall and by SOC and PT
- Study-procedure-related TEAEs overall and by SOC and PT
- Serious TEAEs, overall and by SOC and PT
- Serious Study-treatment-related TEAEs, overall and by SOC and PT
- Serious Study-procedure-related TEAEs, overall and by SOC and PT
- TEAEs by maximum severity, overall and by SOC and PT
- TEAEs by maximum relationship to study treatment, overall and by SOC and PT
- TEAEs by maximum relationship to study procedure, overall and by SOC and PT
- TEAEs leading to study discontinuation, overall and by SOC and PT

All TEAEs and Non-TEAEs will be listed, sorting by subject number, onset date, and end date (placing missing and partial dates first), then alphabetically by SOC and PT within SOC. Serious TEAEs, treatment-related TEAEs, procedure-related TEAEs, and TEAEs leading to study discontinuation will also be listed separately.

9.4. Device Deficiencies

A device deficiency is defined in accordance with ISO 14155 as “inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.” Device deficiencies include malfunctions, use errors, and inadequate labeling.

The number and percentage of subjects with at least one device deficiency, at least one device deficiency that could have led to a serious AE, and at least one device deficiency leading to a serious AE, along with the numbers of these events, will be summarized for the SS. For subjects with at least one device deficiency that could have led to a serious AE, reasons deficiencies could have led to a serious AE will be summarized.

Device Deficiencies will be listed for the SS, sorting by subject number, start date, and end date (placing missing and partial dates first.)

9.5. Injection Site Reaction 30-Day Diary

ISRs following treatment with dermal fillers include redness, pain after injection, tenderness to touch, firmness, swelling, lumps/bumps, bruising, itching, discoloration, and other specified events. Subjects will maintain a diary record of the presence, location, frequency, severity, and duration of any ISR for 30 days after treatment (initial and Touch-up). An example of the ISR 30-Day Diary is available in Protocol Appendix 2.

The ISR 30-Day Diary will be completed by the subject beginning on the day of treatment within 60 minutes post-treatment and daily for 30 consecutive days. Subjects who receive Touch-up treatment will return the original ISR 30-Day Diary completed from initial treatment to Day 14 visit. A new ISR 30-Day Diary will be provided at Day 14 to subjects receiving Touch-up treatment. The subject will begin using the new ISR 30-Day Diary to capture any ISRs that occur following Touch-up treatment with Day 1 of the new ISR 30-Day Diary completed within 60 minutes post-treatment.

ISRs that persist longer than 30 days (i.e., ongoing at the end of the diary period) will be reported as AEs.

ISR 30-Day Diary entries will be listed for the SS.

10. Interim Analyses

An interim analysis will be performed when all patients complete their 6 months visit (or discontinue early). All TFLs detailed in Sections 15 to 17 will be provided using all data available at the time.

11. Changes from Analysis Planned in Protocol

Subject study product compliance was to be summarized using descriptive statistics, but this information was not collected in the database.

12. Reference List

Not applicable.

13. Programming Considerations

All TFLs, and statistical analyses will be generated [redacted] Computer-generated TFLs will adhere to the following specifications.

[redacted]

[redacted]

[redacted]

[redacted]

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. [redacted]

[redacted] Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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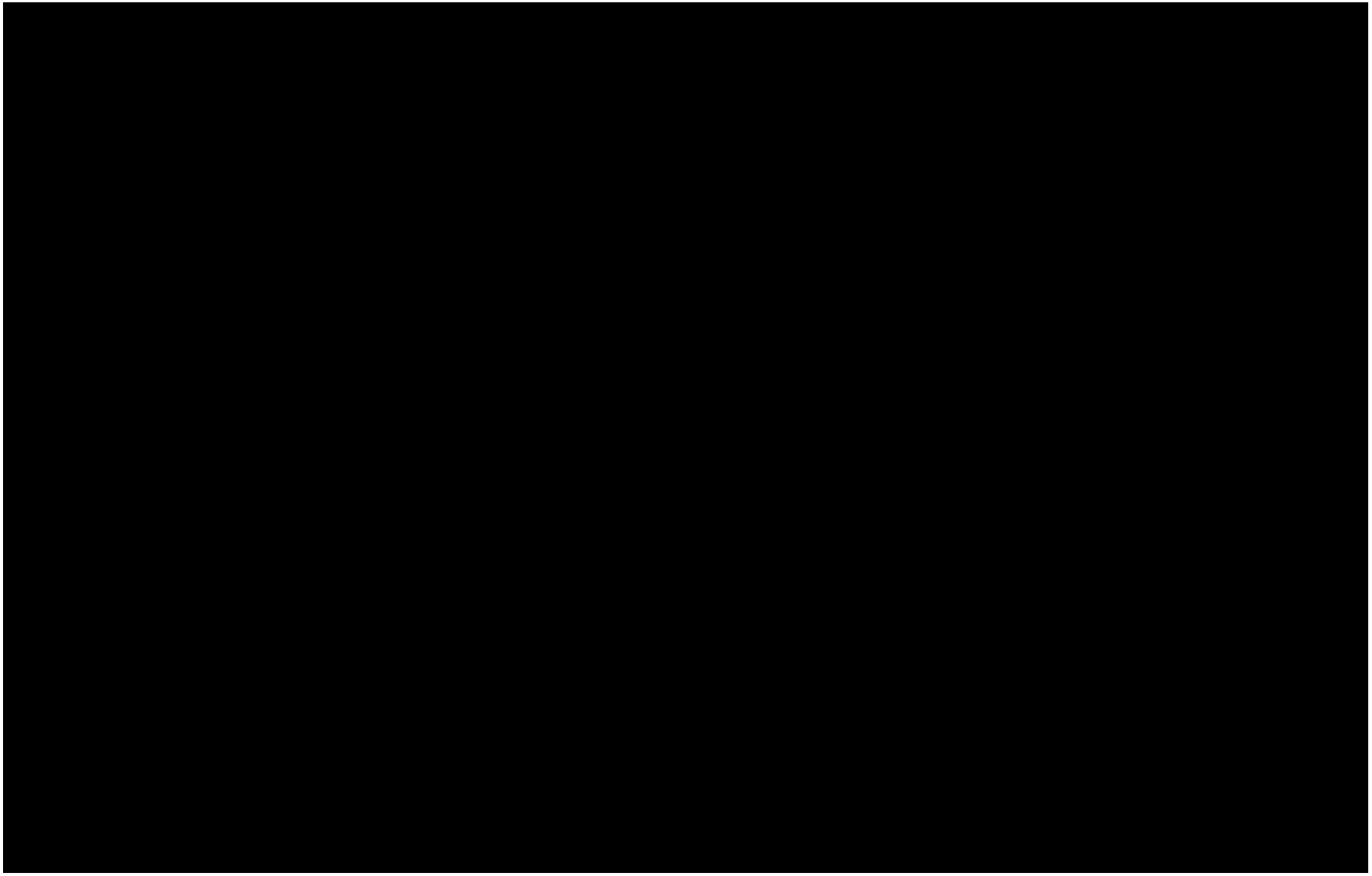
18. Shells

18.1. Table Shells



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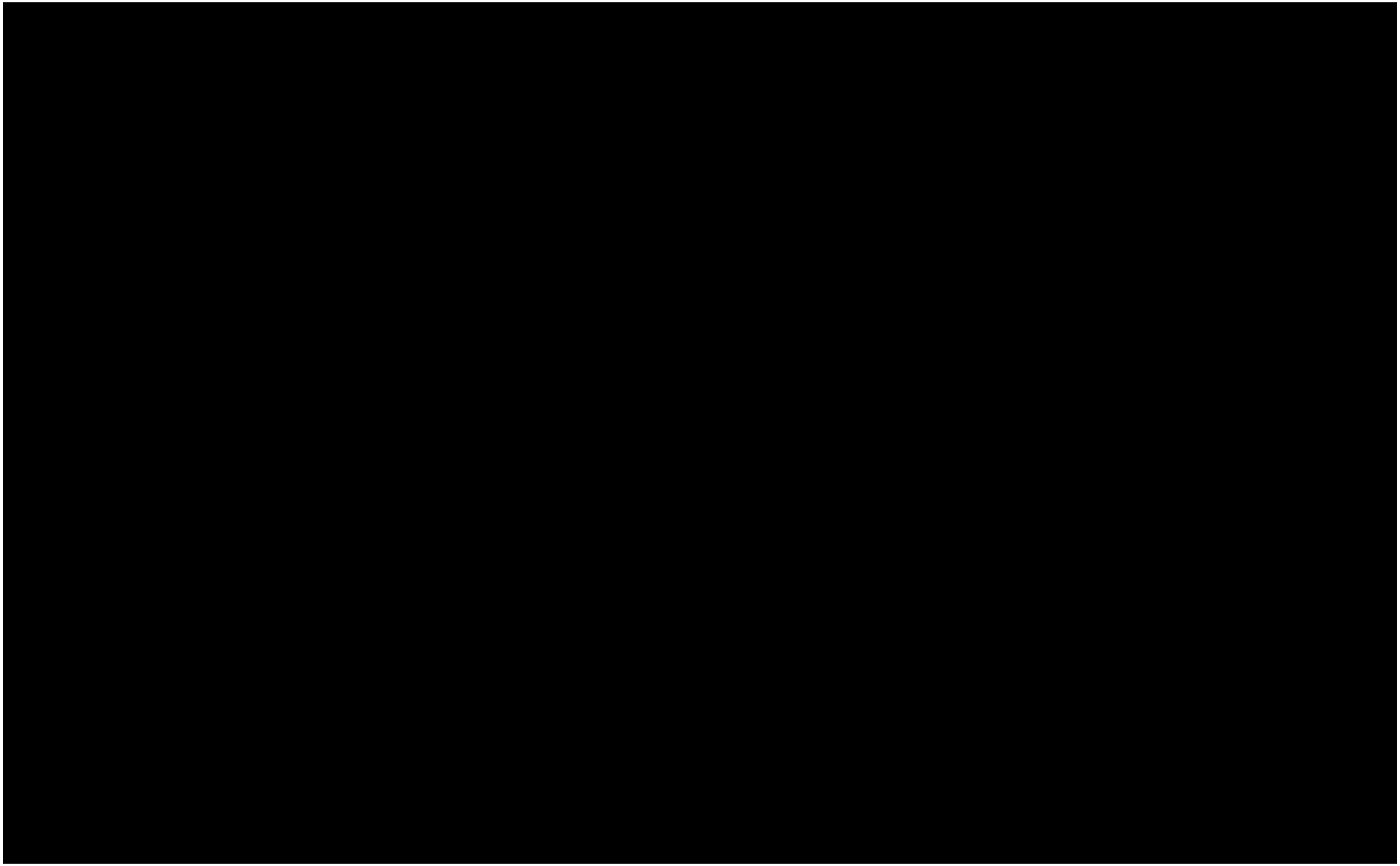

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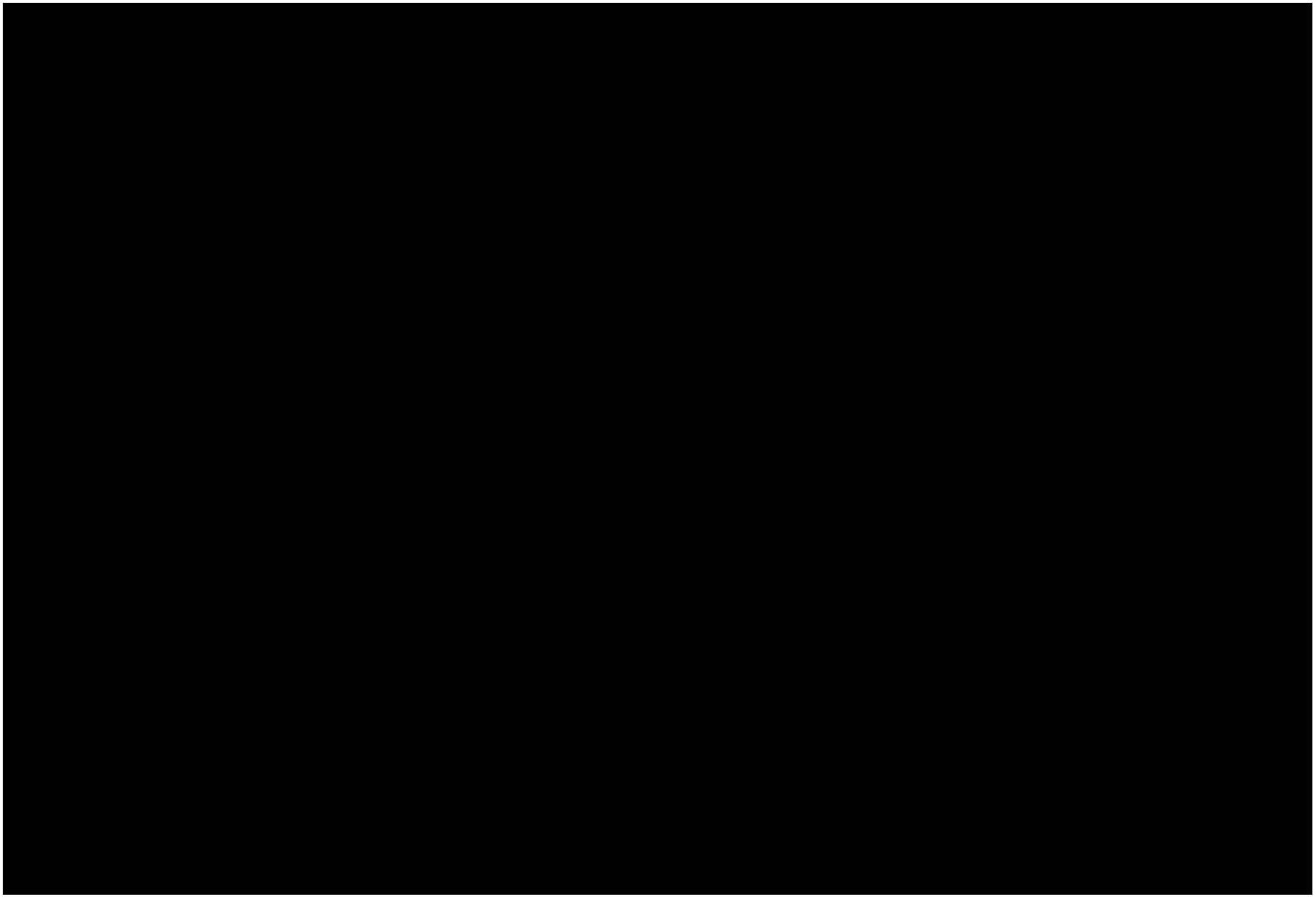

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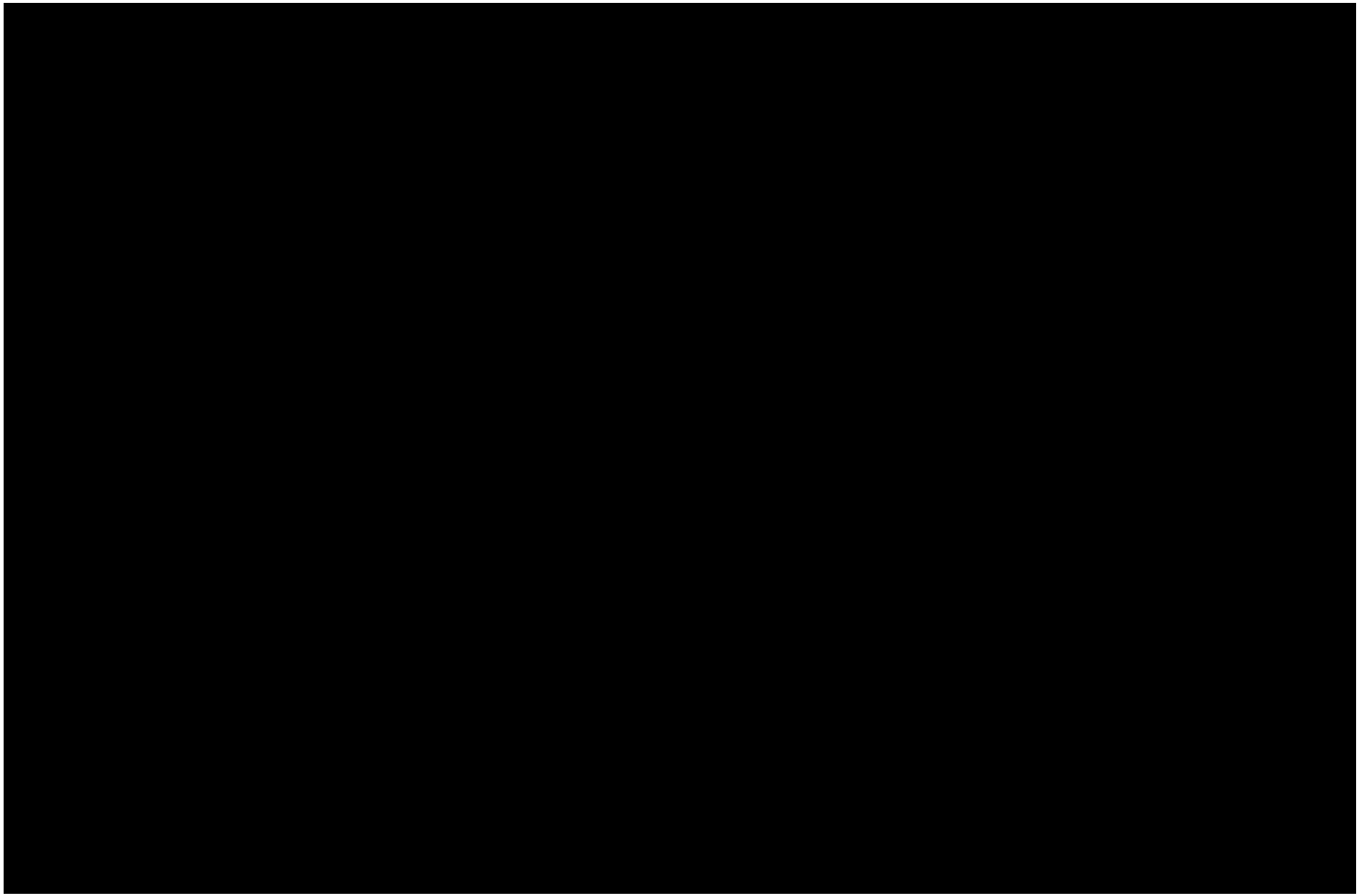

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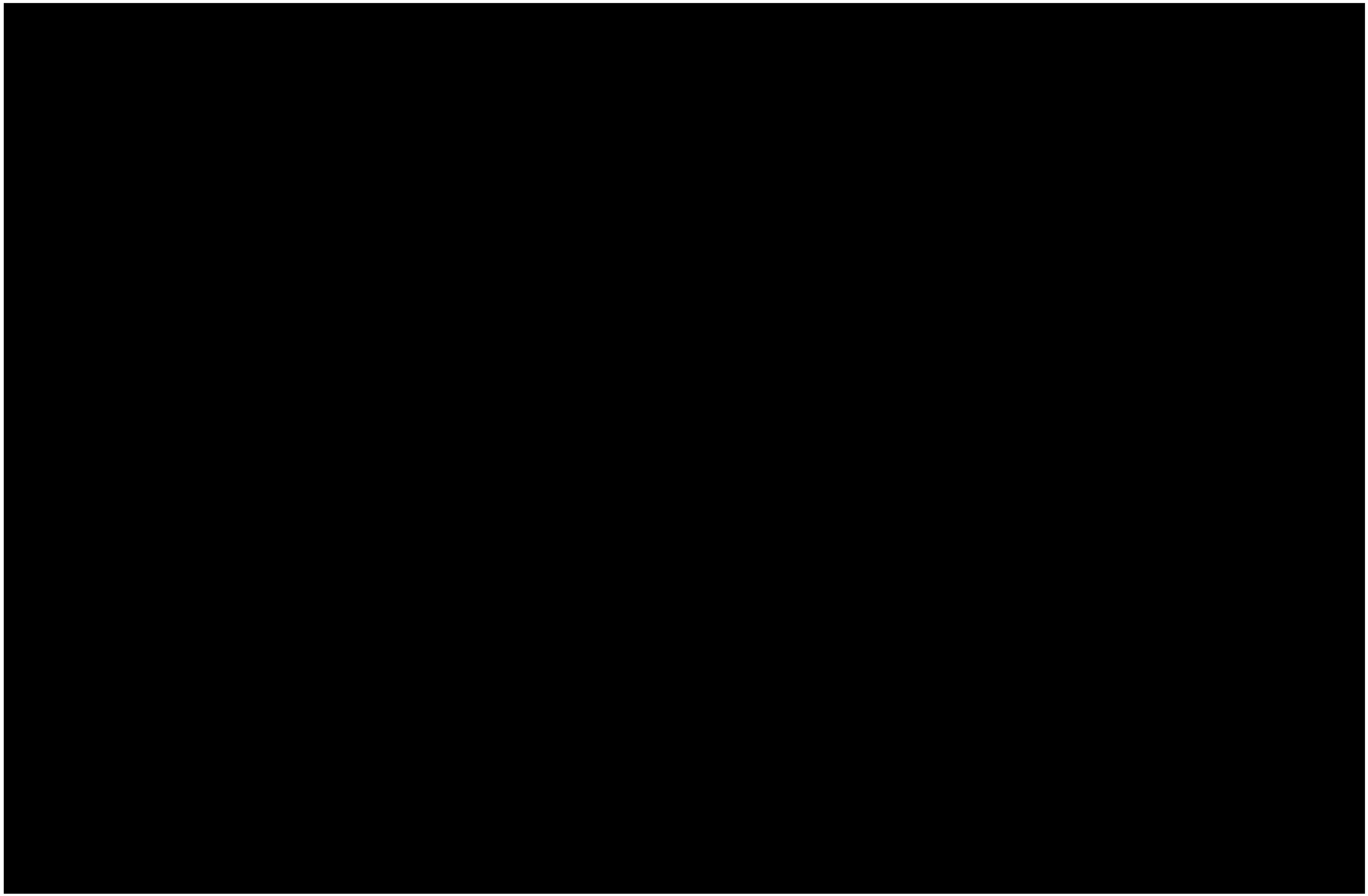

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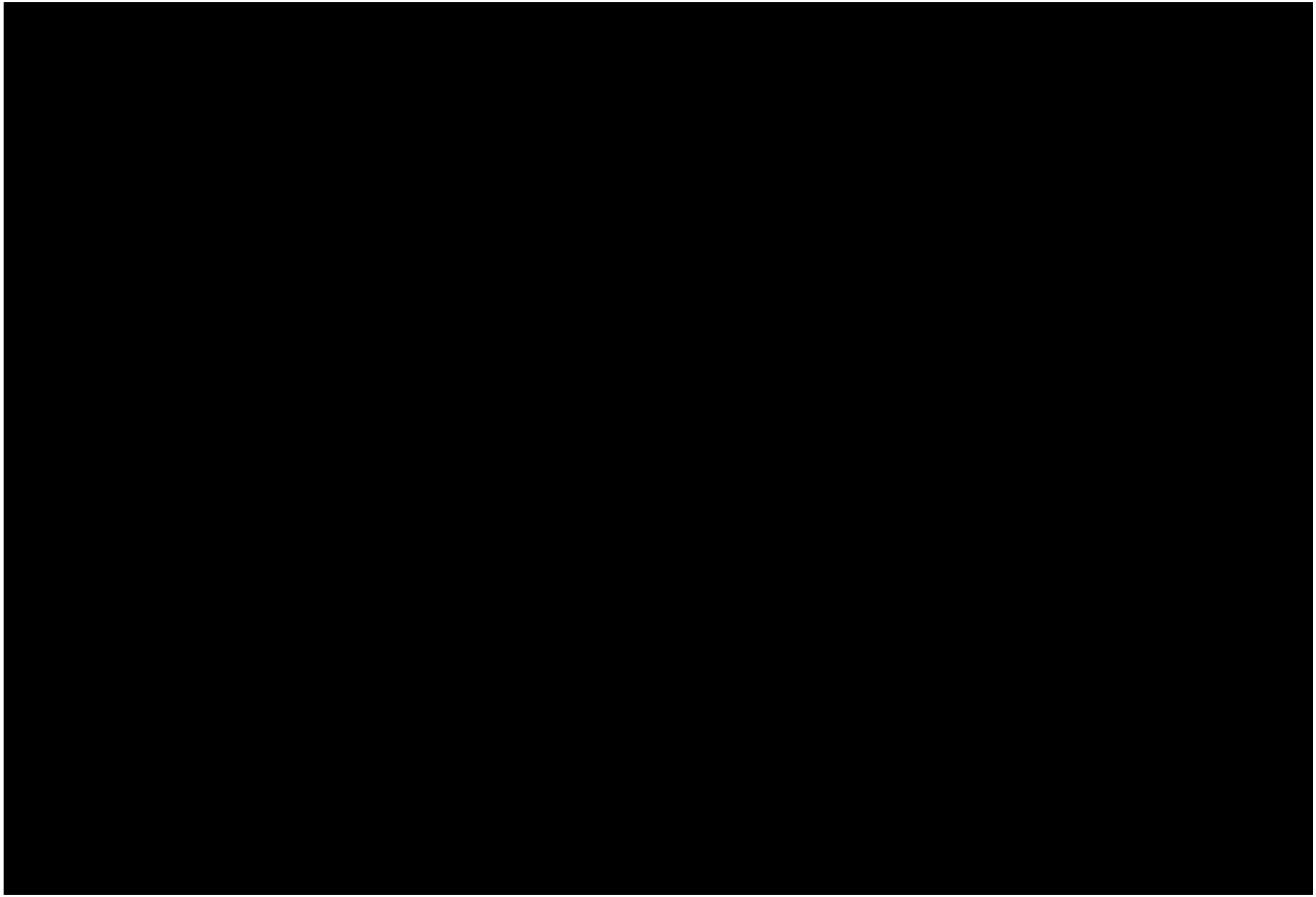

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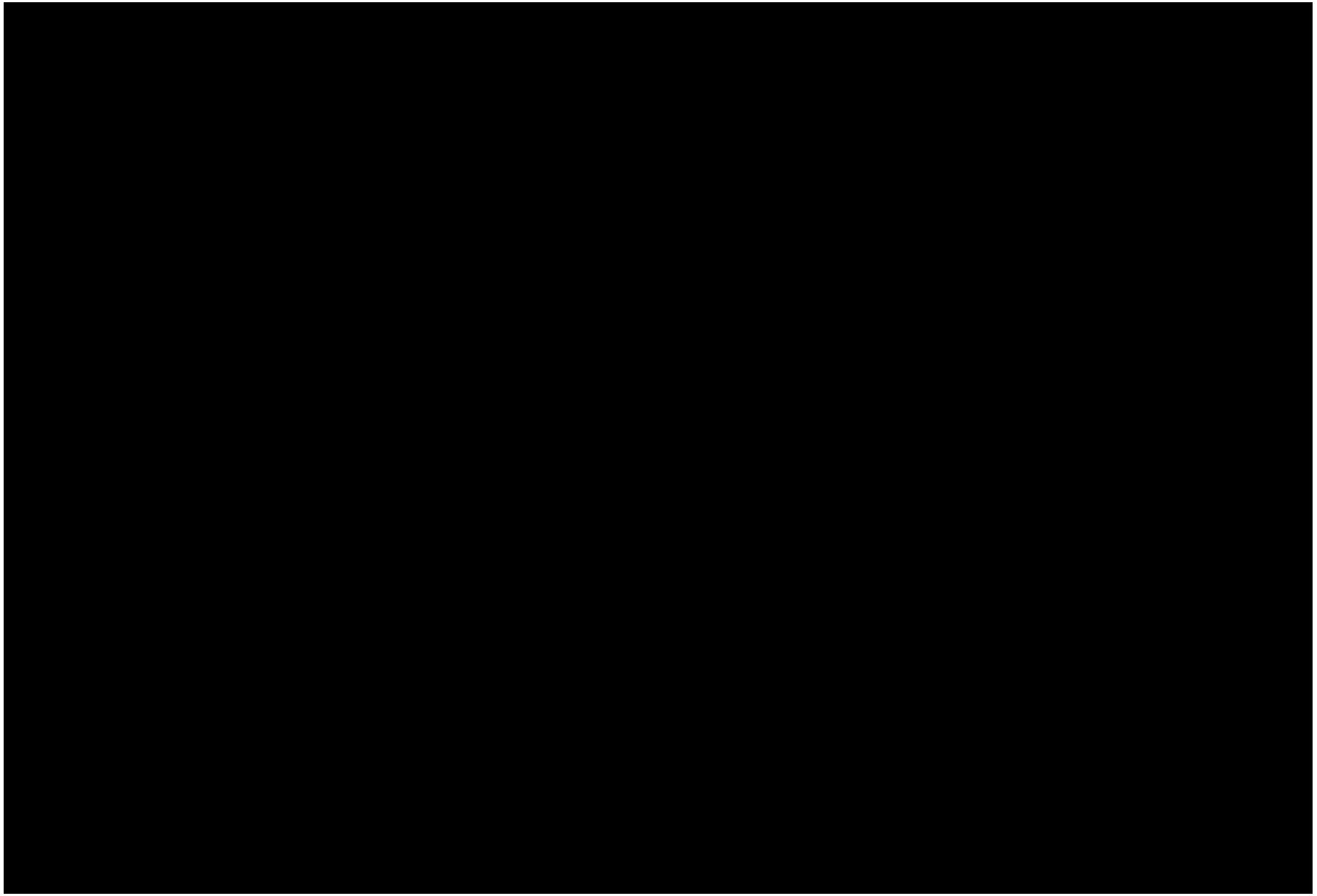

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18.2. Figure Shells

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18.3. Listing Shells

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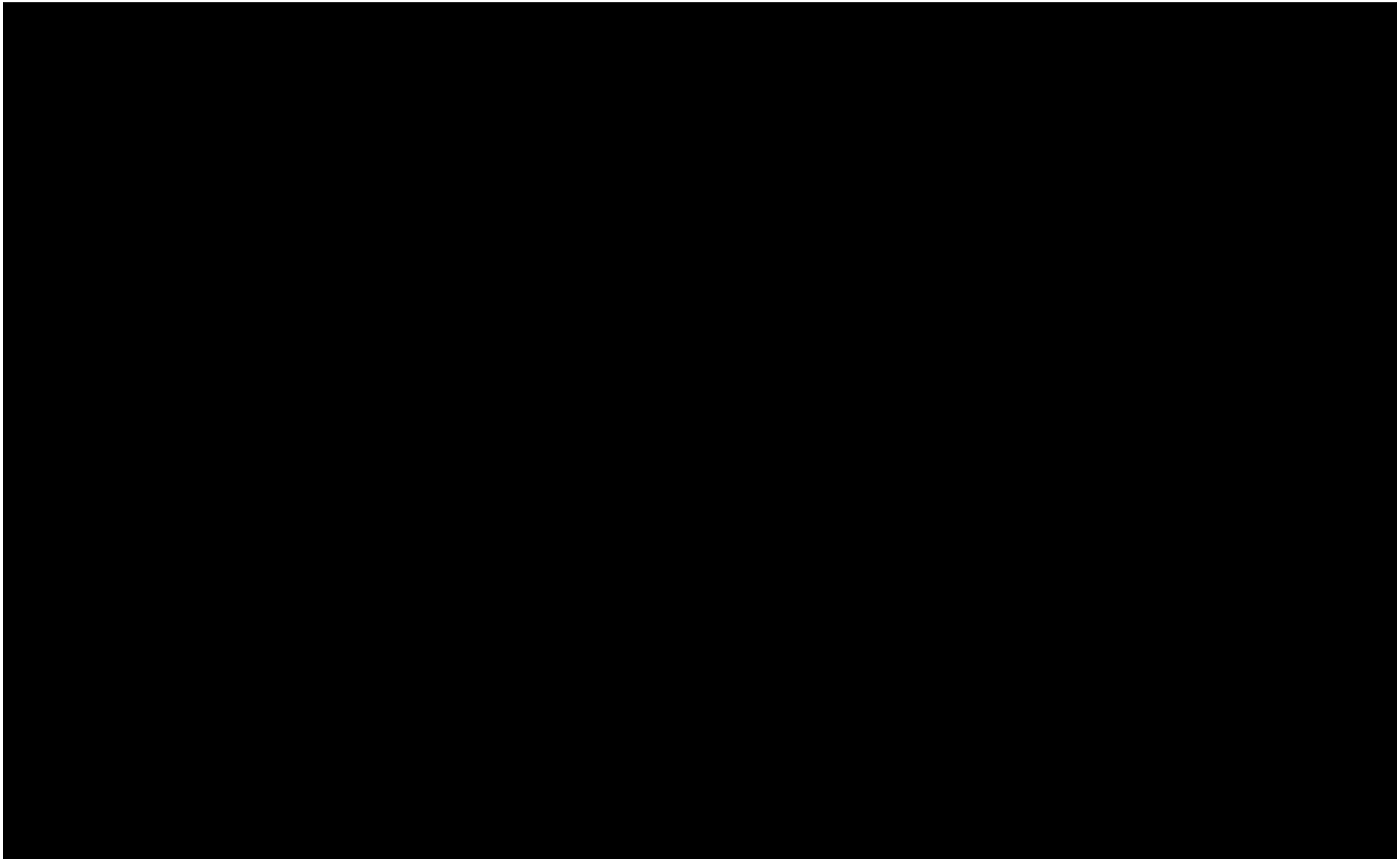

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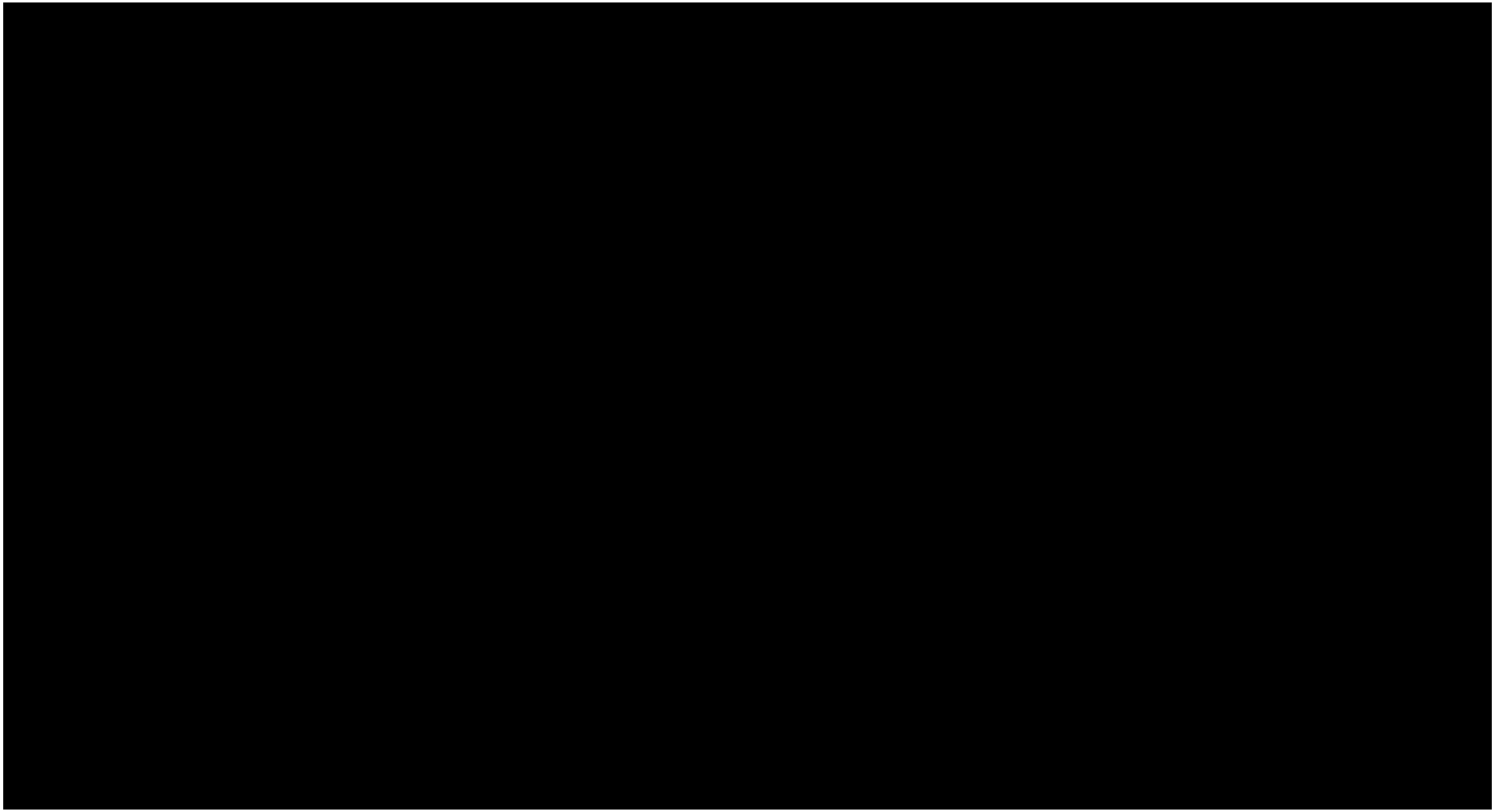

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19. Appendices

Not applicable.