Title Page

Protocol Title: A multicenter, randomized, double-blind, dose-conversion study to evaluate the safety and efficacy of hormone replacement therapy with Armour® Thyroid compared to synthetic T4 (levothyroxine) in previously hypothyroid participants, who are euthyroid on T4 replacement therapy

Protocol Number: 3014-201-002

Amendment Number: 1

Product: Armour Thyroid (AGN-204771)

Brief Protocol Title: A Phase 2, dose-conversion study of Armour® Thyroid compared to synthetic T4 (levothyroxine) in previously hypothyroid participants

Development Phase: 2

Sponsor Name: Allergan Sales, LLC

Legal Registered Address: 5 Giralda Farms, Madison, NJ 07940, USA

Regulatory Agency Identifying Number: IND 105,219: Armour Thyroid (thyroid tablets, USP)

Emergency Telephone Number: Refer to the study contacts page

SAE Reporting Fax Number/Email:

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Allergan	IR-Clinical-SAE@allergan.com	Not applicable	[redacted]

Approval Date: 16 January 2020

Sponsor Signatory:

[redacted]

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	*16 January 2020*
Original Protocol	*24 May 2019*

Amendment 1 (16 January 2020)

Overall Rationale for the Amendment:

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table of Contents

List of Tables

1. Protocol Summary

1.1. Synopsis

Protocol Title: A multicenter, randomized, double-blind, dose-conversion study to evaluate the safety and efficacy of hormone replacement therapy with Armour® Thyroid compared to synthetic T4 (levothyroxine) in previously hypothyroid participants, who are euthyroid on T4 replacement therapy

Protocol Number: 3014-201-002

Brief Protocol Title: A Phase 2, dose-conversion study of Armour® Thyroid compared to synthetic T4 (levothyroxine) in previously hypothyroid participants

Study Phase: 2

Study Rationale:

This study will evaluate the safe and effective dose conversion from synthetic T4 therapy to Armour Thyroid therapy in previously hypothyroid participants who are euthyroid on a stable dose of synthetic T4. This study is designed to demonstrate that treatment with matching doses of Armour Thyroid is noninferior to treatment with synthetic T4, specifically in reference to euthyroid status as determined by TSH measurements. In addition, this study will demonstrate the safe and tolerable use of Armour Thyroid in hypothyroid participants. Finally, symptoms of hypothyroidism will be monitored as exploratory endpoints to evaluate potential differences between Armour Thyroid and synthetic T4.

Objectives and Endpoints:

Objectives	Endpoints
Primary Efficacy	
• To evaluate the efficacy of hormone replacement therapy with matching doses of Armour Thyroid in comparison to synthetic T4 in previously hypothyroid participants who are euthyroid on synthetic T4 replacement therapy (25-200 µg T4 daily)	• The percent of participants who are Sustained TSH Responders, defined as participants whose TSH values are within the normal reference range[a] at both the end of the Titration Period and the end of the Stabilization Period among the randomized participants who received at least 1 dose of study intervention
Secondary Efficacy	
• To evaluate the efficacy of hormone replacement therapy with matching doses of Armour Thyroid in comparison to synthetic T4 in previously hypothyroid participants who are euthyroid on synthetic T4 replacement therapy (25–200 µg T4 daily) based on titration	• The percent of participants who are Titration TSH Responders, defined as participants whose TSH values are within the normal reference range[a] at the end of the Titration Period among the randomized participants who received at least 1 dose of study intervention
Additional Efficacy	
[redacted]	
Safety and Tolerability	
[redacted]	

Armour Thyroid

Overall Study Design:

This is a randomized, double-blinded, parallel-group, active-controlled, multicenter, dose-conversion study in previously hypothyroid participants, who are euthyroid on stable T4 replacement therapy, to evaluate the safety and efficacy of replacement therapy with matching doses of Armour Thyroid in comparison to synthetic T4.

Number of Participants:

Approximately 220 total participants who meet eligibility criteria will be randomly assigned to study intervention in a 1:1 ratio (110 participants per arm).

Number of Sites:

Approximately 20 to 30 study centers in the United States

Intervention Groups and Study Duration:

The study will last approximately 30 to 48 weeks (with a planned minimum of 7 visits and a planned maximum of 15 possible visits if participants require additional dose titration) and will include a Screening Period, double-blinded Titration Period (at least 18 weeks), and a double-blinded Stabilization Period (12 weeks).

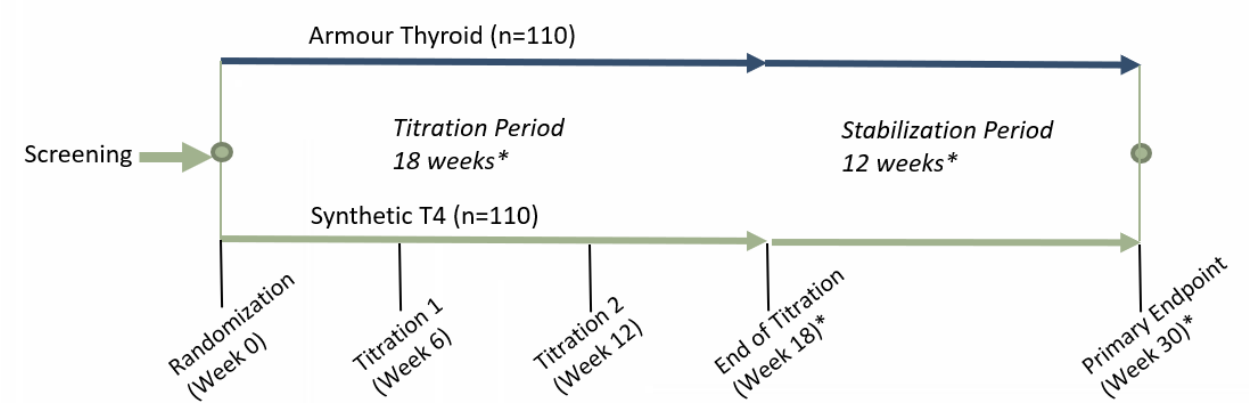
All participants entering the study will be controlled on a stable, FDA-approved, daily dose of synthetic T4 (ie, euthyroid) for at least 3 months and will be randomized to either their same dose of synthetic T4 or a matching dose of Armour Thyroid during the first visit of the Titration Period (Visit 2). [redacted]

During the Titration Period, participants will continue the same dose taken during the last visit or have their dose up- or down-titrated as needed per the Investigators' interpretation of their TSH levels (normal reference range 0.45-4.12 mIU/L, inclusive). [redacted] Other thyroid-related assessments and evaluation of thyroid clinical status will also be completed.

Investigators may only titrate participants' doses, as needed, until the start of the Stabilization Period. Participants will remain on a stable dose during the Stabilization Period until the end of the study.

Data Monitoring Committee: Please refer to Section 8.2.5.

1.2. Schema



* If a participant undergoes up to the maximum of 3 additional dose titrations starting at Week 18, the Titration Period may extend up to Week 36; therefore, the Stabilization Period may extend from Week 36 to Week 48 (remaining 12 weeks in duration). The Primary Endpoint will be measured at the end of the Titration Period and the end of the Stabilization Period.

During the Titration Period, study visits are split into parts "a" and "b" (ie, Visit 3a, Visit 3b, Visit 4a, Visit 4b) to allow for any dose titrations:

- Visits 3a and 4a are mandatory for all participants. Study assessments, including bloodwork for TSH, and study intervention dispensing will be performed.
- Visits 3b and 4b are only required for participants needing a dose titration based on the data obtained from Visits 3a and 4a, respectively. A limited number of assessments and study intervention dispensing will be performed at Visits 3b and 4b.

Visit 5 is designed as a transition visit between the Titration and Stabilization Periods and may consist of a subset of visits (starting with Visit 5a [Week 18] and extending to Visit 5g [Week 36], as needed). The last visit within Visit 5 serves as both the end of the Titration Period and the beginning of the Stabilization Period.

- Participants with TSH levels within normal reference range at Visit 5a may enter the Stabilization Period (ie, their next visit will be Visit 6).
- If participants' TSH levels are out of normal reference range at Visit 5a, participants' doses can be up- or down-titrated per the Investigators' interpretation until their TSH levels are within the normal reference range by continuing the Titration Period beyond Week 18. If the Titration Period is continued, the participants' doses can be up- or down-titrated approximately every 6 weeks until their TSH levels have normalized for up to a maximum of 3 additional titrations (including the titration at Visit 5b). Once their TSH levels are within the normal reference range, participants may enter the Stabilization Period. Participants whose TSH levels have not normalized after the maximum of 3 additional titrations will not enter the Stabilization Period.

[redacted]

[redacted]

1.3. Schedule of Activities

[redacted]

2. Introduction

Hypothyroidism is a disease that affects an estimated 3.7% of the US population, translating to over 8 million patients based on the results of the National Health and Nutrition Examination Survey (NHANES 1999-2002; Aoki 2007). In hypothyroidism, the thyroid gland is underactive and is unable to produce a sufficient amount of thyroid hormone. The principal thyroid hormones are T3 (liothyronine, triiodothyronine [3, 5, 3′- triiodothyronine]) and T4 (levothyroxine, l-thyroxine, thyroxine). Thyroid hormones are required for normal growth, development, and the maintenance of metabolic homeostasis. These hormones enhance oxygen consumption by most tissues of the body and increase the basal metabolic rate and the metabolism of carbohydrates, lipids, and proteins (Armour Thyroid 2018). As such, these hormones exert profound effects on almost every organ in the body and are of particular importance in regard to cardiovascular function, bone metabolism, reproductive function, cognitive function, and in the maturation of the central nervous system (Armour Thyroid 2018, Synthroid 2018).

Hypothyroid patients most commonly present with signs and symptoms of dry skin, fatigue, cold sensitivity, weight gain, constipation, voice changes, and muscle cramps. Patients may also experience neurological disorders such as impaired memory, alterations in mood (eg, depression), and sleep apnea. Because of the deleterious consequences of hypothyroidism during the neonatal period and infancy, including mental retardation or cretinism and impaired growth and development in general, pregnant women and newborns are screened for thyroid hormone deficiency.

Hypothyroidism is typically characterized by high levels of TSH and low levels of T4. T4 is the main hormone produced by the thyroid gland whereas T3 is only secreted by the gland in small amounts. T3 is the metabolically active thyroid hormone and is predominantly produced by the peripheral monodeiodination of T4. The main treatment for hypothyroidism is thyroid hormone replacement therapy. The clinical practice guidelines for treating hypothyroidism, developed by the AACE and ATA, recommend treating hypothyroid patients with synthetic T4 (Garber 2012).

Treatment for hypothyroidism needs to be individualized, as dosing needs are dependent on several factors including a patient's age, sex, body weight, absorption rate, and concomitant medical conditions (Garber 2012, Jonklaas 2014). Therefore, patients with identical baseline TSH values may have varying responses to the same dose of thyroid hormone replacement therapy. An approximate starting dose of synthetic T4 can be estimated using 1.6 µg/kg based on body mass but should be adjusted based on the factors noted above (Synthroid 2018). Approved doses of synthetic T4 range from 25 µg to 300 µg (Synthroid 2018) with multiple incremental doses; however, dosing greater than 200 µg daily could indicate issues with noncompliance or drug absorption (Garber 2012).

The clinical practice guidelines for treating hypothyroidism deem TSH to be the most reliable marker of adequacy of thyroid hormone replacement therapy and recommend incremental dose titrations guided by serum TSH levels (Garber 2012, Jonklaas 2014). Clinical symptoms of hypothyroidism should be followed, but are not recommended for judging adequacy of treatment

as they lack sensitivity and specificity (Jonklaas 2014). Instead, symptoms should be considered in the context of serum TSH values and other potential causes (Jonklaas 2014).

A subgroup of synthetic T4-treated patients continues to have persistent symptoms consistent with hypothyroidism that result in impaired well-being and quality of life despite having TSH levels within normal reference range (Cooper 2003, Kaplan 2003, Saravanan 2002, Walsh 2002, Walsh 2006). One of the reasons why these symptoms persist in patients on T4 therapy may be due to the relative tissue differences in T3 and T4 levels following hormone replacement therapy (Escobar-Morreale 1995, Cooper 2003).

Despite the similar chemical structures of T3 and T4, T3 is the metabolically active hormone and therefore more potent than T4 (McDermott 2012). Intracellular deiodination is an important factor in generating intracellular T3. For instance, animal studies have shown that up to 80% of intracellular T3 in the brain is derived from monodeiodination of circulating T4 and only 20% is derived from T3 secreted by the thyroid gland (Fish 1987). One explanation for the apparent failure of T4 replacement therapy alone to satisfactorily control symptoms of hypothyroidism in some patients may be that T3 levels are not adequately restored in all tissues as was demonstrated in previous studies in thyroidectomized rats (Escobar-Morreale 1995, Escobar-Morreale 1996). Therefore, combined hormone replacement with T3 and T4 may more closely mimic production by the intact thyroid gland compared to T4 monotherapy.

For hypothyroidism patients who have persistent symptoms, signs, or inadequate efficacy despite synthetic T4 treatment, there are few options currently available. Synthetic T3 (brand name, Cytomel) is currently approved for use in the United States as a thyroid replacement hormone and could be used in addition to T4. Desiccated thyroid (porcine-derived) gland is also an option for thyroid hormone replacement that has been widely used for many years and was the predominant treatment choice for hypothyroid patients prior to the development of synthetic T4.

The active ingredient in Armour Thyroid is desiccated, powdered porcine thyroid gland (Thyroid Powder), which contains the protein thyroglobulin. Thyroglobulin is hydrolyzed in vivo to yield the thyroid hormones T3 and T4. Powdered porcine thyroid gland has been available since the early 1900s and is generally recognized as a replacement or supplemental therapy in certain patients with hypothyroidism. Armour Thyroid is currently indicated as treatment in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism in adults (Armour Thyroid 2018). Similar to synthetic T4, dosing for Armour Thyroid needs to be individualized based on clinical response and laboratory parameters. As such, there are incremental doses of Armour Thyroid.

There is a strong demand from physicians as well as patients and advocacy groups for naturally derived T3/T4 products, including Armour Thyroid. A recent hypothyroidism treatment survey completed by 12,146 individuals found a higher median treatment satisfaction with desiccated thyroid compared to other treatments (synthetic T4 or synthetic T3 in addition to synthetic T4) (Peterson 2018). Patients on desiccated thyroid were also less likely to report issues with weight management, fatigue/energy, mood, and memory compared to those taking synthetic T4 alone or in combination with synthetic T3 (Peterson 2018). Despite the availability of synthetic T3 and T4 drug products for the treatment of hypothyroidism, Armour Thyroid was prescribed by over

109,000 physicians (> 4.7 million prescriptions) in the United States for the treatment of hypothyroidism in a 1-year period (August 2017 to July 2018).

2.1. Study Rationale

This study will evaluate the safe and effective dose conversion from synthetic T4 therapy to Armour Thyroid therapy in participants who are euthyroid on a stable dose of synthetic T4. This study is designed to demonstrate that treatment with matching doses of Armour Thyroid is noninferior to treatment with synthetic T4, specifically in reference to euthyroid status as determined by TSH measurements. In addition, this study will demonstrate the safe and tolerable use of matching doses of Armour Thyroid to synthetic T4 in hypothyroid participants. Symptoms of hypothyroidism will be monitored as exploratory endpoints to evaluate potential differences between Armour Thyroid and synthetic T4.

2.2. Background

The number of FDA-approved and commercially available options for the treatment of hypothyroidism are limited. Currently, synthetic T4 is the mainstay of thyroid replacement therapy and is the first-line, guideline-recommended treatment option for hypothyroid patients. If the results of T4 replacement are not satisfactory, then it can be supplemented or replaced with synthetic T3 (which is also FDA approved and commercially available) or desiccated thyroid.

Prior to the advent of synthetic T4 and synthetic T3, patients with hypothyroid disease were treated with desiccated thyroid. Desiccated thyroid is known to contain both thyroid hormones, T3 and T4, and successfully normalize TSH in hypothyroid patients. Although desiccated and purified thyroid has had a long history of therapeutic use, there are a limited number of clinical trials which demonstrate its effectiveness in comparison to the standard of care, synthetic T4.

To date, there has been 1 double-blinded, randomized study which compared desiccated thyroid (Armour Thyroid) to synthetic T4 (Hoang 2013); this single-center study was run by Walter Reed National Military Medical Center and was not sponsored by Allergan. A total of 70 previously hypothyroid patients, then euthyroid on replacement therapy, were enrolled in this cross-over study and were randomized to either synthetic T4 or Armour Thyroid. The primary endpoint of this study showed no difference between synthetic T4 and Armour Thyroid for symptom scores, health questionnaires, or neuropsychological tests. All patients remained within acceptable TSH range at the end of each study period, demonstrating that hypothyroid patients can be safely and effectively switched between synthetic T4 and Armour Thyroid.

2.3. Benefit/Risk Assessment

Participants with hypothyroidism may experience negative symptoms such as fatigue, weight gain, cold sensitivity, dry skin and hair loss as well as neurological symptoms such as impaired memory and mood alterations. Severe and uncontrolled hypothyroidism can lead to serious ailments, such as myxedema coma or crisis. Thus, it is important that all hypothyroid participants receive thyroid replacement therapy to ensure that TSH levels are normalized to a euthyroid status. Due to the risks of uncontrolled hypothyroid disease, this study will be actively controlled to ensure that all participants are receiving thyroid replacement therapy throughout the entirety of the study.

Participants in this study may benefit from the close monitoring of their TSH values, leading to appropriate dose adjustments of either Armour Thyroid or synthetic T4.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of Armour Thyroid may be found in the Investigator's Brochure and the Package Insert (Armour Thyroid 2018).

3. Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
• To evaluate the efficacy of hormone replacement therapy with matching doses of Armour Thyroid in comparison to synthetic T4 in previously hypothyroid participants who are euthyroid on synthetic T4 replacement therapy (25-200 µg T4 daily)	• The percent of participants who are Sustained TSH Responders, defined as participants whose TSH values are within the normal reference range[a] at both the end of the Titration Period and the end of the Stabilization Period among the randomized participants who received at least 1 dose of study intervention
Secondary Efficacy	
• To evaluate the efficacy of hormone replacement therapy with matching doses of Armour Thyroid in comparison to synthetic T4 in previously hypothyroid participants who are euthyroid on synthetic T4 replacement therapy (25–200 µg T4 daily) based on titration	• The percent of participants who are Titration TSH Responders, defined as participants whose TSH values are within the normal reference range[a] at the end of the Titration Period among the randomized participants who received at least 1 dose of study intervention
Additional Efficacy	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	

GMT)

4. Study Design

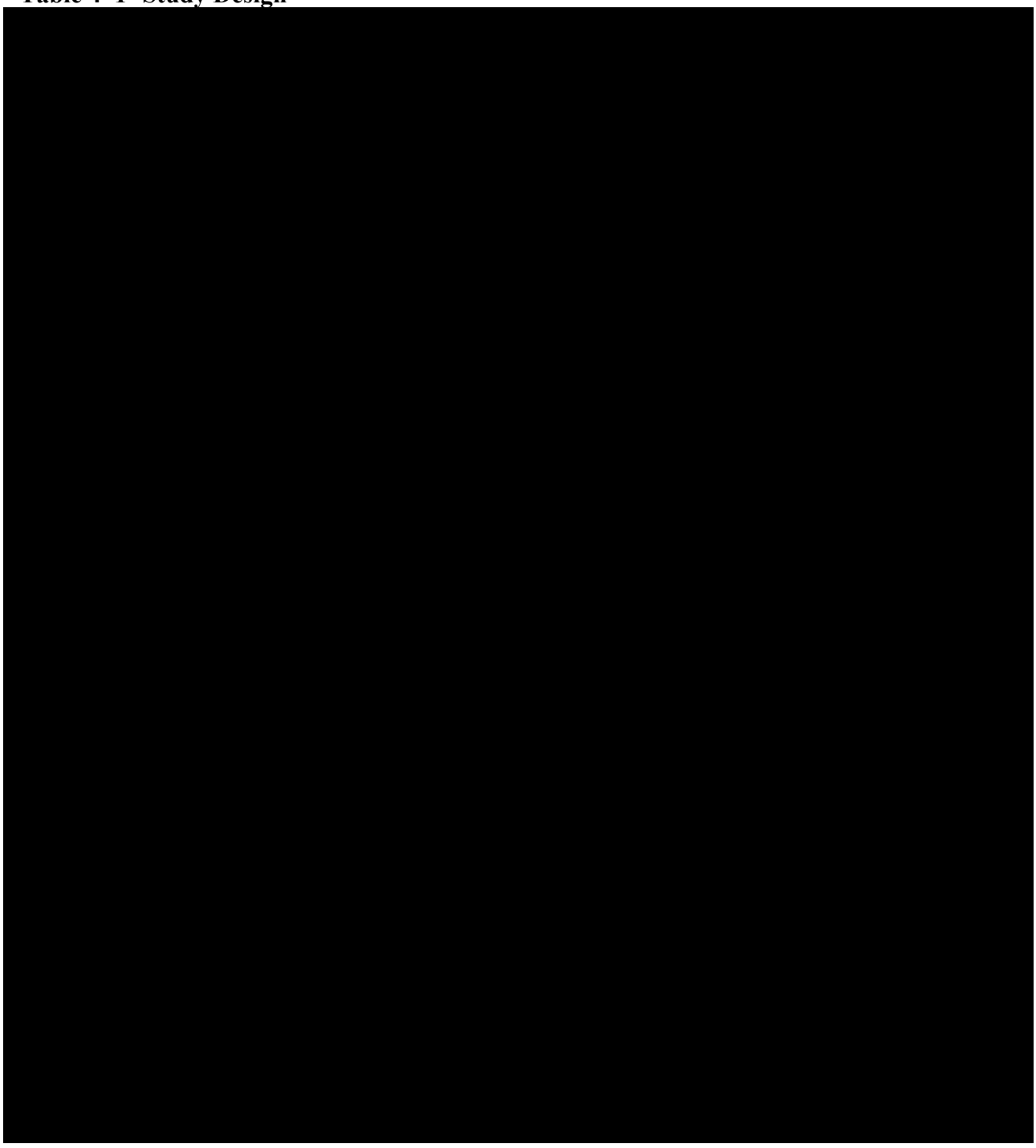
4.1. Overall Design

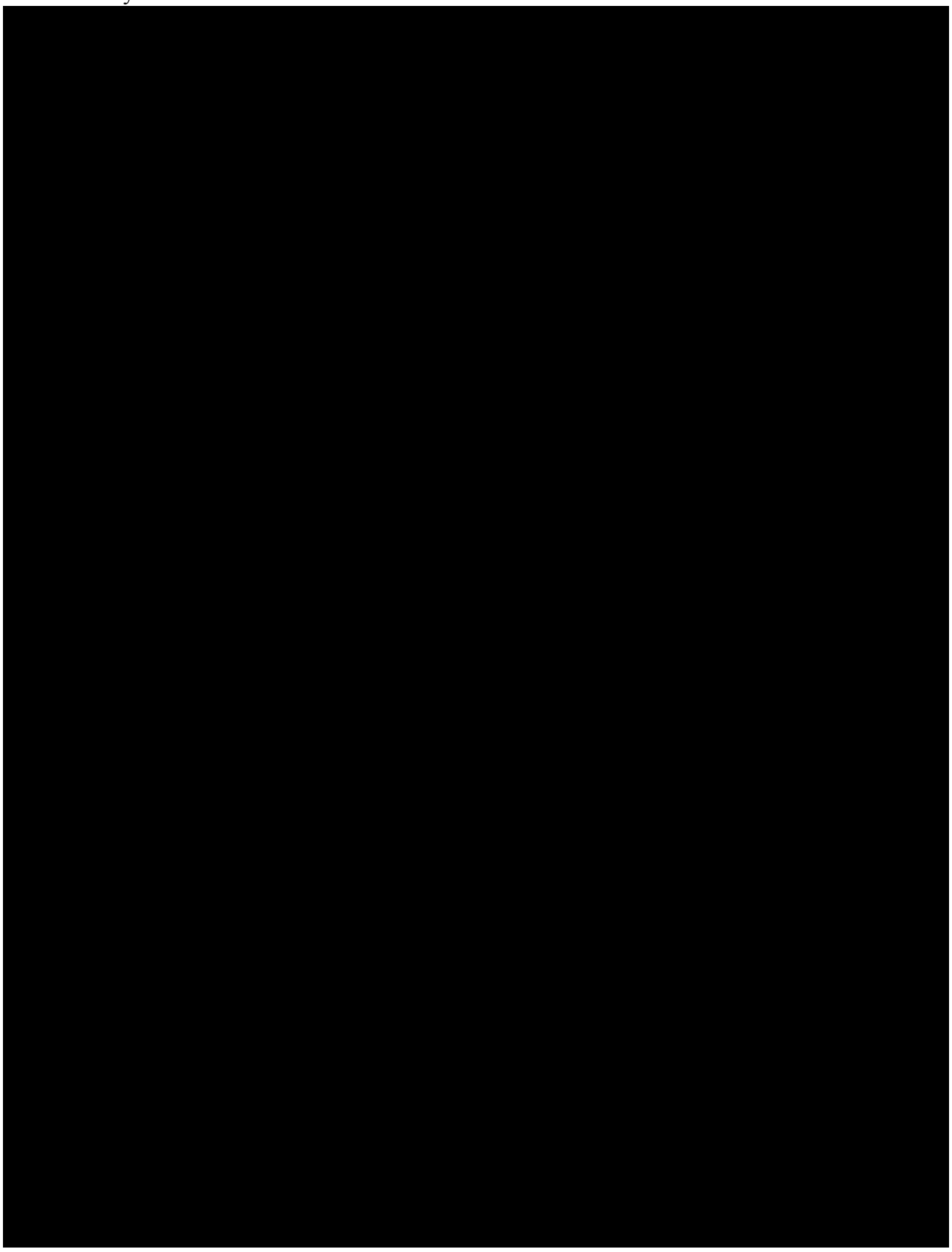
This is a randomized, double-blinded, parallel-group, active-controlled, multicenter, dose-conversion study in previously hypothyroid participants, who are euthyroid on a stable dose of T4 replacement therapy, to evaluate the efficacy and safety of replacement therapy with matching doses of Armour Thyroid in comparison to synthetic T4.

Approximately 220 total participants who meet eligibility criteria will be randomly assigned to study intervention in a 1:1 ratio (110 participants per arm) at approximately 20 to 30 study centers in the United States.

[redacted]

Table 4–1 Study Design





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4.1.1. Clinical Hypotheses

Participants treated with Armour Thyroid will show a similar ability to sustain a normal TSH level (ie, TSH response) as participants receiving synthetic T4. The safety and tolerability in participants receiving Armour Thyroid will be similar to participants receiving synthetic T4. It is expected that this study will validate the dose-conversion table of synthetic T4 and Armour Thyroid (Section 10.10, Appendix 10).

4.2. Scientific Rationale for Study Design

This is a randomized, double-blind, parallel-group, active-controlled, multicenter, dose-conversion study in order to assess the efficacy and safety of matching doses of Armour Thyroid in comparison to synthetic T4 for thyroid hormone replacement in previously hypothyroid participants. This study will also evaluate a safe and effective dose conversion from synthetic T4 to Armour Thyroid in participants who are euthyroid on a stable dose of synthetic T4. The use of active control is justified because synthetic T4 is the standard of care for thyroid hormone replacement. All participants entering the study will be controlled on a stable FDA-approved, daily dose of synthetic T4 for at least 3 months and will be randomized to either their same dose of synthetic T4 or a matching dose of Armour Thyroid (Section 10.10, Appendix 10).

4.3. Justification for Dose and/or Study Intervention Administration

Participants will be randomized to either their pre-randomized dose of synthetic T4 or a matching dose of Armour Thyroid (Section 10.10, Appendix 10) during the first visit of the Titration Period (Visit 2). For each available dose of synthetic T4, up to 200 µg, a matching dose of Armour Thyroid will be employed in this clinical study.

The Titration Period will be comprised of at least 18 weeks during which the study participants will complete a study visit approximately after every 6 weeks to have assessments performed, including the measurement of TSH. During the Titration Period, Investigators will have the option to either maintain, up-, or down-titrate the dose of study intervention based on participants' TSH levels. The clinical practice guidelines for treating hypothyroidism in adults recommend dose adjustments to be guided by serum TSH levels (Garber 2012, Jonklaas 2014).

At the end of the Titration Period, participants with TSH levels within normal reference range may enter the Stabilization Period.

[redacted]

4.4. End of Study Definition

The EOS is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the study.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Participant must be 18 to 75 years of age, inclusive, at the time of signing the informed consent.
2.	**Type of Participant and Disease Characteristics**
2.01	Participants who have a diagnosis of primary hypothyroidism made ≥ 12 months before study entry (Visit 1).
	Note: Participants who have undergone total thyroidectomy for treatment of thyroid cancer may be eligible for enrollment if they: a. are > 5 years from the date of total thyroidectomy (or last thyroid surgery), b. have had no clinical evidence of recurrence, and c. have had serial measurements of thyroglobulin and anti-thyroglobulin since the time of surgery or treatment with radioactive iodine. All thyroglobulin values should have been undetectable and anti-thyroglobulin values within the normal reference range after surgery or starting 6 months after treatment with radioactive iodine (including values obtained at the Screening Visit [Visit 1])
2.02	Be on continuous thyroid replacement therapy with synthetic T4 for primary hypothyroidism for at least 12 months immediately prior to the Screening Visit (Visit 1).
2.03	Be on a stable FDA-approved daily dose of synthetic T4 for a minimum of 3 months prior to the Screening Visit (Visit 1). Must enter the study on the same stable dose.
2.04	Have euthyroid status indicated by at least 1 documented TSH value within normal reference range (0.45-4.12 mIU/L, inclusive) at a minimum of 6 weeks and maximum of 12 months prior to the Screening Visit (Visit 1). Also have a confirmed TSH value within the normal reference range drawn at the Screening Visit (Visit 1)
2.05	Have vision and hearing (hearing aid permissible) sufficient for compliance with testing procedures.
3.	**Weight and Body Mass Index**
3.01	Participants must have a BMI between 18 and 40 (inclusive) at Screening Visit (Visit 1).

4.	**Sex**
4.01	Male or female
5.	**Contraceptives**
5.01	Male participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period (35 days after last dose of study intervention).
	A male participant must agree to use contraception as detailed in Appendix 7 of this protocol starting at the Screening Visit (Visit 1), during the study intervention period and for at least 35 days after the last dose of study intervention and refrain from donating sperm during this period.
5.02	Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period (35 days after last dose of study intervention).
	A female participant is eligible to participate if she is not pregnant (has a negative serum pregnancy result at the Screening Visit (Visit 1) and a negative urine pregnancy result at Baseline (Visit 2) prior to randomization; see Appendix 7), not breastfeeding, and at least 1 of the following conditions applies: a. Not a female of CBP as defined in Appendix 7 OR b. A female of CBP who agrees to follow the contraceptive guidance in Appendix 7 of this protocol starting at the Screening Visit (Visit 1) and for at least 35 days after the last dose of study intervention.
6.	**Informed Consent**
6.01	Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
6.02	Written informed consent from the participant has been obtained prior to any study-related procedures.
6.03	Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable.
7.	**Other**
7.01	Able, as assessed by the Investigator, and willing to follow study instructions and likely to complete all required study visits.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Any clinical condition or previous surgery that might affect the absorption, distribution, biotransformation, or excretion of Armour Thyroid or synthetic T4.
1.02	History of alcohol or other substance abuse within the previous 5 years.
1.03	Known or suspected allergy or intolerance to any ingredients of Armour Thyroid, including its excipients, levothyroxine (T4), other thyroid replacement medications, or pork products.
2.	**Prior/Concomitant Therapy**
2.01	Have taken any prohibited concomitant medication that cannot meet the requirements prior to Baseline (Visit 2) as outlined in Section 6.5.1.
2.02	Have received active treatment with an investigational drug within 30 days or 5 half-lives, whichever is longer, of Screening Visit (Visit 1).
2.03	Participant cannot be taking a daily dose of synthetic T4 that exceeds 200 µg at Screening Visit (Visit 1).
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 60 days of entry into this study.
4.	**Diagnostic Assessments**
4.01	Clinically significant results according to the Investigator or designee, on physical examination, medical history, ECG, hematology, clinical chemistry, or urinalysis that may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study.
4.02	Sitting systolic BP [≥ 140 mm Hg or ≤ 90 mm Hg] or sitting diastolic BP [≥ 90 mm Hg or ≤ 50 mm Hg] at the Screening Visit. Note: A total of 3 readings of BP and pulse will be taken. The first reading should be rejected. If either the second or third reading meets exclusion criteria, the participant should be excluded.

4.03	Abnormal ECG results thought to be potentially clinically significant according to the Investigator or designee, or QT prolongation (QTcF ≥ 450 msec for male participants or ≥ 470 msec for female participants) at the Screening Visit (Visit 1).
5.	**Other**
5.01	The participant has a concurrent disease, condition, or is in a situation which, in the Investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study.
5.02	Directly or indirectly involved in the conduct and administration of this study as an Investigator, sub-investigator, study coordinator, or other study staff member; or employee of the Sponsor or a first-degree family member, significant other, or relative residing with 1 of the above persons involved directly or indirectly in the study; or enrolled in the study at another clinical site.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

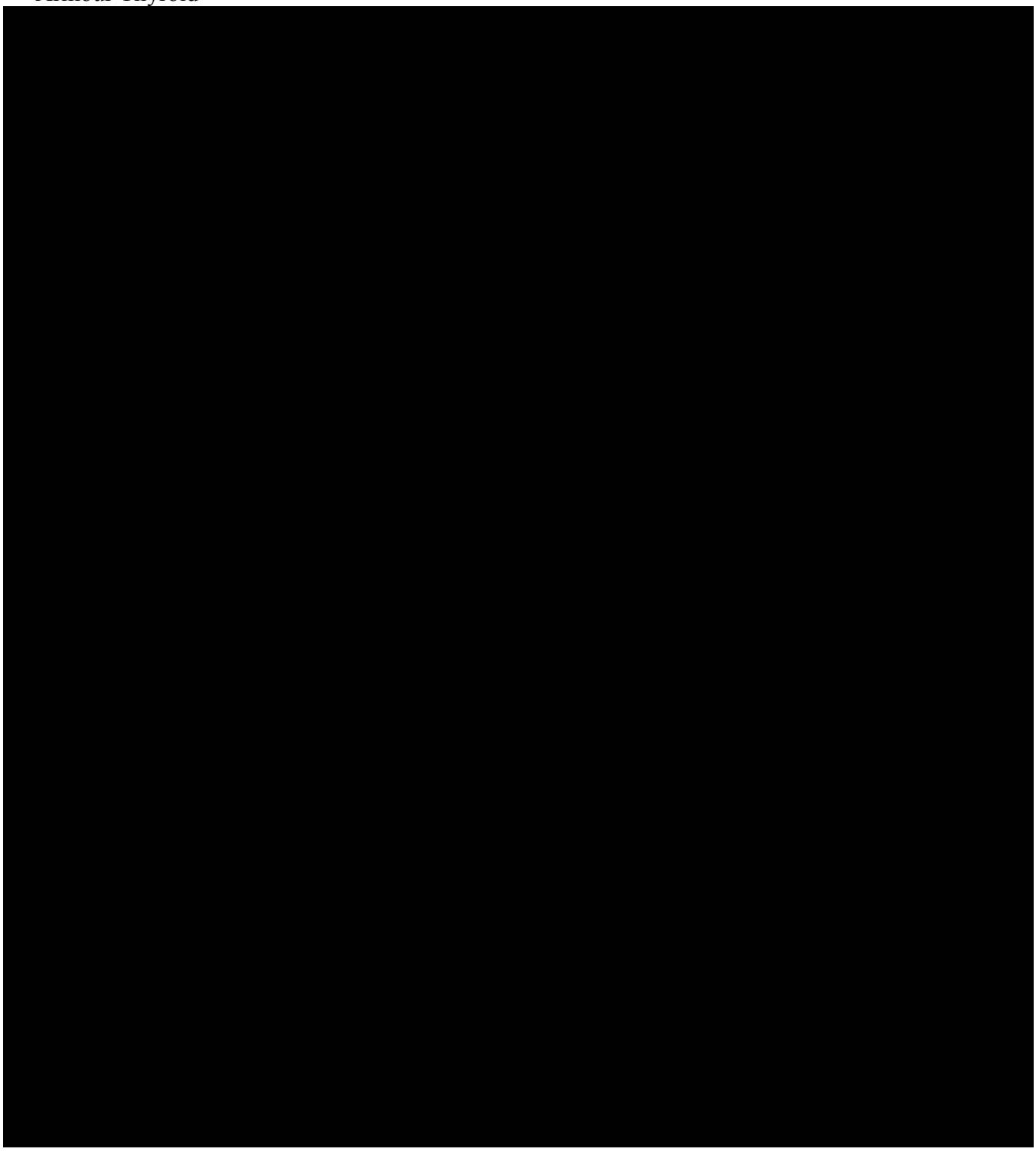
Participants will be required to undergo an overnight (minimum 5 hours) fast for all visits where laboratory assessments will be performed and will need to maintain a fasted condition for an additional 30 to 60 minutes after administration of study intervention for these visits.

1. Study intervention will be taken at least 30 to 60 minutes prior to the first meal with approximately 1 glass of water; water will be provided for participants at other times as desired.
2. Blood samples (with the exception of post-dose PK sampling) and thyroid-related assessments (specifically TSH, T3, T4, FT3, FT4) will be measured prior to study intervention administration.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT (Consolidated Standards of Reporting Trials) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened once after Sponsor approval.



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6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator or study center is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

All unused study intervention and used kits must be returned to the Sponsor/designee or destroyed on site per site policy by the termination of the study. Final accountability will be performed when the study intervention is returned or prior to destruction.

[redacted]

6.4. Study Intervention Compliance

Study intervention compliance will be assessed at each visit starting with Visit 2 (Baseline) and through the remainder of the study. The compliance assessment at Baseline (Visit 2) will evaluate the participants having taken their own synthetic T4 between the Screening Visit (Visit 1) and Visit 2.

Study intervention compliance will be closely monitored by counting the units of study intervention dispensed and returned. Before dispensing new study intervention at each visit, study center personnel will make every effort to collect all unused study intervention and used kits.

The study center will keep an accurate drug disposition record that specifies the amount of study intervention dispensed to each participant and the date of dispensation.

6.5. Concomitant Therapy

The use of any concomitant medication, prescription or over-the-counter medication, is to be recorded on the participant's eCRF at each visit along with the reason the medication is taken.

At all study visits, study center staff will question each participant specifically on the use of concomitant medications. Study center staff must notify the Sponsor immediately if a participant consumes any concomitant medications not permitted by the protocol. Participants who admit to using prohibited concomitant medications may be discontinued from the study at the discretion of the Investigator or the Sponsor.

6.5.1. Prohibited Interventions Before the Study

Participants must discontinue any of the medications listed in the table below for the specified period prior to Baseline (Visit 2). These medications are prohibited for the duration of the study.

Thyroid Replacement Therapy	Minimum Duration that Participants must be off Treatment Prior to Baseline
Synthetic T4	0 days
Thyroid supplements	12 months
Synthetic T3	12 months
Desiccated thyroid	12 months

The Investigator or Sponsor reserves the right to exclude a participant from participation in the study if a medication taken 14 or more days before the study start may interfere with the study outcome (eg, a drug with prolonged half-life).

All medication taken since informed consent will be recorded in the eCRF.

The decision to administer a prohibited medication/intervention during the study period is done with the safety of the study participant as the primary consideration. When possible, the Sponsor is to be notified before the prohibited medication/intervention is administered.

6.5.2. Permitted Interventions

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Therapy considered necessary for the participant's welfare may be given at the discretion of the Investigator. If the permissibility of a specific medication/intervention is in question, please contact the Sponsor.

The Sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

Any medication taken during the study between the date of the first dose of study intervention and the date of the EOS visit will be recorded in the eCRF as a concomitant medication; any medication started after the EOS visit will not be considered a concomitant medication and should not be captured in the eCRF.

6.5.3. Rescue Medicine

Rescue medicine is not applicable.

6.6. Dose Modification

The clinical practice guidelines for treating hypothyroidism in adults recommend dose adjustments guided by serum TSH levels (Garber 2012, Jonklaas 2014).

Participants will be randomized to either their pre-randomized dose of synthetic T4 or a corresponding dose of Armour Thyroid (Section 10.10, Appendix 10) during the first visit of the Titration Period (Visit 2).

During the Titration Period, Investigators will have the option to up- or down-titrate participants' doses as needed per their interpretation of the participants' TSH levels (normal reference range 0.45-4.12 mIU/L, inclusive). For example, Investigators should up-titrate the dose if the TSH value is above 4.12 mIU/L and down-titrate the dose if the TSH value is below 0.45 mIU/L during the Titration Period.

At Week 18, if participants' TSH levels are not within the normal reference range, the Investigator may up- or down-titrate participants' doses by continuing the Titration Period beyond Week 18. If the Titration Period is continued, the participants' doses can be up- or down-titrated approximately every 6 weeks until their TSH levels are within the normal reference range for up to a maximum of 3 additional titrations (including the titration at Visit 5b). Participants whose TSH levels have not normalized after the maximum 3 additional titrations will not enter the Stabilization Period.

At the end of the Titration Period, participants who are euthyroid based on TSH levels may enter the Stabilization Period.

Armour Thyroid

Dose modification will be prohibited during the Stabilization Period of the study.

6.7. Intervention after the End of the Study

Intervention after the EOS is not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and receives intervention ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Reasons for discontinuation from the study intervention and/or the study may include the following commonly used or other acceptable terms (definitions are provided in Appendix 5):

- Adverse event
- Death
- Lost to follow-up
- Non-compliance with study drug
- Other
- Physician decision
- Pregnancy
- Site terminated by Sponsor
- Study terminated by Sponsor
- Withdrawal by participant

7.1. Discontinuation of Study Intervention

If a clinically significant finding is identified after enrollment, the Investigator or qualified designee will determine if the participant can continue treatment with the study intervention and if any change in the participant's management is needed. Any new clinically relevant finding should be reported as an AE. All efforts should be made to follow the participant until the EOS to minimize the occurrence of missing data.

If a pregnancy is reported, see Appendix 7 and Section 8.3.5 (Pregnancy) for procedures.

See the Schedule of Activities for data to be collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records. The Investigator should also notify the Sponsor so that any untested samples can be destroyed.
- See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the Schedule of Activities. A detailed listing of study assessments by study visit is presented in Appendix 8.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

According to Clinical Practice Guidelines for Hypothyroidism in Adults, participants with hypothyroidism being treated with synthetic T4 should have an upper limit of normal of 4.12 mIU/L and a lower limit of 0.45 mIU/L for TSH level (Garber 2012). Based on these guidelines, the normal reference range of 0.45 to 4.12 mIU/L will be used to determine TSH responders.

8.1.1. Study Intervention Administration Assessments

Planned timepoints for all efficacy assessments are provided in the Schedule of Activities (Section 1.3).

[redacted]

8.1.3. Secondary Endpoint

The percent of participants who are Titration TSH Responders defined as participants whose TSH values are within the normal reference range (defined in Section 3) at the end of the

Titration Period among the randomized participants who received at least 1 dose of study intervention (Section 9.3).

Assessment	Timing	Measurement
Titration TSH Responder	End of Titration Period	TSH values measured at the end of the Titration Period to determine if the values are within the normal reference range.

[redacted]

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities.

8.2.1. Physical Examinations

- A complete physical examination will be performed and will include assessment of the following: general appearance, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, respiratory, cardiovascular, abdomen, musculoskeletal (including spine and extremities), and neurological systems. Height will be measured at screening; weight will be measured at screening and end of study. BMI (kg/m^2) will be calculated as the ratio of weight in kg/(height in $cm/100)^2$. BMI will be calculated at screening and end of study.

- Physical examinations will be completed by a trained physician or health professional licensed to perform physical examinations.

8.2.2. Vital Signs

Vital signs will be assessed as follows:

- BP, pulse rate, respiratory rate, and oral temperature will be assessed.
- BP will be assessed using a sphygmomanometer.
- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be taken before blood collection for laboratory tests. A total of 3 readings of BP and pulse will be taken consecutively, at least 1 to 3 minutes apart. The first reading should be rejected. The second and third readings will be used to make any study-related decisions. All three readings will be recorded. During the screening visit, if either the second or third reading meets exclusion criteria, the participant should be excluded.
- Pre-dose vital signs must be assessed within a window of 0 to 120 minutes prior to study intervention dosing.

8.2.3. Electrocardiograms

- The Sponsor will receive ECG data, including cardiologist assessments, in the data transfer.
- Single 12-lead ECG will be performed and obtained as outlined in the Schedule of Activities (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.
- Pre-dose ECGs must be performed within a window of 0 to 120 minutes prior to study intervention dosing.
- The ECG tracing will be kept at the study center. Measurements will be recorded for the following parameters: heart rate, PR interval, QRS duration, QT interval, and QTc. All ECGs will be clinically interpreted by the Investigator or sub-investigator.
- At screening, participants who have an abnormal QTcF according to the ranges specified in Section 5.2 will be excluded from the study.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the Schedule of Activities for the timing and frequency.
- At screening, the Investigator or sub-investigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.

- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significant during participation in the study or at the EOS should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.
    - Serum pregnancy tests and urine dipsticks are to be used to conduct pregnancy tests by the study personnel or designee at timepoints specified in the Schedule of Activities. Urine dipstick results will be read locally.

8.2.5. Safety Data Monitoring

Safety data will be monitored during the study. If an unblinded safety review is needed, a data review committee (DRC) will be created in advance to review unblinded safety data. The purpose and procedure for this safety data review will be detailed in a DRC Charter and a companion analysis plan prior to the unblinded safety data review, should this review be performed. The methods to maintain study integrity, including restrictions of access to unblinded safety results before study completion will also be described in the DRC Charter.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs from the signing of the ICF until 35 days after the last dose of study intervention will be collected at the time points specified in the Schedule of Activities (Section 1.3), and as observed or reported spontaneously by study participants.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Armour Thyroid

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- An Investigator who receives an investigator safety report describing an SAE from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 35 days after the last dose of study intervention.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

Hypersensitivity has been identified as an AESI. Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. Hypersensitivity reactions to active constituents may also occur.

Reports of this AESI warrant ongoing monitoring and prompt communication by the Investigator to the Sponsor as outlined in Appendix 3.

8.3.7. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study intervention
- Wrong dose/kit (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study intervention.

Overdose: Unintentional administration of a quantity of the study intervention given that is above the maximum recommended dose according to the protocol for the study intervention.

Underdose: Unintentional administration of a quantity of the study intervention given that is under the minimum recommended dose according to the protocol.

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than the maximum protocol-recommended dose will be considered an overdose.

Information on the treatment of overdose may be found in the Armour Thyroid Investigator's Brochure and the package insert for Synthroid (Synthroid 2018).

In the event of an overdose, the Investigator/treating physician should:

1. Contact the medical safety physician immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically.
3. Obtain a blood sample for analysis if requested by the medical safety physician (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the medical safety physician based on the clinical evaluation of the participant.

[redacted]

[redacted]

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Biomarkers are not evaluated in this study.

8.9. Health Economics and Outcomes

No additional health outcomes are evaluated in this study beyond those already stated as exploratory endpoints (Section 3).

9. Statistical Considerations

9.1. Statistical Hypotheses

The null hypothesis is that the TSH responder of Armour Thyroid is inferior to the TSH responder of synthetic T4 at the end of the Stabilization Period. The alternative hypothesis is that the TSH responder of Armour Thyroid is noninferior to the TSH responder of synthetic T4 at the end of the Stabilization Period. [redacted]

[redacted]

9.3. Populations for Analyses

The analysis populations will consist of participants as defined below:

- The ITT population includes all randomized participants who received at least 1 dose of study intervention.

- The Safety population includes all participants who take ≥ 1 dose of study intervention.
- The PK population includes all participants who have at least 1 evaluable PK sample.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and unblinding, and will describe the participant populations to be included in the analyses, the detailed analyses of all analysis parameters for the study report, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, additional, and exploratory endpoints.

9.4.1. Efficacy Analyses

The primary and secondary efficacy analysis will be performed on the ITT Population. Additional efficacy parameters on the ITT Population will be summarized descriptively by treatment group or by treatment dose level at each visit.

9.4.1.1. Analysis Endpoints

The primary, secondary, additional, and exploratory efficacy endpoints are listed below. Analyses will be defined in the following sections.

Primary efficacy endpoint:

The primary efficacy endpoint is the percent of participants who are Sustained TSH Responders, defined as participants whose TSH values are within the normal reference range of 0.45 to 4.12 mIU/L, inclusive at both the end of the Titration Period and the end of the Stabilization Period among those participants in the ITT Population. If a participant is missing the TSH value at either the end of the Titration Period or at the end of the Stabilization Period, then this participant will be considered a sustained TSH non-responder.

Secondary efficacy endpoint (see Section 8.1.3):

The secondary efficacy endpoint is the percent of participants who are Titration TSH Responders defined as participants whose TSH values are within the normal reference range at the end of the Titration Period among those participants in the ITT Population. If a participant is missing the TSH value at the end of the Titration Period, then this participant will be considered a titration non-responder.

[redacted]

9.4.1.2. Primary Analyses

The noninferiority hypothesis test for the primary efficacy parameter, based on the ITT Population, will be performed at a 1-sided 2.5% level of significance. The null hypothesis is that Armour Thyroid is inferior to synthetic T4, which will be tested against the alternative hypothesis that Armour Thyroid is noninferior to synthetic T4, as follows:

H0: $rT - rR \leq -\Delta$ versus Ha: $rT - rR > -\Delta$

Where: rT and rR are the proportions of TSH responders in the Armour Thyroid and synthetic T4 study intervention groups, respectively, at the end of the double-blind Stabilization Period; Δ is the noninferiority margin, which is assumed to be 10%.

The primary analysis of the primary efficacy endpoint will be performed on the ITT population based on a stratified method using Mantel-Haenszel (MH) weighted. Within the framework of this method, the difference proportions of sustained TSH responders (Armour Thyroid group minus T4 group) and the corresponding 95% confidence interval for the non-inferiority testing will be computed. Specifically, the confidence intervals for stratified proportion differences will be calculated using the MH-weighted method with the age group (age < 65 years or ≥ 65 years) as a stratification factor as described in Agresti (2013, p. 231). [redacted]

A sensitivity analysis of the 2-sided 95% confidence interval for stratified proportion difference will also be performed on the ITT population using stratified Newcombe confidence (Yan 2010).

Sensitivity analyses, based on the ITT population, for participants who are missing TSH values either at the end of the Titration Period or at the end of the Stabilization Period will be provided in detail in the SAP as follows:

- Sustained TSH responder for missing TSH values either at the end of the Titration Period or at the end of the Stabilization Period will be imputed.
- Missing values under an assumption of missing at random will be imputed by multiple imputation approach.
- Tipping-point analysis will be performed to investigate the impact of missing data on the study results.
- The noninferiority between Armour Thyroid and synthetic T4 will be established in the complete-case, which excludes participants who have not completed the study or who are missing TSH values either at the end of the Titration Period or at the end of the Stabilization Period.

9.4.1.3. Secondary Efficacy Analyses

Similar to the primary analysis, the 2-sided 95% CI for the stratified proportion difference for the secondary efficacy endpoint will also be performed on the ITT population.

9.4.1.4. Estimand Framework for Primary Endpoint

Population

The target study population comprises previously hypothyroid patients who are presently euthyroid on a stable dose of synthetic T4 at the time of randomization, and who also meet the inclusion and exclusion criteria as specified in Sections 5.1 and 5.2, respectively.

The analysis population is the ITT population as defined in Section 9.3.

Variable

The variable is the primary efficacy endpoint, a sustained TSH responder endpoint defined as the TSH value within the normal reference range both at the end of Titration Period and at the end of the Stabilization Period.

Accounting for Intercurrent Events

Intercurrent events and their handling rules are as follows.

- Participants who discontinue study treatment due to any reason will have their data collected after discontinuation of study treatment and included in the study database and analysis, whenever possible.
- If a participant is missing TSH values either at the end of Titration Period or at the end of the Stabilization Period, the participant will be considered a TSH non-responder for the study.

Population-level Summary

The population-level summary will be a 2-sided 95% confidence interval in stratified proportion difference for the primary study responder endpoint.

The estimand framework for the secondary endpoint will be handled using the same approach as described for the primary.

9.4.1.5. Multiple Comparisons Procedure

The overall study Type 1 error will be controlled for the primary and secondary efficacy endpoints using the fixed sequential procedure to control the overall type I error rate at 0.05 level:

- Step 1: Testing for non-inferiority of sustained THS responder
- Step 2: Testing for non-inferiority of titration THS responder

[redacted]

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population based on a whole study and different periods separately and will be fully defined in the SAP. The safety parameters will include AEs, clinical laboratory measurements including fasting T3 and T4 (both total and free

T3 and T4 taken prior to study intervention dose that day), vital sign values, ECG parameters, and physical examination findings. For each safety parameter of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter.

9.4.2.1. Adverse Events

An AE will be considered a TEAE if:

- The AE began on or after the date of the first dose of study intervention; or
- The AE was present before the date of the first dose of study intervention, but increased in severity or became serious on or after the date of the first dose of study intervention

An AE that occurs more than 35 days after the last dose of study intervention will not be counted as a TEAE.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criteria.

The number and percentage of participants reporting TEAEs in each study intervention group will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants reporting treatment related TEAEs in each study intervention group will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Summary tables will be provided for participants with SAEs and participants with AEs leading to discontinuation if 5 or more participants reported such events. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

The definitions of an AE and SAE can be found in Appendix 3.

9.4.2.2. Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline (screening) and changes from baseline at each assessment will be presented by study intervention for each clinical laboratory assessment.

The criteria for PCS laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by study intervention at each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.2.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic BP, pulse rate, weight, respiration rate, and temperature) at baseline (screening) and changes from baseline at each assessment will be presented by study intervention.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline-value criteria that will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by study intervention for each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.2.4. Electrocardiograms

Descriptive statistics for ECG parameters (heart rate, PR interval, QRS duration, QT interval, and QTc) at baseline, EOS, changes from baseline at EOS, interim ECG parameters at baseline (pre-dose at each period), and changes from baseline at post-dose will be presented by study intervention.

The criteria for PCS ECG values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline ECG values will be tabulated by study intervention for EOS assessments and interim assessments. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided, including the participant number and baseline and postbaseline values, for the safety population.

9.4.3. Pharmacokinetic Analyses

Serum concentrations of total and free T3 and T4 will be listed by participant. Descriptive statistics will be provided for each analyte by visit and time (pre-dose and post-dose).

9.4.4. Other Analyses

[redacted]

9.5. Interim Analyses

No interim analysis is planned.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH/ISO GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded in eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study.

10.1.7. Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

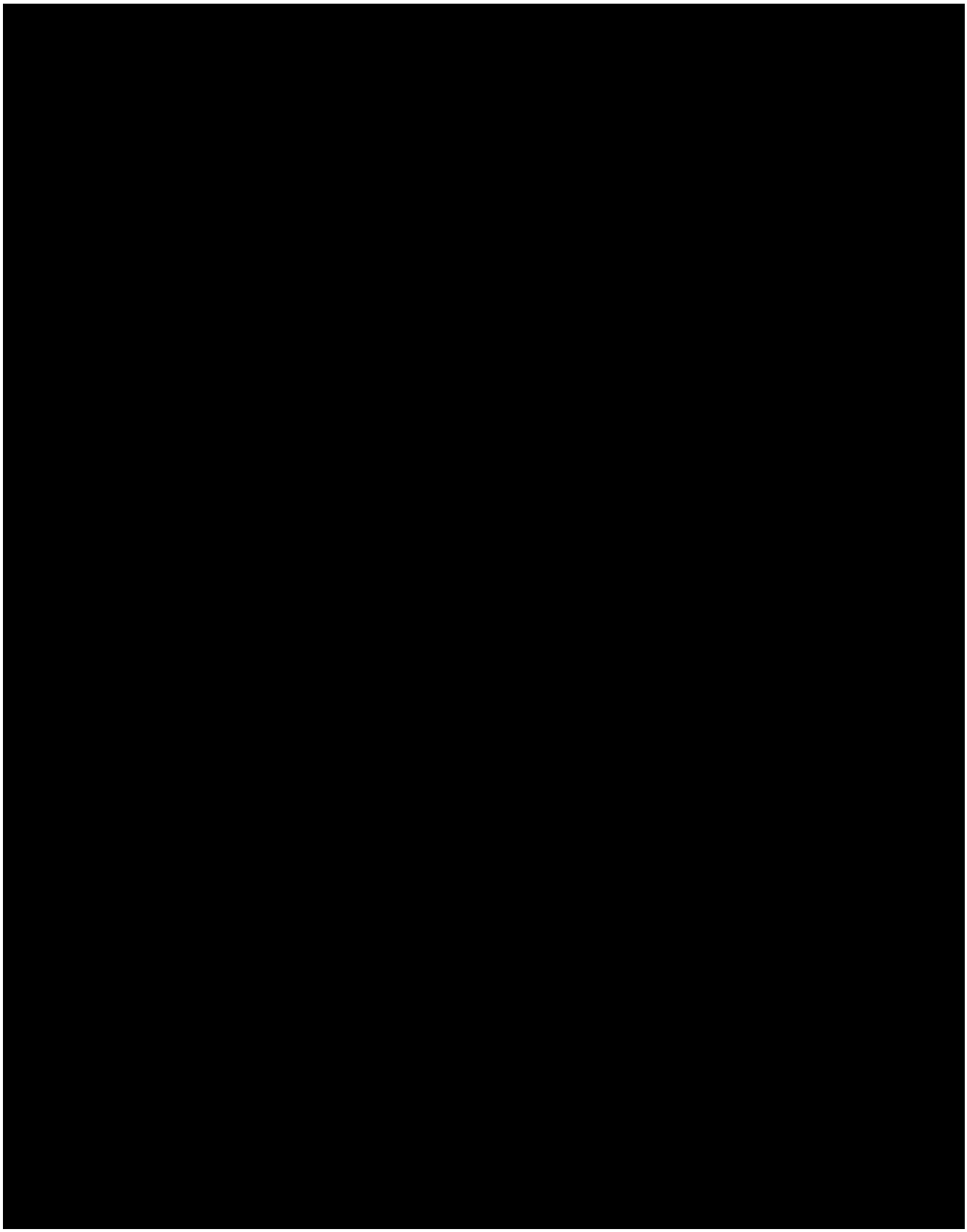
10.1.8. Publication Policy

- Allergan as the Sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect cooperation between multiple Investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.9. Compliance with Protocol

The Investigator is responsible for compliance with the protocol at the investigational site. A representative of the Sponsor will make frequent contact with the Investigator and his/her research staff and will conduct monitoring visits to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the Investigator upon identification. The use of the data collected for the participant will be discussed to determine if the data are to be included in the analysis. The Investigator will enter data that may be excluded from analysis as defined by the protocol deviation specifications. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.



10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. **AE of Special Interest** An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the Sponsor's study intervention or program, which warrants ongoing monitoring and prompt communication by the Investigator to the Sponsor. Such an event might warrant further investigation in order to characterize and understand it. The following AESI has been identified for the study intervention in this protocol: hypersensitivity. Serious AESIs should be reported to the Sponsor within 24 hours via the Serious Adverse Event/Serious Adverse Event of Special Interest form. Nonserious AESIs should be recorded in a timely fashion on the appropriate page of the eCRF.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease); for example:
  - The test result is associated with accompanying symptoms, and/or
  - The test result requires additional diagnostic testing or medical/surgical intervention, and/or
  - The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
  - The test result is considered to be an AE by the Investigator or Sponsor.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/ self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE. • The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen • Study endpoints: Study endpoints where there is no reasonable possibility of attribution to the study intervention(s) will not be reported as AEs or SAEs to the Sponsor. Rather, these will be collected in the eCRF. If there is a reasonable possibility of a causal relationship of the study endpoint to the study intervention(s), this endpoint should be reported as an endpoint as described above and as an AE or SAE as per Section 8.3, respectively. For a list of the endpoints in this study, refer to Section 9.4.1.1.

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE or SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE Reporting
• Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

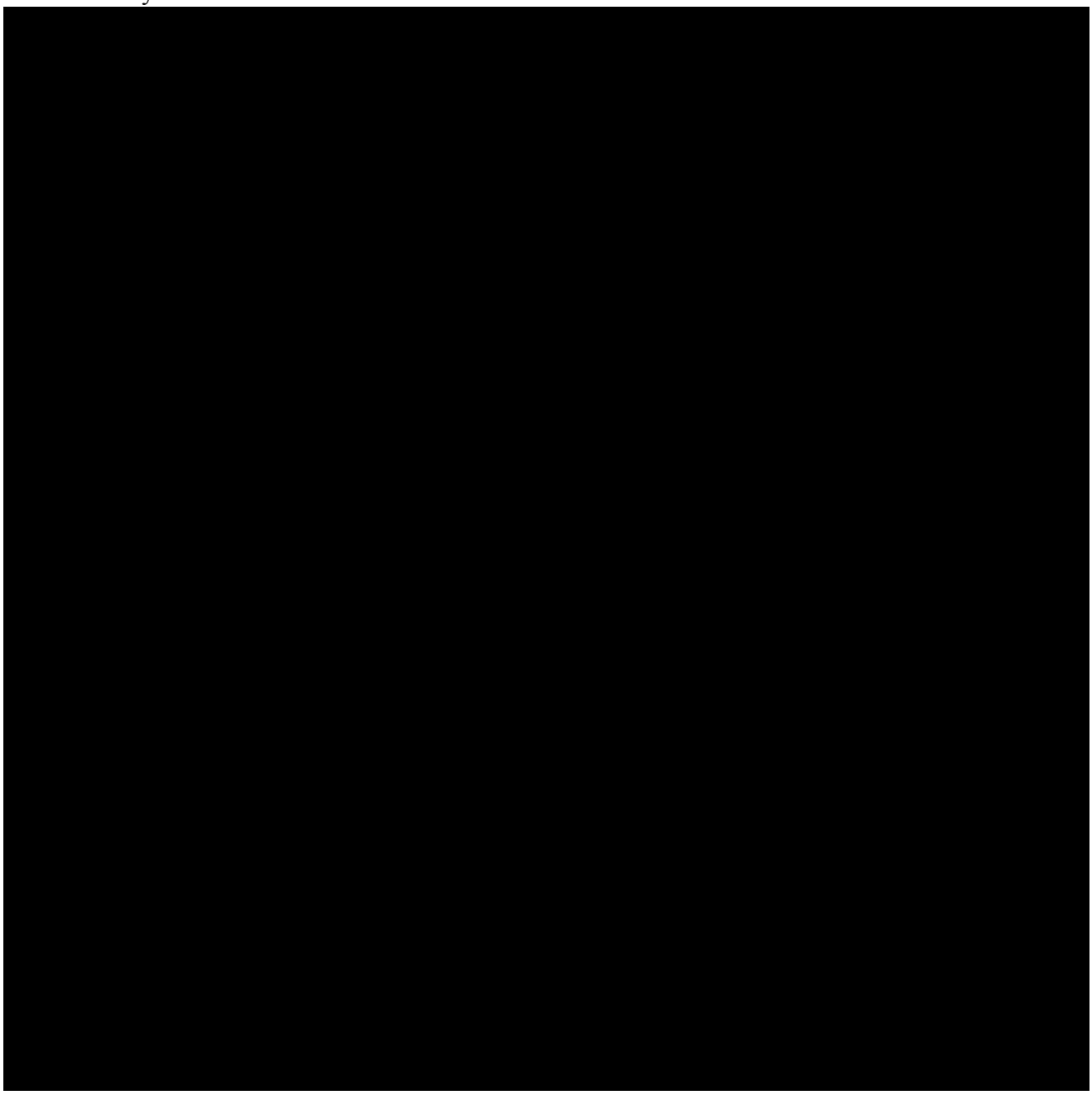
10.4. Appendix 4: Abbreviations

Abbreviation/Term	Definition
AACE	American Association of Clinical Endocrinologists
AE	adverse event
AESI	adverse event of special interest
ATA	American Thyroid Association
BMI	body mass index
BP	blood pressure
CBP	childbearing potential
CFR	Code of Federal Regulations
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EOS	end of study
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
FT3	free T3
FT4	free T4
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web response system
MH	Mantel-Haenszel
PCS	potentially clinically significant
PK	pharmacokinetic
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/[RR]^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
T3	liothyronine, triiodothyronine (3, 5, 3′-triiodothyronine)
T4	levothyroxine, l-thyroxine, thyroxine

Abbreviation/Term	Definition
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TSH	thyroid-stimulating hormone
USP	United States Pharmacopeia

10.5. Appendix 5: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by Sponsor	An indication that a clinical study was stopped at a particular site by its Sponsor (NCI)
Study terminated by Sponsor	An indication that a clinical study was stopped by its Sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)



10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Female of Childbearing Potential (CBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Females in the following categories are not considered of CBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Contraception Guidance:

Male Participants

Nonvasectomized male participants with female partners of CBP are eligible to participate if they agree to the following during the protocol-defined timeframe in Section 5.1:

- Agree to use a male condom with spermicide plus partner use of a highly effective or acceptable method of contraception as described in Table 10-2, when having penile-vaginal intercourse with a woman of CBP who is not currently pregnant.

In addition, nonvasectomized male participants must refrain from donating sperm for the duration of the study and through 35 days after the last dose of study intervention.

Nonvasectomized male participants with a pregnant or breastfeeding partner must agree to use a male condom during each episode of penile penetration during the protocol-defined timeframe.

Female Participants

Female participants of CBP are eligible to participate if they agree to use a highly effective or acceptable method of contraception consistently and correctly as described in Table 10-2.

Table 10-2 Highly Effective and Acceptable Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen[b]- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) • Bilateral tubal occlusion (eg, Essure®, bilateral tubal ligation) • Intrauterine copper contraceptive (ie, ParaGard®)
Acceptable Methods *Acceptable birth control methods that result in a failure of more than 1% per year include:*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with spermicide • Cap, diaphragm, or sponge with spermicide • Nonhormonal intrauterine device A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[a] Typical use failure rates may differ from those experienced when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Estrogen-containing oral contraceptives may increase serum thyroxine-binding globulin (TBG) concentration.

Pregnancy Testing:

- Female participants should be enrolled only after a negative serum pregnancy test at screening and a negative urine test (or serum test, if required by local regulation or IRB/IEC) at Visit 2.
- Additional pregnancy testing should be performed at each study visit as defined in the Schedule of Activities in Section 1.3.
- Serum pregnancy testing will be performed whenever pregnancy is suspected.

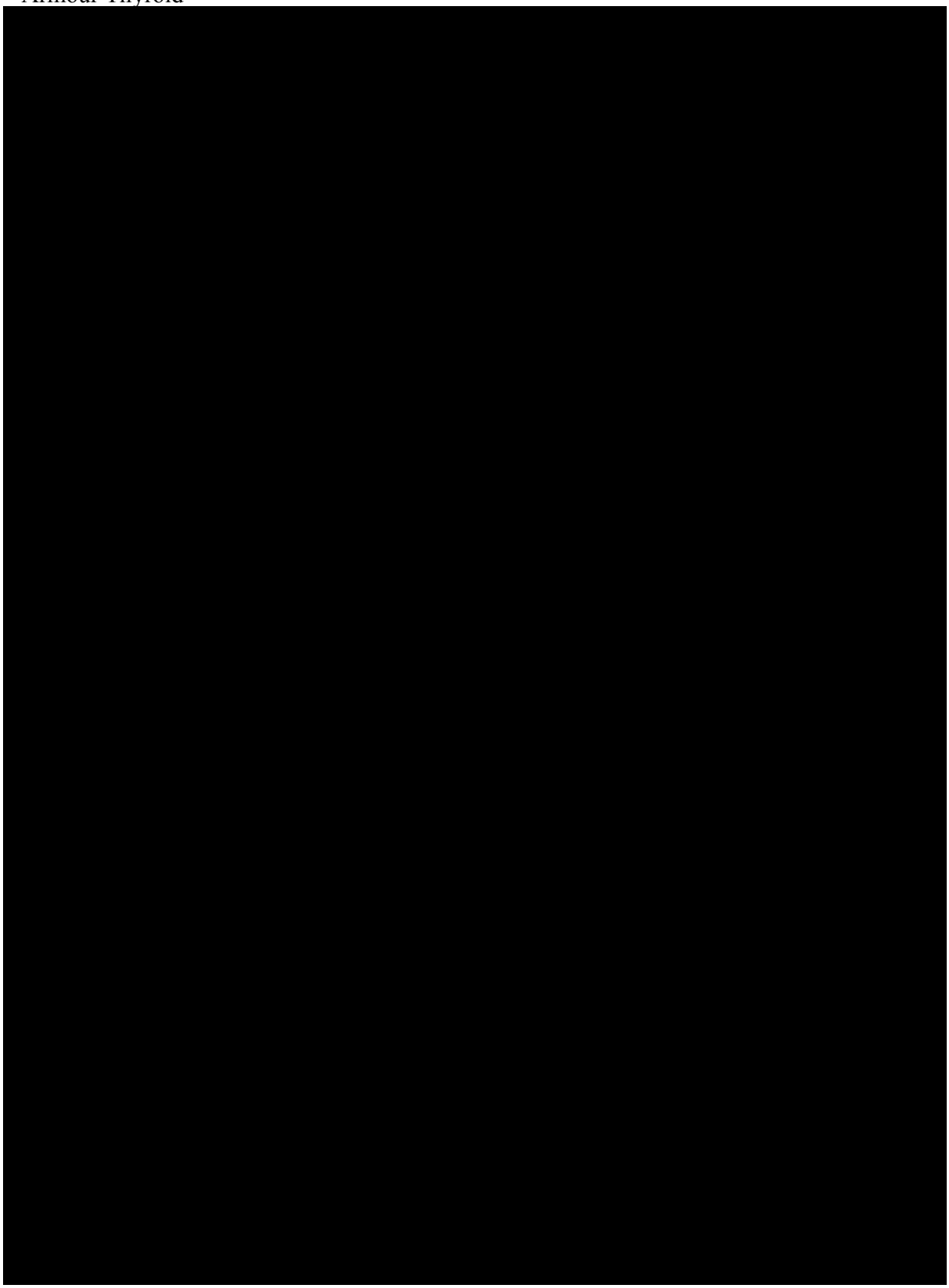
Collection of Pregnancy Information:

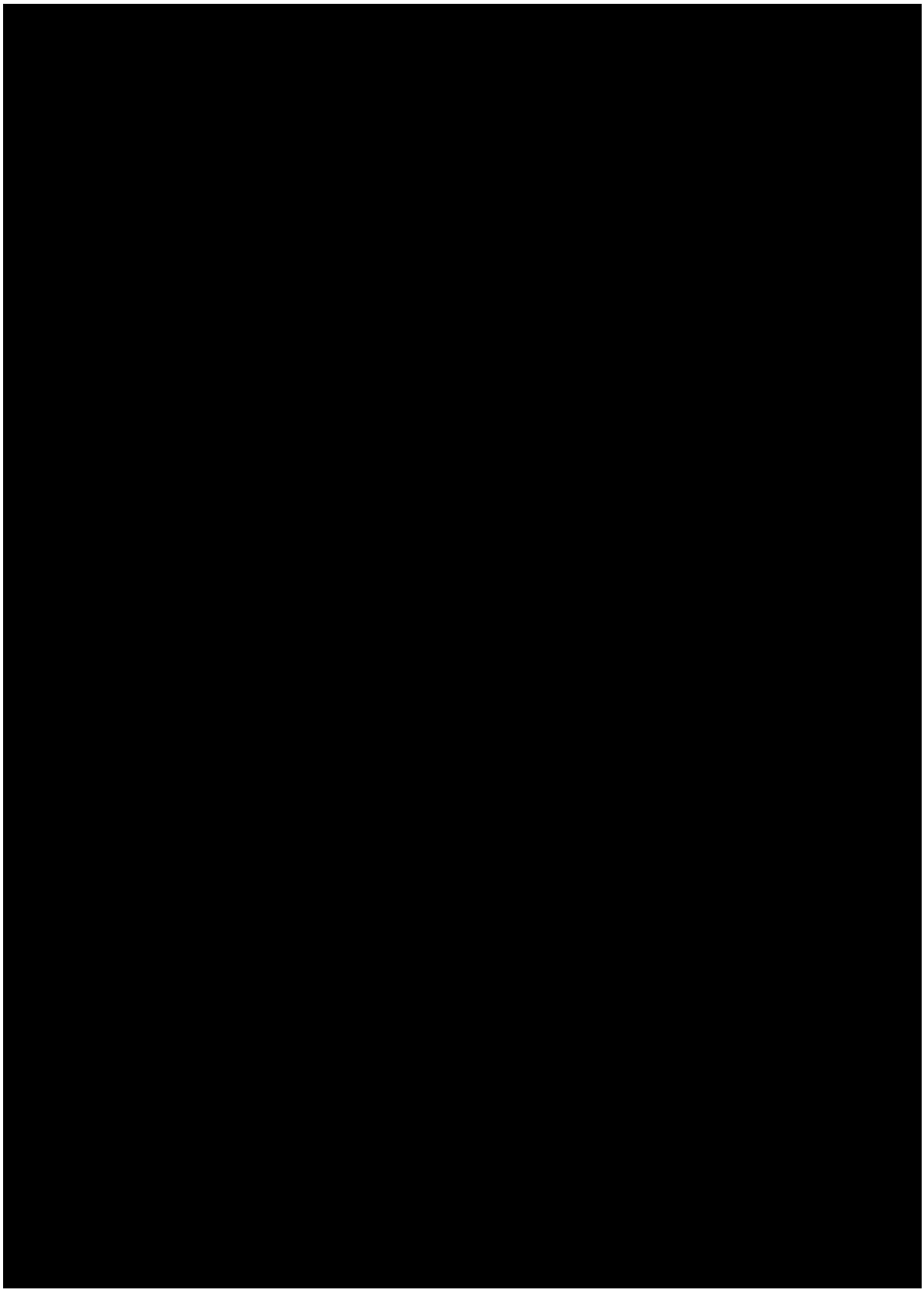
Male Participants with Partners Who Become Pregnant

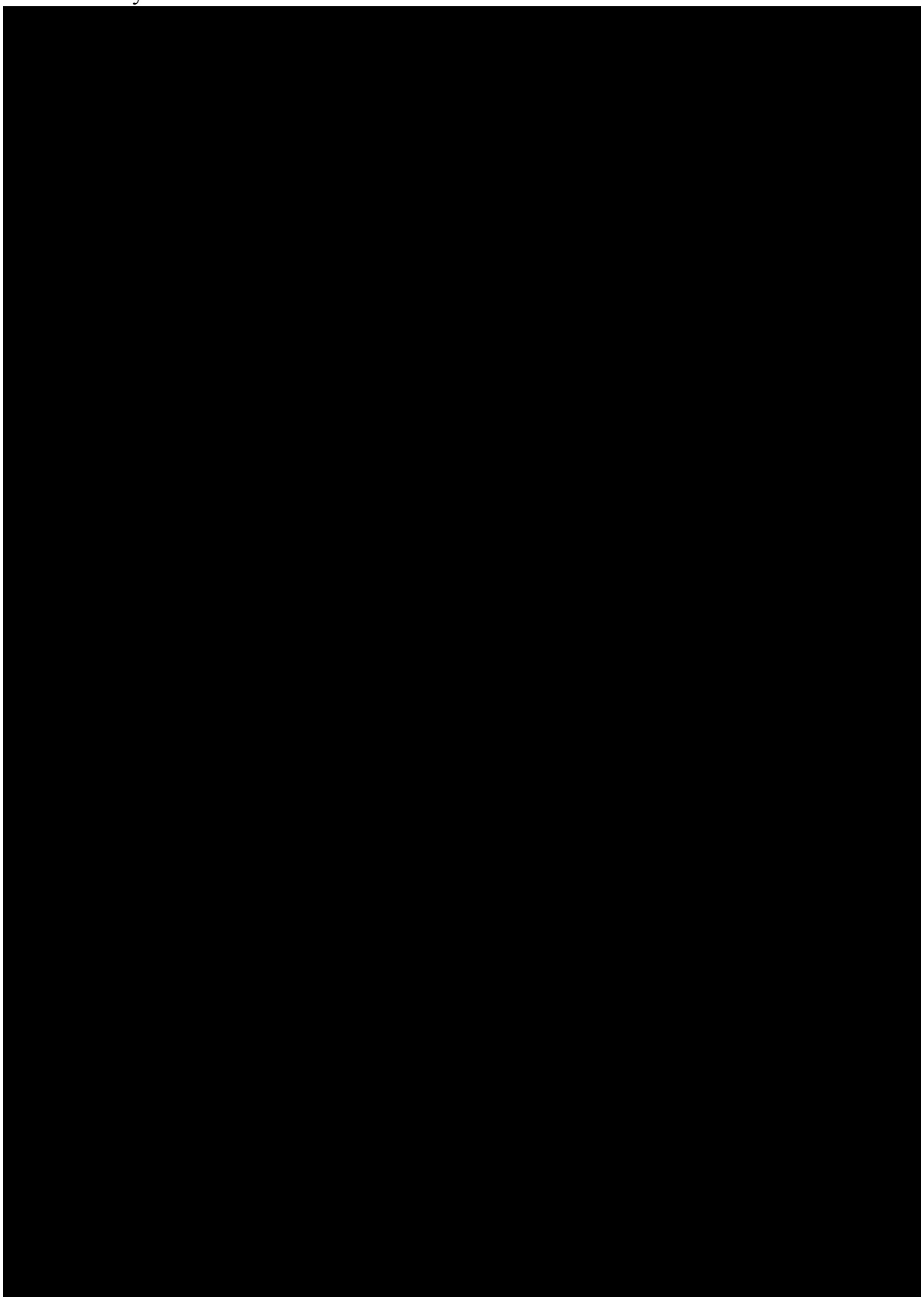
- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- The Investigator should inform the Sponsor within 24 hours of learning of the pregnancy. After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.







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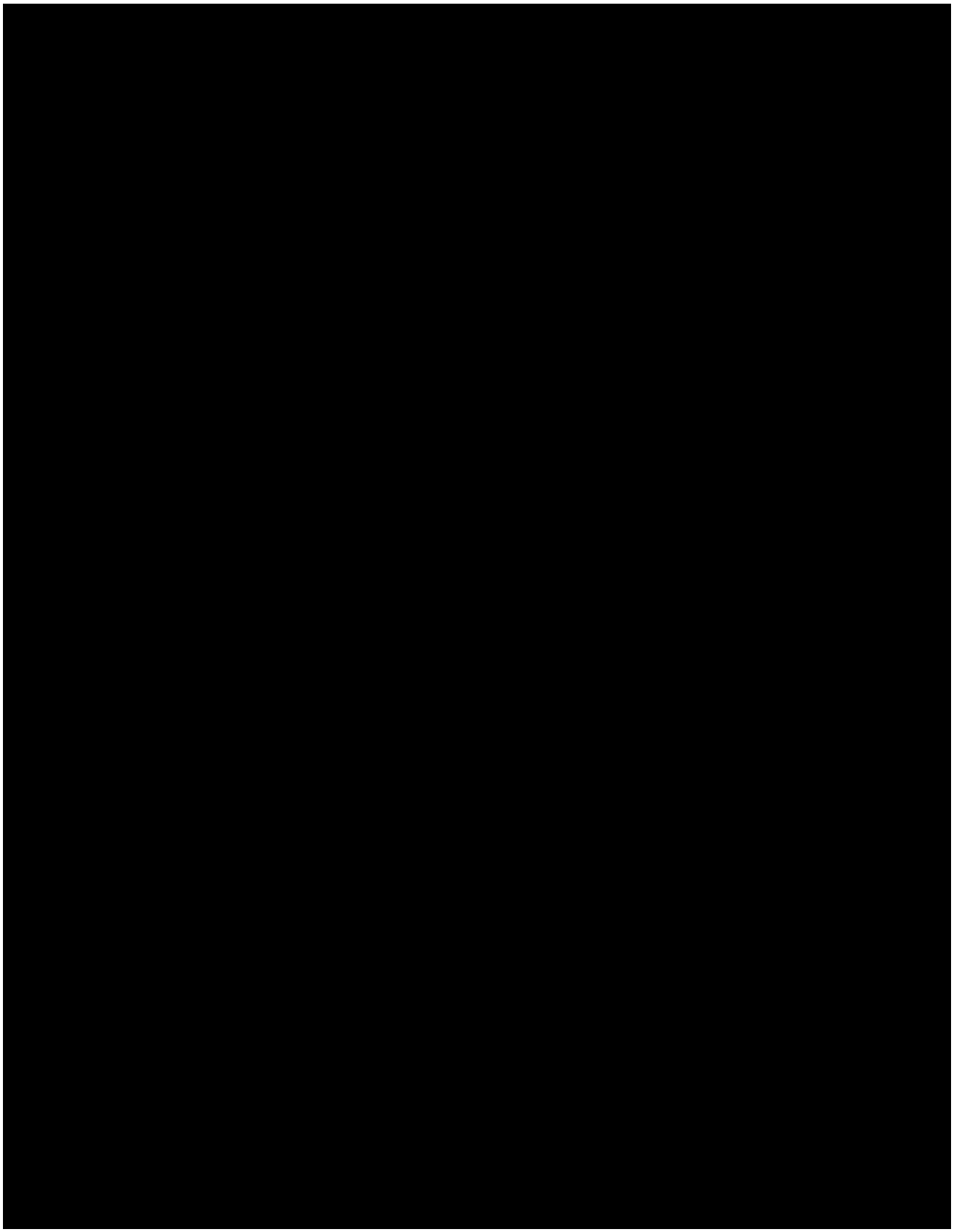

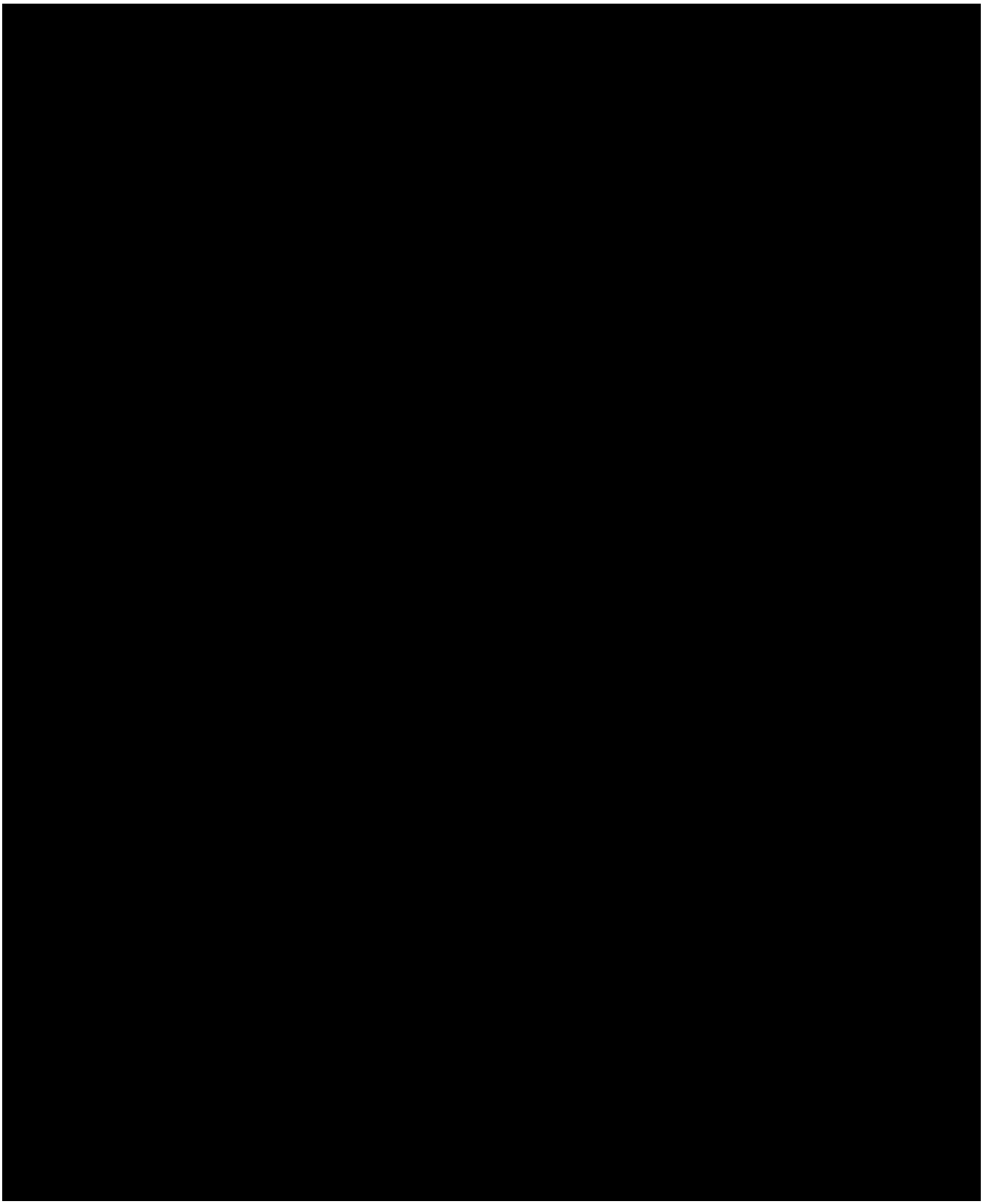

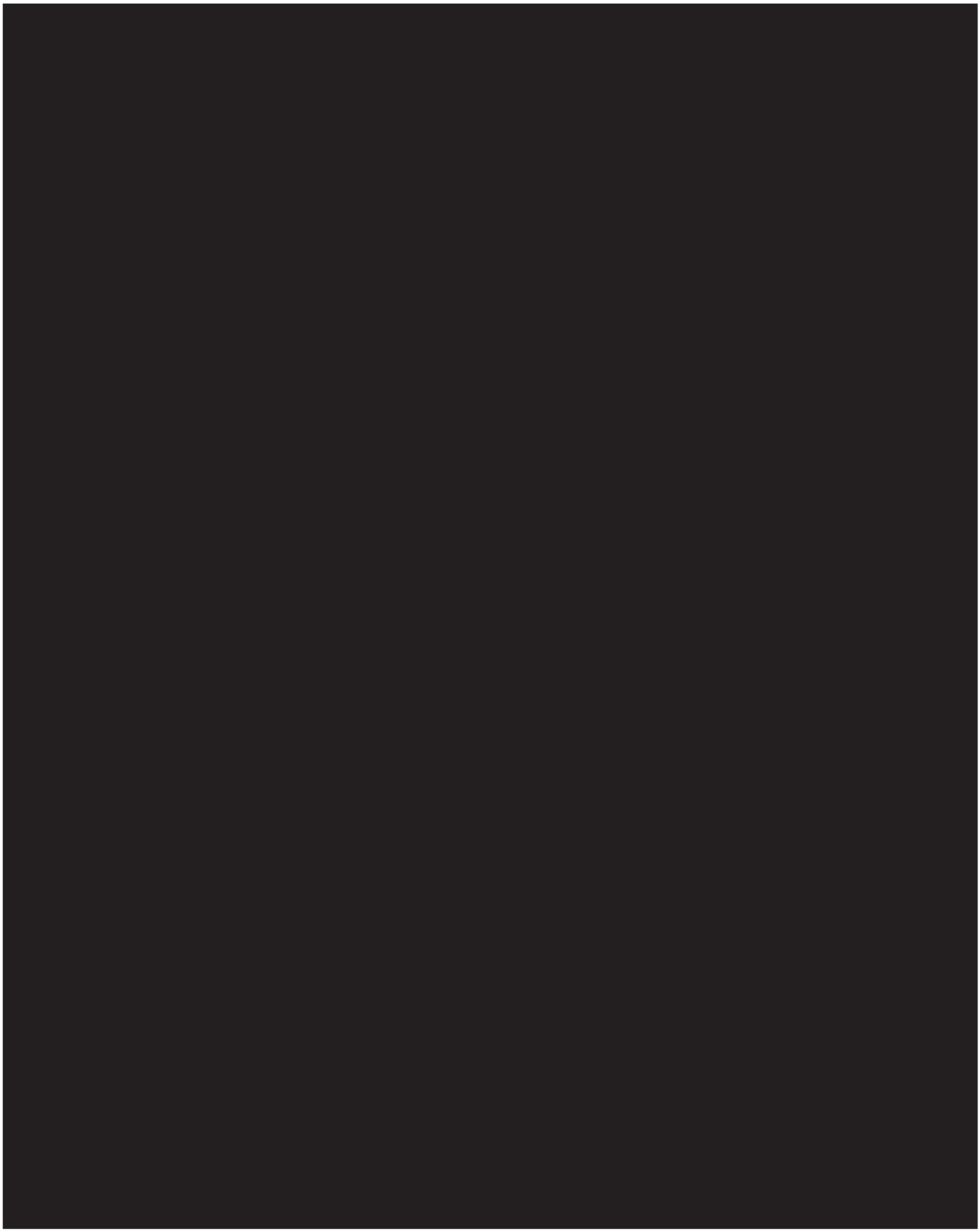

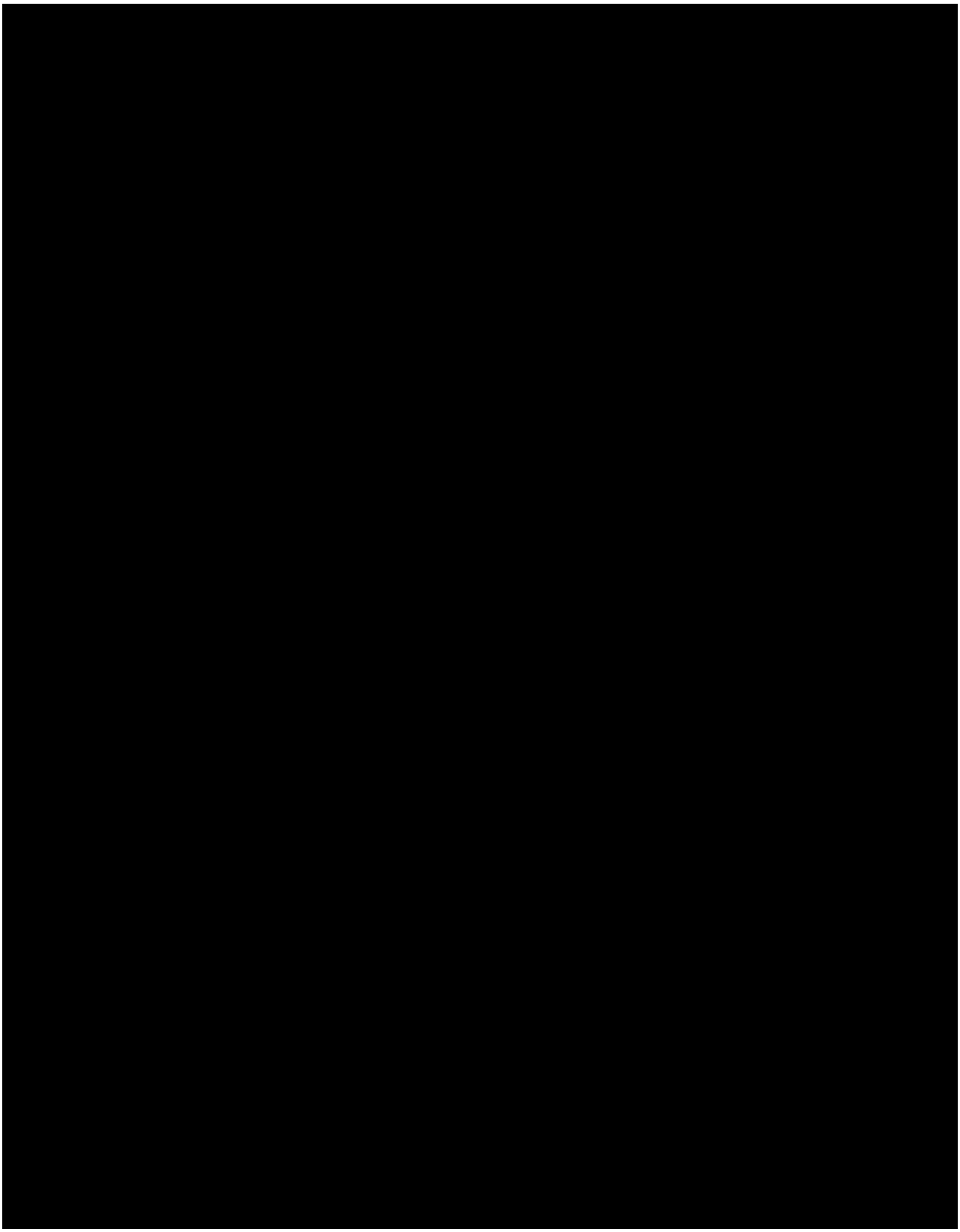

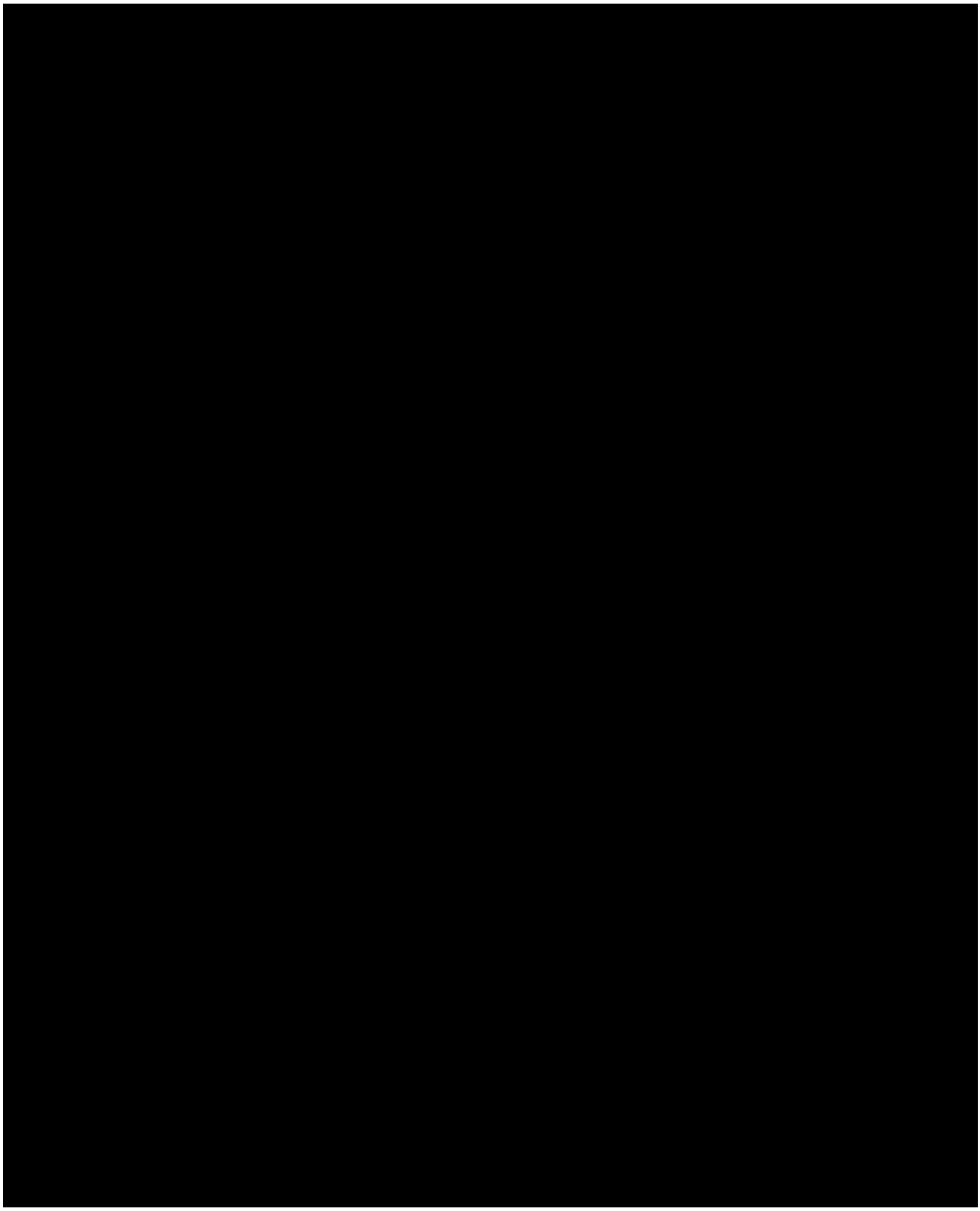

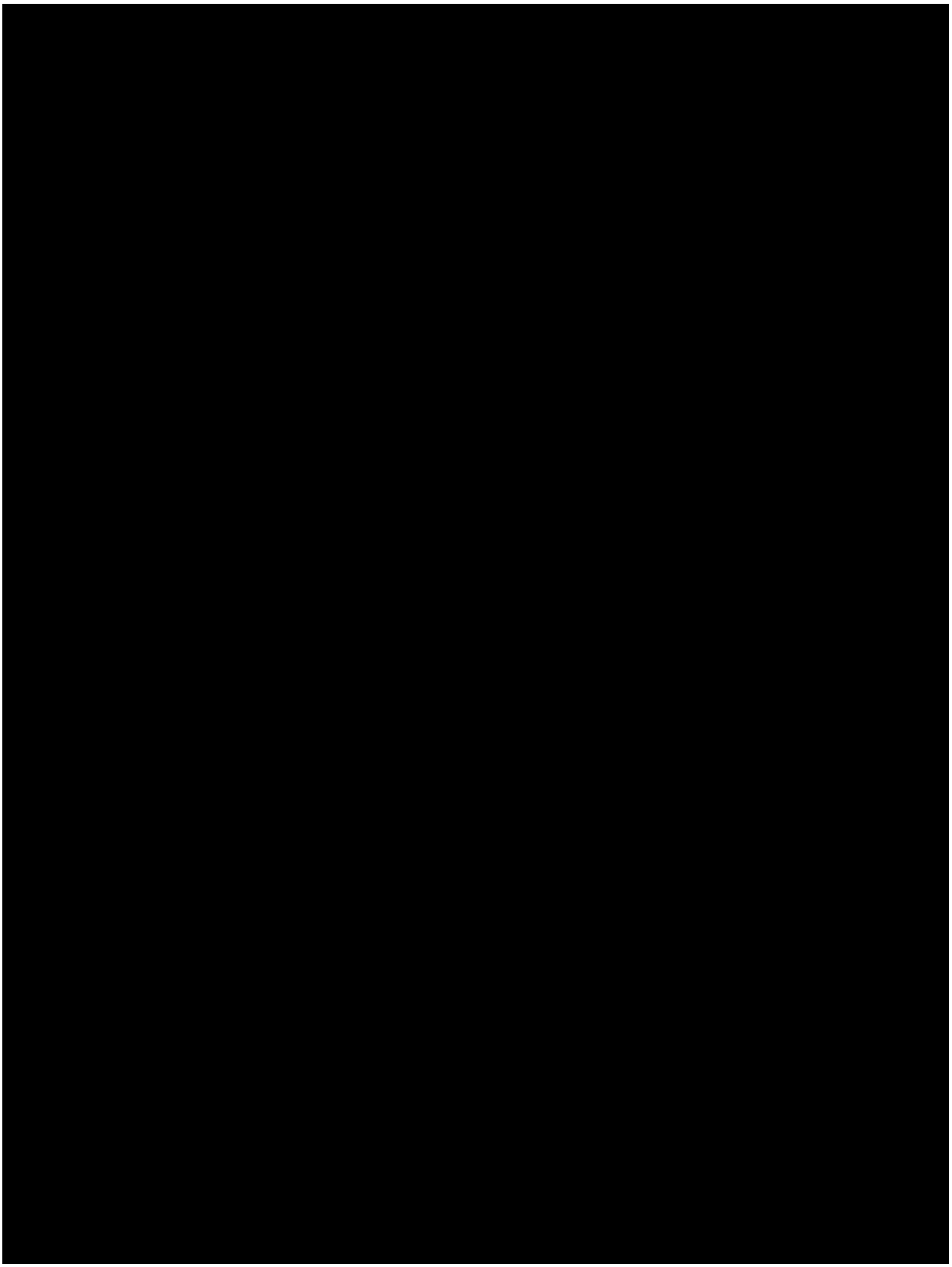

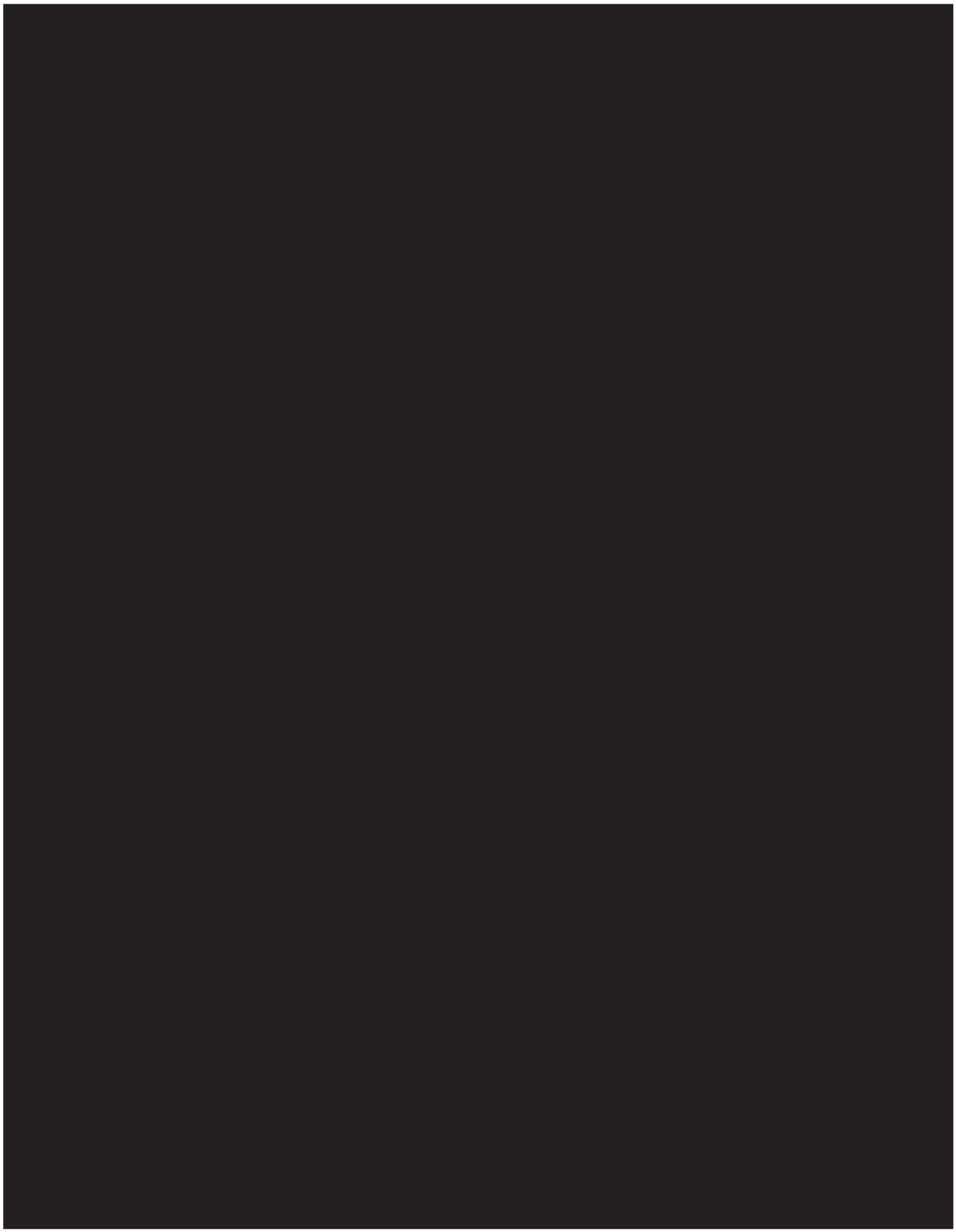

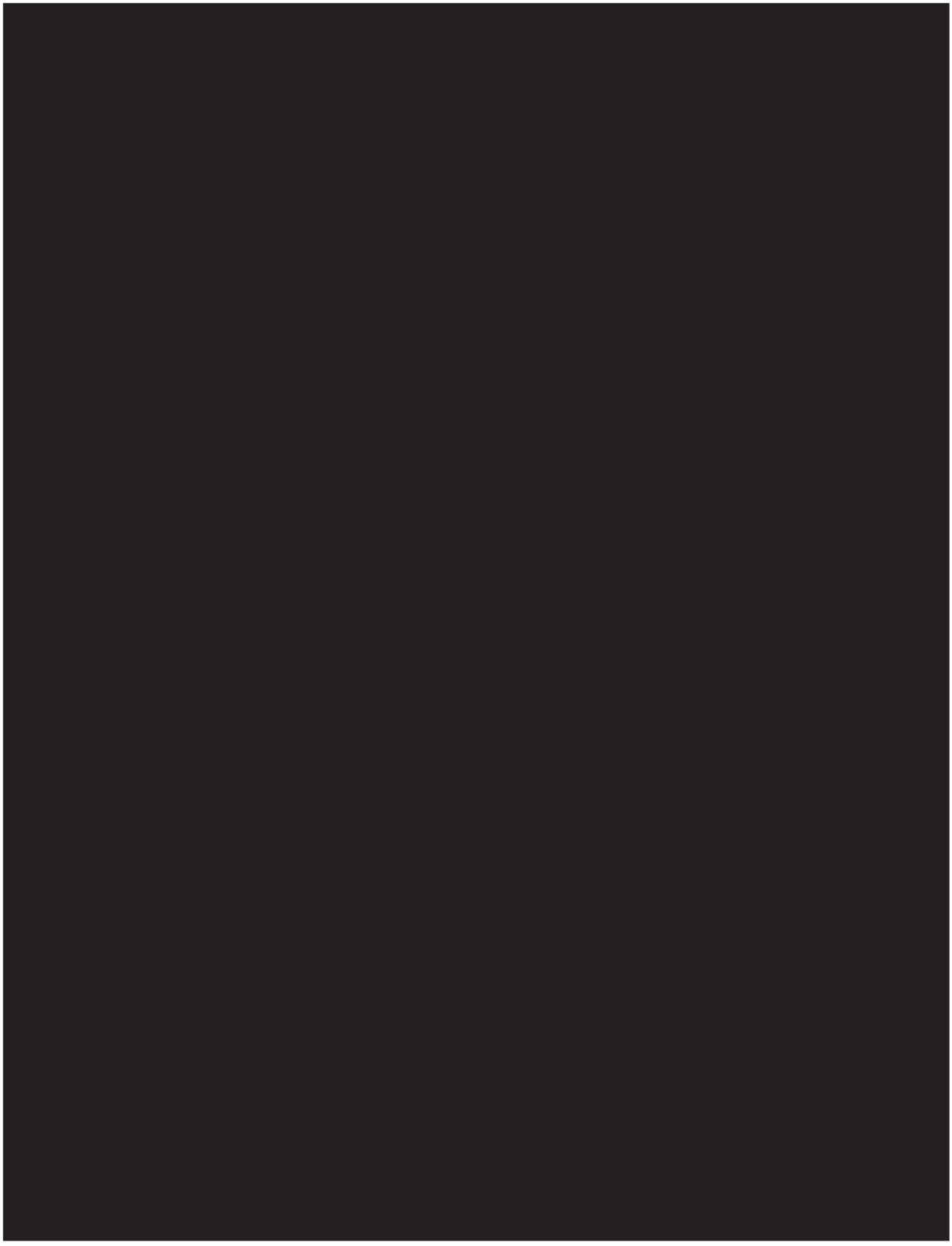

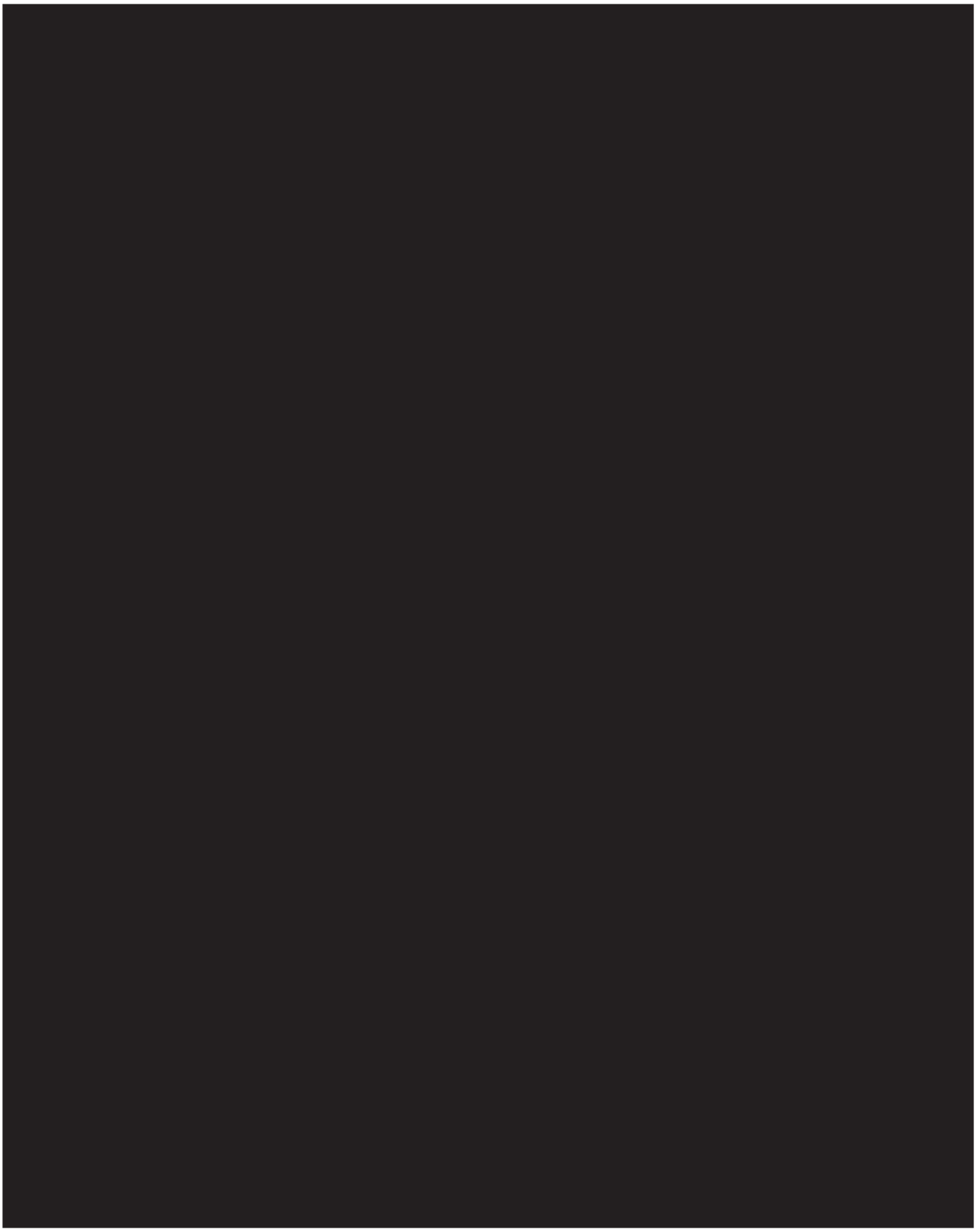

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