A MULTI-CENTER, OPEN-LABEL PHASE 2 CLINICAL TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF ADX-629 ADMINISTERED ORALLY TO SUBJECTS WITH PLAQUE PSORIASIS

PROTOCOL NUMBER:	ADX-629-PS-001
[redacted]PROJECT NUMBER:	249-12851-201
IND NUMBER:	[redacted]
ORIGINAL PROTOCOL:	October 23, 2020
PROTOCOL VERSION:	3.0
[redacted]	
FILENAME:	[redacted]
SPONSOR:	Aldeyra Therapeutics, Inc. 131 Hartwell Avenue, Suite 320 Lexington, MA, 02421, U.S.A.
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PROJECT MANAGER:	[redacted]

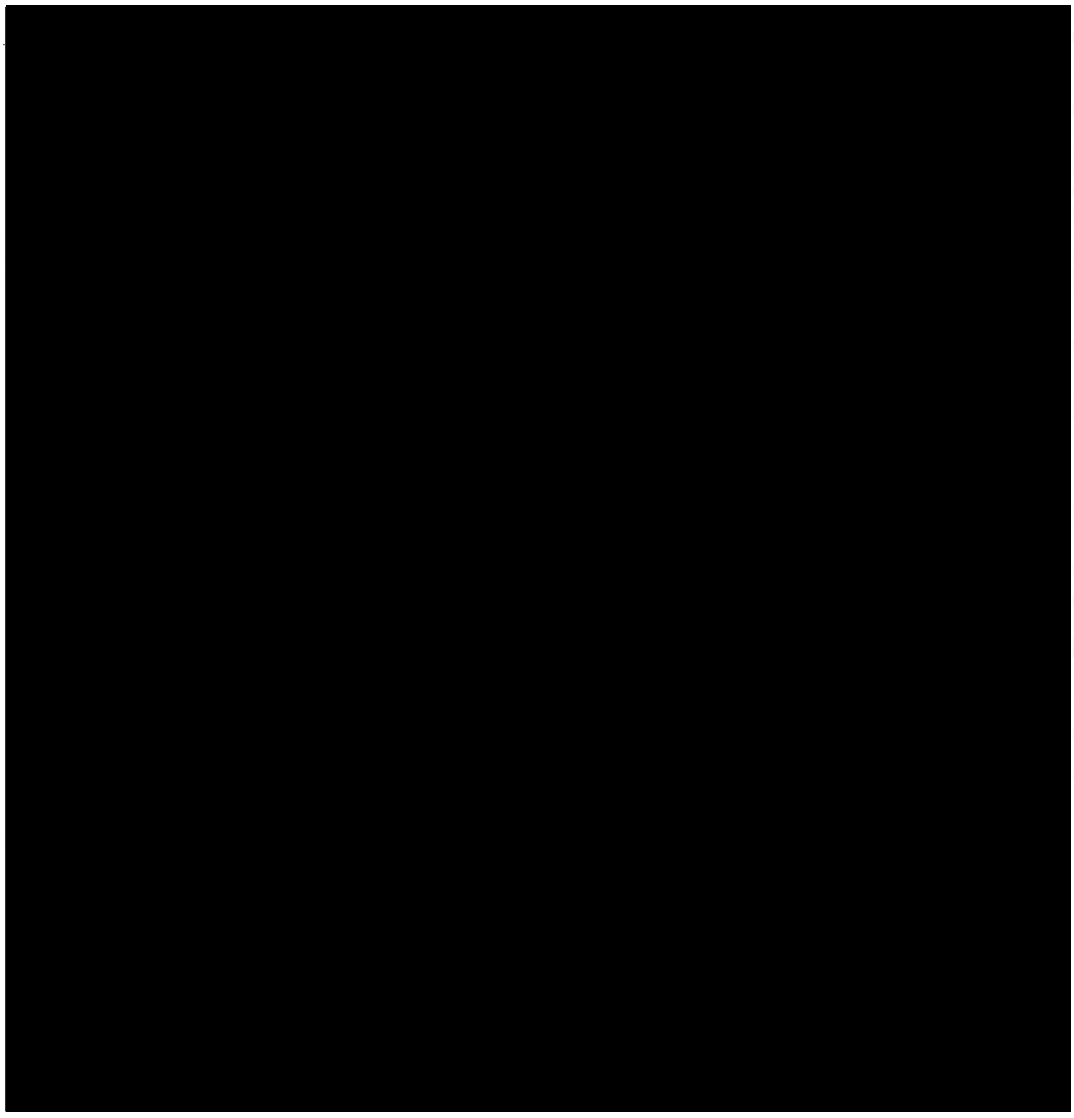
24 Hour Emergency Telephone Number

[redacted]

[redacted]

PROTOCOL APPROVAL

The following individuals approve version 3.0 of the ADX-629-PS-001 protocol dated June 9, 2021. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.



TRIAL ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to Aldeyra Therapeutics, Inc.

I have read this protocol, agree that it contains all the details necessary to conduct the trial as described, and will conduct this trial following this protocol.

I will provide the contents of this protocol to trial staff under my direct supervision that need to know the contents to conduct the trial. I will discuss this information with the trial staff to ensure they are fully informed about the trial and the test article. I will provide the contents of the protocol to the responsible Institutional Review Board(s). These disclosures may be made; provided the contents are not used in any other clinical trial and they are not disclosed to any other person or entity without prior written consent from Aldeyra Therapeutics, Inc. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to Aldeyra Therapeutics, Inc. of any such disclosure.

I understand the trial may be terminated or enrollment suspended at any time by Aldeyra Therapeutics, Inc., with or without cause, or by me if it becomes necessary to protect the interests of the trial subjects.

Any additional information added to this protocol is also confidential and proprietary to Aldeyra Therapeutics, Inc. and must be treated in the same manner as the contents of this protocol.

_____
Printed Name of Principal Investigator

_____ _____
Signature of Principal Investigator Date

Protocol number: ADX-629-PS-001 Site number: _____

PROTOCOL SYNOPSIS

Title	A Multi-Center, Open-Label, Phase 2 Clinical Trial to Evaluate the Safety, Tolerability, and Efficacy of ADX-629 Administered Orally to Subjects with Plaque Psoriasis
Trial Type	Phase 2a
Test Article	ADX-629
Trial Objective	To evaluate the safety, tolerability, and efficacy of ADX-629 in subjects with plaque psoriasis
Trial Design	Multi-center, open-label.
Treatment Groups	After enrollment in the trial, all subjects will be assigned to 250 mg of ADX-629 orally (PO) twice daily (BID).
Duration of Treatment	Approximately 12 weeks
Duration of Trial	Approximately 15 weeks
Trial Population	Male or female subjects 18 years of age or older with plaque psoriasis
Total Number of Subjects	Approximately 10 subjects will be enrolled.
Number of Sites	Approximately 2 sites will participate in the trial.
Inclusion Criteria	To enter the trial, a subject must meet the following criteria: 1. Subject is a male or non-pregnant female 18 years of age or older. 2. Subject has provided written informed consent.

	3. Females must be post-menopausal[1], surgically sterile[2], or use a highly effective method of birth control[3,4] during the trial and for 30 days after the last administration of test article. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)[5] at Visit 1/Screening and Visit 2/Baseline. 4. Male subjects who are not surgically sterile (e.g., vasectomy performed at least 6 months prior to trial entry) and are sexually active with a female partner who is of childbearing potential[6] must agree to use an effective form of birth control[7] for the duration of the trial and for 90 days after completion of treatment. 5. If male, subject agrees to refrain from sperm donation during the trial and for 90 days after completion of treatment. 6. Subject has a clinical diagnosis of moderate to severe stable plaque psoriasis for at least 6 months with a Psoriasis Area and Severity Index (PASI) score ≥ 12, an Investigator's Global Assessment (IGA)

[1] Defined as spontaneous amenorrhea for at least 1 year in women 50 years of age and older.

[2] Hysterectomy, bilateral tubal ligation, salpingectomy, or bilateral oophorectomy at least 26 weeks prior to Visit 2/Baseline.

[3] Highly effective forms of birth control for FEMALE subjects include 1) intrauterine device (IUD; copper or hormonal); 2) implantable hormonal contraception; 3) monogamous relationship with a partner who is sterile (e.g., vasectomy [performed at least 6 months prior to study entry]); 4) total abstinence; or 5) using one of each of the following a) hormonal contraceptives [other than IUD or implantable, e.g., oral, transdermal, injectable, or vaginal ring] and b) double barrier methods [i.e., male or female condom, diaphragm with spermicidal foam/gel/film/cream/vaginal suppository, cervical cap with spermicides, or contraceptive sponge]. Also see next footnote for the required duration of birth control prior to test article application. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the trial must agree to use a highly effective form of birth control for the duration of the trial.

[4] WOCBP taking hormonal therapy must be on treatment prior to trial entry, continued per label, and must not change their dosing regimen during the trial; highly effective birth control forms must be for (1) oral: at least 1 complete cycle (e.g., 4 to 8 weeks); (2) transdermal, injectable (e.g., Depo-Provera), implantable, vaginal ring (e.g., NuvaRing), IUD: at least 1 week; or (3) total abstinence: at least 1 complete cycle (e.g., 4 to 8 weeks) prior to initiation of test article.

[5] UPT must have a minimum sensitivity of 25 mIU ß-hCG/mL.

[6] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, salpingectomy, or bilateral oophorectomy at least 26 weeks prior to Visit 2/Baseline) or is not postmenopausal (defined as amenorrhea for at least 1 year in women 50 years of age and older).

[7] Effective forms of birth control for MALE subjects include: 1) male condom with spermicide; or 2) use by the female sexual partner of a) hormonal contraceptives [e.g., oral stabilized for at least 1 complete cycle (e.g., 4 to 8 weeks); transdermal, injectable (e.g., Depo-Provera), implantable, or vaginal ring (e.g., NuvaRing) stabilized for at least 1 week prior to trial entry or initiation of sexual relations], b) IUD (with or without hormones) for at least 1 week prior to test article dosing, or c) a barrier method [e.g., female condom, contraceptive sponge, diaphragm, or cervical cap] with spermicide. Abstinence is also an acceptable method of birth control for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a female partner who is of childbearing potential during the trial must agree to use an effective form of birth control for the duration of the trial and for 90 days after completion of treatment.

	score of ≥ 3, and an affected body surface area (BSA) of ≥ 8% at Visit 2/Baseline. 7. Subject has normal renal function at Visit 1/Screening, defined[8] as an estimated glomerular filtration rate (eGFR) of ≥ 90 mL/min/1.73 m^2 calculated by Chronic Kidney Disease Epidemiology Collaboration equation in the absence of hematuria, proteinuria, or glycosuria on urine analysis by dipstick. Urine albumin must be < 30 mg/gram creatinine by laboratory measurement. 8. Subject agrees to avoid smoking tobacco and all other nicotine containing products (e.g., vaping, gum, patches, chewing, or dip products, etc.) for the duration of the trial. 9. [redacted] 10. Subject agrees to avoid taking the following concomitant medications: strong CYP1A2, 2B6, and 3A4 inhibitors for the duration of the trial. 11. Subject is willing and able to administer the test article(s) as directed, comply with trial instructions, and commit to all follow-up visits for the duration of the trial. 12. Subject, in the investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of plaque psoriasis or exposes the subject to an unacceptable risk by trial participation.
Exclusion Criteria	A subject is ineligible to enter the trial if he/she meets one or more of the following criteria: 1. Subject is pregnant, lactating, or is planning to become pregnant during the trial. 2. Subject has guttate, pustular, erythrodermic, drug-induced, or other non-plaque forms of psoriasis. 3. Subject has a physical condition which, in the investigator's opinion, might impair evaluation of plaque psoriasis or which exposes the subject to an unacceptable risk by trial participation. 4. Subject has acute or chronic renal disease or medical history of renal disease that, in the opinion of the investigator, could compromise the subject's safety. 5. Subject has a history or presence of gastrointestinal, hepatic, or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs. 6. Subject has an active infection at Visit 2/Baseline that precludes the subject's participation in the opinion of the investigator.

[8] If eGFR and/or urine albumin lab assessments are close to, but outside of the limits specified and the lab results are deemed not to be clinically significant by the Investigator, the Investigator may request a review by the Medical Monitor of the lab finding(s) in writing to determine the subject's eligibility. The Medical Monitor will review the subject's medical history and concomitant medications in conjunction with the lab results. If the Medical Monitor concurs with the Investigator's assessment of the lab results and assuming that the subject is otherwise qualified to participate, the subject may be enrolled in the study upon receipt of a written approval of the Medical Monitor prior to enrollment.

	7. Subject has a history of cancer, with the exception of cancers considered nonmelanoma skin cancers (e.g., squamous cell carcinoma, basal cell carcinoma) in the opinion of the investigator. 8. Subject has clinically significant laboratory results at Visit 1/Screening that precludes the subject's participation in the opinion of the investigator. 9. Subject has used any phototherapy (including laser), photo-chemotherapy, or other forms of photo based therapy for the treatment of their psoriasis within 90 days prior to Visit 2/Baseline. 10. Subject has used systemic tofacitinib, apremilast, methotrexate, retinoids, systemic corticosteroids (including intralesional, intra-articular, and intramuscular corticosteroids), cyclosporine, or analogous products within 90 days prior to Visit 2/Baseline. 11. Subject has used any systemic immunosuppressant biologic therapy (i.e., FDA-approved or experimental therapy) within 5 half-lives of the biologic prior to Visit 2/Baseline. Published or documented half-life of the product provided by the commercial supplier or Sponsor should be used to establish this value. 12. Subject is taking concomitant medication or therapy that affects renal or hepatic function, in the opinion of the investigator. 13. Subject has had prolonged exposure to natural or artificial sources of ultraviolet radiation within 30 days prior to Visit 2/Baseline or is intending to have such exposure during the trial which, in the opinion of the investigator, is thought to modify the subject's disease. 14. Subject has used topical body psoriasis therapy (including coal tar, anthralin, steroids, retinoids, and vitamin D analogs) within 14 days prior to Visit 2/Baseline. 15. Subject has used emollients/moisturizers on areas to be treated within 4 hours prior to clinical evaluation at Visit 2/Baseline. 16. Subject is currently using lithium or Plaquenil (hydroxychloroquine). 17. [redacted] 18. Subject is currently enrolled in an investigational drug, biologic, or device trial. 19. Subject has used an investigational drug, investigational biologic, or investigational device treatment within 30 days prior to Visit 2/Baseline. 20. Subject has a history of sensitivity to any of the ingredients in the test article (see Section 6.1).

	21. Subject is known to be noncompliant or is unlikely to comply with the requirements of the trial protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.
Trial Procedures	ADX-629-PS-001 will consist of 7 visits: 5 in-person visits and 2 phone calls. At every in-person visit, assessments should be completed in the following order: vital signs, subject self-evaluation (Patient Global Impression of Change [PGIC]), clinical evaluations (IGA first, then BSA and PASI), and then remaining assessments. Visit 1 (Day –21 to –3): Screening. Subjects can be screened up to 21 days prior to Baseline. If applicable, qualified subjects can washout from prohibited medications and/or therapies prior to Baseline (after obtaining informed consent). Subjects who require washout for longer than 30 days will be reconsented. The trial requirements and procedures will be reviewed and written informed consent must be obtained prior to the initiation of any trial-related procedures. Demographics, inclusion/exclusion criteria, medical history, and concomitant medications and concurrent procedures/therapies will be reviewed to determine eligibility. Vital signs will be measured. Clinical evaluations (IGA first, then BSA and PASI) will be performed by the investigator. A physical examination and electrocardiogram (ECG) will be performed. Blood and urine samples will be taken for serology, clinical laboratory tests (chemistry, hematology, and urinalysis), and a UPT for all females (test results must be negative for the subject to be eligible for the trial). If fasting samples cannot be collected at this time, the subject may return to the clinic for sample collection such that the results of the clinical laboratory tests are available for review prior to Visit 2/Baseline. The subject will be scheduled for Visit 2. Visit 2 (Day 1): Baseline. The subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies. Eligibility will be confirmed. Vital signs will be measured. Clinical evaluations (IGA first, then BSA and PASI) will be performed by the investigator. Physical examination and an ECG will be performed. Blood samples will be taken for baseline blood biomarker analysis (prior to first test article administration) and clinical laboratory tests (chemistry, hematology), and urine samples will be taken for urinalysis and UPT for WOCBP (post-menopausal status must also be confirmed with FSH test results from Visit 1/Screening; UPT results must be negative for the subject to be eligible for the trial). Non-invasive skin samples will be collected from non-lesional (perilesional) and lesional skin. Subject Instruction Sheet will be dispensed. Test article accountability will be documented. The first dose will be administered at the site under supervision of trial staff. Adverse events (AEs) will be recorded. The subject will be scheduled for the next visit. Visit 3 (Day 15 ± 2): Phone Call. The site staff will contact the subject by telephone and query the subject for any changes in health status, including

	concomitant medications and concurrent procedures/therapies. The site staff will remind the subject to continue to take 1 tablet twice daily until the next clinic visit. Any AEs will be discussed with the investigator to determine if the subject should return to the study site for an unscheduled visit. The next visit will be confirmed. Visit 4 (Day 29 ± 3): Week 4, One day prior to the visit, the site staff will contact the subject to remind them that if the subject chooses to take the morning dose of test article at home on the day of their clinic visit, the subject should: 1) take the morning dose of test article approximately 2 hours prior to the study visit AND 2) note the time of dosing on the Subject Instruction Sheet. Subject will also be informed that if the subject chooses to take the morning dose of test article in the clinic, the subject will need to remain in the clinic for 2 hours after dosing. On the day of the visit, the subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies. Vital signs will be measured. Subject evaluation (PGIC) will be performed by the subject and clinical evaluations (IGA first, then BSA and PASI) will be performed by the investigator. A targeted physical examination based on subject symptoms and an ECG will be performed. A non-invasive skin sample will be collected from lesional skin (same area collected at baseline). Test article accountability will be documented. Subjects who did not take their morning dose at home will take the morning dose of test article under supervision of study staff and will wait 2 hours before blood and urine sample collection. Time of dosing will be recorded. Blood samples will be taken for biomarker analysis (including drug metabolism) and clinical laboratory tests (chemistry, hematology) and urine samples will be taken for urinalysis, a UPT (for WOCBP), and urine drug metabolite analysis between 2 and 4 hours after test article dosing. Subject will be reminded to continue to take 1 tablet twice daily until the next clinic visit. AEs will be recorded. The subject will be scheduled for the next visit, as appropriate. Visit 5 (Day 57 ± 3): Week 8. One day prior to the visit, the site staff will contact the subject to remind them to note the time of dosing on the Subject Instruction Sheet if the subject chooses to take the morning dose of test article on the day of their clinic visit at home and to inform them that if the subject chooses to take the morning dose of test article in the clinic, the subject will need to remain in the clinic for 1 hour after dosing. On the day of the visit, the subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies. Vital signs will be measured. Subject evaluation (PGIC) will be performed by the subject and clinical evaluations (IGA first, then BSA and PASI) will be performed by the investigator. A targeted physical examination based on subject symptoms and an ECG will be performed. Test article accountability will be documented. Subjects who did not take their morning dose at home will take the morning dose of test article under supervision of study staff and will wait 1 hour before blood sample collection. Time of dosing will be recorded. Blood samples will be taken for biomarker analysis and clinical laboratory

	tests (chemistry, hematology) and urine samples will be taken for urinalysis and a UPT (for WOCBP). Subject will be reminded to continue to take 1 tablet twice daily until the next clinic visit. AEs will be recorded. The subject will be scheduled for the next visit, as appropriate. Visit 6 (Day 85 ± 3): Week 12/End of Treatment [EOT]. One day prior to the visit, the site staff will contact the subject to remind them to note the time of dosing on the Subject Instruction Sheet if the subject chooses to take the morning dose of test article on the day of their clinic visit at home and to inform them that if the subject chooses to take the morning dose of test article in the clinic, the subject will need to remain in the clinic for 1 hour after dosing. On the day of the visit, the subject will return to the clinic and be queried for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies. Vital signs will be measured. Subject evaluation (PGIC) will be performed by the subject and clinical evaluations (IGA first, then BSA and PASI) will be performed by the investigator. A targeted physical examination based on subject symptoms and an ECG will be performed. Non-invasive skin samples will be collected from non-lesional (perilesional) and lesional skin (same areas collected at baseline). Test article accountability will be documented and all test articles will be collected. Subjects who did not take their morning dose at home will take the morning dose of test article under supervision of study staff and will wait 1 hour before blood sample collection. Time of dosing will be recorded. Blood samples will be taken for biomarker analysis and clinical laboratory tests (chemistry, hematology) and urine samples will be taken for urinalysis and a UPT (for WOCBP). AEs will be recorded. The subject will be scheduled for the End of Study (EOS) phone call follow-up visit 3 days after this visit. Visit 7 (3 days after EOT Visit): EOS. The investigator or designee will call and query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies, and document any AEs. The subject will exit the study.
Trial Measurements	Safety: Vital signs, physical examinations, 12-lead ECGs, clinical laboratory tests, UPTs, and AEs will be recorded per the schedule of events. Metabolite Profiling: Urine and plasma drug metabolite analysis will take place according to the schedule of events. Clinical and Biomarker: *Skin Biomarker Analysis* Skin tape strips will be collected from all participants for whole RNA transcript analysis. The purpose of these analyses will be to retrospectively evaluate biomarkers predictive of subject response at baseline, prior to test article administration, as well as to potentially identify additional correlative and pharmacodynamic biomarkers.

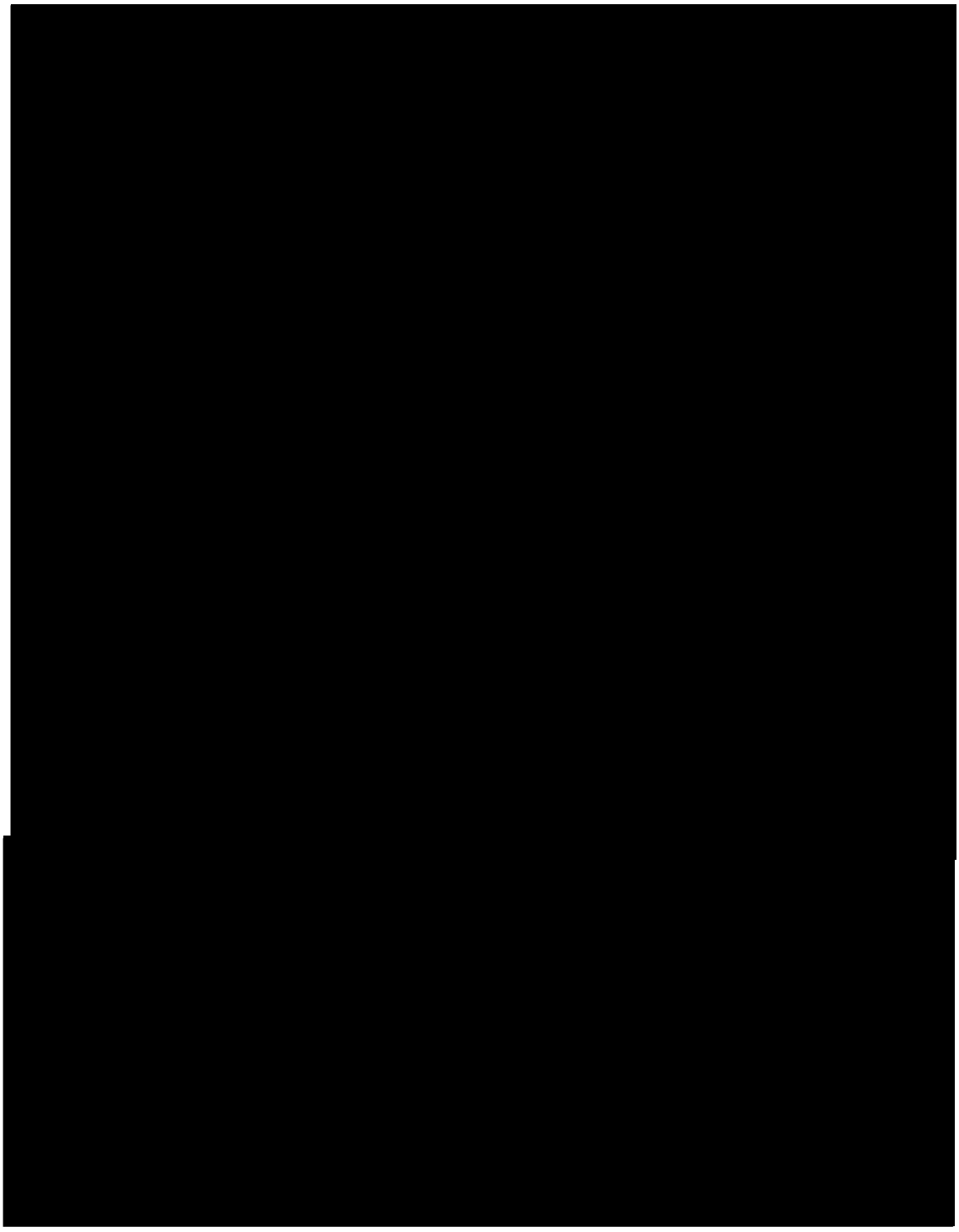
	[redacted] Sera and plasma will be further analyzed for changes from baseline in circulating inflammatory mediators. *Psoriasis Area and Severity Index* The severity of plaque psoriasis by body region (head, upper limbs, trunk, and lower limbs) and the percentage area affected by body region will be assessed. For each body region, erythema, induration/thickness, and scaling will be graded using a 5-point scale (0=clear, 1=slight (mild), 2=moderate, 3=severe, 4=very severe) and the percent involvement of each body region will be assigned a numeric score (from the BSA assessment described below): 0% (0), 1% – 9% (1), 10% – 29% (2), 30% – 49% (3), 50% – 69% (4), 70% – 89% (5) or 90% – 100% (6). The sign scores for each body region will be summed and multiplied by the Area Score, and then multiplied by the amount of body surface area assigned to that body region (0.1 for head, 0.2 for upper limbs, 0.3 for trunk, and 0.4 for lower limbs). The sum of PASI scores by body region will give the total PASI score, which may range from zero (0) to a maximum of 72. *Investigator's Global Assessment* The IGA is a single item measure that assesses the investigator's impression of overall severity of the subject's plaque psoriasis. The evaluation takes into consideration the 3 individual characteristics of psoriasis (plaque elevation, scaling, and erythema) with the IGA score at each visit representing the average degree of plaque elevation, scaling, and erythema that is present amongst all of the lesions using a 5-point visual rating scale ranging from 0 (clear) to 4 (severe). *Body Surface Area* Calculation of the PASI score requires an area score in 4 anatomic regions of the body (head; upper limbs; trunk; and lower limbs). To calculate the total BSA, the Investigator or designee will determine the absolute percent BSA of psoriasis involved skin disease in each of the 4 anatomic regions. Then, the total BSA will be calculated as the sum of the values in each of the 4 anatomic regions. BSA in each anatomic region will be determined using the hand method, whereby the subject's hand surface area (palm with fingers held in juxtaposition to each other) represents about 1% of the subject's BSA. All assessments will be recorded in the electronic case report form (eCRF). This BSA assessment in each region shall include 1 decimal point of precision (e.g., 11.0, 1.3). The amount of BSA involved in each of the 4 anatomic regions will (i) be used to assign the Area Score in the calculation of the PASI score and (ii) be summed to provide a Total BSA for the subject (at Visit 1/Screening and Visit 2/Baseline). The assignment of these values (i.e., Area Scores for the PASI assessment and Total BSA) will be "determined" by the electronic data capture (EDC) software based upon the Investigator's (or designee) assignment of the absolute percent BSA of

	diseased psoriasis skin within each of the 4 anatomic regions of the body (head; upper limbs; trunk; and lower limbs). *Patient Global Impression of Change* The PGIC is a single item measure that assesses the subject's impression of overall change from Baseline of plaque psoriasis signs and symptoms at the time the questionnaire is administered, using a 7-point visual rating scale ranging from 1 (much improved) to 7 (much worse).
Trial Endpoints	Safety Endpoints: 1. Incidence (severity and causality) of any local and systemic AEs 2. Changes from Baseline in vital signs at Days 29, 57, and 85/EOT 3. Changes from Baseline in clinical laboratory tests (chemistry, hematology, and urinalysis) at Days 29, 57, and 85/EOT 4. Changes from Baseline in overall interpretation of the ECG at Days 29, 57, and 85/EOT Metabolite Profiling Endpoint: 1. Presence/absence of urine and plasma drug metabolite(s) at Day 29 Clinical Endpoints: 1. Change from Baseline in PASI score at Day 85/EOT 2. Proportion of subjects with PASI-50 (defined as a reduction of $\geq$ 50% from Baseline) at Days 29, 57, and 85/EOT 3. Proportion of subjects with PASI-75 (defined as a reduction of $\geq$ 75% from Baseline) at Days 29, 57, and 85/EOT 4. Changes from Baseline in IGA score at Days 29, 57, and 85/EOT 5. PGIC score at Days 29, 57, and 85/EOT Biomarker Endpoints: 1. Analyses of biomarkers in peripheral blood and skin tape strips 2. Change from Baseline in the expression of select biomarkers in the skin and peripheral blood
Sample Size Calculations	Sample size calculations were not performed, as this is primarily a safety and tolerability trial. The number of subjects (N=10) to be enrolled is standard for trials of this type.
Statistical Methods	All statistical processing will be performed using SAS®. Summary tables (descriptive statistics and/or frequency tables) will be provided for screening and/or baseline variables, clinical and biomarker variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data. **Trial Population:** The Safety population will include all enrolled subjects who received and administered the test article. **Safety Analyses:** The safety analyses will be conducted on the Safety population.

	Extent of Exposure Descriptive statistics will be used to summarize the extent of exposure in the Safety population. The total number of doses taken will be assessed by tablet counts. Vital Signs Descriptive statistics of vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) at Days 29, 57, 85/EOT as well as change from Baseline will be provided. Physical Examinations Clinically significant findings from physical examinations will be recorded in medical history (from assessment at Screening and Baseline) or as AEs (from assessment at Days 29, 57, 85/EOT, if applicable at those visits). Electrocardiograms ECGs will be evaluated for any material changes during the trial period. Descriptive statistics of ECG parameters will be provided. Changes in overall interpretation of the ECG from Baseline to Days 29, 57, and 85/EOT will be examined using shift tables. Clinical Laboratory Tests Clinical laboratory tests will be evaluated for any material changes during the trial period. All laboratory data (chemistry, hematology, and urinalysis) will be listed and reported in the units received by the laboratory. Shift tables by analyte and by out of range flag will be presented to facilitate the evaluation of change from Baseline to Days 29, 57, and 85/EOT. Adverse Events All AEs reported during the trial will be listed, documenting course, severity, investigator assessment of the relationship to the test article, and outcome. Verbatim terms on the eCRFs will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities mapping system. The PTs and SOC will then be tabulated. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article. **Metabolite Profiling Analysis:** The metabolic profiling analysis will be conducted on the Safety population. Drug Metabolite Analysis Results from urine and plasma drug metabolite analysis at Day 29 will be provided in a listing. **Clinical and Biomarker Endpoint Analyses:** The clinical and biomarker endpoint analyses will be conducted on the Safety population using summary statistics. Statistical analyses for clinical and biomarker endpoints will be detailed in the Statistical Analysis Plan, which will dominate statistical language herein.

	Dosing Compliance: Descriptive statistics will be used to summarize the total number of doses for the Safety population. Subjects who take at least 80% of the expected total number of doses and have no other evidence of material dosing non-compliance will be considered to be compliant with test article dosing.

SCHEDULE OF EVENTS



ABBREVIATIONS

ACE	Angiotensin-converting Enzyme
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
β-hCG	Beta-Human Chorionic Gonadotropin
BID	Bis In Die (Twice daily)
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum Concentration
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FSH	Follicular Stimulating Hormone
GGT	Gamma-Glutamyltransferase
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
I/E	Inclusion/Exclusion
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
IUD	Intrauterine Device
L	Liter
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
MAD	Multiple Ascending Dose
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDA	Malondialdehyde
mIU	Milli International Units

mL	Milliliter
NOAEL	No-Observed-Adverse-Effect Level
OTC	Over-the-Counter
PASI	Psoriasis Area Severity Index
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PO	Per Os (Orally)
PT	Preferred Term
RASP	Reactive Aldehyde Species
RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width
RNA	Ribonucleic Acid
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
$t_{1/2}$	Half Life
TI	Therapeutics, Incorporated
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
WBC	White Blood Cells
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

TABLE OF CONTENTS

1. BACKGROUND

Reactive aldehyde species (RASP) such as 4-hydroxynonenal and malondialdehyde (MDA) are toxic mediators of the mammalian immune system and are implicated in numerous disease states. The Sponsor has developed ADX-629, a proprietary new chemical entity for the treatment of immune-mediated diseases, including psoriasis, asthma, inflammatory bowel disease, alcoholic and non-alcoholic hepatitis, acute respiratory distress syndrome, and other diseases that are thought to be caused or exacerbated by elevated concentrations of RASP.

MDA is elevated in the plasma of patients with psoriasis [1], reaching levels of approximately 4μM, roughly twice that of healthy subjects. A recent review [2] highlights the correlation of MDA levels with psoriasis area severity index (PASI), as well as increased levels of MDA in patients with genetic polymorphisms that increase the risk of psoriasis.

[redacted]

In addition to nonclinical safety studies, Phase 1 safety testing has been conducted in 85 healthy human volunteers in a single ascending dose (SAD) and a multiple ascending dose (MAD) clinical trial. In the SAD portion of the clinical trial, 41 subjects received drug and 13 received placebo across all cohorts. In the MAD portion of the clinical trial, 23 subjects received drug and 8 received placebo across all cohorts for 10 days. Overall, ADX-629 was found to be safe and tolerable at the doses explored, including the maximum single dose of 1200 mg and the maximum multiple dose of 600 mg BID for 10 days. The adverse event profile of ADX-629 was favorable compared to placebo. A total of 6 (9.4%) subjects receiving ADX-629 had treatment emergent adverse events compared to 4 (19.1%) subjects who received placebo. None of the subjects had an interruption or discontinuation of the trial drug.

Although PK variability was observed, a linear correlation was evident in C_{max} and AUC as dose increased. The half-life ($t_{1/2}$) was consistent across cohorts and days, with mean values in multiple day exposures ranging between 3.49 to 6.83 hours, supportive of BID administration. Little to no accumulation of the drug was seen across all cohorts. At the top dose (600 mg BID), a C_{max} of 1920 ng/mL (approximately 9.5 μM) was consistent with an adequate molar ratio to achieve stoichiometric efficacy against elevated RASP in psoriasis, as described above. Importantly, MDA levels in drug-treated subjects were statistically lower than those of placebo-treated subjects, and inflammation following ingestion of a fatty meal at Day 10, as assessed by lipid profiling, was statistically lower in the drug group relative to the placebo group.

In summary, mechanistic, preclinical, and clinical data suggest that administration of the RASP inhibitor ADX-629 to subjects with plaque psoriasis may sufficiently mitigate the inflammatory response to modify levels of inflammatory mediators and reduce clinical severity.

2. RATIONALE

The starting dose for ADX-629 is based on the doses studied in nonclinical studies and the Phase 1 healthy volunteer clinical trial. In nonclinical studies, the human equivalent of 250 mg BID PO for 91 days resulted in acceptable safety profiles. In the Phase 1 clinical trial, the highest multiple dose tested of 600 mg BID for a period of 10 days was found to be safe and tolerable with no adverse events of clinical concern noted. Based on the Phase 1 clinical trial PK results, the anticipated C_{max} at 250 mg BID is approximately 3.3 μM, which, based on preclinical results in models of severe inflammation and published levels of MDA in patients with psoriasis, is in the range of active concentrations.

3. OBJECTIVE

The objective of ADX-629-PS-001 is to evaluate the safety, tolerability, and efficacy of ADX-629 in subjects with plaque psoriasis.

4. TRIAL DESIGN

ADX-629-PS-001 is a multi-center, open-label trial of ADX-629 in adult subjects with stable plaque psoriasis. Approximately 10 subjects with stable moderate to severe plaque psoriasis (Investigator's Global Assessment [IGA] score $\geq$ 3, PASI score of $\geq$ 12, and body surface area [BSA] $\geq$ 8%) who fulfill the inclusion/exclusion (I/E) criteria will be enrolled at approximately 2 trial sites in the United States. All subjects will be assigned to the following treatment group in an open-label manner.

- ADX-629, 250 mg BID for 12 weeks

All subjects will administer the test article orally (PO) BID.

Subjects will have 7 trial visits: 5 in-person visits and 2 phone calls. Activity will be assessed via PASI, Skin Biomarker Analysis, Blood Biomarker Analysis (RASP enzyme-linked immunosorbent assays [ELISAs] and cytokine levels), IGA, and Patient Global Impression of Change (PGIC). Safety will be assessed by vital signs, physical examinations, clinical laboratory tests, electrocardiogram (ECG), and adverse events (AEs). Metabolite profiling will be assessed by urine and plasma drug metabolite analysis.

5. TRIAL POPULATION

5.1 Subject Eligibility

To be included in the trial, subjects must meet the following inclusion and none of the exclusion criteria.

5.1.1 Inclusion Criteria

1. Subject is a male or non-pregnant female 18 years of age or older.
2. Subject has provided written informed consent.

3. Females must be post-menopausal[9], surgically sterile[10], or use a highly effective method of birth control[11,12] during the trial and for 30 days after the last administration of test article. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)[13] at Visit 1/Screening and Visit 2/Baseline.
4. Male subjects who are not surgically sterile (e.g., vasectomy performed at least 6 months prior to trial entry) and are sexually active with a female partner who is of childbearing potential[14] must agree to use an effective form of birth control[15] for the duration of the trial and for 90 days after completion of treatment.
5. If male, subject agrees to refrain from sperm donation during the trial and for 90 days after completion of treatment.
6. Subject has a clinical diagnosis of moderate to severe stable plaque psoriasis for at least 6 months with a PASI score ≥ 12, an IGA of ≥ 3, and an affected BSA of ≥ 8% at Visit 2/Baseline.

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[9] Defined as spontaneous amenorrhea for at least 1 year in women 50 years of age and older.

[10] Hysterectomy, bilateral tubal ligation, salpingectomy, or bilateral oophorectomy at least 26 weeks prior to Visit 2/Baseline.

[11] Highly effective forms of birth control for FEMALE subjects include 1) intrauterine device (IUD; copper or hormonal); 2) implantable hormonal contraception; 3) monogamous relationship with a partner who is sterile (e.g., vasectomy [performed at least 6 months prior to study entry]); 4) total abstinence; or 5) using one of each of the following a) hormonal contraceptives [other than IUD or implantable, e.g., oral, transdermal, injectable, or vaginal ring] and b) double barrier methods [i.e., male or female condom, diaphragm with spermicidal foam/gel/film/cream/vaginal suppository, cervical cap with spermicides, or contraceptive sponge]. Also see next footnote for the required duration of birth control prior to test article application. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the trial must agree to use a highly effective form of birth control for the duration of the trial.

[12] WOCBP taking hormonal therapy must be on treatment prior to trial entry, continued per label, and must not change their dosing regimen during the trial; highly effective birth control forms must be for (1) oral: at least 1 complete cycle (e.g., 4 to 8 weeks); (2) transdermal, injectable (e.g., Depo-Provera), implantable, vaginal ring (e.g., NuvaRing), IUD: at least 1 week; or (3) total abstinence: at least 1 complete cycle (e.g., 4 to 8 weeks) prior to initiation of test article.

[13] UPT must have a minimum sensitivity of 25 mIU ß-hCG/mL.

[14] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, salpingectomy, or bilateral oophorectomy at least 26 weeks prior to Visit 2/Baseline) or is not postmenopausal (defined as amenorrhea for at least 1 year in women 50 years of age and older).

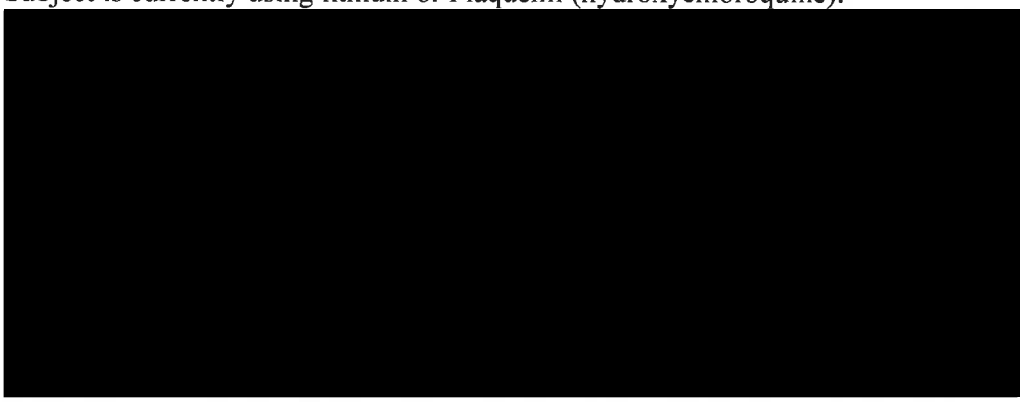
[15] Effective forms of birth control for MALE subjects include: 1) male condom with spermicide; or 2) use by the female sexual partner of a) hormonal contraceptives [e.g., oral stabilized for at least 1 complete cycle (e.g., 4 to 8 weeks); transdermal, injectable (e.g., Depo-Provera), implantable, or vaginal ring (e.g., NuvaRing) stabilized for at least 1 week prior to trial entry or initiation of sexual relations], b) IUD (with or without hormones) for at least 1 week prior to test article dosing, or c) a barrier method [e.g., female condom, contraceptive sponge, diaphragm, or cervical cap] with spermicide. Abstinence is also an acceptable method of birth control for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a female partner who is of childbearing potential during the trial must agree to use an effective form of birth control for the duration of the trial and for 90 days after completion of treatment.

7. Subject has normal renal function at Visit 1/Screening, defined[16] as an estimated glomerular filtration rate (eGFR) of ≥ 90 mL/min/1.73 m^2 calculated by Chronic Kidney Disease Epidemiology Collaboration equation in the absence of hematuria, proteinuria, or glycosuria on urine analysis by dipstick. Urine albumin must be < 30 mg/gram creatinine by laboratory measurement.
8. Subject agrees to avoid smoking tobacco and all other nicotine containing products (e.g., vaping, gum, patches, chewing, or dip products, etc.) for the duration of the trial.
9. [redacted]
10. Subject agrees to avoid taking the following concomitant medications: strong CYP1A2, 2B6, and 3A4 inhibitors for the duration of the trial.
11. Subject is willing and able to administer the test article(s) as directed, comply with trial instructions, and commit to all follow-up visits for the duration of the trial.
12. Subject, in the investigator's opinion, is in good general health and free of any disease state or physical condition that might impair evaluation of plaque psoriasis or exposes the subject to an unacceptable risk by trial participation.

5.1.2 Exclusion Criteria

1. Subject is pregnant, lactating, or is planning to become pregnant during the trial.
2. Subject has guttate, pustular, erythrodermic, drug-induced, or other non-plaque forms of psoriasis.
3. Subject has a physical condition which, in the investigator's opinion, might impair evaluation of plaque psoriasis or which exposes the subject to an unacceptable risk by trial participation.
4. Subject has acute or chronic renal disease or medical history of renal disease that, in the opinion of the investigator, could compromise the subject's safety.
5. Subject has a history or presence of gastrointestinal, hepatic, or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
6. Subject has an active infection at Visit 2/Baseline that precludes the subject's participation in the opinion of the investigator.
7. Subject has a history of cancer, with the exception of cancers considered nonmelanoma skin cancers (e.g., squamous cell carcinoma, basal cell carcinoma) in the opinion of the investigator.

[16] If eGFR and/or urine albumin lab assessments are close to, but outside of the limits specified and the lab results are deemed not to be clinically significant by the Investigator, the Investigator may request a review by the Medical Monitor of the lab finding(s) in writing to determine the subject's eligibility. The Medical Monitor will review the subject's medical history and concomitant medications in conjunction with the lab results. If the Medical Monitor concurs with the Investigator's assessment of the lab results and assuming that the subject is otherwise qualified to participate, the subject may be enrolled in the study upon receipt of a written approval of the Medical Monitor prior to enrollment.

8. Subject has clinically significant laboratory results at Visit 1/Screening that precludes the subject's participation in the opinion of the investigator.
9. Subject has used any phototherapy (including laser), photo-chemotherapy, or other forms of photo based therapy for the treatment of their psoriasis within 90 days prior to Visit 2/Baseline.
10. Subject has used systemic tofacitinib, apremilast, methotrexate, retinoids, systemic corticosteroids (including intralesional, intra-articular, and intramuscular corticosteroids), cyclosporine, or analogous products within 90 days prior to Visit 2/Baseline.
11. Subject has used any systemic immunosuppressant biologic therapy (i.e., FDA-approved or experimental therapy) within 5 half-lives of the biologic prior to Visit 2/Baseline. Published or documented half-life of the product provided by the commercial supplier or Sponsor should be used to establish this value.
12. Subject is taking concomitant medication or therapy that affects renal or hepatic function, in the opinion of the investigator
13. Subject has had prolonged exposure to natural or artificial sources of ultraviolet radiation within 30 days prior to Visit 2/Baseline or is intending to have such exposure during the trial which, in the opinion of the investigator, is thought to modify the subject's disease.
14. Subject has used topical body psoriasis therapy (including coal tar, anthralin, steroids, retinoids, and vitamin D analogs) within 14 days prior to Visit 2/Baseline.
15. Subject has used emollients/moisturizers on areas to be treated within 4 hours prior to clinical evaluation at Visit 2/Baseline.
16. Subject is currently using lithium or Plaquenil (hydroxychloroquine).
17. 
18. Subject is currently enrolled in an investigational drug, biologic, or device trial.
19. Subject has used an investigational drug, investigational biologic, or investigational device treatment within 30 days prior to Visit 2/Baseline.
20. Subject has a history of sensitivity to any of the ingredients in the test article (see Section 6.1).
21. Subject is known to be noncompliant or is unlikely to comply with the requirements of the trial protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.

5.1.3 Subject Withdrawal Criteria

Procedures for handling subjects who are discontinued from the trial are described in Section 13.2. Subjects who are discontinued will not be replaced.

6. TEST ARTICLES AND REGIMEN

6.1 Description

[redacted]

ADX-629 will be supplied as 250 mg tablets for oral delivery.

Drug/biologic name: ADX-629
Active ingredient: ADX-629

[redacted]

6.2 Instructions for Use and Administration

Subject kits will contain bottles containing tablets of test article. The first dose will be taken at the clinic on Day 1. Note: If subject's Day 1 visit is in the evening (i.e., later in the day), and the subject is unlikely to have at least an 8-hour separation between the dose taken at the clinic and the second Day 1 dose, then the dose taken at the clinic will be considered their evening dose and the subject will not dose again until the following morning. Subjects will be instructed to take 1 tablet by mouth twice daily for 12 weeks, once in the morning and once in the evening, with at least 8 hours and preferably 12 hours between doses. Each subject will be provided with a Subject Instruction Sheet providing further dosing details (see Appendix 2).

[redacted]

For Visit 4, the morning dose of test article may be taken by the subject at home or may be taken at the site under supervision of the site staff. One day prior to the visit, the site staff will contact the subject to remind them that if the subject chooses to take the morning dose of test article at home on the day of their clinic visit, the subject should: **1)** take the morning dose of test article approximately 2 hours prior to the study visit AND **2)** note the time of dosing on the Subject Instruction Sheet. Subject will also be informed that if the subject chooses to take the morning dose of test article in the clinic, the subject will need to remain in the clinic for 2 hours after dosing. Time of dosing will be recorded, such that time (in minutes) from test article dosing to blood draw for blood biomarker analysis and urine draw for drug metabolism analysis can be calculated.

For Visit 5 and Visit 6, the morning dose of test article may be taken by the subject at home or may be taken at the site under supervision of the site staff. One day prior to the visit, the site staff will contact the subject to remind them to note the time of dosing in the Subject Instruction Sheet if the subject chooses to take the morning dose of test article on the day of their clinic visit at home and to inform them that if the subject chooses to take the morning dose of test article in the clinic, the subject will need to remain in the clinic for 1 hour after dosing. Time of dosing will be recorded, such that time (in minutes) from test article dosing to blood draw for blood biomarker analysis can be calculated.

Subjects will be instructed to bring all test article bottles (used and unused) to each trial visit. At each visit, tablets will be counted.

6.3 Warnings, Precautions, and Contraindications

Subjects with a known sensitivity to any of the ingredients in the test article should not participate in ADX-629-PS-001.

In case of accidental ingestion, subjects should contact the investigator immediately.

The effects of the test article in nursing mothers, pregnant women, and their unborn children are unknown. WOCBP must not be pregnant or planning a pregnancy during the trial period.

7. RANDOMIZATION ASSIGNMENT

Subjects will not be randomized, as ADX-629-PS-001 is an open-label trial.

8. PRIOR AND CONCOMITANT THERAPIES

Current medications/therapies and any medications/therapies taken in the 30 days prior to the start of the trial (Visit 1/Screening) will be recorded as concomitant medications or concurrent procedures, respectively, with the dose (for medications only) and corresponding indication. The medications to be recorded include prescription and over-the-counter (OTC) medications; vitamins, minerals, and herbal, holistic, and dietary supplements will only be recorded as concomitant medications if being taken for a therapeutic indication. All medications taken on a regular basis must be recorded on the electronic case report forms (eCRFs). All concomitant medications will be coded with the current version of the WHO Drug Dictionary. Therapies to be recorded include any non-drug therapy used to treat a medical condition. Procedures which occurred prior to Visit 2/Baseline will be recorded as Medical History.

Any changes in concomitant medications and/or procedures/therapies during the trial must be recorded. The reason for any changes in concomitant medications and/or therapies should be reported and should reflect either a baseline medical condition documented in the medical history or in conjunction with an AE.

8.1 Prohibited Medications or Therapies

Prior to entry into the trial, subjects must not use the medications or procedures/therapies as specified in Section 5.1.2.

8.2 Allowed Medications or Therapies

Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health and will not be recorded in the eCRFs. Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the trial for the treatment or prevention of disease or to maintain good health. Non-prohibited chronic therapies being used at Visit 1/Screening may be continued, but must be recorded.

Approved bland moisturizers/emollients (as detailed on a list of such products to be provided by the sponsor or their designee) may be used once daily, but must be recorded as a concurrent procedure. Use of bland moisturizers/emollients more than once daily must be approved by written permission of the Medical Monitor.

OTC shampoo products containing selenium sulfide, zinc pyrithione, and/or salicylic acid as active ingredient(s) may be used to help control inflammatory scalp conditions including scalp psoriasis, but must be recorded as a concomitant medication.

9. TRIAL PROCEDURES

Specific activities for each trial visit are listed below.

9.1 Visit 1 (Day –21 to –3): Screening

At this visit, the investigator or designee will:

- Obtain a signed, written informed consent.
- Record demographics.
- Review I/E criteria.
- Record medical history.
- Record prior and/or concomitant medications and concurrent procedures/therapies.
- Measure vital signs (including height and weight). See Section 10.7.1.
- Perform clinical evaluations (IGA first, then BSA and PASI). See Section 10.3, Section 10.5, and Section 10.4, respectively.
- Perform a brief physical exam (see Section 10.7.2). Record abnormalities in medical history.
- Perform ECG (see Section 10.7.3).
- Collect blood sample for serology (i.e., human immunodeficiency virus (HIV), hepatitis B, and hepatitis C).
- Collect blood and urine samples for clinical laboratory tests (chemistry, hematology, and urinalysis). Subjects must be fasting for approximately 8 hours. If fasting samples cannot be collected at the time of other Visit 1/Screening procedures, the subject may return to the clinic for sample collection such that the results of the clinical laboratory tests are available for review prior to Visit 2/Baseline; such testing will still be considered "Visit 1/Screening" labs.
- Perform a UPT for all females. The result must be negative for the subject to be eligible for the trial.
- Schedule the next visit.

9.2 Visit 2 (Day 1): Baseline

Prior to this visit, the investigator or designee will:

- Review laboratory results to determine if subject is eligible to enroll in the trial.

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies, and document the findings.
- Confirm I/E criteria.
- Review and update medical history, if needed.
- Measure vital signs (see Section 10.7.1).
- Perform clinical evaluations (IGA first, then BSA and PASI). See Section 10.3, Section 10.5, and Section 10.4, respectively.
- Perform a brief physical exam (see Section 10.7.2). Record any findings in medical history.
- Perform ECG (see Section 10.7.3).
- Collect blood for baseline blood biomarker analysis (RASP ELISAs and cytokines) prior to first test article administration (see Section 12.3).
- Collect blood and urine samples for clinical laboratory tests (chemistry, hematology, and urinalysis). If possible, subjects should be fasting for approximately 8 hours.
- Perform a UPT for all WOCBP[17]. The result must be negative for the subject to be enrolled in the trial.
- Identify a lesion area for skin sampling (this location will be used for all subsequent assessments during the study). Collect non-invasive skin samples from lesional and non-lesional (perilesional to the lesional sample) skin (see Section 12.2).
  Note: Be sure to capture and document location of collection for future collections.
- Dispense Subject Instruction Sheet.
- Document Test Article Accountability and dispense the test article.
- Supervise the first dose of test article in the clinic.
- Document any AEs.
- Schedule the next visit.

9.3 Visit 3 (Day 15 ± 2): Phone Call

During this phone call, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies, and document the findings.
- Remind the subject to continue to take 1 tablet twice daily until the next clinic visit.
- Discuss any AEs to determine if the subject should return to the study site for an unscheduled visit.

[17] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, salpingectomy, or bilateral oophorectomy at least 26 weeks prior to Visit 2/Baseline) or is not postmenopausal (defined as amenorrhea for at least 1 year in women 50 years of age and older).Post-menopausal status must also be confirmed with FSH test results from Visit 1/Screening.

- Confirm the next visit.

9.4 Visit 4 (Day 29 ± 3): Week 4

One day prior to the visit, the site staff will contact the subject to remind them that if the subject chooses to take the morning dose of test article at home on the day of their clinic visit, the subject should: 1) take the morning dose of test article approximately 2 hours prior to the study visit AND 2) note the time of dosing on the Subject Instruction Sheet. Subject will also be informed that if the subject chooses to take the morning dose of test article in the clinic, the subject will need to remain in the clinic for 2 hours after dosing.

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies, and document the findings.
- Measure vital signs (see Section 10.7.1).
- Have the subject perform the subject evaluation (PGIC). See Section 10.6.
- Perform clinical evaluations (IGA first, then BSA and PASI). See Section 10.3, Section 10.5, and Section 10.4, respectively.
- Perform a targeted physical exam (see Section 10.7.2). Record any new or worsening clinically significant abnormalities as AEs.
- Perform ECG (see Section 10.7.3).
- From the same area collected at baseline, collect non-invasive skin sample from lesional skin for subjects (see Section 12.2).
- Review compliance.
- Document Test Article Accountability; all test articles will be collected and tablets will be counted.
- If the subject chose to take the test article in the clinic, administer the morning dose of test article to the subject.
- Record dosing time. Note: dosing time can be obtained verbally from the subject, from the Subject Instruction Sheet, or from administration in the clinic.
- Collect blood for blood biomarker analysis (metabolite analysis, RASP ELISAs, and cytokines) **between 2 and 4 hours after** test article administration (see Section 12.3).
- Collect blood and urine samples for clinical laboratory tests (chemistry, hematology, and urinalysis). If possible, subjects should be fasting for approximately 8 hours.
- Collect urine sample for urine drug metabolism analysis **between 2 and 4 hours after** test article administration (see Section 12.4).
- Perform a UPT for all WOCBP. The result must be negative for the subject to continue dosing with test article.
- Document any AEs.

- Schedule the next visit.

9.5 Visit 5 (Day 57 ± 3): Week 8

One day prior to the visit, the site staff will contact the subject to remind them to note the time of dosing in the Subject Instruction Sheet if the subject chooses to take the morning dose of test article on the day of their clinic visit at home and to inform them that if the subject chooses to take the morning dose of test article in the clinic, the subject will need to remain in the clinic for 1 hour after dosing.

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies, and document the findings.
- Measure vital signs (see Section 10.7.1).
- Have the subject perform the subject evaluation (PGIC). See Section 10.6.
- Perform clinical evaluations (IGA first, then BSA and PASI). See Section 10.3, Section 10.5, and Section 10.4, respectively.
- Perform a targeted physical exam (see Section 10.7.2). Record any new or worsening clinically significant abnormalities as AEs.
- Perform ECG (see Section 10.7.3).
- Review compliance.
- Document Test Article Accountability; all test articles will be collected and tablets will be counted.
- If the subject chose to take the test article in the clinic, administer the morning dose of test article to the subject.
- Record dosing time. Note: dosing time can be obtained verbally from the subject, from the Subject Instruction Sheet, or from administration in the clinic.
- Collect blood for blood biomarker analysis (RASP ELISAs and cytokines) **no earlier than 1 hour after** test article administration (see Section 12.3).
- Collect blood and urine samples for clinical laboratory tests (chemistry, hematology, and urinalysis). If possible, subjects should be fasting for approximately 8 hours.
- Perform a UPT for all WOCBP. The result must be negative for the subject to continue dosing with test article.
- Document any AEs.
- Schedule the next visit.

9.6 Visit 6 (Day 85 ± 3): Week 12/End of Treatment

One day prior to the visit, the site staff will contact the subject to remind them to note the time of dosing in the Subject Instruction Sheet if the subject chooses to take the morning dose of test article on the day of their clinic visit at home and to inform them

that if the subject chooses to take the morning dose of test article in the clinic, the subject will need to remain in the clinic for 1 hour after dosing.

At this visit, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit, including concomitant medications and concurrent procedures/therapies, and document the findings.
- Measure vital signs (see Section 10.7.1).
- Have the subject perform the subject evaluation (PGIC). See Section 10.6.
- Perform clinical evaluations (IGA first, then BSA and PASI). See Section 10.3, Section 10.5, and Section 10.4, respectively.
- Perform a targeted physical exam (see Section 10.7.2). Record any new or worsening clinically significant abnormalities as AEs.
- Perform ECG (see Section 10.7.3).
- From the same areas collected at baseline, collect non-invasive skin samples from lesional and non-lesional (perilesional to the lesional sample) skin (see Section 12.2).
- Document Test Article Accountability; all test articles will be collected and tablets will be counted.
- If the subject chose to take the test article in the clinic, administer the morning dose of test article to the subject.
- Record dosing time. Note: dosing time can be obtained verbally from the subject, from the Subject Instruction Sheet, or from administration in the clinic.
- Collect blood for blood biomarker analysis (RASP ELISAs and cytokines) **no earlier than 1 hour after** test article administration (see Section 12.3).
- Collect blood and urine samples for clinical laboratory tests (chemistry, hematology, and urinalysis). If possible, subjects should be fasting for approximately 8 hours.
- Perform a UPT for all WOCBP.
- Document any AEs.
- Schedule the subject for a phone call follow-up visit 3 days after this visit.

9.7 Visit 7 (3 days after Visit 6): End of Study

During this phone call, the investigator or designee will:

- Query the subject for any changes in health status since the previous visit including concomitant medications and concurrent procedures/therapies, and document the findings.
- Document any AEs.
- In the event that 3 days after Visit 6 occurs on a weekend, the site may call the subject on the Monday to follow as/if necessary.
- Exit the subject from the study.

10. CLINICAL EVALUATIONS

The following clinical evaluations will be performed according to the Schedule of Events. The same expert grader who has received training on how to properly perform the IGA and PASI clinical evaluations should ideally complete the evaluations for a given subject throughout the trial. If this is not possible (e.g., scheduling conflict), a different expert grader with overlapping experience with the subject and the trial should complete the evaluations.

10.1 Skin Biomarker Analysis

Skin tape strips will be collected from all participants for whole RNA transcript analysis, respectively. The purpose of these analyses will be to retrospectively evaluate biomarkers predictive of subject response at baseline, prior to test article administration, as well as to potentially identify additional correlative and pharmacodynamic biomarkers [5].

10.2 Blood Biomarker Analysis

Plasma will be collected, stored at –70°C, and sent under frozen conditions to Charles River Laboratories (Senneville, Quebec, Canada) for RASP ELISA and cytokine assays.

Sera and Plasma will be further analyzed for changes from baseline in circulating inflammatory mediators.

10.3 Investigator's Global Assessment

The IGA score is a static evaluation of the overall severity or "average" degree of severity of a subject's disease, taking into account all of the subject's psoriatic lesions (excluding those on the face, scalp, groin, axillae, and other intertriginous areas) by the investigator or designee as the subject appears on the day of the evaluation. The evaluation takes into consideration the 3 individual characteristics of psoriasis (plaque elevation, scaling, and erythema) with the IGA score at each visit representing the average degree of plaque elevation, scaling, and erythema that is present amongst all of the lesions.

The investigator should NOT refer to any other assessments to assist with this evaluation. This evaluation is NOT a comparison with the IGA at any other visit or a mathematical calculation based on the clinical signs of psoriasis scores. At every trial visit, the investigator or designee will evaluate all active psoriasis plaques in the subject's entire body) and report the one whole integer score that describes the average IGA using the following scale:

CLEAR (0)	
Plaque elevation	No evidence of plaque elevation above normal skin level.
Scaling	No evidence of scaling.
Erythema	No erythema (hyperpigmentation may be present).

ALMOST CLEAR (1)	
Plaque elevation	No more than a very slight elevation above normal skin level, easier felt than seen.
Scaling	No more than limited amount of very fine scales partially covers some of the plaques.
Erythema	No more than faint red coloration.

MILD (2)	
Plaque Elevation	No more than a slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped, on some of the plaques.
Scaling	No more than mainly fine scales; some plaques are partially covered.
Erythema	No more than light red coloration.

MODERATE (3)	
Plaque Elevation	No more than a moderate elevation with rounded or sloped edges on most of the plaques.
Scaling	No more than somewhat coarser scales predominate; most plaques are partially covered.
Erythema	No more than moderate red coloration.

SEVERE (4)	
Plaque elevation	Marked elevation with hard sharp edges on virtually all of the plaques.
Scaling	Coarse, thick tenacious scales predominate; virtually all or all plaques are covered; rough surface.
Erythema	Dusky to deep red coloration.

10.4 Psoriasis Area and Severity Index

The severity of plaque psoriasis by body region (head, upper limbs, trunk, and lower limbs) and the percentage area affected by body region will be assessed. For each body region, erythema, induration/thickness, and scaling will be graded using a 5-point scale (0=clear, 1=slight (mild), 2=moderate, 3=severe, 4=very severe) and the percent involvement of each body region will be assigned a numeric score (from the BSA assessment described below): 0% (0), 1% – 9% (1), 10% – 29% (2), 30% – 49% (3), 50% – 69% (4), 70% – 89% (5) or 90% – 100% (6). The sign scores for each body region will be summed and multiplied by

the Area Score, and then multiplied by the amount of body surface area assigned to that body region (0.1 for head, 0.2 for upper limbs, 0.3 for trunk, and 0.4 for lower limbs). The sum of PASI scores by body region will give the total PASI score, which may range from zero (0) to a maximum of 72. See Appendix 3.

10.5 Body Surface Area

Calculation of the PASI score requires an area score in 4 anatomic regions of the body (head; upper limbs; trunk; and lower limbs). To calculate the total BSA, the Investigator or designee will determine the absolute percent BSA of psoriasis involved skin disease in each of the 4 anatomic regions. Then, the total BSA will be calculated as the sum of the values in each of the 4 anatomic regions. BSA in each anatomic region will be determined using the hand method, whereby the subject's hand surface area (palm with fingers held in juxtaposition to each other) represents about 1% of the subject's BSA. All assessments will be recorded in the eCRF. This BSA assessment in each region shall include 1 decimal point of precision (e.g., 11.0, 1.3). The amount of BSA involved in each of the 4 anatomic regions will (i) be used to assign the Area Score in the calculation of the PASI score and (ii) be summed to provide a Total BSA for the subject (at Visit 1/Screening and Visit 2/Baseline). The assignment of these values (i.e., Area Scores for the PASI assessment and Total BSA) will be "determined" by the electronic data capture (EDC) software based upon the Investigator's (or designee) assignment of the absolute percent BSA of diseased psoriasis skin within each of the 4 anatomic regions of the body (head; upper limbs; trunk; and lower limbs).

10.6 Patient Global Impression of Change

The PGIC is a single item measure that assesses the subject's impression of overall change from Baseline in plaque psoriasis signs and symptoms at the time the questionnaire is administered, using a 7-point visual rating scale ranging from 1 (much improved) to 7 (much worse). See Appendix 4.

Please select the response below that best describes the overall change in your psoriasis since you started taking the trial drug.

Grade	Description
1	Much improved
2	Moderately improved
3	A little improved
4	Stayed the same
5	A little worse

Grade	Description
6	Moderately worse
7	Much worse

10.7 Safety Evaluations

10.7.1 Vital Signs

Vital signs including temperature, systolic and diastolic blood pressure, heart rate, and respiration rate will be measured. Assessments will be made after the subject has rested in a seated position for at least 5 minutes. Height and weight will also be measured at Visit 1/Screening.

10.7.2 Physical Examination

Brief physical examinations at Visit 1/Screening and Visit 2/Baseline will include examination of head and neck, dermatologic (except the indication being studied), cardiovascular, respiratory, gastrointestinal (abdomen), and gross motor and gait. Clinically significant abnormalities at Visit 1/Screening and Visit 2/Baseline will be recorded as medical history. A targeted physical examination will be conducted at follow-up visits driven by the subject's signs and symptoms. Any new or worsening clinically significant abnormalities at any post-Baseline visits will be recorded as AEs.

10.7.3 Electrocardiogram

12-lead ECGs will be performed after the subject has rested for at least 10 minutes in the supine position.

The investigator must review all the ECG reports in a timely manner. Note: The investigator will initial and date each ECG report to indicate his/her review. The investigator will note, directly on the report, whether or not any abnormal findings are clinically significant. The investigator must complete an appropriate AE form for any new or worsening abnormal test results that are identified as clinically significant after Baseline.

11. PHOTOGRAPHY

Photography documentation is not required in ADX-629-PS-001. However, the investigator may elect to photograph the subject to document the effects of treatment, AEs, or other findings during the trial. All photographs taken as part of ADX-629-PS-001 are for informational purposes only and are not to assist in grading or for any other assessment.

Any photographs taken of readily identifiable features (e.g., the face) will be de-identified (i.e., a masking bar over the eyes). In addition, subject identifiers (i.e., codes) will be used to identify photographs to the appropriate subject.

Note: Subjects may decline to have photographs taken during the conduct of the trial. If a subject initially consents to photographs, then declines further photography, the Sponsor may use the photographs taken under consent for the purposes noted above.

12. LABORATORY TESTS

12.1 Blood Chemistries, Hematology, and Urinalysis

Blood and urine specimens will be collected at every clinic visit for chemistry, hematology, and urinalysis. At Visit 1/Screening, serology will be performed for HIV, hepatitis B, and hepatitis C (i.e., HepB-sAg and Hep C-Ab) in all subjects and FSH levels will be evaluated in all females. The post-menopausal range for FSH will be based on the central laboratory's range [typically ≥ 40 IU/L]). Subjects must be fasting (approximately 8 hours) for Visit 1/Screening and, if possible, for all post-Screening visits. If fasting samples cannot be collected at the time of other Visit 1/Screening procedures, the subject may return to the clinic for sample collection such that the results of the clinical laboratory tests are available for review prior to Visit 2/Baseline; such testing will still be considered "Visit 1/Screening" labs. If a subject arrives at the clinic for any post-Screening visit without fasting for at least 8 hours, laboratory specimens may be collected as non-fasting, at the discretion of the investigator, and with the appropriate fasting status documented on the lab requisition form.

The following laboratory tests will be performed:

LABORATORY TESTS		
Chemistries	**Hematology**	**Urinalysis**
Albumin	Hemoglobin	Color
Alkaline phosphatase	Hematocrit	Appearance/Clarity
ALT (SGPT)	MCV	Albumin
AST (SGOT)	MCH	Creatinine
Bilirubin, total	MCHC	Bilirubin
Calcium	RBC (Erythrocytes)	Blood
Carbon Dioxide §	WBC (Leucocytes)	Glucose
Chloride	RDW	Ketones
Creatinine	Differential count	Leukocyte Esterase
GGT	Basophils	Nitrite
Glucose (fasting)	Eosinophils	pH

LABORATORY TESTS		
Chemistries	**Hematology**	**Urinalysis**
LDH	Lymphocytes	Protein
Phosphate	Monocytes	Specific gravity
Potassium	Neutrophils	Urobilinogen
Protein, total	Platelets	Microscopic analysis (if needed)
Sodium		Microalbumin/Creatinine Ratio*
Urea (BUN)		
Uric acid		
eGFR*		
Lipid Panel		
Cholesterol, total		
HDL		
Direct LDL		
Triglycerides		

§ Bicarbonate may be substituted if the participating lab does not perform assay for carbon dioxide.

* If eGFR and/or urine albumin lab assessments are close to, but outside of the limits specified in inclusion #7 and the lab results are deemed not to be clinically significant by the Investigator, the Investigator may request a review by the Medical Monitor of the lab finding(s) in writing to determine the subject's eligibility. The Medical Monitor will review the subject's medical history and concomitant medications in conjunction with the lab results. If the Medical Monitor concurs with the Investigator's assessment of the lab results and assuming that the subject is otherwise qualified to participate, the subject may be enrolled in the study upon receipt of a written approval of the Medical Monitor prior to enrollment.

Sample collection, handling, labeling, and shipping should be done following the instructions provided by the relevant certified laboratory in their lab manual (or equivalent document) and the applicable local regulations.

The investigator must review all the subject's laboratory reports in a timely manner. **NOTE**: The investigator will initial and date each laboratory report to indicate his/her review. The investigator will note, directly on the laboratory report, whether or not any abnormal test results are clinically significant or not clinically significant. Clinical significant laboratory abnormalities that are present at Screening and/or Baseline must be documented in the subject's medical history. In addition, the investigator must complete an appropriate AE form for any new or worsening abnormal test results that are identified as clinically significant after Baseline.

AEs that may be associated with venipuncture and that must be included in the informed consent include:

- Pain
- Bruising
- Bleeding at the puncture site
- Fainting
- Inflammation of the vein

12.2 Lesional and Non-Lesional Skin Assessments

Non-invasive patch-based skin sampling will be taken from psoriasis lesion and non-lesional (perilesional) skin, chosen at the discretion of the investigator at Baseline to be representative of the subject's overall plaque psoriasis, and sent to DermTech (La Jolla, CA) for RNA isolation and transcriptomic analysis by a blinded independent evaluator.

Please refer to the DermTech Manual for specifics regarding the harvesting and handling of these samples.

12.3 Blood Biomarker Analysis

Plasma samples will be collected, stored at -70°C, and sent under frozen conditions to Charles River Laboratories for cytokine assays and RASP ELISAs for malondialdehyde and 4-hydroxynonenal (Senneville, Quebec, Canada).

At Visit 4 only, a plasma sample (taken from subjects between 2 and 4 hours after test article dosing) will also be sent to Charles River Laboratories (Mattawan, MI) for drug metabolite analysis. Note: the laboratory designated to perform these services is subject to change based on availability or other factors.

Further details will be provided in a laboratory manual.

12.4 Urine Drug Metabolite Analysis

At Visit 4 only, urine samples will be taken from subjects between 2 and 4 hours after test article dosing and sent to Charles River Laboratories (Mattawan, MI) for urine drug metabolite analysis.

Further details will be provided in a laboratory manual.

12.5 Urine Pregnancy Tests

The UPTs will be performed at the trial site as permitted by applicable local and national health authority laws and regulations. In the United States, the site must be registered and conform to CLIA regulations for such testing (possesses a current valid CLIA Certificate

of Waiver or higher), or at an appropriately registered reference laboratory. The investigator will report the UPT results on the eCRFs, in the subject's medical records, and in independent records maintained at the trial site. The UPT used must have a minimum sensitivity of 25 mIU of β-hCG/mL.

13. END OF TRIAL CRITERIA

At the end of each subject's participation in the trial, the investigator will complete an End of Study Disposition form for all completed and discontinued subjects.

13.1 Completion of the Trial

Subjects who complete the 12-week course of treatment and Visit 6/EOT procedures as specified in the protocol will be considered to have completed the trial.

13.2 Subject Discontinuation

A subject may be withdrawn from the trial prior to completion for any of the following reasons:

- AEs
- Death
- Lack of efficacy[18]
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Progressive disease[19]
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject; NOTE: if the subject decides to withdraw from the trial due to an AE then it should be classified as withdrawal due to an AE
- Other (e.g., any reason that may affect the outcome of the trial or safety of subjects)

If a subject withdraws from the trial prematurely for any reason, the site should make every effort to have the subject return to the clinic to perform all of the required visit activities and to collect and reconcile all test articles (if applicable). If the subject will not return to the clinic, the site should make every attempt to contact the subject; otherwise the subject will be considered lost to follow-up.

[18] Defined as the lack of expected or desired effect related to a therapy.
[19] Defined as a disease process that is increasing in extent or severity.

When a subject is withdrawn from the trial for a test article related AE (as defined in Section 14.2), when possible, the subject should be followed until resolution or stabilization of the AE. If the subject is discontinued from the trial due to pregnancy, the pregnancy and its outcome should be followed.

Subjects who are prematurely withdrawn or discontinued from the trial will not be replaced.

13.3 Trial Termination

The trial may be terminated by the investigator or the Sponsor. If, in the opinion of the investigator, clinical observations made during the trial suggest that it may be unwise to continue, he or she may stop the trial. A trial termination by the investigator will be reported to the Sponsor.

In addition, a written statement fully documenting the reasons for trial termination will be submitted to the Sponsor by the investigator within 5 working days.

In the event that the Sponsor chooses to discontinue or terminate the trial, appropriate notification will be given to the investigator.

14. ADVERSE EVENT REPORTING

14.1 Adverse Event Definitions

An **adverse event** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with any drug) and from any route of administration, formulation, or dose, including an overdose.

A **suspected adverse reaction** is any AE for which there is a reasonable possibility that the drug caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. For the purposes of prescription drug labeling, the term adverse reaction means an undesirable effect, reasonably associated with the use of a drug that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, the event is considered "unexpected" if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Timely and complete reporting of all AEs assists the Sponsor and/or their designee (e.g., Therapeutics, Inc. [TI]) in identifying any untoward medical occurrence, thereby allowing:

1) protection of the safety of trial subjects;
2) a greater understanding of the overall safety profile of the test article;
3) recognition of dose-related test article toxicity;
4) appropriate modification of trial protocols;
5) improvements in trial design or procedures; and
6) adherence to worldwide regulatory requirements.

14.2 Adverse Event Details

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. All AEs must be recorded on the AE eCRF. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of test article or those experiencing AEs that are present at the end of their participation in the trial should receive follow-up as appropriate. AEs should be followed to resolution or stabilization (if possible) and, if they become serious, reported as serious adverse events (SAEs, see Section 14.4). If possible, the outcome of any AEs that caused permanent discontinuation or that were present at the end of the trial, especially those considered by the investigator to be related to the test article, should be reported.

Information on the medical condition of subjects should begin following the subject's written informed consent to participate in the trial and a medical history should be taken at screening. During any wash out and screening periods, any changes in the health of subjects should be recorded as changes in medical history unless an event occurred as a result of a trial-related procedure and is unanticipated; in such cases, the event should be recorded as an AE and reported to the Institutional Review Board (IRB) as an "unanticipated problem" in accordance with local procedures. Other changes in subject health information becomes AE data when the subject begins dosing with the test article; therefore AE data should be

collected from the date of the first dose of test article until the date of the final trial visit. These data are considered treatment-emergent AEs.

In clinical trials in healthy humans exposed to ADX-629, AEs deemed unrelated to test article included sinus congestion, headache, nasal congestion, upper respiratory tract infection, and rhinitis. One AE deemed possibly related to test article included syncope of moderate intensity.

The investigator will instruct the subject to report any AEs that may occur during the trial. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject's overall health status since the previous visit.

The investigator must determine the relationship of the AE to the test article according to the following categories:

Definitely Related: An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage, and reappearance of the event on repeated exposure (re-challenge).

Probably Related: An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage of the test article; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.

Possibly Related: An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern

to the test article; but may have been caused by concurrent/underlying illness, other drug, procedure, or other causes.

Unlikely Related: An event that does not follow a reasonable temporal sequence from administration of the test article; that does not follow a known or expected response pattern to the test article, or most likely was caused by concurrent/underlying illness, other drug, procedure, or other causes, because of their known effects.

Not Related: An event almost certainly caused by concurrent/underlying illness, other drug, procedure, or other causes.

The investigator should categorize the outcome of the AE according to the following categories:

Fatal: Termination of life as a result of an AE.

Not Recovered/Not Resolved: AE has not improved or the subject has not recuperated.

Recovered/Resolved: AE has improved or the subject has recuperated.

Recovered/Resolved with Sequelae: Subject recuperated but retained the pathological conditions resulting from the prior disease or injury.

Recovering/Resolving: AE is improving or the subject is recuperating.

Unknown: Not known, not observed, not recorded or subject refused.

14.3 Subject Stopping Rules

Safety and tolerability data will be reviewed on an ongoing basis by the Medical Monitor and stopping rules will be applicable starting with dosing of the first subject.

Subjects will be discontinued from dosing, but will continue to be followed in the trial, if any of the following occurs:

- ≥ Grade 3 (Common Terminology Criteria for Adverse Events [CTCAE] v5.0) AE or clinically significant laboratory abnormality OR ≥ Grade 2 (CTCAE v5.0) AE (or Grade 3 if a qualified subject is enrolled at Baseline with Grade 2 findings) for the system organ classes (SOCs) of cardiac disorders and/or blood and lymphatic disorders, considered related to trial drug. Any clinically significant laboratory or ECG abnormalities that may trigger a subject stopping rule must be repeated promptly to ensure accuracy and confirm the event meets stopping rule requirements.
- Severe anaphylactic reaction, including bronchospasm;

- Moderate to severe renal impairment, defined as an eGFR ≤ 50 mL/min/1.73m^2;
  Note: Dosing will be suspended until eGFR exceeds 50 mL/min/1.73m^2 for at least 2 consecutive measurements within 24 hours, at which time dosing may be resumed. A subject with out-of-range value(s) may be re-tested once before dosing is discontinued. Re-testing must occur promptly of an abnormal laboratory value(s).
- Requirement for hemodialysis; and/or
- Significant hepatic impairment, defined as an ALT or AST level > 3 times the upper limit of normal (ULN) or a total bilirubin > 2 times the ULN for more than 24 hours, confirmed on re-testing.
  Note: A subject with out-of-range value(s) may be re-tested once before dosing is discontinued. Re-testing must occur promptly of an abnormal laboratory value(s).

Subjects will be monitored until the AEs resolve or stabilize.

In the event that any of the following are encountered, the Medical Monitor will determine if the trial must stop enrollment:

- SAE considered related to trial drug;
- ≥ Grade 3 (CTCAE v5.0) reaction considered related to trial drug;
- ≥ 2 subjects are discontinued from treatment for safety reasons pertaining to trial drug; and/or
- ≥ 2 subjects experience similar SAEs or Grade 3 (CTCAE v5.0) AEs related to trial drug.

14.4 Serious Adverse Event

An event that is serious must be recorded on the AE eCRF and on the TI SAE Report Form, and requires expeditious handling to comply with regulatory requirements.

An AE or suspected adverse reaction is considered "serious" if, in the opinion of either the investigator or Sponsor, it results in any of the following outcomes:

- Death; the event must be the cause of death for the SAE to meet this serious criterion.
- Life-threatening event; an event in which the subject was at risk of death at the time of the event and not an event that hypothetically might have caused death if it had been more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization (for ≥24 hours).
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical events; a medical event(s) that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical

intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events NOT considered to be SAEs are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen; and
- Treatment on an emergency, outpatient basis, for an event not fulfilling any of the definitions of "serious" given above and not resulting in hospital admission.

AEs classified as "serious" by either the investigator or the Sponsor require expeditious handling and reporting to TI to comply with regulatory requirements. **All SAEs, whether related or unrelated to test article, must be immediately reported by telephone to the Medical Monitor and, in the event that he/she is unavailable, to the Project Manager listed on the first page of the protocol.** Written notification of all SAEs should be sent to the Project Manager by email or confirmed facsimile transmission. These include those SAEs listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the test article caused the event.

Any suspected adverse reactions that are serious and unexpected represent especially important safety information that must be reported more rapidly to Health Authorities; therefore, it is important that the Investigator submit any information requested by the Sponsor or designee (e.g., TI) as soon as it becomes available.

If only limited information is initially available, follow-up reports are required. Should the investigator become aware of an SAE (regardless of its relationship to test article) that occurs within 30 days after stopping the test article, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to TI, if available.

As required, the Sponsor or designee (e.g., TI) will notify participating investigators of all suspected adverse reactions that are serious and unexpected. This notification will be in the form of an IND safety report of potential serious risks as soon as possible but no later than 15 calendar days after the Sponsor determines that the information is "reportable" according to the criteria listed in 21 CFR Section 312.32. These are:

i) Serious and unexpected suspected adverse reactions;
ii) Findings from other studies including epidemiological studies, pooled analyses, or other clinical studies that suggest a significant risk in humans exposed to the test articles;
iii) Findings from animal or in vitro tests that suggest a significant risk to humans exposed to the test articles, or reports of significant organ toxicity at or near the expected human exposure; and

iv) Clinically important increases in the rate of occurrence of serious suspected adverse reactions.

Upon receiving such notices, the investigator must review and retain the notice with the IB and promptly submit a copy of this information to the responsible IRB according to local regulations. The investigator and IRB will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of safety updates by the investigator to Health Authorities should be handled according to local regulations.`

The Sponsor or designee may be required to report certain SAEs to regulatory authorities (e.g., United States FDA, National Health Authorities) within seven calendar days of being notified about the event; therefore, it is important that investigators submit any information requested by the Sponsor or designee as soon as it becomes available.

14.5 Laboratory Test Abnormalities

Any clinically significant laboratory test result that meets the criteria for an AE (see Section 14.1) or SAE (see Section 14.4) must be recorded on the AE eCRF, in addition to being recorded on the appropriate laboratory test results eCRF and the original laboratory report, as applicable. In these cases, TI will typically require additional information about the clinically significant abnormality, including information regarding relationship to test article, any action taken, and outcome. Clinically significantly laboratory abnormalities that qualify as SAEs must be reported to the Sponsor and IRB as per Section 14.4.

14.6 Pregnancy

WOCBP (see Schedule of Events for definition of WOCBP) must have a UPT prior to trial enrollment. Post-menopausal status must also be confirmed with FSH test results from Visit 1/Screening. Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during the trial and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If a subject or investigator suspects that a subject may be pregnant at any time during the trial, the test article must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or administer further test article and must be discontinued from the trial unless the Medical Monitor elects to retain the subject for all or part of the remaining trial period to follow the subject for safety.

If following initiation of trial treatment, it is subsequently discovered that a subject was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the Medical Monitor and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to TI. The investigator will also report

any pregnancy associated with the trial treatment as required by their IRB and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the trial must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated, including counseling of the subject by the investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the investigator must report to TI, on the appropriate pregnancy surveillance form(s), any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs or SAEs (if they fulfill the SAE criteria). Offspring should be followed for a minimum of 8 weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to the test article(s) should be recorded as a SAE with details documented in the pregnancy surveillance form. Abortion, whether accidental, therapeutic, or spontaneous should be reported as an SAE.

Male subjects who are not surgically sterile (e.g., vasectomy performed at least 6 months prior to trial entry) and are sexually active with a female partner who is of childbearing potential[20] must agree to use an effective form of birth control[21] for the duration of the trial and for 90 days after completion of treatment. Male subjects must also agree to refrain from sperm donation during the study and for 90 days after completion of treatment. Prior to trial enrollment, subjects must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

During the trial, all subjects should be instructed to contact the investigator immediately if they suspect that their sexual partner might be pregnant (e.g., female sexual partner has missed or late menstrual period).

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[20] WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, salpingectomy, or bilateral oophorectomy at least 26 weeks prior to Visit 2/Baseline) or is not postmenopausal (defined as amenorrhea for at least 1 year in women 50 years of age and older).

[21] Effective forms of birth control for MALE subjects include: 1) male condom with spermicide; or 2) use by the female sexual partner of a) hormonal contraceptives [e.g., oral stabilized for at least 1 complete cycle (e.g., 4 to 8 weeks); transdermal, injectable (e.g., Depo-Provera), implantable, or vaginal ring (e.g., NuvaRing) stabilized for at least 1 week prior to trial entry or initiation of sexual relations], b) an IUD (with or without hormones) for at least 1 week prior to test article dosing, or c) a barrier method [e.g., female condom, contraceptive sponge, diaphragm, or cervical cap] with spermicide. Abstinence is also an acceptable method of birth control for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a female partner who is of childbearing potential during the trial must agree to use an effective form of birth control for the duration of the trial and for 90 days after completion of treatment.

If the subject suspects that their sexual partner may be pregnant at any time during the trial, or if following initiation of trial treatment, it is subsequently discovered that a trial subject's sexual partner was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the IRB of any pregnancy associated with the trial treatment and keep careful source documentation of the event, including abortion (accidental, therapeutic, or spontaneous) and birth of offspring. Offspring should be followed for a minimum of 8 weeks and any congenital anomaly/birth defect in a child born to a subject's sexual partner that was exposed to the test article(s) should be documented.

15. BLINDING/UNBLINDING

This is an open-label trial.

16. CLINICAL SUPPLIES

16.1 Test Article Information

Test article will be packaged and labeled by the Sponsor or designee. Detailed information on the packaging/labeling, storage and preparation, dispensing, accountability, etc. is included in Appendix 1.

16.2 Supplies Provided by Therapeutics, Inc.

- eCRFs
- Source document draft templates
- Site regulatory binder
- UPT kits
- List of approved bland moisturizers/emollients

16.3 Supplies Provided by Investigator

- Urine collection containers for UPTs
- Centrifuge to process blood samples
- ECG machine

16.4 Supplies Provided by the Clinical Laboratory

- Supplies to collect and transport urine and blood samples to the clinical laboratory

17. STATISTICAL CONSIDERATIONS

17.1 Sample Size

Sample size calculations were not performed, as this is primarily a safety and tolerability trial. The number of subjects (N=10) to be enrolled is standard for trials of this type.

17.2 Endpoints

17.2.1 Safety Endpoints

1. Incidence (severity and causality) of any local and systemic AEs
2. Changes from Baseline in vital signs at Days 29, 57, and 85/EOT
3. Changes from Baseline in clinical laboratory tests (chemistry, hematology, and urinalysis) at Days 29, 57, and 85/EOT
4. Changes from Baseline in overall interpretation of the ECG at Days 29, 57, and 85/EOT

17.2.2 Metabolite Profiling Endpoint

1. Presence/absence of urine and plasma drug metabolite(s) at Day 29

17.2.3 Clinical and Biomarker Endpoints

Clinical Endpoints will include:

1. Change from Baseline in PASI score at Day 85/EOT
2. Proportion of subjects with PASI-50 (defined as a reduction of $\geq 50\%$ from Baseline) at Days 29, 57, and 85/EOT
3. Proportion of subjects with PASI-75 (defined as a reduction of $\geq 75\%$ from Baseline) at Days 29, 57, and 85/EOT
4. Changes from Baseline in IGA score at Days 29, 57, and 85/EOT
5. PGIC score at Days 29, 57, and 85/EOT

Biomarker Endpoints will include:

1. Analyses of biomarkers in peripheral blood and skin tape strips
2. Change from Baseline in the expression of select biomarkers in the skin and peripheral blood

17.3 Statistical Methods

All statistical processing will be performed using SAS®. Summary tables (descriptive statistics and/or frequency tables) will be provided for screening and/or baseline variables, clinical and biomarker variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data.

Trial Population:
The Safety population will include all enrolled subjects who received and administered the test article.

17.3.1 Safety Analyses

The safety analyses will be conducted on the Safety population.

17.3.1.1 Extent of Exposure

Descriptive statistics will be used to summarize the extent of exposure in the Safety population. The total number of doses taken will be assessed by tablet counts.

17.3.1.2 Vital Signs

Descriptive statistics of vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) at Day 29, 57, 85/EOT as well as change from Baseline will be provided.

17.3.1.3 Physical Examination

Clinically significant findings from physical examinations will be recorded in medical history (from assessment at Screening and Baseline) or as AEs (from assessment at Days 29, 57, and 85/EOT, if applicable at those visits).

17.3.1.4 Electrocardiograms

ECGs will be evaluated for any material changes during the trial period. Descriptive statistics of ECG parameters will be provided. Changes in overall interpretation of the ECG from Baseline to Days 29, 57, and 85/EOT will be examined using shift tables.

17.3.1.5 Clinical Laboratory Tests

Clinical laboratory tests will be evaluated for any material changes during the trial period. All laboratory data (chemistry, hematology, and urinalysis) will be listed and reported in the units received by the laboratory. Shift tables by analyte and by out of range flag will be presented to facilitate the evaluation of change from Baseline to Days 29, 57, and 85/EOT.

17.3.1.6 Adverse Events

All AEs reported during the trial will be listed, documenting course, severity, investigator assessment of the relationship to the test article, and outcome. Verbatim terms on the eCRFs will be linked to preferred terms (PTs) and SOC using the Medical Dictionary for Regulatory Activities mapping system. The PTs and SOC will then be tabulated. All

reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article.

17.3.2 Metabolite Profiling Analysis

The metabolite profiling analysis will be conducted on the Safety population.

17.3.2.1 Drug Metabolite Analysis

Results from urine and plasma drug metabolite analysis at Day 29 will be provided in a listing.

17.3.3 Clinical and Biomarker Endpoint Analyses

The clinical and biomarker endpoint analyses will be conducted on the Safety population using summary statistics.

17.3.3.1 Clinical and Biomarker Endpoint Analyses

Statistical analyses for clinical and biomarker endpoints will be detailed in the Statistical Analysis Plan, which will dominate statistical language herein.

17.3.3.2 Dosing Compliance

Descriptive statistics will be used to summarize the total number of doses for the Safety population. Subjects who take at least 80% of the expected total number of doses and have no other evidence of material dosing non-compliance will be considered to be compliant with test article dosing.

17.3.3.3 Subgroup Analyses

No subgroup analyses are planned.

17.4 Interim Analyses

No interim analyses are planned.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Compliance with Good Clinical Practice

ADX-629-PS-001 will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice guidelines and with other applicable regulations. The investigator and all trial staff will conduct the trial in compliance with this protocol. The protocol, informed consent documents, recruitment advertisements, and any amendments to these items will have IRB approval, where required, prior to trial initiation.

Voluntary informed consent will be given by every subject prior to the initiation of any trial-related procedures. The rights, safety and well-being of the trial subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of ADX-629-PS-001 must be qualified by education, training, and experience to perform their assigned responsibilities. Contact information for each site and any clinical laboratories used in the trial will be maintained up to date in a separate reference document.

18.2 Institutional Review Board and Informed Consent

Before trial initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to the subject. The investigator should also provide the IRB with a copy of the product labeling, information to be provided to the subject and any updates. The investigator will submit documentation of the IRB approval to TI.

The IRB approved consent form must include all elements required by FDA or other national health authorities, state, and local regulations, and may include appropriate additional elements.

The investigator/designee will explain the trial to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The investigator must provide the subject with a copy of the consent.

The investigator will maintain documentation that informed consent was obtained prior to the initiation of any trial-specific procedures.

18.3 Protocol Compliance

The IRB approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

18.4 Protocol Revisions

TI must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding ADX-629-PS-001 must be sent to TI.

New or altered consent forms required by the IRB due to a protocol change must be signed by all subjects currently enrolled in the trial and must be used for any subsequent subject enrollment.

18.5 Trial Monitoring

This study will include both on site and remote monitoring activities. Representatives of TI and/or the Sponsor must be allowed to visit all trial sites, to review trial records, and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the trial conduct with the investigator and trial staff, and to verify that the investigator, trial staff, and facilities remain acceptable for the conduct of the trial. To facilitate remote monitoring visits the Investigator or designee will upload requested source documents to a secure file share portal. Protected health information will be de-identified using the safe harbor method defined in 45 CFR 164.514.

Representatives of government regulatory authorities may also evaluate the trial records, source documents, investigator, trial staff, and facilities.

The investigator should immediately notify TI of any audits of ADX-629-PS-001 by any regulatory agency and must promptly provide copies of any audit reports.

18.6 Case Report Form Requirements

For eCRFs, validated 21 CFR Part 11 compliant EDC software will be used to collect data. All requested information must be entered on the eCRFs in the areas provided in a timely manner. When changes or corrections are made in the eCRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change, and the reason for the change. Only individuals who have completed EDC training and are listed on the Delegation of Responsibilities Log with responsibility for eCRF completion will be provided usernames and passwords in order to access the system and make entries on the eCRF.

The investigator or physician sub-investigator must electronically sign and date each subject's eCRF. Individuals who will be providing electronic signatures must first submit documentation with a handwritten signature acknowledging that their electronic signature is a legally binding equivalent to their handwritten signature.

18.7 Reports to Institutional Review Board

The investigator should provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements or Institution procedures.

18.8 Quality Assurance Audits

Representatives from TI and/or the Sponsor or a third party selected by the Sponsor may conduct a quality assurance audit of ADX-629-PS-001. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA, National Health Authorities, or other regulatory authorities, the investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The investigator must notify TI in the event of a site audit by the FDA and/or other regulatory authority.

18.9 Records Retention

The investigator must maintain all trial records (including test article disposition, informed consents/assents, eCRFs, source documents, correspondence, regulatory documents, contracts, etc.) for the maximum period required by TI or the institution where the trial is conducted, whichever is longer. Original Test Article Accountability Logs and original Label Pages (only applicable if have 2-part label with detachable panel typically used for double-blind studies) must be kept with trial records at the site.

The investigator must contact TI or the Sponsor prior to destroying any records associated with ADX-629-PS-001.

If the investigator withdraws from the trial, the records shall be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to TI.

18.10 Record Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject or the subject's parent/guardian (if appropriate), except as necessary for monitoring by TI or the Sponsor, the FDA, National Health Authorities, or other regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with ADX-629-PS-001 shall not disclose or use for any purpose other than performance of the trial, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from TI or the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

19. REFERENCES

APPENDIX 1 TEST ARTICLE INFORMATION

A 1.1 Test Article Packaging and Labeling

The test article will be packaged and labeled by the Sponsor or designee. The test article will be packaged in bottles capped with a child-resistant closure liner with an induction seal. Each subject will be assigned a subject number and provided with sufficient test article in standard packaging for the designated treatment period during the trial.

Each bottle of the test article will contain, at a minimum, the following information: the protocol number, subject identifiers (e.g., subject number and initials), the contents, the bottle number, an investigational test article disclaimer (e.g., Caution: New Drug Limited by United States law to investigational use), and the appropriate storage conditions for the test article.

Bottles of the test article will be contained in subject kits. When kits are dispensed to the subjects, the Subject Kit label must be completed entirely with the necessary information and recorded in the Test Article Accountability Log at the investigational site.

A 1.2 Test Article Storage and Preparation

Test articles will be stored under secure conditions until they are dispensed to the subjects. Test articles should be stored in accordance with the temperature specified on the label.

A 1.3 Dispensing Test Article

The test article must be dispensed only to trial subjects and only at trial sites specified on the signed 'Statement of Investigator' (e.g., Form FDA 1572 or equivalent) required by applicable regulations and guidelines.

Sufficient test article for the designated treatment period will be dispensed to the subject and the information recorded on the Test Article Accountability Log. The subjects will be instructed to bring all bottles of the test article (used and unused) to each clinic visit.

At each post-Baseline visit, site staff will collect all bottles (used and unused) of the test article, count the number of remaining tablets, and record the necessary information in the Test Article Accountability Log. Site staff will review the test article dosing procedure and subjects will be counseled on test article compliance, as necessary. Partially used bottles will be redispensed and additional bottles of the test article will be dispensed to the subject, as needed, to ensure that each subject has sufficient test article for the designated treatment period.

A 1.4 Test Article Supply Records at Trial Sites

It is the responsibility of the investigator to ensure that a current record of test article disposition is maintained. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of the person responsible for each product inventory entry/movement.
- Amount (number and units) dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-trial disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor.
- Amount destroyed at trial site, if applicable.

TI will provide forms to facilitate inventory control if the staff at the trial site does not have an established system that meets these requirements.

A 1.5 Dose Modifications

The subject should not modify the treatment regimen without consultation with the investigator. In the event that the investigator believes that dose modification is necessary (e.g., problems with tolerance), the subject's care should be discussed with the Medical Monitor prior to making any dose modifications. All dose modifications must be reported on the appropriate eCRF.

A 1.6 Documentation of Administration and Compliance

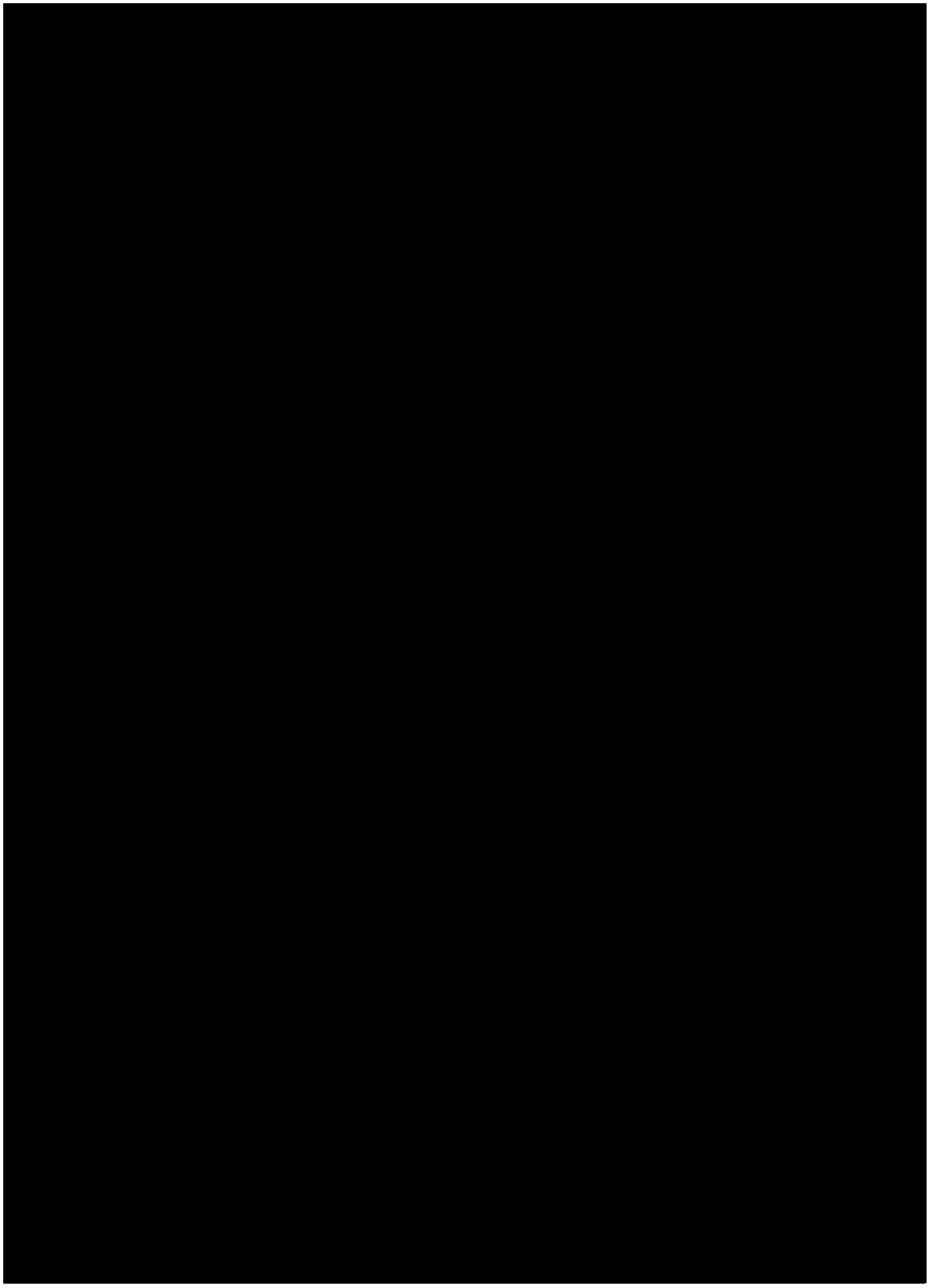
The date of the first and final dose of the test article will be recorded on the appropriate eCRF. An eCRF will also be used to record any changes from the dosing specified in the protocol (e.g., investigator directed reduction in dosing frequency or drug holiday).

A 1.7 Return and Destruction of Test Article Supplies

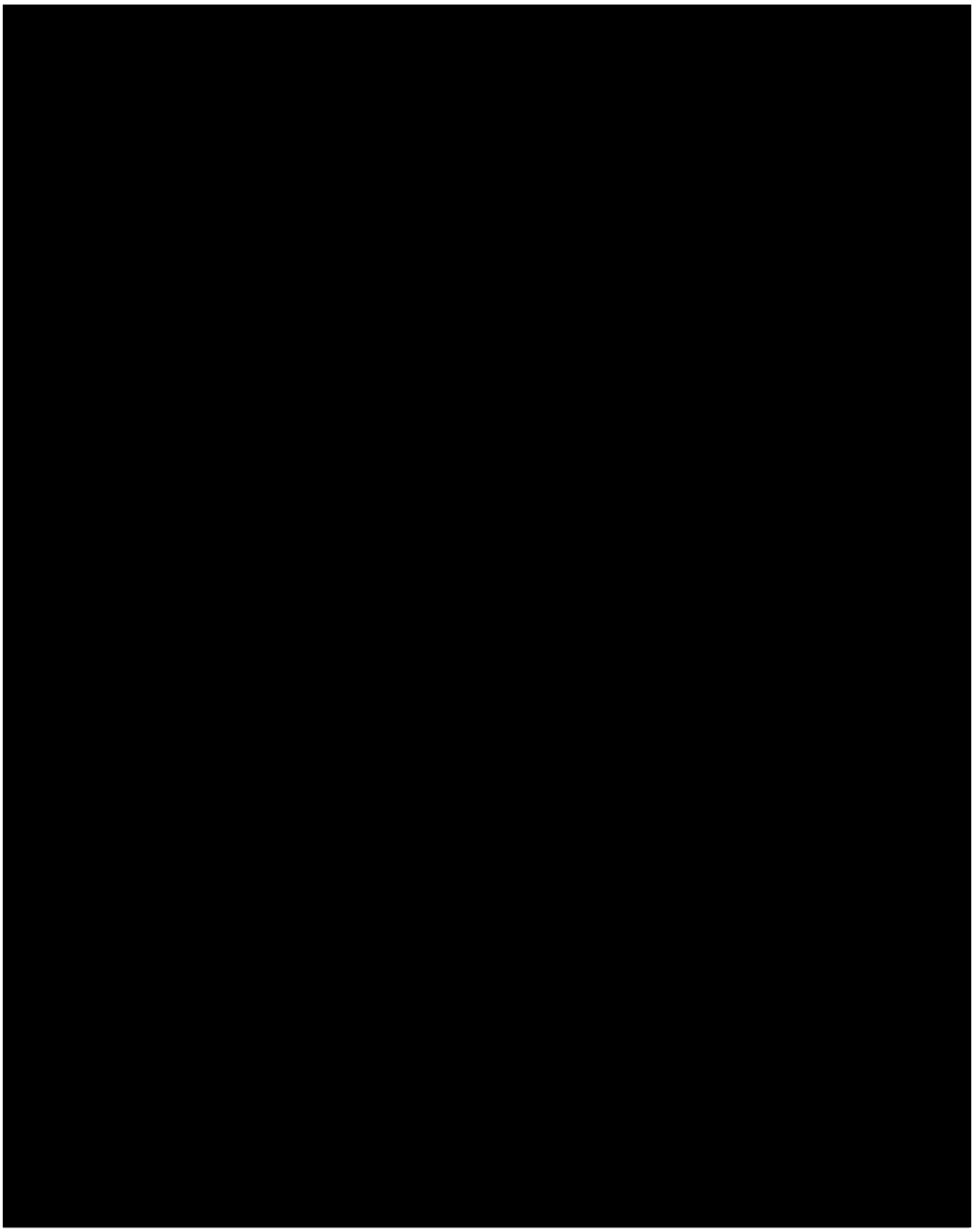
Upon completion or termination of the trial, all remaining test article containers must be a) returned to Sponsor or designee by a traceable method for final accountability and destruction or b) appropriately destroyed in accordance with applicable regulations with the provision of a certificate of destruction. All missing containers of test article must be explained on the completed Test Article Accountability Log. A copy of the Test Article Accountability Log and Label Pages (if applicable) will be returned to TI or designee.

APPENDIX 2 SAMPLE SUBJECT INSTRUCTION SHEET

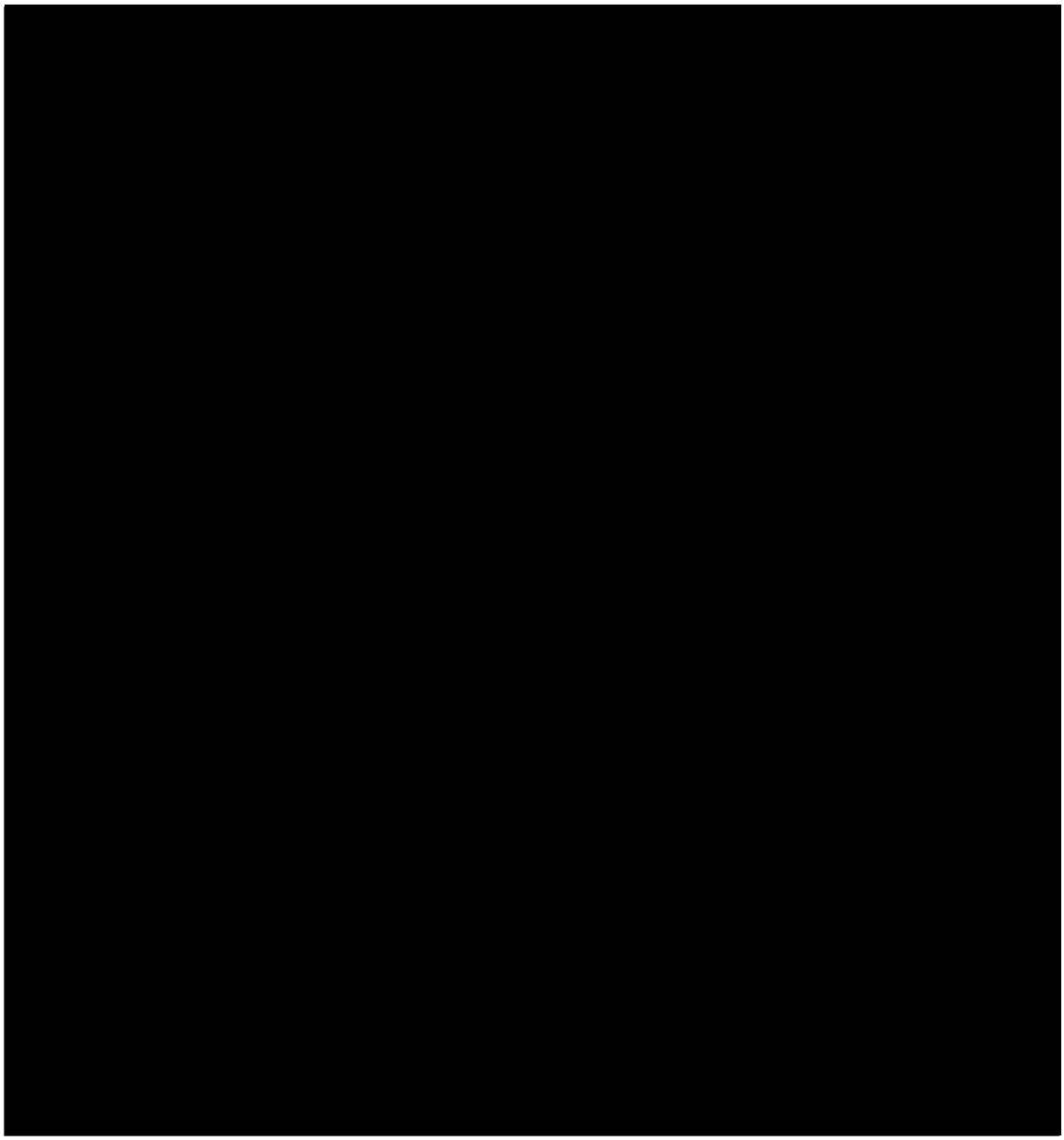
Copies of the following sample subject instructions will be provided to the study site. The investigator must give each subject a copy of this instruction sheet at Visit 2/Baseline.



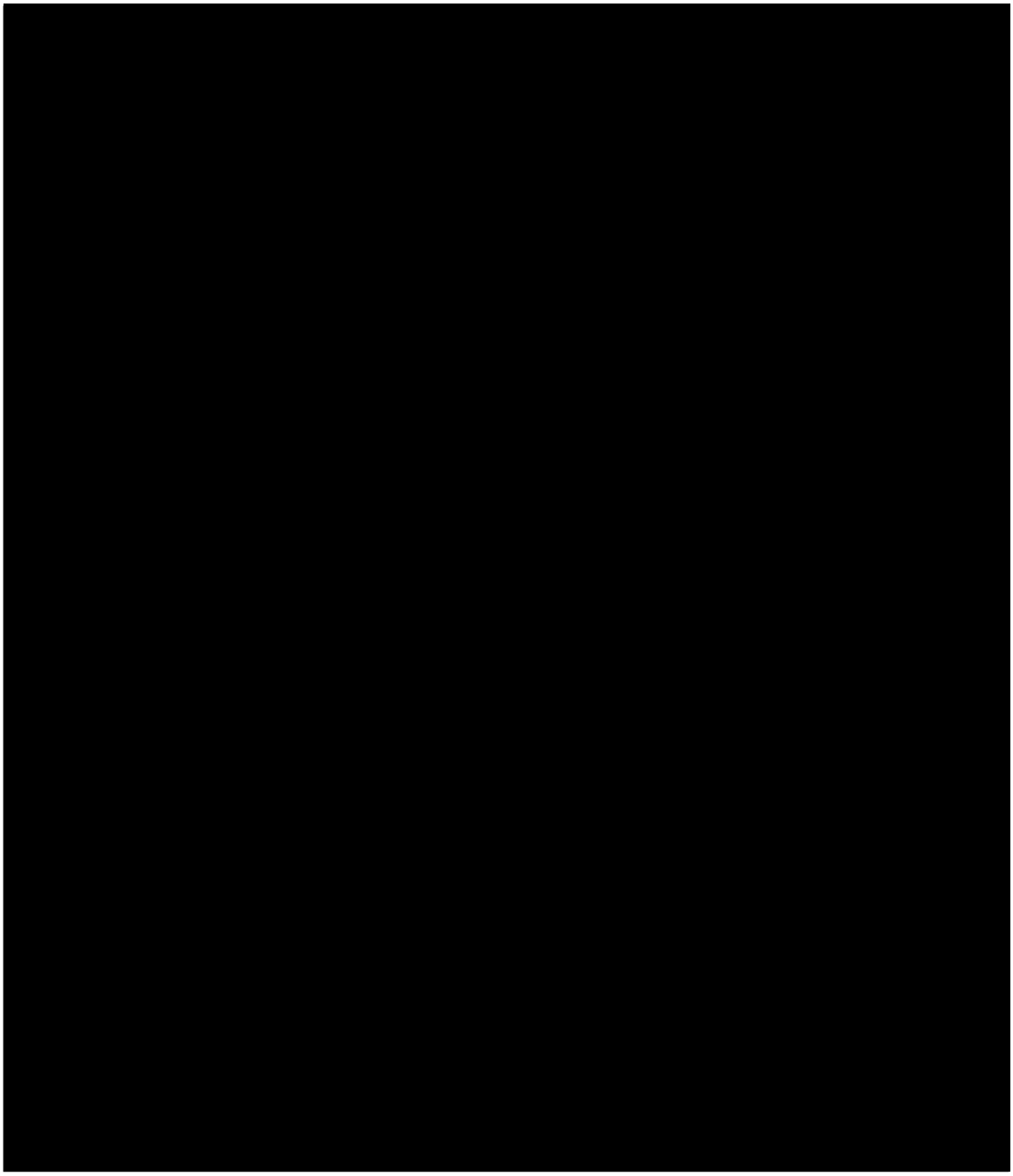
APPENDIX 3 PSORIASIS AREA AND SEVERITY INDEX

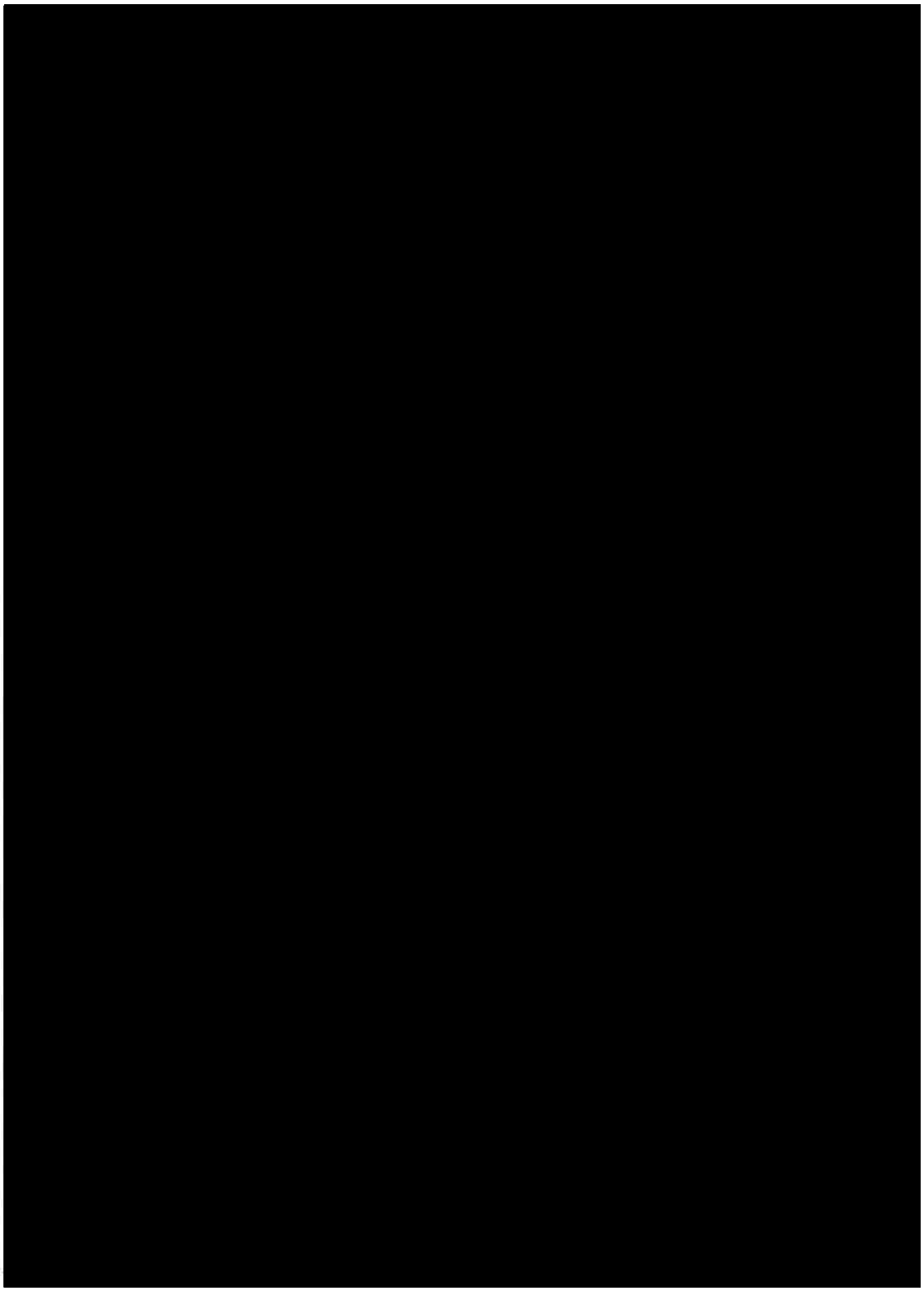


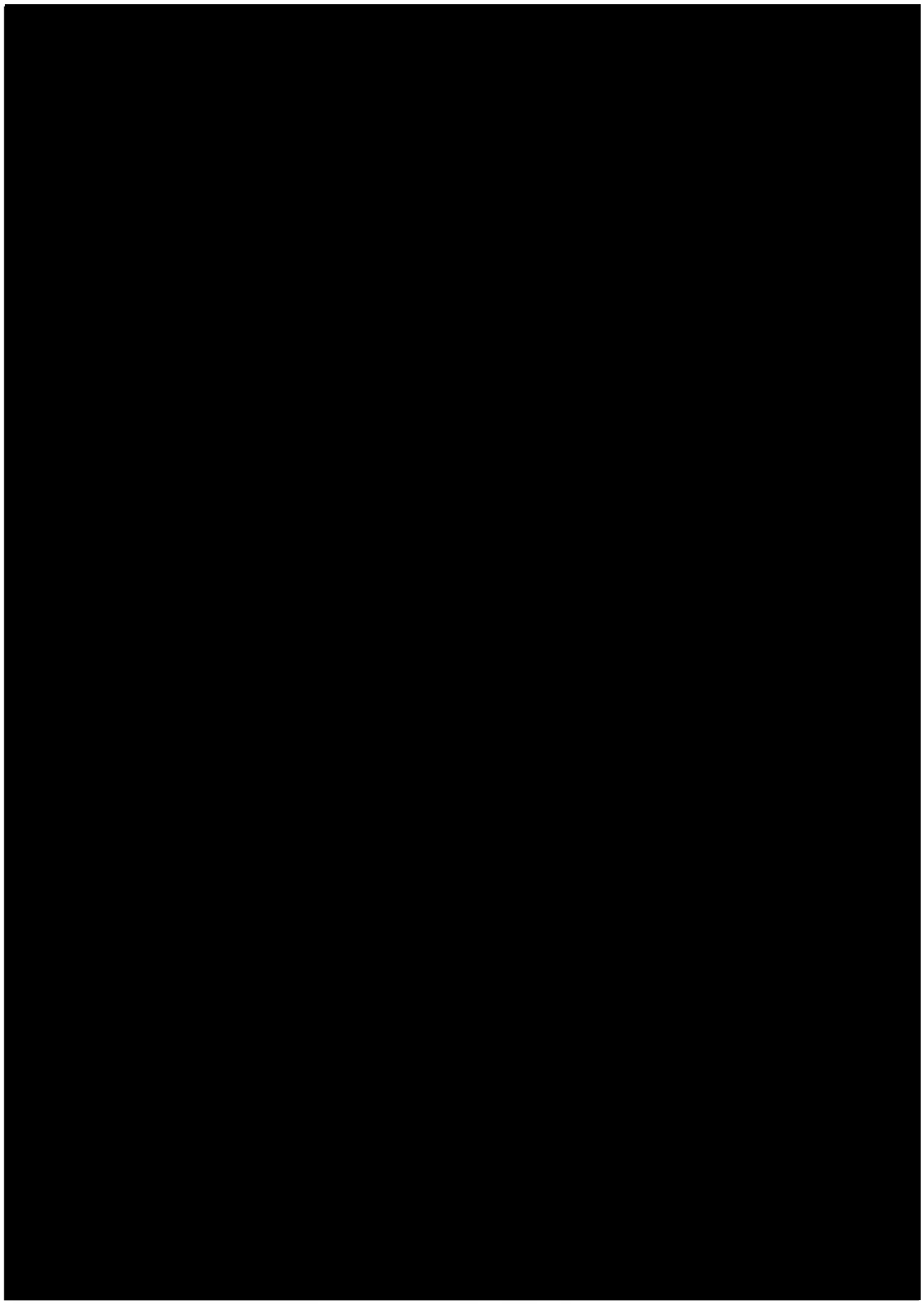
APPENDIX 4 PATIENT GLOBAL IMPRESSION OF CHANGE QUESTIONNAIRE

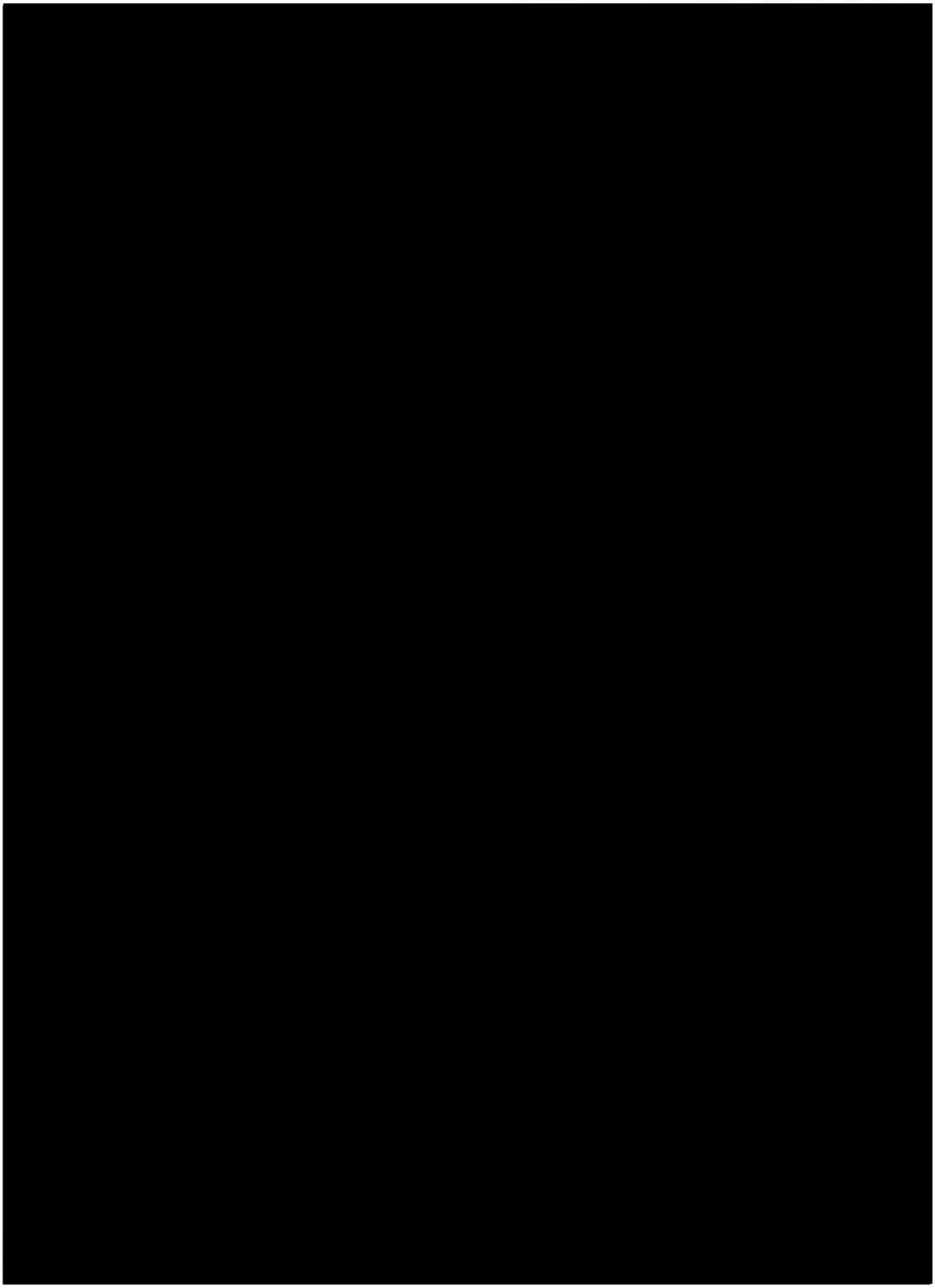


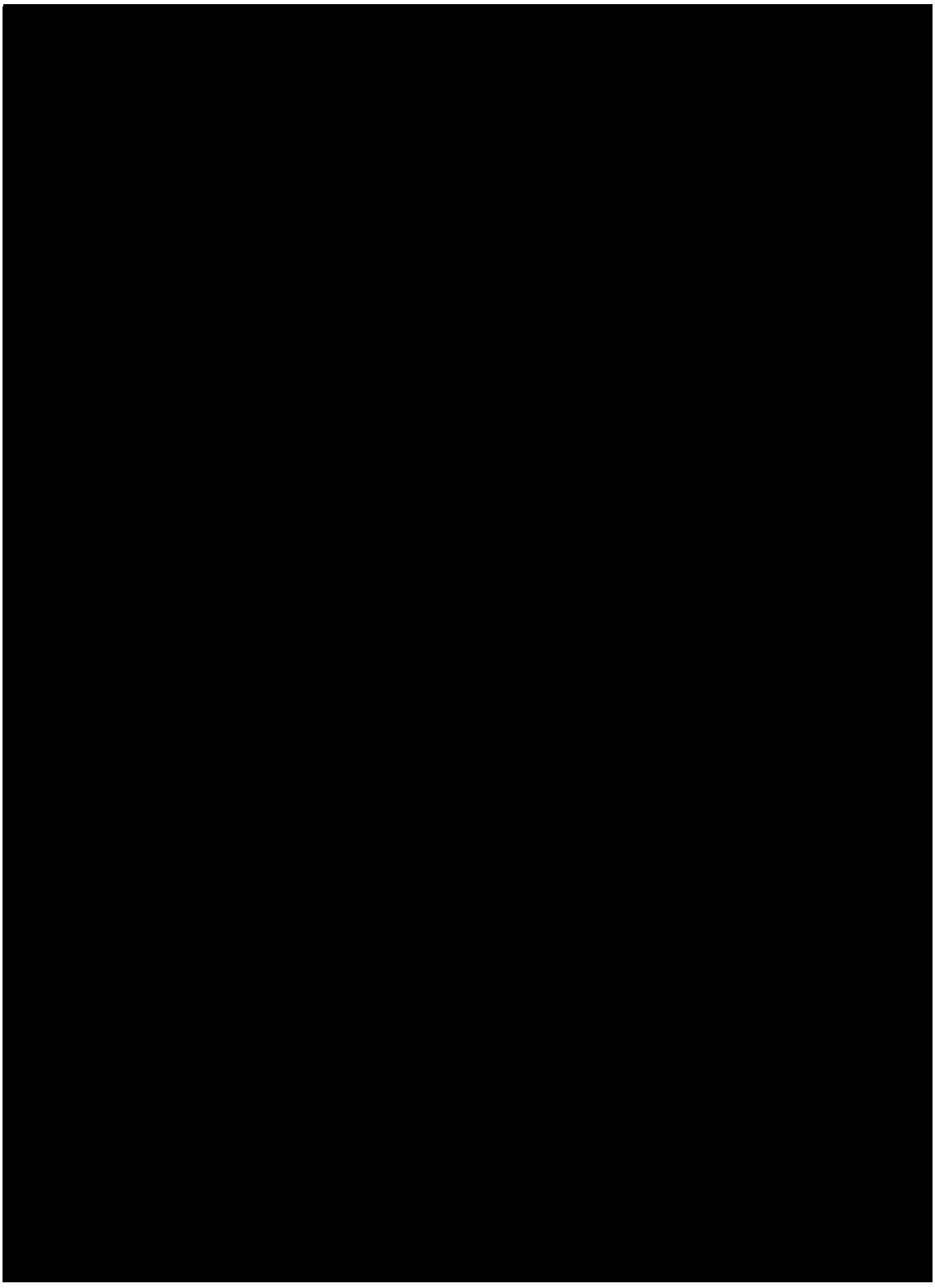
APPENDIX 5 PROTOCOL AMENDMENTS

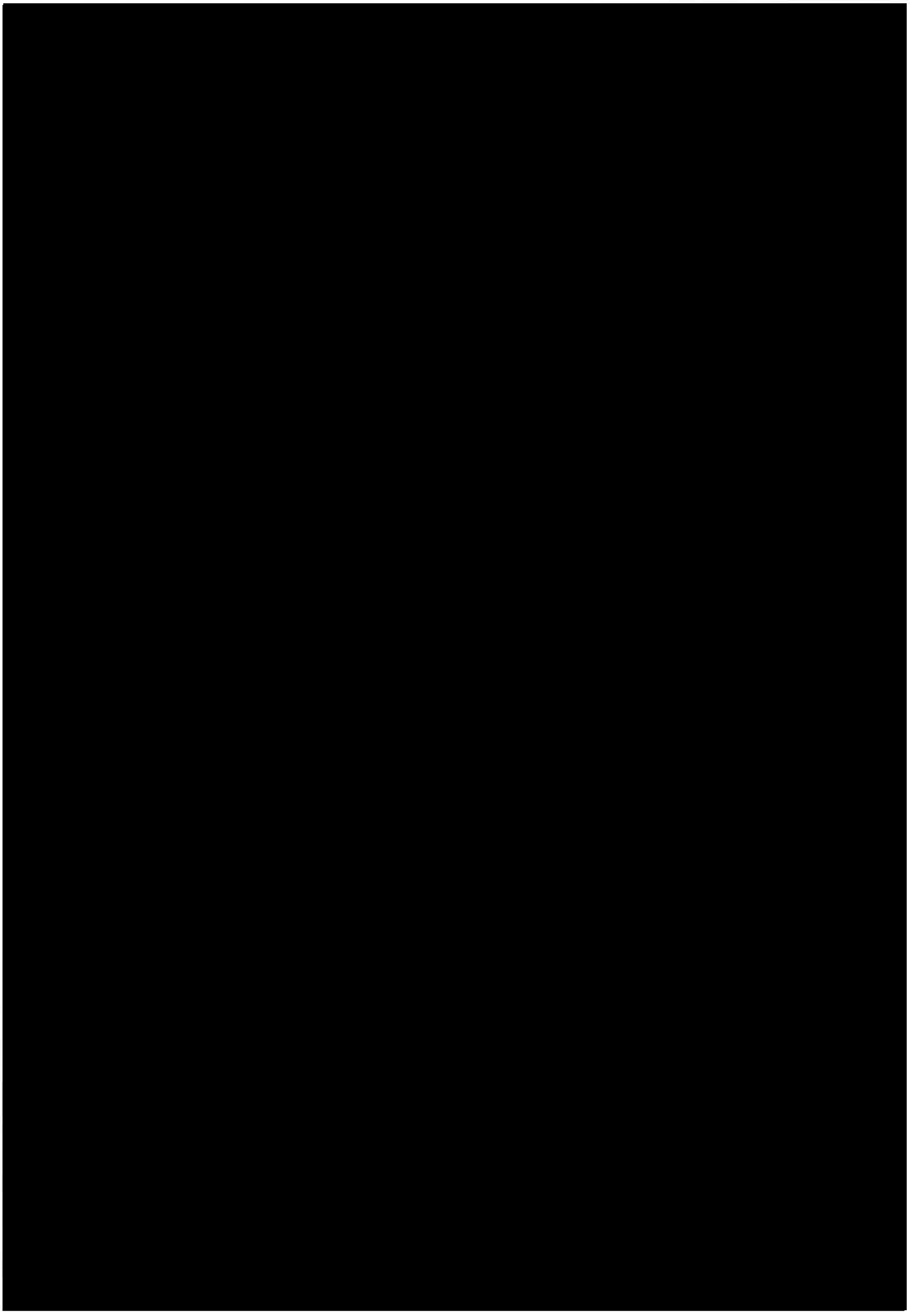


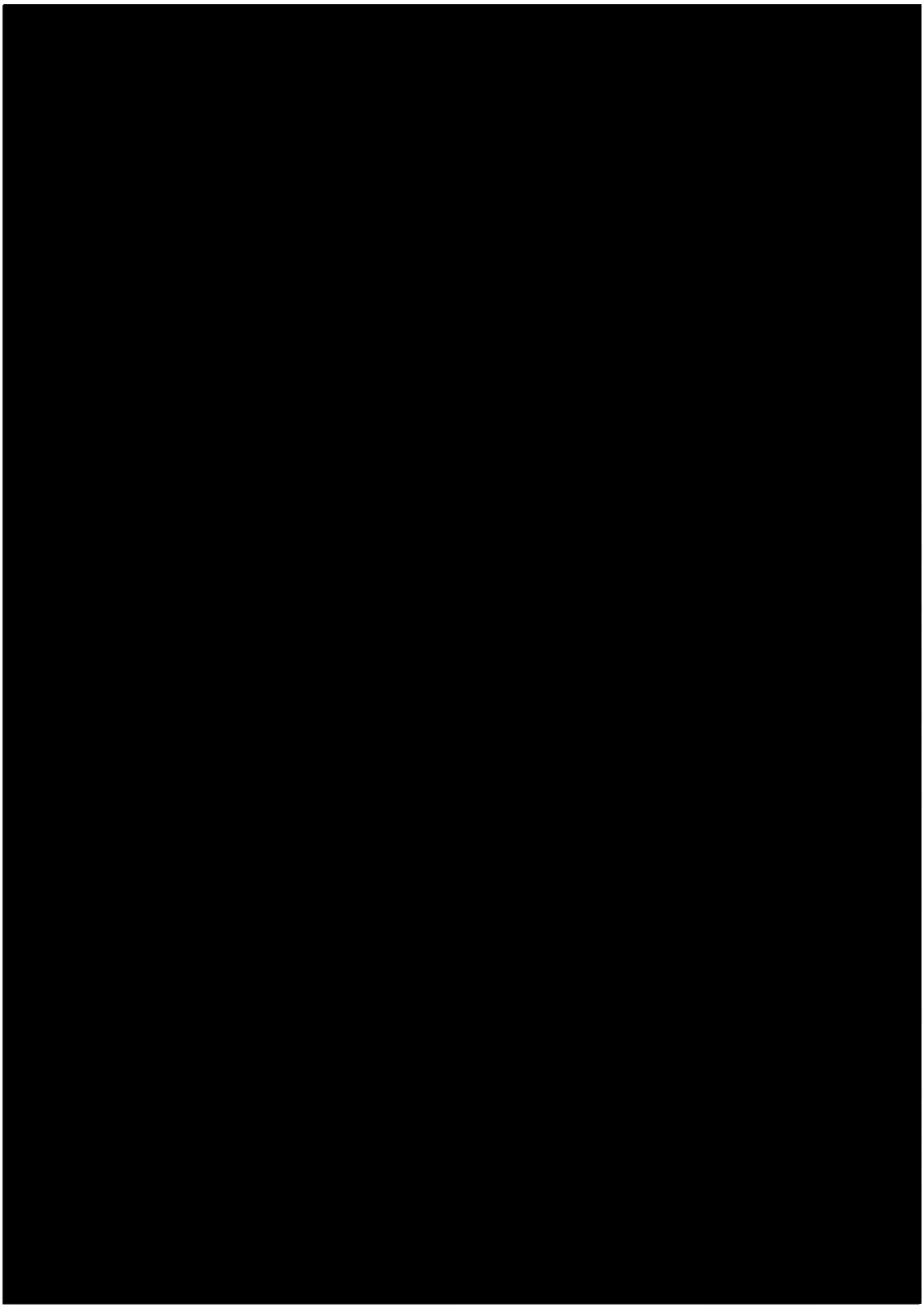


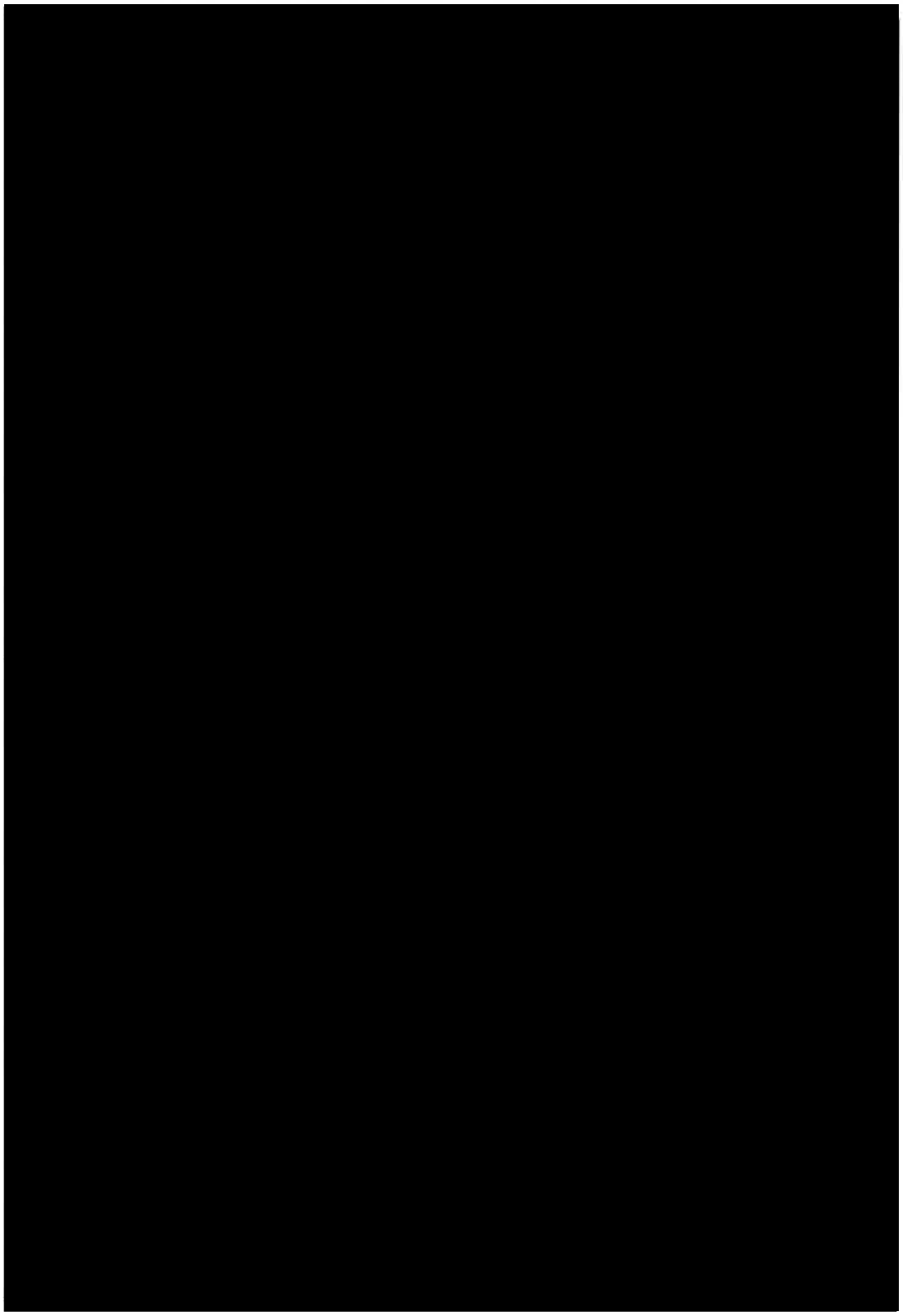


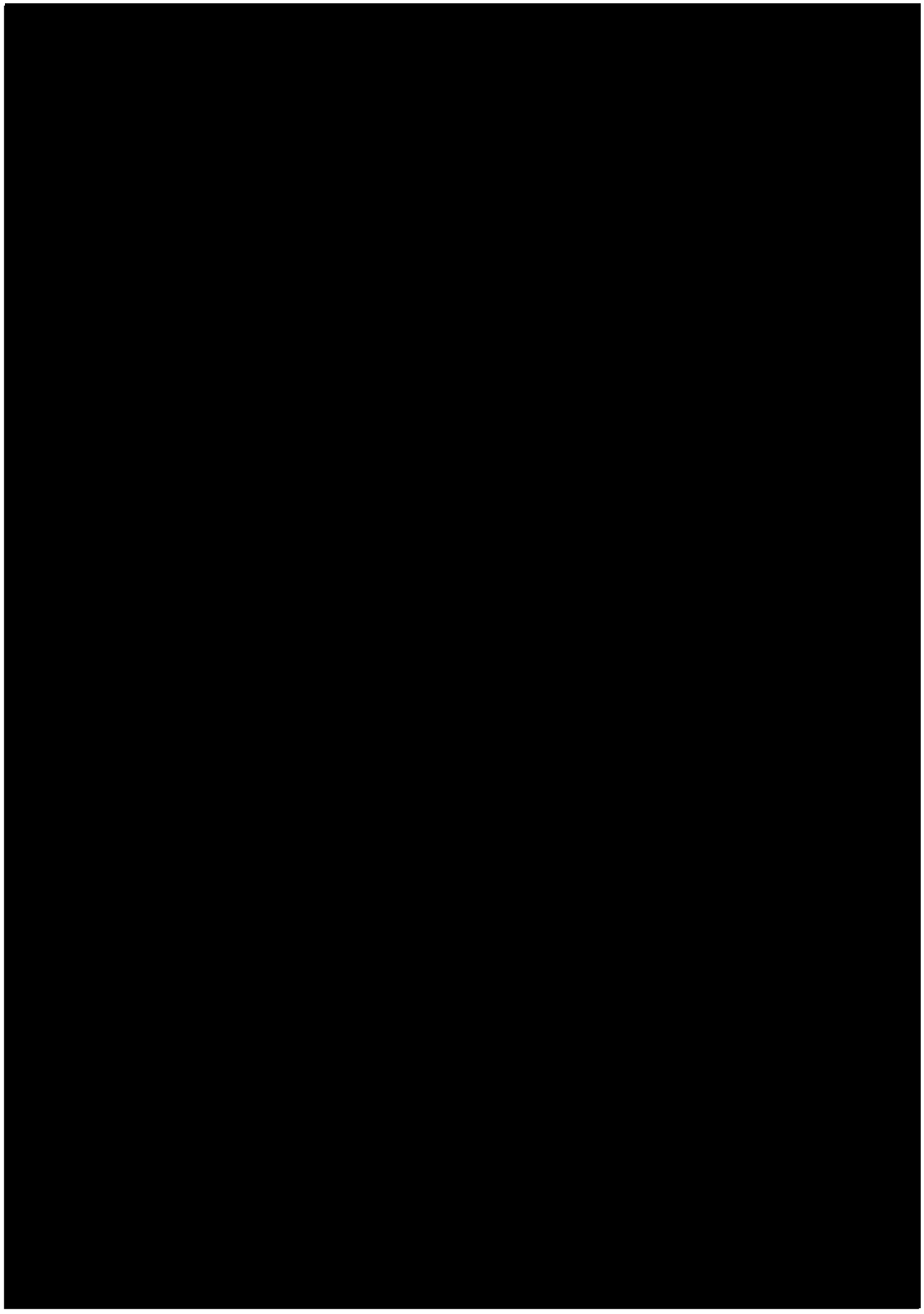


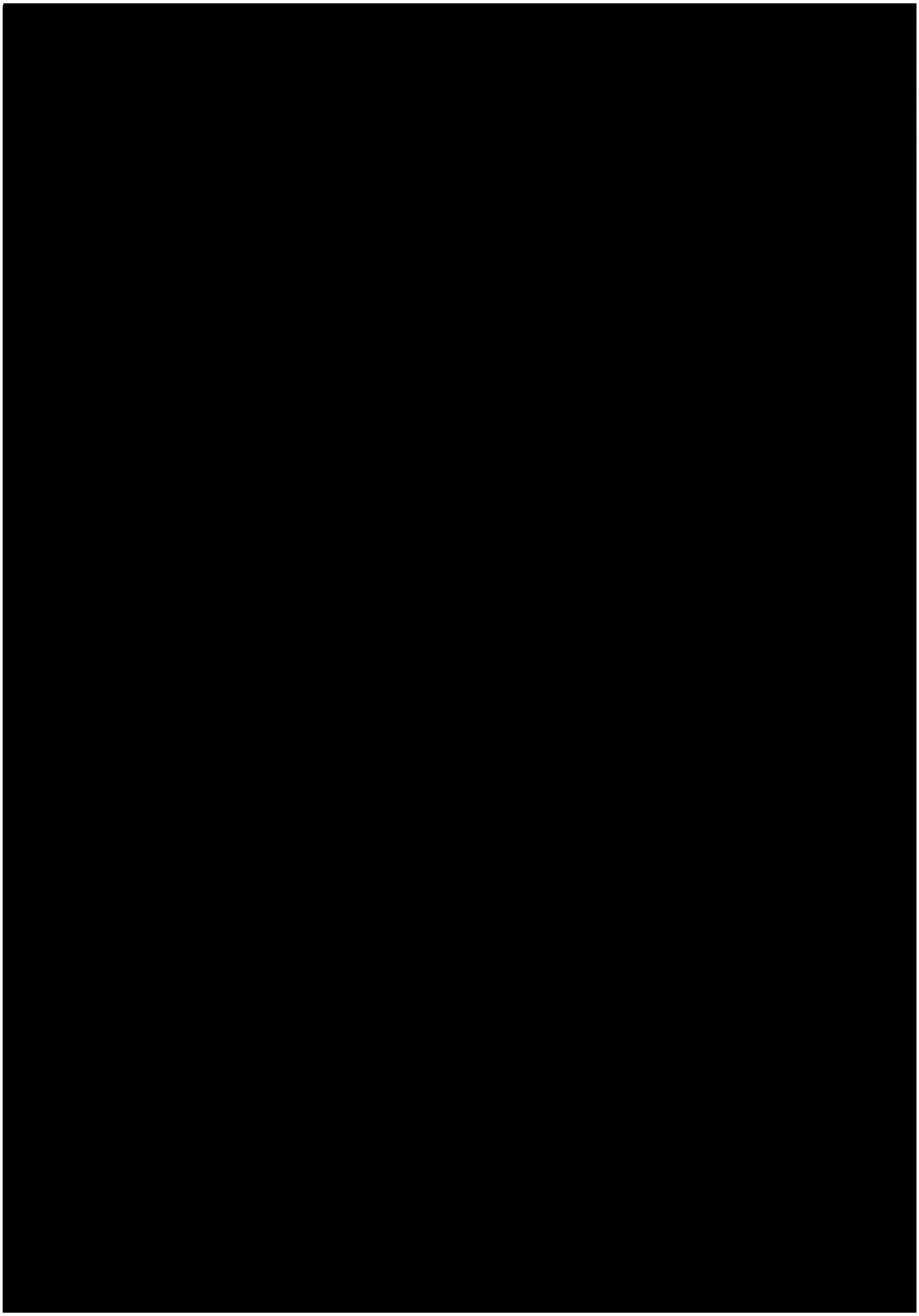


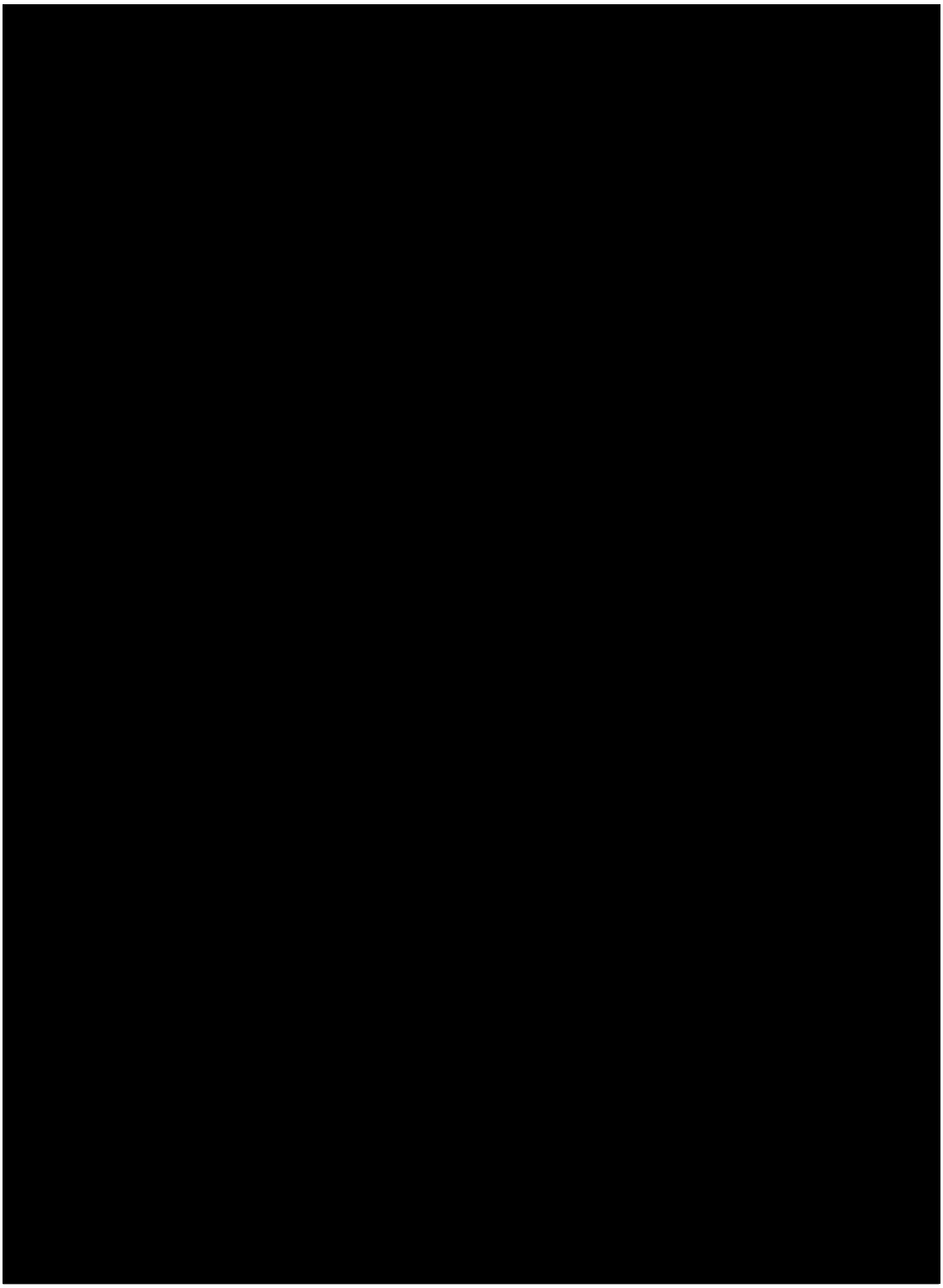


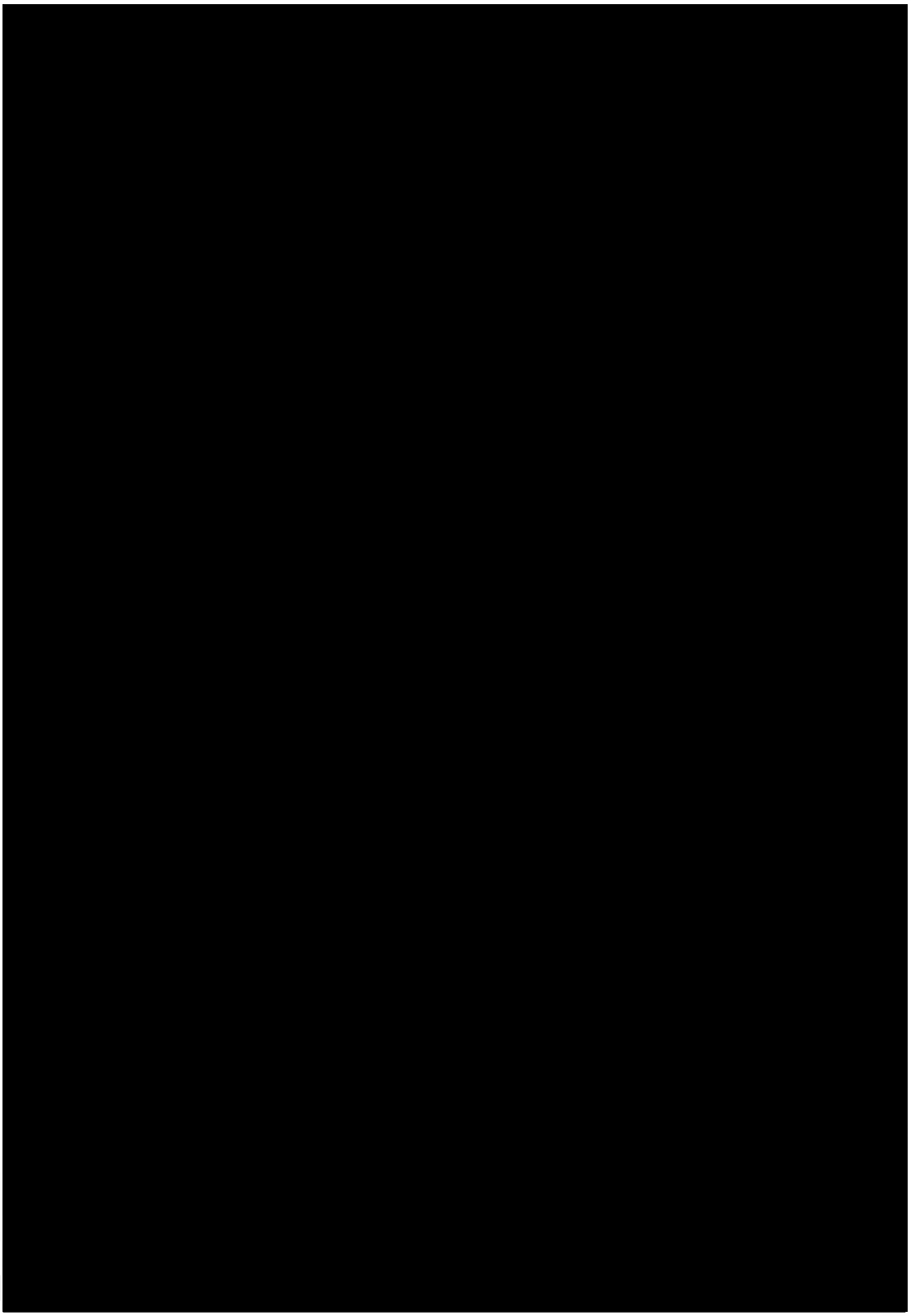


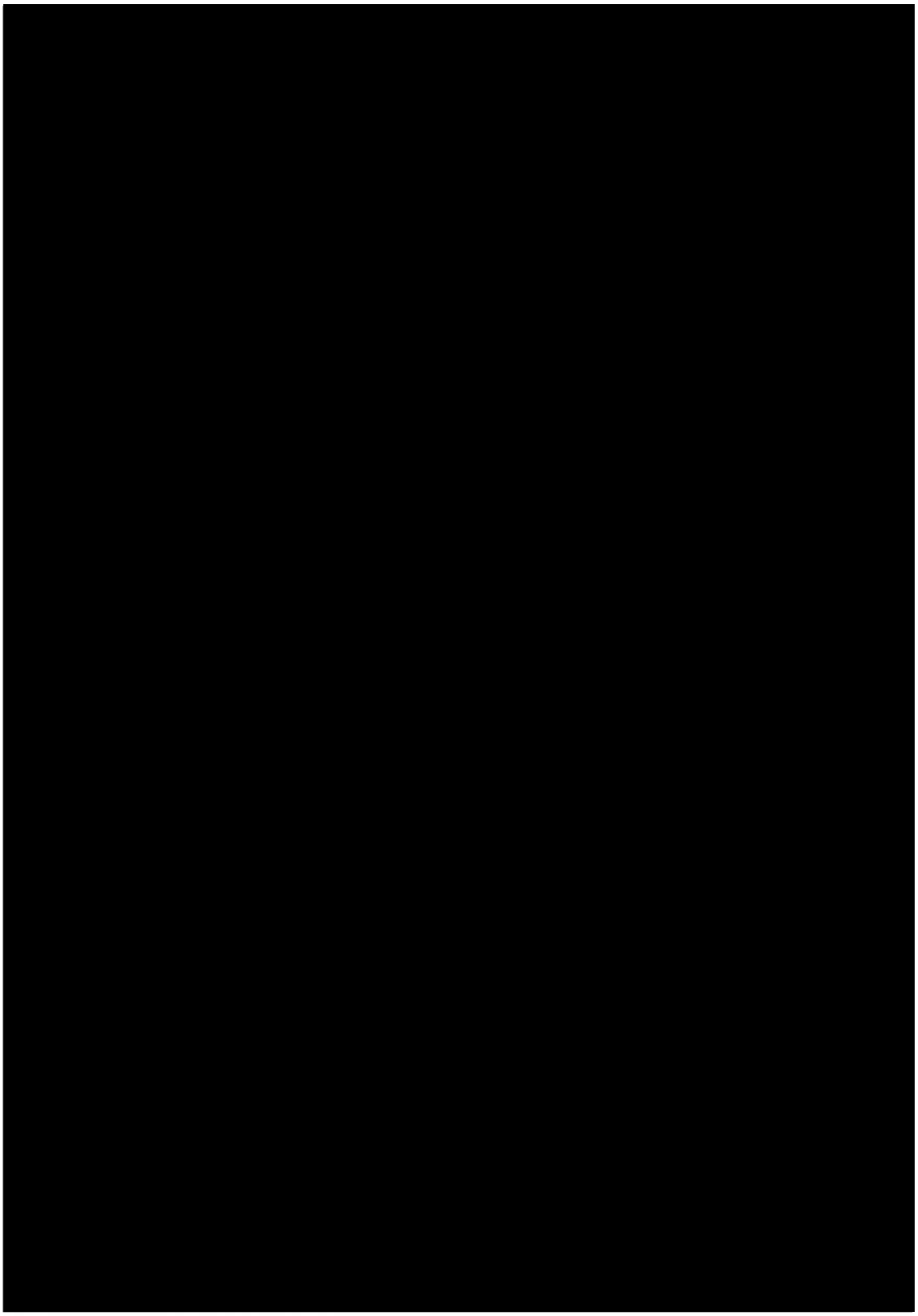


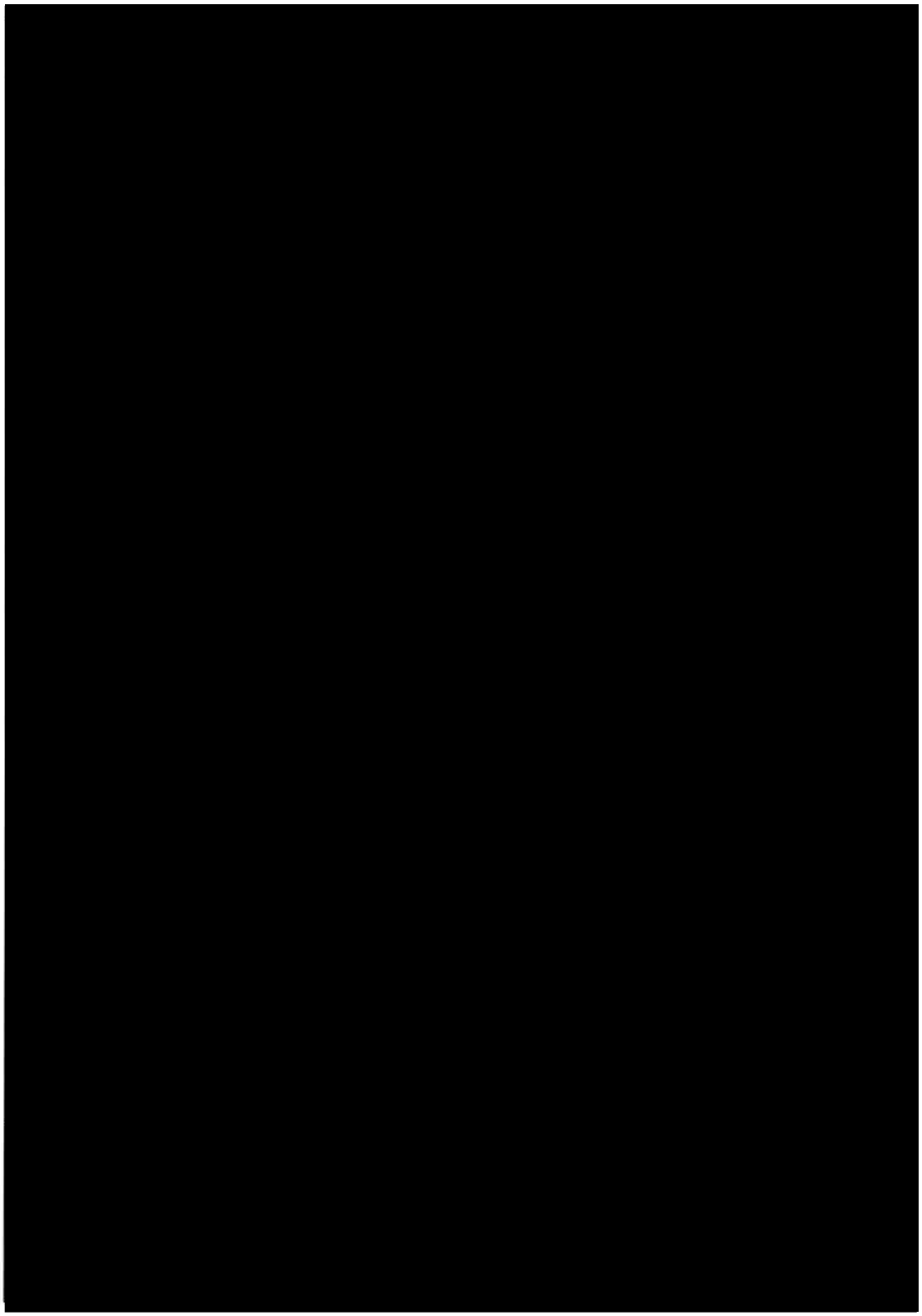


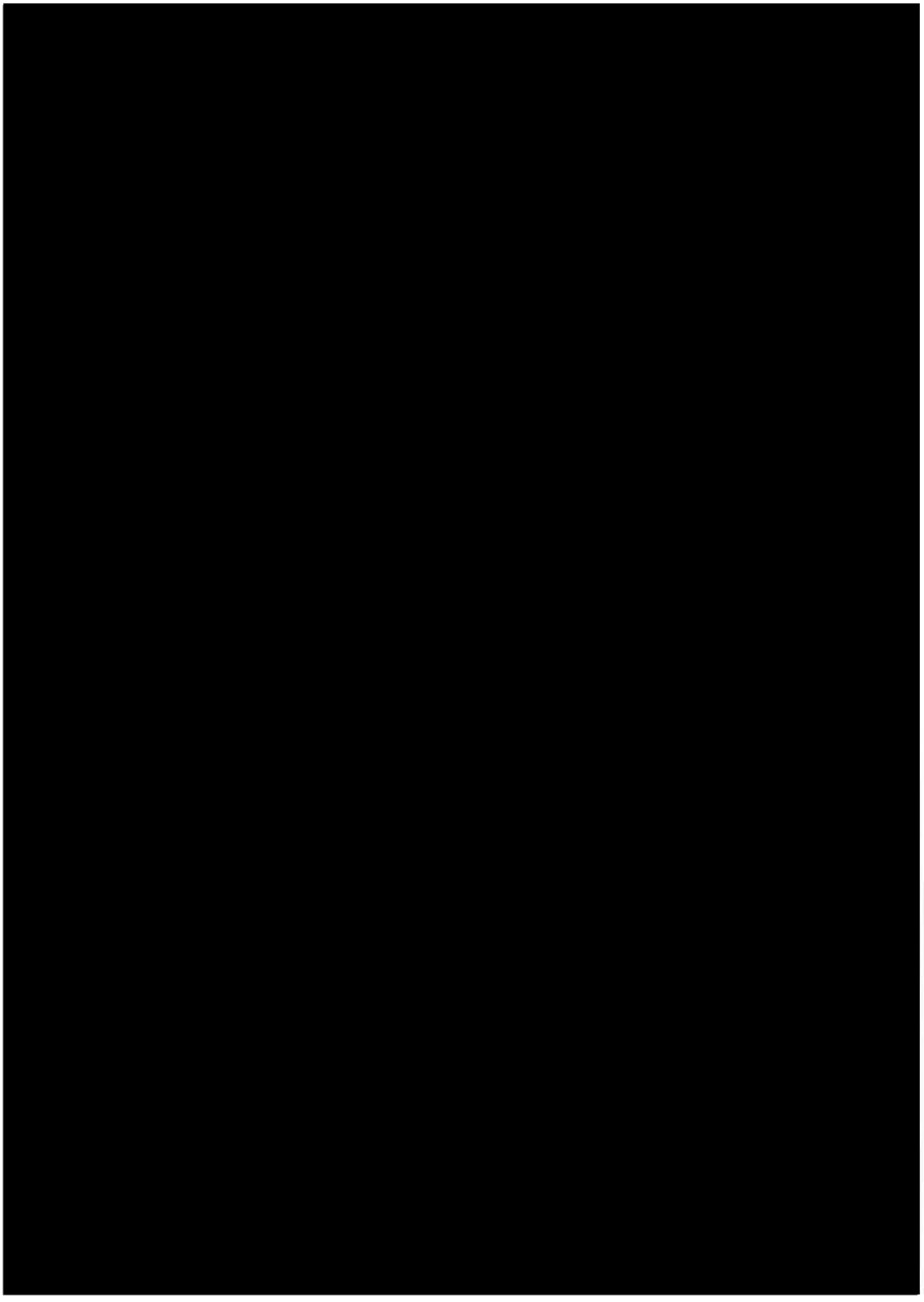


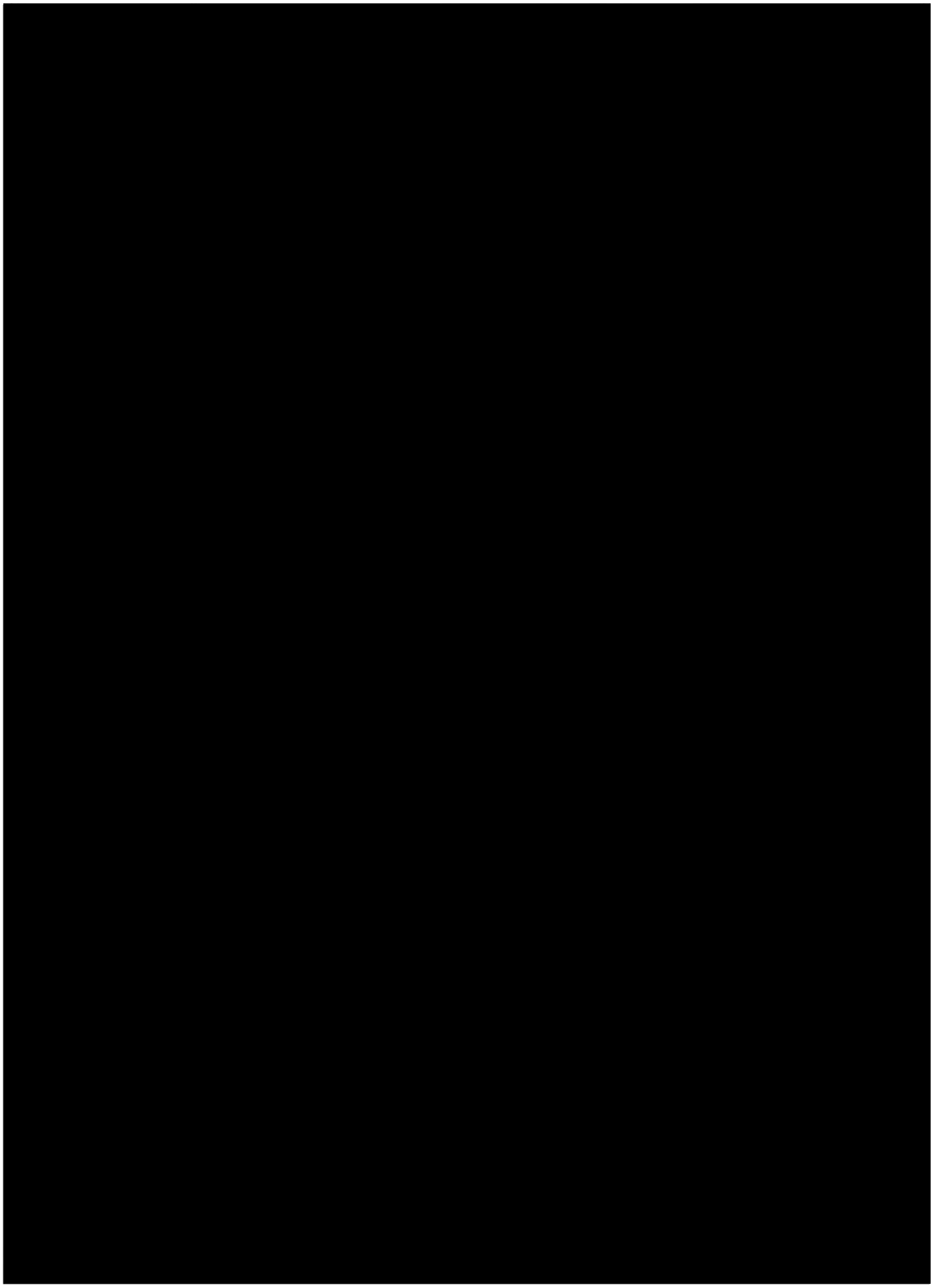












A 5.2 Protocol Amendment # 2