AMENDED CLINICAL TRIAL PROTOCOL 03

Protocol title:	**A Phase 2, open-label, multicenter, 2-stage sequential cohort, dose escalation study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of subcutaneous SAR442501 in pediatric participants with Achondroplasia**
Protocol number:	**DRI16646**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR442501**
Brief title:	**Safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of SAR442501 in pediatric participants with Achondroplasia**
Acronym:	**upreACH-2**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Developpement**
Legal registered address:	**82 avenue Raspail 94250 Gentilly France** **Local Sponsor for US: Sanofi US Services Inc** **55 Corporate Drive, Bridgewater, NJ 08807, USA**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	[redacted]
NCT:	NCT06067425
WHO:	U1111-1280-5374
EUDAMED:	Not applicable
EU trial number:	2023-503677-37
Other:	Not applicable

Date: 08-Apr-2024 Total number of pages: 176

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	All	08 April 2024, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02	All	01 December 2023, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01	All	28 August 2023, version 1 for review (electronic 1.0)
Original Protocol		28 February 2023, version 1 (electronic 2.0)

Amended protocol 03 (08 April 2024)

This Amended protocol 03 (Amendment 03) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or rights of the participants or the reliability and robustness of the data generated in the clinical trial.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to align with feedback received from a health authority (MHRA CTA).

Protocol amendment summary of changes

Section # and Name	Description of Change	Brief rationale
Section 10.1.5.1 Data monitoring committee	Brief summary of the committee composition added	To address MHRA CTA questions

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LIST OF ABBREVIATIONS

%CV:	coefficient of variation
25(OH)D:	25-hydroxy-vitamin D
ACH:	achondroplasia
AEs:	adverse events
AESIs:	adverse events of special interest
AGV:	annualized growth velocity
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AP:	anterior-posterior
AST:	aspartate aminotransferase
AUC:	area under curve
BIW:	twice weekly
BMI:	body mass index
C_{ave_ss}:	average steady state concentration
C_{max}:	maximum serum concentration observed
[redacted]	
CSA:	central sleep apnea
CSCR:	central serous chorioretinopathy
CSICF:	Core Study Informed Consent Form
CSR:	central serous retinopathy
CTX:	collagen-Type I C-telopeptide
DBL:	database lock
DMC:	data monitoring committee
DTP:	direct to participant
DXA:	dual energy X-ray absorptiometry
eCRF:	electronic case report form
ENT:	ear, nose, throat
FGFR:	fibroblast in growth factor receptor
FIH:	first in human
GLP:	Good Laboratory Practice
IB:	Investigator's brochure
ICH-GCP:	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use Good Clinical Practice
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	interactive response technology
ITT:	intent-to-treat
MAD:	multiple ascending dose
MOA:	mechanism of action
MRI:	magnetic resonance imaging
NHP:	nonhuman primates
NMPA:	National Medical Products Administration

NOAEL:	no observed adverse effect level
OCT:	ocular coherence tomography
OSA:	obstructive sleep apnea
P1NP:	procollagen 1 intact N-terminal peptide
PA:	posterior-anterior
PCSA:	potentially clinically significant abnormalities analyses
PD:	pharmacodynamic
PedsQL:	pediatric quality of life
PK:	pharmacokinetic
PopPK:	population PK
PT:	preferred term
Q3Q4:	every 3 days alternating with every 4 days
QD:	once a day
QoL:	quality of life
QSP:	quantitative systems pharmacology
RPED:	retinal pigment epithelia detachment
RSI:	reference safety information
SAD:	single ascending dose
SAEs:	serious adverse events
SC:	subcutaneously
SD:	standard deviation
SDB:	sleep disordered breathing
SoA:	schedule of activities
STEMS:	Screening Tool for Everyday Mobility and Symptoms
SUSAR:	suspected unexpected serious adverse reaction
TE:	treatment-emergent
TEAEs:	treatment-emergent adverse events
TSH:	thyroid stimulating hormone
ULN:	upper limit of normal
WOCBP:	woman of childbearing potential

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 2, open-label, multicenter, 2-stage sequential cohort, dose escalation study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of subcutaneous SAR442501 in pediatric participants with Achondroplasia

Brief title:

Safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of SAR442501 in pediatric participants with Achondroplasia

Regulatory agency identifier number(s):

IND:	[redacted]
NCT:	NCT06067425
WHO:	U1111-1280-5374
EUDAMED:	Not applicable
EU trial number:	2023-503677-37
Other:	Not applicable

Rationale:

SAR442501 is a monoclonal antibody that binds the [redacted] of Fibroblast Growth Factor Receptor 3 (FGFR3), which directly inhibits FGFR3 activity, thereby preventing the inhibition of chondrocyte proliferation and differentiation. This is expected to correct the underlying skeletal pathophysiology of Achondroplasia (ACH) and therefore to improve not only growth velocity but also clinically relevant complications, including body proportionality and foramen magnum size.

Nonclinical studies have demonstrated preliminary efficacy of SAR442501 on growth. Specifically, inhibition of the [redacted] with SAR442501 and [redacted] (mouse surrogate Fab), in a mouse model, resulted in increased chondrocyte proliferation and differentiation in the growth plate and improvement in skeletal parameters (increased growth plate volume, growth plate thickness and increased bone length in the skull, foramen magnum area, vertebral column, and long bones). Similar effects on bone growth were observed after repeated subcutaneous dosing in healthy juvenile NHP.

The completed Phase 1, first in human (FIH) single and multiple ascending dose (MAD) studies (TDU16639/TDR16640) demonstrated that SAR442501 is safe and well tolerated in healthy adult volunteers when administered subcutaneously (SC) at doses of [redacted] twice weekly (BIW) for 29 days. There were 18 cases of hyperphosphatemia in SAR442501-treated and 1 case in placebo-treated participants. All hyperphosphatemia events were mild (Grade 1) and asymptomatic, did not require treatment, resolved spontaneously, and did not result in investigational medicinal product (IMP)

discontinuation. Taken together, the efficacy findings from the preclinical studies and safety results from the Phase 1 studies support the initiation of this first study of SAR442501 in pediatric participants with ACH. All eligible participants will have participated in the OBS16647 study (Section 5.1 Inclusion criteria), a non-interventional study designed to collect longitudinal baseline growth measurements.DRI16646 is designed to assess the safety, tolerability, and efficacy of BIW subcutaneous SAR442501 administration to pediatric participants from birth to age <12 years with ACH. This study will assess the effects of SAR442501 in improving linear growth and also clinically important complications of ACH, including body proportionality and foramen magnum size. The study will be divided into 2 stages.

In Stage 1, efficacy will be assessed by change from baseline to Week 26 and Week 52 in those between ages ≥3 to <12 years in annualized growth velocity (AGV) Z-score, AGV, height Z-score, and body proportions. In Stage 2, efficacy will be assessed by change from baseline to Week 26 and Week 52 in those from birth to age <3 years in AGV Z-score, AGV, height Z-score, body proportions, and foramen magnum parameters (at Week 52 only). In both stages, additional secondary endpoints will include pharmacokinetic (PK) and pharmacodynamic (PD) parameters, changes from baseline to Week 26 and 52 in immunogenicity, neurological exam, pediatric quality of life (PedsQL), Screening Tool for Everyday Mobility and Symptoms (STEMS) rating score, and developmental milestone achievement (in those ages birth to <3 years at Week 52 only). [redacted].

Objectives and endpoints:

Objectives	Endpoints
Primary	
To assess the safety and tolerability of SAR442501 administered SC twice weekly for 52 weeks in participants from birth to <12 years of age with ACH	The occurrence of AEs, SAEs, and AESIs during the TE period
Secondary	
To evaluate changes in growth parameters following twice weekly SC injections of SAR442501	Change from baseline to Week 26 and Week 52 in AGV Z-score Change from baseline to Week 26 and Week 52 in AGV (cm/year) Change from baseline to Week 26 and Week 52 in height Z-score
To evaluate changes in body proportionality following twice weekly SC injections of SAR442501 for 52 weeks	Change from baseline to Week 26 and Week 52 in the following calculated ratios: - Upper to lower body segment ratio - Upper to lower extremity ratio - Sitting to standing height ratio (crown-to-rump length to total length for infants) - Arm span to height ratio - Upper arm to forearm length ratio - Upper leg to lower leg ratio - Head circumference to height ratio

Objectives	Endpoints
To evaluate changes in foramen magnum parameter via magnetic resonance imaging (MRI) following twice weekly SC injections of SAR442501 (Stage 2 only)	Change from baseline to Week 52 in brainstem, skull, and spine morphometric and volumetric parameters in participants birth to age <3 years (Stage 2 only)
To evaluate changes in health-related QoL as measured by the PedsQL Inventory Generic Core Scale	Change from baseline to Week 26 and Week 52 in social, emotional, and school functioning scores as well as the Psychosocial Health Summary Score, Physical Health Summary Score, and Total Score pooled across instrument versions by age
To evaluate changes in mobility as measured by the STEMS	Change from baseline to Week 26 and Week 52 (those ages ≥5 at enrollment) in mobility and symptom rating (STEMS) score
To evaluate changes in fatigue as measured by the PedsQL Multidimensional Fatigue Scale	Change from baseline to Week 26 and Week 52 in general fatigue, sleep/rest fatigue and cognitive fatigue scores and Total Score pooled across instrument versions by age
To evaluate changes in pain as measured by the PedsQL Pediatric Pain Questionnaire	Change from baseline to Week 26 and Week 52 in PPQ score pooled across instrument versions by age
To collect developmental milestone data as measured by the Achondroplasia Developmental Recording Form	Change from baseline to Week 52 (those ages birth to <3 years at enrollment) in achievement of gross motor, fine motor, communication, and feeding milestones
To evaluate the pharmacokinetic profile of SAR442501 following twice weekly SC injections	Plasma concentration and parameters of SAR442501
• To characterize changes from baseline in bone/collagen biomarkers following twice weekly SC injections of SAR442501	Change from baseline to Week 26 and Week 52 in CXM, osteocalcin, bone-specific alkaline phosphatase, P1NP, CTX levels
To evaluate the immunogenicity of SAR442501 administered as twice weekly SC injections	Number of participants with TE anti-drug antibodies (ADA), number of treatment-induced ADAs, number of treatment-boosted ADAs from baseline to Week 26 and Week 52, ADA status at each visit, ADA titer at each visit
To evaluate clinical signs and symptoms of foramen magnum stenosis following twice weekly injections of SAR442501 (Stage 2)	Number and percentages of participants with changes in neurological examination findings from baseline to Week 26 and Week 52 (Stage 2 only)
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: ACH = Achondroplasia; ADA = Anti-drug antibody; AEs= adverse events; AESIs = adverse events of special interest; AGV = Annualized growth velocity; CTX = collagen-Type 1 C-Telopeptide; CXM = collagen X biomarker; P1NP = procollagen type 1 N-terminal propeptide; PedsQL = Pediatric Quality of Life; [redacted]; PPQ= present pain and worst pain rating; MRI= magnetic resonance imaging; QoL = Quality of life; SAEs= serious adverse events; SC = subcutaneous; STEMS = Screening Tool for Everyday Mobility and Symptoms; TE = Treatment-emergent.

For China, please see Section 10.8 details.

Overall design synopsis:

This is a Phase 2 open-label, multicenter, 2-stage sequential cohort dose escalation study to evaluate the safety, tolerability, PK, PD, and efficacy of SAR442501 in pediatric participants with genetically confirmed ACH. Participants will be enrolled across approximately 15 sites. However, this site number is subject to change based on recruitment.

Participants who have completed at least 24 weeks (or 12 weeks for those younger than age 6 months at the time of OBS16647 enrollment) of data collection in the OBS16647, a longitudinal study to evaluate growth measurements and digital biomarkers in pediatric participants with ACH, will be eligible to enroll in this DRI16646 study (see inclusion/ exclusion criteria in Section 5).

The study will have two stages:

- In Stage 1 pediatric participants between the ages ≥3 to <12 years will enroll in a 52-week sequential cohort dose escalation period (primary treatment period) followed by an extended treatment period.
- In Stage 2 pediatric participants between the ages birth to <3 years will enroll in a 52-week sequential cohort dose escalation period (primary treatment period) followed by an extended treatment period.

In both stages, after the Week-52 visit, participants will enter the extended treatment period. During the extended treatment period, each participant will return for on-site visits every 12 weeks until the last participant enrolled in the study completes 52 weeks of the extended treatment period. Therefore, the duration of the extended treatment period will vary per participant. It will last between approximately 52 and 216 weeks.

In Stage 1, the participants will be divided into 2 age cohorts based on the ages of participants at the time of enrollment (date of first dose of IMP), and each age cohort will be divided into [redacted] subgroups [redacted]. Cohort 1 will include children with ACH between the ages of ≥6 to <12 years, and Cohort 2 will include children with ACH between the ages of ≥3 to <6 years.

In Stage 2, the participants (Cohort 3) will be between birth and age <3 years at the time of enrollment (date of first dose of IMP). These participants will be divided into [redacted] subgroups [redacted].

Enrollment will proceed as follows (see Figure 1):

Stage 1:

Initial dosing with [redacted] will occur in Cohort 1A, comprising the oldest participants (ie, between ≥6 and <12 years). Two participants in Cohort 1A will be enrolled and monitored. The accumulated safety data, including treatment-emergent adverse events (TEAEs) will be reviewed by the data monitoring committee (DMC) after both participants have completed at least 8 weeks of treatment. After review and approval by the DMC, then the following cohorts/

subgroups may open for enrollment in the manner detailed below:

- Cohort 1B: 2 participants between the ages ≥6 and <12 years will be enrolled to receive the dose of [redacted].
- Cohort 1C: After the 2 participants have been enrolled in Cohort 1B, then the next 12 participants eligible between the ages of ≥6 and <12 years will be randomized in a [redacted] manner into Cohort 1C to receive either [redacted] of study intervention. No additional DMC meeting is required between the opening of Cohorts 1B and 1C.
- Cohort 2A: In parallel with Cohort 1B enrollment, Cohort 2A enrollment will start: 2 participants between the ages ≥3 and <6 years will be enrolled to receive the dose of [redacted].

The accumulated safety data available from all these cohorts (Cohorts 1A, 1B, 1C, and 2A), including TEAEs, will be reviewed by the DMC after both participants in Cohorts 1B and 2A have completed at least 8 weeks of treatment. If the stopping criteria are not met, and after review and approval by the DMC (see Section 10.1.5.2 Study stopping criteria), the following may occur:

- Cohort 2B: 2 participants between the ages of ≥3 and <6 years will be enrolled to receive the dose of [redacted].
- Cohort 2C: After the 2 participants have been enrolled in Cohort 2B as above, then the next 4 participants eligible between the ages of ≥3 and <6 years will be randomized in a [redacted] manner into Cohort 2C to receive [redacted] the dose of [redacted] No additional DMC meeting is required between the opening of Cohorts 2B and 2C.

The accumulated safety data available from all cohorts (Cohorts 1A, 1B, 1C, 2A, 2B, and 2C) including TEAEs, will be reviewed by the DMC after all participants in Cohorts 1A, 1B, 1C, 2A, 2B, and 2C have completed at least 26 weeks of treatment. [redacted]

Stage 2:

Initial dosing with [redacted] will occur in Cohort 3A, comprising participants between birth and age <3 years. Two participants in Cohort 3A will be enrolled and monitored. The accumulated safety data, including TEAEs will be reviewed by the DMC after both participants have completed at least 8 weeks of treatment. If the stopping criteria are not met, and after review and approval by the DMC (see Section 10.1.5.2 Study stopping criteria), then the following cohorts/ subgroups may open for enrollment in the manner detailed below:

- Cohort 3B: Two participants between birth and age <3 years will be enrolled to receive the dose of [redacted].
- Cohort 3C: After the 2 participants have been enrolled in Cohort 3B as above, then the next 8 participants eligible between birth and age <3 years will be randomized in a [redacted] manner into Cohort 3C to receive [redacted] the dose of [redacted]. No additional DMC meeting is required between the opening of Cohorts 3B and 3C.

Extended Treatment Period:

After the second interim analysis (see Section 9.3), the Investigator will be permitted to discuss the option of treatment discontinuation or a dose change (depending on the results of prior interim analyses) if the participant has experienced lack of improvement on the originally assigned dose. "Lack of improvement" will be defined as no change or a decrease from baseline AGV Z-score as established by data collected in the OBS16647 study. If the Investigator wishes to discontinue the IMP or change the participant's dose due to suspected "lack of improvement," the investigator should inform the Sponsor so that the Sponsor biostatistical team may calculate the individual change in AGV Z-score for the participant to confirm whether "lack of improvement" is valid per the definition above. Otherwise, the participant will remain on the dose assigned at enrollment throughout the entire study including the extended treatment period.

Safety monitoring:

Comprehensive safety monitoring will be conducted for all participants throughout the duration of the study. Safety monitoring includes vital signs, laboratory assessments, ophthalmological testing, bone age X-ray, lower extremity X-ray, spine X-rays, dual energy X-ray absorptiometry (DXA) scan (Stage 1 only), and adverse events (AEs) collection at the frequency specified in the schedule of activities (SoA). Laboratory and ophthalmological assessment safety data will be performed both as scheduled and as needed throughout the treatment period. Participants may be observed for a longer duration and/or additional visits may be added for further safety assessment at the discretion of the Investigator and in consultation with the Sanofi Medical Monitor.

Study intervention administration:

The first [redacted] administrations of study intervention will be done at the study site. After adequate training and approval by the Investigator and Sponsor, if no injection site reactions or AEs has occurred or is suspected, and appropriate medical training, evaluation of participant's/caregiver's/home healthcare professional's injection capability and technique are completed, then (please refer to pharmacy manual) SC injections of SAR442501 from Week 1 onward can be performed between visits at an alternate location, including the participant's home by these trained individuals per local regulations. In case of any injection site reactions or other AEs, the participant must contact the site as soon as possible for reporting, timely monitoring of any worsening of the events, and decision for best evaluation/treatment by the Investigator (including on-site visit if needed). The Investigator may also proactively contact the participant the day of injection to assure absence of any events or to assure their best management if such occur. Phone/telemedicine calls may be performed between study site visits to assess AEs, record concomitant medications, confirm drug compliance, and to answer questions throughout the duration of the study when needed. Please refer to the SoA for additional details.

Efficacy assessments:

There will be a total of at least 11 required on study site visits throughout the study. **Visit 1/Screening, Visit 2/Week 0/Days 1 to 4, Visit 3/Week 8/Day 57, Visit 4/ Week 13/ Day 92, Visit 5/Week 26/Day 183, Visit 6/ Week 39/ Day 274, and Visit 7/Week 52/ Day 365** will take place during the primary treatment period. After the Week 52 visit, participants will

enter the extended treatment period. During this, each participant will return for on-site visits every 12 weeks until the last participant enrolled completes 52 weeks of the extended treatment period. Therefore, the duration and number of visits during the extended treatment period will vary per participant. After the final visit during the extended treatment period, participants will enter a 4 week post-treatment observation phase, after which the end-of-study visit or phone call will take place. To reduce their burden, participants will have the option to have several visits replaced by decentralized visits, if permitted by the local regulations and based on study site/participant's decision as per SoAs in Section 1.3. All procedures planned in-between the on-site visits may be performed remotely. Please see the SoA (Section 1.3) for details.

Brief summary:

This is an open-label sequential cohort dose escalation, Phase 2, 2-stage, multicenter study to evaluate the safety, tolerability, PK, PD, and efficacy of SAR442501 treatment in pediatric participants with genetically confirmed ACH.

Number of participants:

In Stage 1 approximately 24 participants will be enrolled. In Stage 2 approximately 12 participants will be enrolled. Participants who discontinue study treatment or withdraw from the study may be replaced.

Note: Enrolled participants are all participants who had been screened and allocated to study intervention regardless of whether the intervention was received or not.

Study arms and duration:

All participants will receive open-label SAR442501 at [redacted].

Study intervention:

SAR442501

Investigational medicinal product

- Formulation: SAR442501 is currently supplied as a [redacted]

Posttrial access to study medication: Not applicable

Duration of study intervention

Up to approximately 275 weeks: 3 weeks Screening + 52 weeks primary treatment period + up to approximately 216 weeks extended treatment period+ 4 weeks follow-up.

Statistical considerations:

- **Primary endpoint:**

  Assessment of AEs, serious adverse events (SAEs), and TEAEs and adverse events of special interest (AESIs) during the TE period.

- **Main secondary endpoints:**

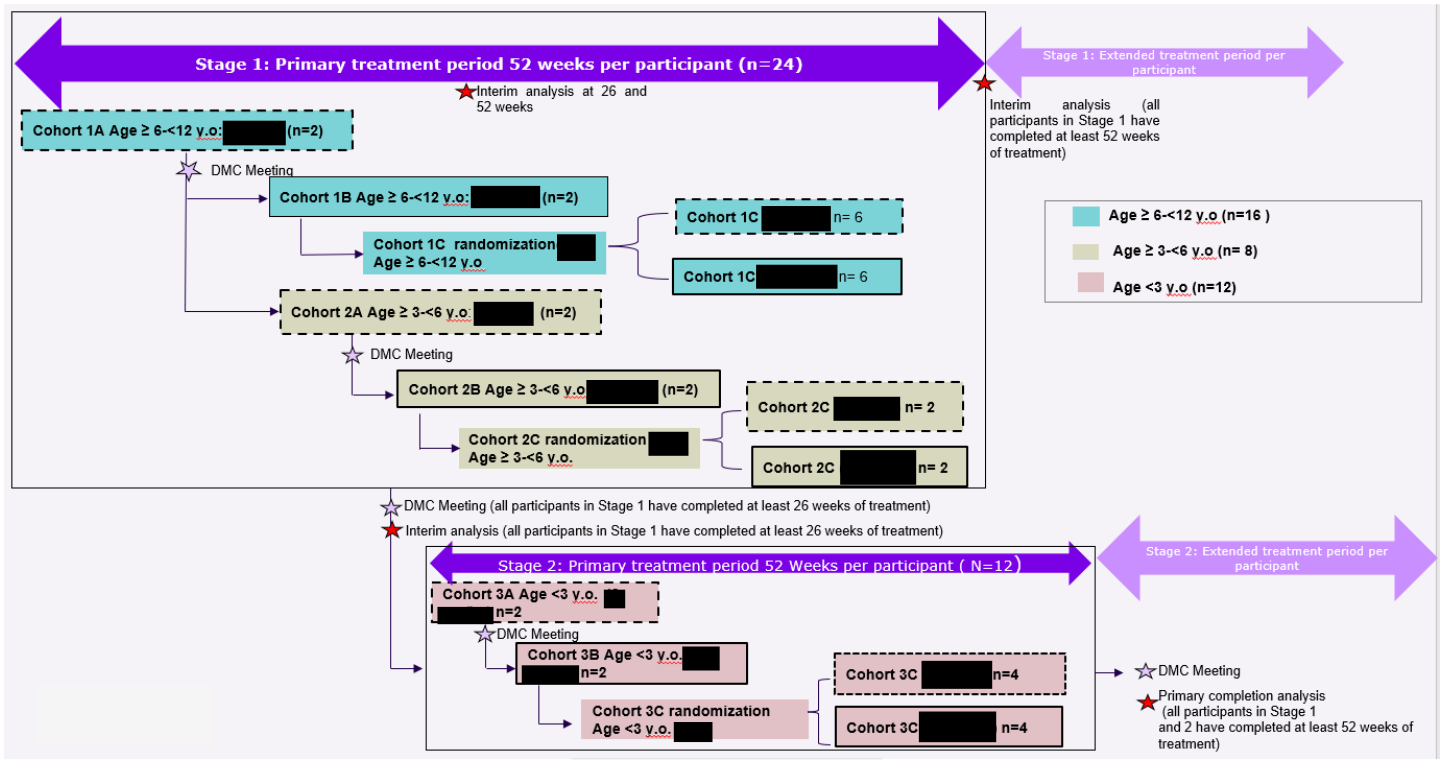
  Change in AGV, AGV Z-score, and height Z-score, after 26 and 52 weeks of treatment.

Data Monitoring/Other committee: Yes

A Data Monitoring Committee (DMC) has been appointed for this study. The DMC is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for efficacy, for harm, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
Please see Section 10.1.5.1 for details.

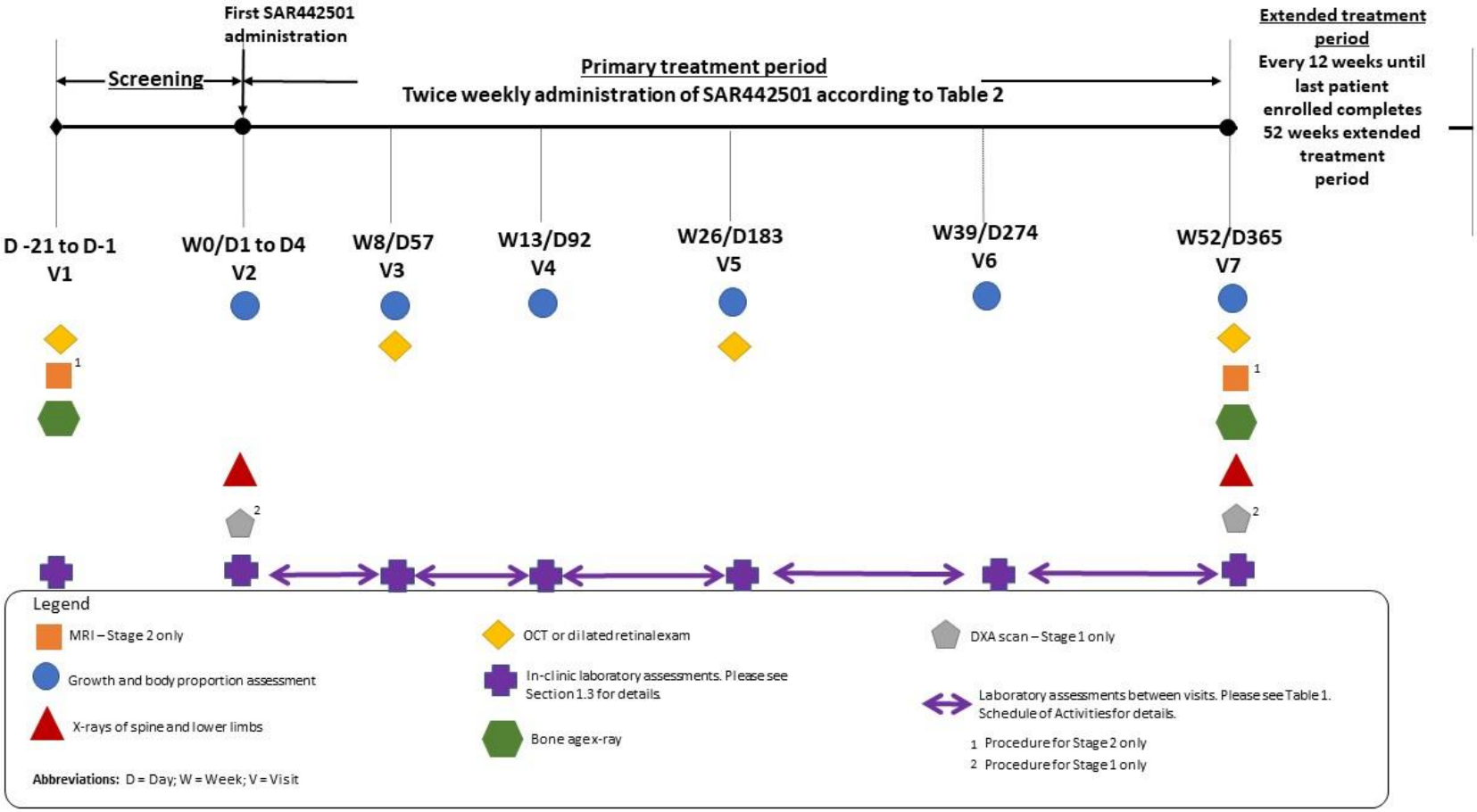
1.2 SCHEMA

Figure 1 - Dose escalation schematic



Abbreviations: n= number of subjects; y.o= years old.

Figure 2 - Screening and treatment period study assessments schematic



1.3 SCHEDULE OF ACTIVITIES (SOA)

Assessments	Screen-ing	Primary treatment period[a,b]																Extended treatment period	Post-treatment observation	
	D -21 to D -1 Visit 1[aa]	W0/D1 to D4/ Visit 2[c,jj]				W1 to W7[d,jj]	W8/ D57-D60 Visit 3 (+/- 3 days)[gg,jj]				W9 to W12[d,jj]	W13/D92/Visit 4 (± 3 days)[jj]	W14 to W25[d,jj]	W26/ D183/ Visit 5 (±3 days)[hh,jj]	W27 to W38[d,jj]	W39/ D 274/ Visit 6 (± 3 days)[jj]	W40 to W51[d,jj]	W52/ D365/ Visit 7 (± 3 days)[z,jj]	W64/ D449/ Visit 8, then every 12 weeks (+/- 3 days)[ff,jj]	Early Treatment Discontinu-ation Visit	End of Study Phone Call or Visit (4 weeks +/- 3 days)[e]
		D1	D 2	D 3	D 4		D 57	D 58	D 59	D 60												
Visit at clinical site	X	X	X		X		X	X		X		X		X		X		X	X	X	X	(X)[e]
Informed consent	X																					
Inclusion and exclusion criteria	X	X																				
Demographic information	X																					
Medical history, including surgical history, growth history and ACH-related history	X																					
Prior/concomitant medication/ therapies	←==========→																					

Assessments	Screen-ing	Primary treatment period[a,b]																	Extended treatment period	Post-treatment observation	
	D -21 to D -1 Visit 1[aa]	W0/D1 to D4/ Visit 2[c,jj]				W1 to W7[d,jj]	W8/ D57-D60 Visit 3 (+/- 3 days)[gg,jj]				W9 to W12[d,jj]	W13/D92/Visit 4 (± 3 days)[jj]	W14 to W25[d,jj]	W26/ D183/ Visit 5 (±3 days)[hh,jj]	W27 to W38[d,jj]	W39/ D 274/ Visit 6 (± 3 days)[jj]	W40 to W51[d,jj]	W52/ D365/ Visit 7 (± 3 days)[z,jj]	W64/ D449/ Visit 8, then every 12 weeks (+/- 3 days)[ff,jj]	Early Treatment Discontinu-ation Visit	End of Study Phone Call or Visit (4 weeks +/- 3 days)[e]
		D1	D 2	D 3	D 4		D 57	D 58	D 59	D 60											
Safety assessments																					
Neurological examination[f]	X	X					X					X		X		X		X	X	X	
Physical examination[g]	X	X					X					X		X		X		X	X	X	
Vital signs[h]	X	X					X					X		X		X		X	X	X	
ECG		X					X					X		X		X		X	X	X	
AE collection, including ACH-related events of interest[i]	←==========→																				
Ophthalmological assessments																					
Amsler grid and visual acuity test[j]	X						X							X				X	X[l]	X	

Assessments	Screen-ing	Primary treatment period[a,b]																Extended treatment period	Post-treatment observation	
	D -21 to D -1 Visit 1[aa]	W0/D1 to D4/ Visit 2[c,jj]				W1 to W7[d,jj]	W8/ D57-D60 Visit 3 (+/- 3 days)[gg,jj]				W9 to W12[d,jj]	W13/D92/Visit 4 (± 3 days)[jj]	W14 to W25[d,jj]	W26/ D183/ Visit 5 (±3 days)[hh,jj]	W27 to W38[d,jj]	W39/ D 274/ Visit 6 (± 3 days)[jj]	W40 to W51[d,jj]	W52/ D365/ Visit 7 (± 3 days)[z,jj]	W64/ D449/ Visit 8, then every 12 weeks (+/- 3 days)[ff,jj]	Early Treatment Discontinu-ation Visit	End of Study Phone Call or Visit (4 weeks +/- 3 days)[e]
		D1	D 2	D 3	D 4		D 57	D 58	D 59	D 60												
OCT or dilated retinal examination[k]	X						X							X				X	X[l]	X	
Laboratory assessments																					
Clinical laboratory (hematology, chemistry, thyroid function tests - TSH)[m,n]	See Table 1 - Laboratory sampling schedule																				
25-hydroxy-vitamin D level, 1,25-dihydroxy-vitamin D, calcitonin, parathyroid hormone levels[m,n]	See Table 1 - Laboratory sampling schedule																				
FGF23	See Table 1 - Laboratory sampling schedule																				

Assessments	Screen-ing	Primary treatment period[a,b]																Extended treatment period	Post-treatment observation	
	D -21 to D -1 Visit 1[aa]	W0/D1 to D4/ Visit 2[c,jj]				W1 to W7[d,jj]	W8/ D57-D60 Visit 3 (+/- 3 days)[gg,jj]				W9 to W12[d,jj]	W13/D92/Visit 4 (± 3 days)[jj]	W14 to W25[d,jj]	W26/ D183/ Visit 5 (±3 days)[hh,jj]	W27 to W38[d,jj]	W39/ D 274/ Visit 6 (± 3 days)[jj]	W40 to W51[d,jj]	W52/ D365/ Visit 7 (± 3 days)[z,jj]	W64/ D449/ Visit 8, then every 12 weeks (+/- 3 days)[ff,jj]	Early Treatment Discontinu-ation Visit	End of Study Phone Call or Visit (4 weeks +/- 3 days)[e]
		D1	D 2	D 3	D 4		D 57	D 58	D 59	D 60												
Pregnancy test[o]	X	X					X					X		X		X		X	X	X	
Radiological assessments[q]																			X[p]		
MRI[n,bb]	X																	X	X[cc]	X	
DXA scan[cc]		X[cc]																X	X[cc]	X	
Bone Age X ray (PA X-ray of hand and wrist)	X[n]																	X	X[dd]	X	
AP lower extremity X-ray		X																X	X[dd]	X	
Lateral thoraco-lumbar spine X-ray		X																X	X[dd]	X	
AP X-ray of spine		X																X	X[dd]	X	
Growth measurements																					
Height		X					X					X		X		X		X	X	X	

Assessments	Screen-ing	Primary treatment period[a,b]																Extended treatment period	Post-treatment observation	
	D -21 to D -1 Visit 1[aa]	W0/D1 to D4/ Visit 2[c,jj]				W1 to W7[d,jj]	W8/ D57-D60 Visit 3 (+/- 3 days)[gg,jj]				W9 to W12[d,jj]	W13/D92/Visit 4 (± 3 days)[jj]	W14 to W25[d,jj]	W26/ D183/ Visit 5 (±3 days)[hh,jj]	W27 to W38[d,jj]	W39/ D 274/ Visit 6 (± 3 days)[jj]	W40 to W51[d,jj]	W52/ D365/ Visit 7 (± 3 days)[z,jj]	W64/ D449/ Visit 8, then every 12 weeks (+/- 3 days)[ff,jj]	Early Treatment Discontinu-ation Visit	End of Study Phone Call or Visit (4 weeks +/- 3 days)[e]
		D1	D 2	D 3	D 4		D 57	D 58	D 59	D 60												
Arm span		X					X					X		X		X		X	X	X	
Weight		X					X					X		X		X		X	X	X	
Circumference (chest, head, and waist)		X					X					X		X		X		X	X	X	
Length (head, upper arm, forearm, hand, palm, middle finger, upper leg, lower leg, foot, upper and lower body segment, upper and lower body extremity)		X					X					X		X		X		X	X	X	
Tanner stage (sexual maturity rating)[r]		X					X					X		X		X		X	X	X	

Assessments	Screen-ing	Primary treatment period[a,b]																	Extended treatment period	Post-treatment observation	
	D -21 to D -1 Visit 1[aa]	W0/D1 to D4/ Visit 2[c,jj]				W1 to W7[d,jj]	W8/ D57-D60 Visit 3 (+/- 3 days)[gg,jj]				W9 to W12[d,jj]	W13/D92/Visit 4 (± 3 days)[jj]	W14 to W25[d,jj]	W26/ D183/ Visit 5 (±3 days)[hh,jj]	W27 to W38[d,jj]	W39/ D 274/ Visit 6 (± 3 days)[jj]	W40 to W51[d,jj]	W52/ D365/ Visit 7 (± 3 days)[z,jj]	W64/ D449/ Visit 8, then every 12 weeks (+/- 3 days)[ff,jj]	Early Treatment Discontinu-ation Visit	End of Study Phone Call or Visit (4 weeks +/- 3 days)[e]
		D1	D 2	D 3	D 4		D 57	D 58	D 59	D 60											
Study intervention administration and compliance																					
Drug administration[a]		See Table 2 - Weekly Study intervention Administration Schedule																			
Assessment of drug compliance[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone/telemedicine call[t]						X					X		X		X		X		X	X	X
Clinical Outcome Assessments (COAs)																					
Achondroplasia Developmental Recording Form (Stage 2 only)		X					X					X		X		X		X	X	X	

Assessments	Screen-ing	Primary treatment period[a,b]																Extended treatment period	Post-treatment observation	
	D -21 to D -1 Visit 1[aa]	W0/D1 to D4/ Visit 2[c,jj]				W1 to W7[d,jj]	W8/ D57-D60 Visit 3 (+/- 3 days)[gg,jj]				W9 to W12[d,jj]	W13/D92/Visit 4 (± 3 days)[jj]	W14 to W25[d,jj]	W26/ D183/ Visit 5 (±3 days)[hh,jj]	W27 to W38[d,jj]	W39/ D 274/ Visit 6 (± 3 days)[jj]	W40 to W51[d,jj]	W52/ D365/ Visit 7 (± 3 days)[z,jj]	W64/ D449/ Visit 8, then every 12 weeks (+/- 3 days)[ff,jj]	Early Treatment Discontinu-ation Visit	End of Study Phone Call or Visit (4 weeks +/- 3 days)[e]
		D1	D 2	D 3	D 4		D 57	D 58	D 59	D 60												
Screening Tool for Everyday Mobility and Symptoms (STEMS)[u]		X					X					X		X		X		X	X	X	
PedsQL Core Scale, PedsQL Fatigue Inventory, PedsQL Pain Questionnaire[v]		X					X					X		X		X		X	X	X	
[redacted]																						

Assessments	Screen-ing	Primary treatment period[a,b]																Extended treatment period	Post-treatment observation	
	D -21 to D -1 Visit 1[aa]	W0/D1 to D4/ Visit 2[c,jj]				W1 to W7[d,jj]	W8/ D57-D60 Visit 3 (+/- 3 days)[gg,jj]				W9 to W12[d,jj]	W13/D92/Visit 4 (± 3 days)[jj]	W14 to W25 [d,jj]	W26/ D183/ Visit 5 (±3 days) [hh,jj]	W27 to W38[d,jj]	W39/ D 274/ Visit 6 (± 3 days)[jj]	W40 to W51 [d,jj]	W52/ D365/ Visit 7 (± 3 days) [z,jj]	W64/ D449/ Visit 8, then every 12 weeks (+/- 3 days)[ff,jj]	Early Treatment Discontinu-ation Visit	End of Study Phone Call or Visit (4 weeks +/- 3 days)[e]
		D1	D 2	D 3	D 4		D 57	D 58	D 59	D 60												
PK/PD assessments																						
PK samples		See Table 3 - PK sample collection schedule for details																				
CXM, osteocalcin, bone alkaline phosphatase, CTX, P1NP[b]	See Table 1 - Laboratory sample collection schedule for details																					
ADA level[y]		See Table 1 - Laboratory sample collection schedule for details.																				

Abbreviations: aBMD= areal bone mineral density; AE= adverse event; ACH= Achondroplasia; ADA= anti-drug antibody; AP=antero-posterior; BIW= twice weekly; COA= clinical outcome assessments; [redacted] CTX= collagen-Type 1 C-Telopeptide; CXM= collagen X biomarker; CV= cardiovascular; D= Day; DXA= dual energy X-ray absorptiometry; ECG=electrocardiogram; GI= gastrointestinal; GU= genitourinary; HEENT= head, eyes, ears, nose, and throat; IMP= investigational medicinal product; MRI= magnetic resonance imaging; MSK= musculoskeletal; OCT= optical coherence tomography; PA= posteroanterior; PD= pharmacodynamic; PedsQL= pediatric quality of life; [redacted]; PK= pharmacokinetic; PROs= patient reported outcomes; P1NP = procollagen type 1 N-terminal propeptide; STEMS= screening tool for everyday mobility and symptoms; TSH= thyroid stimulating hormone; W= week.

a During the primary treatment period and extended treatment period, study intervention will be administered BIW starting at Week 0/Day 1/Visit 2. The first two drug administrations, on Day 1 and Day 4, will be administered and monitored on-site. The first BIW drug administrations of study Week 8 and Week 13 will also be administered on-site at those respective visits. [redacted] Each time the medication is administered on site, the participant will be monitored for 30 minutes after the injection by study staff trained in recognizing acute hypersensitivity reactions. Medication and equipment to treat such reactions must be readily available at the study site.

b Unless specified otherwise, during on-site visits, assessments are completed before administering SAR442501. See Table 1 for laboratory sampling schedule for sampling collection windows. When multiple assessments are required, the order should be vital signs before PK or blood draw.

c Week 0/Visit 2 activities, including study intervention administration and [redacted] the participant may be offered lodging near the site on a case by case basis if local regulations permit.

d For laboratory assessments between required study site visits, please see Table 1 for details. These assessments can be performed remotely if local regulations permit.

e An end-of-study phone/telemedicine call or visit will be conducted approximately 4 weeks (+/- 3 days) after the last dose of study intervention is administered. The choice of phone call or in study site visit will be at the Investigator's discretion.

f A full neurological exam including motor, reflexes, sensory, and cranial nerve assessments should be performed.

g Complete physical examination includes all major body systems, including assessment of general appearance; CV; dermatologic; HEENT; lymphatic; respiratory; GI; MSK; and GU.

h During each visit, vital sign measurements will be taken at the beginning of each study site visit prior to all visit procedures including study intervention administration and lab draws (if due at that visit).

i Achondroplasia related events of interest to be recorded include, but are not limited to, bone fractures, ear infections, tonsillectomies, adenoidectomies, cervical medullary decompression surgeries, any orthopedic surgeries, sleep apnea diagnosis, and other events the Investigator deems relevant to the disease course. Adverse events collection will take place throughout the study. Sites may administer phone calls to assess AEs.

j For participants who are capable of complying with the Amsler grid and visual acuity tests, assessments should be performed at the indicated visits and may be performed at any point during the study at the Investigator's discretion. Participants who are not capable of complying with the Amsler grid and visual acuity tests will not have these assessments.

k For participants ages ≥5 years, OCT will be performed, and for participants ages <5 years, the dilated retinal examination will be used. These assessments will be conducted at the visits indicated, or at any time during the study per the Investigator's judgment. This assessment should be performed prior to study intervention administration. Whether sedation should be used for either examination is at the discretion of the Investigator.

l Amsler grid, visual acuity test, and OCT or dilated retinal examination should be performed every 24 weeks during the extended treatment period starting at Week 78.

m Detailed laboratory sampling schedule is provided in Table 1 - Laboratory sampling schedule.

n Results from the Screening MRI (Stage 2 only), bone age X-ray (wrist), long chemistry panel and TSH levels must be available prior to enrollment to ensure participant meets eligibility criteria.

o Female participants who are postmenarchal at the time of screening must have a negative pregnancy test at the screening visit. Those who are postmenarchal or start menses during the study must be willing to have additional pregnancy tests during the study. Female participants of childbearing potential will have a urine or serum pregnancy test at the time points specified. Start date of menses will be captured. Serum pregnancy tests will be performed in the event that urine pregnancy test results are positive or equivocal. Female participants with a positive serum pregnancy test at any time will be withdrawn from SAR442501 treatment.

p Collected every 48 weeks.

q Should subjects' imaging assessment yield any concerns, additional imaging may be conducted; this will be determined by the Investigator in conjunction with the Sponsor Medical Monitor and the DMC if indicated.

r The Tanner stage of pubertal development will be assessed only in participants ≥5 years of age at the time of assessment.

s Study intervention compliance will be assessed during all study site visits. if there are remote visits, compliance will be assessed by the healthcare provider, or via a diary or phone/telemedicine call.

t Phone/telemedicine calls may be performed between study site visits approximately weekly to assess AEs, record concomitant medications and confirm drug compliance.

u The STEMS assessment will be collected in participants ages ≥5 years age at the time of assessment.

v Clinical outcome assessments will include the following: PedsQL Inventory Generic Core Scale (on participants ages ≥2 years), PedsQL Multidimensional Fatigue Inventory (on participants ages ≥2 years), PedsQL Pediatric Pain Questionnaire (on participants ages ≥5 years old), [redacted] (all participants). Caregivers will complete the PedsQL Core Scale and Multidimensional Fatigue Scale for participants ages ≥2 years and the Pediatric Pain Questionnaire for participants ages ≥5 years. In addition, participants ages ≥8 years will complete the PedsQL child self-report for all PedsQL scales. PedsQL scales will be completed as summarized by the age ranges in Table 7. [redacted].

w [redacted]

x [redacted] should be administered AFTER IMP administration during the Week 0 Day 1 visit.

y ADA sampling should be done before SAR442501 administration, at the indicated visits. Participants who show evidence of treatment-emergent immunogenicity (ie, ADA) at the last visit during which IMP is administered or Early treatment discontinuation visit (whichever comes first) will return at least once within 45 days following the last visit during which IMP is administered or Early treatment discontinuation visit (whichever comes first) for additional evaluation.

z If study intervention is permanently discontinued prior to the Week 52 visit, but after the Week 26 visit, a follow-up visit at Weeks 52 should occur in addition to the Early treatment discontinuation visit and 4-week follow-up visit. At this Week 52 visit, only growth parameters (including height, weight, and body proportionality measurements) should be collected.

aa This visit may be combined with the final visit of the OBS16647 study.

bb Stage 2 only.

cc Stage 1 only.

dd X-rays, MRI (Stage 2 only), and DXA (Stage 1 only) during the extended treatment period will be collected every 48 weeks (+/- 3 days) during the extended treatment period.

ee At Visit 2/ Week 0/ Day 1 documentation of historical aBMD results collected per standard of care within 3 months of Visit 2/ Week 0/ Day 1 is acceptable in place of on-site assessment.

ff The extended treatment period for all participants will end when the last participant enrolled has completed 52 weeks of treatment in the extended treatment period.

gg Week 8/Visit 3 activities, including study intervention administration and [redacted] the participant may be offered lodging near the site on a case by case basis if local regulations permit. Additionally, the Day 58 24-hour and Day 60 72-hr laboratory samples may be collected remotely if local regulations permit.

hh If study intervention is permanently discontinued prior to the Week 26 visit, follow-up visits at Weeks 26 and 52 should occur in addition to the Early treatment discontinuation visit and 4-week follow-up visit. At these Week 26 and Week 52 visits, only growth parameters (including height, weight, and body proportionality measurements) should be collected.

ii X-rays, MRI (Stage 2 only), and DXA (Stage 1 only) during the extended treatment period will be collected every 48 weeks (+/- 3 days) during the extended treatment period.

jj IRT allocation should occur at W0 and +/- 3 days at: W4, W8, W13, W17, W21, W26, W30, W34, W39, W43, W52 and every 4 weeks during the extension period. If direct to patient (DTP) is authorized, IMP will be dispensed by the site at visits W0, W8, W13, W26, W39, W52, and every 12 weeks and IMP may be shipped by DTP at W0, W4, W8, W17, W21, W26, W30, W34, W39, W43, W47, W52 and every 4 weeks. If DTP is not authorized, IMP will be dispensed in the clinic at W0, W4, W8, W13, W17, W21, W26, W30, W34, W39, W43, W47, W52 and every 4 weeks.

Table 1 - Laboratory sampling schedulee

Activity	Screening: Day -21 to Day -1	W0	W1	W2	W3	W4	W6	W8	W13		W17	W21	W26	W30	W34	W39	W43	W47	W52	W64, then every 12 weeks[f]	ETDV
Visit at clinical site	X	X						X	X				X			X			X	X	X
Safety																					
Long chemistry panel[a]	X	X						X	X				X			X			X	X	X
CBC and differential		X						X	X				X			X			X	X	X
TSH with reflex[a]	X												X						X	X	X
Short chemistry panel[b]			X	X		X	X				X	X		X	X		X	X			
25-hydroxy-vitamin D level, 1,25-dihydroxy-vitamin D		X						X					X			X			X	X	X
Parathyroid hormone (PTH) level		X						X					X			X			X	X	X
Calcitonin		X						X					X			X			X	X	X
FGF23[c]		←==========FGF23 will be performed when required (see Footnote c)==========→																			
Treatment, PK, PD																					
PK[d]		See Table 3. PK and ADA sample collection schedule																			
PD (CXM, osteocalcin, bone alkaline phosphatase, CTX, P1NP)		X				X		X	X				X			X			X	X	X

Activity	Screening: Day -21 to Day -1	W0	W1	W2	W3	W4	W6	W8	W13		W17	W21	W26	W30	W34	W39	W43	W47	W52	W64, then every 12 weeks[f]	ETDV
Immunogenicity																					
ADA levels			See Table 3. PK and ADA sample collection schedule																		

Abbreviations= ADA = Anti-drug antibody, ALT = alanine aminotransferase; AST= aspartate aminotransferase; BUN = blood urea nitrogen; CBC= complete blood count, CTX = collagen-type 1 C-Telopeptide; CXM = collagen X biomarker, ETDV = early treatment discontinuation visit, FGF23= Fibroblast Growth Factor Receptor 23, PK= pharmacokinetics, PD= pharmacodynamics; PTH= parathyroid hormone; P1NP= procollagen 1 intact N-terminal peptide, T3= triiodothyronine; T4= thyroxine; TSH=thyroid stimulating hormone; ULN= upper limit of normal; W= week.

a Long chemistry panel includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, magnesium, phosphorous, glucose, ALT, alkaline phosphatase, AST, direct bilirubin, indirect bilirubin, total bilirubin, albumin. TSH with reflex: a TSH value outside the standard reference range will prompt assay of free T4 and total T3.

b Short chemistry panel: (calcium, magnesium, phosphorous, albumin).

c FGF23 will only be assessed on those with hyperphosphatemia defined as serum phosphorous level ≥1.3 × ULN.

d See Table 3 for PK sample collection schedule for details.

e All laboratory assessments between on-site visits may be performed remotely per local regulations.

f The extended treatment period for all participants will end when the last participant enrolled has completed 52 weeks of treatment in the extended treatment period.

Table 2 - Weekly study intervention administration schedule

	D1	D2	D3	D4	D5	D6	D7
Study intervention administration[a]	X			X			

Abbreviations: D = Day.

a This is a study intervention administration schedule for each week of the study treatment period. The interval between 2 consecutive doses should be between 60 hours and 120 hours. The remainder of the primary treatment and extended treatment periods should follow the same schedule of BIW administration.

Table 3 - PK and ADA sample collection schedule

Activity	Week 0						Week 1		Week 4		Week 8							Week 13		Week 26		Week 39		Week 52		W64, then every 12 weeks[a]		ETD Visit
	D1			D2	D3	D4	D8		D29		D57					D 58	D60 (Optional)	D92		D183		D274		D365		D449, then every 84 days		
	Pre-dose	0 hr	6 hr (± 1 hr)	24 hr (±2 hr)		72 hr (within 2 hr before dose)	Pre-dose	0 hr	Pre-dose	0 hr	Pre-dose	0 hr	3 hr (± 30 min)	6 hr (± 1 hr)	12 hr (± 1 hr)	24 hr (±2 hr)[b]	72 hr (within 2 hr before dose)[b]	Pre-dose	0 hr	Pre-dose	0 hr	Pre-dose	0 hr	Pre-dose	0 hr	Pre-dose	0 hr	
On-site visit	X			X		X					X					X	X	X		X		X		X		X		X
Study intervention administration		X				X		X		X		X					X		X		X		X		X		X	
ADA sample	X						X		X		X					X	X	X		X		X		X	X	X	X	X

Abbreviations: D= Day, PK= Pharmacokinetics, ETD=Early Treatment Discontinuation, W= week.

a The extended treatment period for all participants will end when the last participant enrolled has completed 52 weeks of treatment in the extended treatment period.

b The Day 58 24-hour and Day 60 72-hr laboratory samples may be collected remotely if local regulations permit.

c See Table 2 for Weekly study intervention administration schedule.

d Only for participants with age ≥3 to <12 years old.

2 INTRODUCTION

SAR442501 is a monoclonal antibody that binds the [redacted] of FGFR3 thus inhibiting receptor activity. In preclinical studies, SAR442501 has demonstrated an ability to significantly improve the growth abnormalities that characterize ACH.

2.1 STUDY RATIONALE

SAR442501 directly inhibits FGFR3 activity, thereby preventing the inhibition of chondrocyte proliferation and differentiation. This therapy is expected to correct the underlying skeletal pathophysiology of ACH and therefore improve not only absolute growth but also clinically relevant complications, including body proportionality and foramen magnum size.

Nonclinical studies have demonstrated preliminary efficacy of SAR442501 on growth. Specifically, inhibition of the [redacted] with SAR442501 and [redacted], in a mouse model, resulted in increased chondrocyte proliferation and differentiation in the growth plates and improvement in skeletal parameters (increased growth plate volume, growth plate thickness and increased bone length in the skull, foramen magnum area, vertebral column, and long bones). Similar effects on bone growth were demonstrated after repeated subcutaneous dosing in healthy juvenile NHP.

The completed Phase 1, FIH single ascending dose (SAD) and MAD studies (TDU16639/TDR16640) demonstrated that SAR442501 is safe and well tolerated in healthy adult volunteers when administered SC at doses of [redacted] daily for 14 days, as well as [redacted] BIW for 29 days. There were 18 cases of hyperphosphatemia in SAR442501-treated and 1 case in placebo-treated participants. All hyperphosphatemia events were mild (Grade 1) and asymptomatic, did not require treatment, resolved spontaneously, and did not result in IMP discontinuation. Taken together, the efficacy findings from the preclinical studies and safety results from the Phase 1 studies support the initiation of this first study of SAR442501 in pediatric participants with ACH.

DRI16646 is designed to assess the safety, tolerability, and efficacy of BIW subcutaneous SAR442501 administration to pediatric participants ages birth to <12 years with ACH. This study will assess the effects of SAR442501 in improving linear growth and also clinically important complications of ACH, including body proportionality and foramen magnum size. The study will be divided into 2 stages.

2.2 BACKGROUND

Achondroplasia is caused by a mutation in the FGFR3 gene. The incidence is 1 in 25 000 births worldwide with a prevalence of 250 000 to 385 000 (47). Achondroplasia is diagnosed at birth clinically by virtue of the newborn's prominent head size and disproportionately short limbs. Achondroplasia can also be diagnosed by ultrasound in the second trimester of pregnancy based on the participant's family history. The diagnosis can be confirmed genetically by the

identification of a heterozygous pathogenic variant in FGFR3, especially in individuals who may have atypical or uncertain findings (48). Additional clinical features of ACH might include thoracolumbar kyphosis, lumbar lordosis and bowed legs (47, 48, 49).

The most common mutation (p.G380R) is found in the transmembrane domain of FGFR3 of approximately 98% of ACH participants. This mutation results in hyperactivation of the receptor by increasing the residence time of the receptor on the membrane thereby contributing to increased signaling (50, 51, 52). Increased FGFR3-mediated signaling inhibits differentiation of the growth plate chondrocytes of long bones and select intramembranous bones leading to short stature, foramen magnum stenosis, spinal stenosis, and recurrent ear infections.

Although ACH is an autosomal dominant disease, the majority (approximately 80%) of reported cases are a result of de novo mutations (48). Clinical manifestations of ACH are wide ranging and contribute to both an increase in mortality and morbidity. Complications of the axial skeleton encompass dysplasia and hypoplasia of the skull, facial bones, and vertebrae, manifesting as hydrocephaly, foramen magnum stenosis, delayed speech, ataxia, sleep apnea, and disability (53). Additionally, dysfunctional vertebral growth results in scoliosis, kyphosis/lordosis, nerve compression, paralysis/neuralgia, and spinal cord stenosis. These serious complications have necessitated frequent surveillance imaging and corrective surgeries. A recent retrospective study, also the largest natural history study to date, CLARITY, found that in a cohort of 1374 participants between 1957 and 2017, 91% had at least 1 X-ray, computed tomography, MRI, or ultrasound in their medical record (54). Nearly 80% had at least one ear, nose, throat (ENT), brain, foramen magnum, spine, or extremity surgery (54).

Higher mortality and morbidity rates associated with ACH have been established as detailed below:

Achondroplasia is associated with increased mortality, especially in infants

Among age groups the standardized mortality ratio (mortality of disease population compared to healthy population within the age group) was highest among infants ages 0 to 4 years, with deaths most frequently attributed to sudden infant death related to respiratory complications. Studies have reported up to a 6-fold higher mortality among infants <1 year of age compared to the general population in recent decades (55, 56). High infant mortality has been attributed to the increased prevalence of sudden infant death and sleep disordered breathing (SDB). Both are likely related to spinal cord compression at the cervicomedullary junction at the foramen magnum. Compared to age-matched controls, the mean foramen magnum diameter in ACH participants is significantly lower (57, 58). Considering that the greatest increase in growth rate of the foramen magnum occurs by 2 years of age and reaches final adult size by 5 years of age in healthy children (58), transversal and sagittal diameters are approximately 45% and 35% lower, respectively, in children with ACH aged 5 years compared to matched controls, amounting to an approximately 60% smaller foramen magnum area in this age group (58, 59).

Overall survival and the average life expectancy have been reported to be decreased by up to 10 years compared to healthy populations (60). Among adults with ACH age 25 to 35 years, heart disease-related deaths contributed most significantly to mortality (60).

Achondroplasia has a heavy burden of multiorgan system morbidity over a lifetime

The skeletal growth abnormalities in ACH can result in significant respiratory complications, most notably a high prevalence of SDB. Specifically, central or obstructive sleep apnea (OSA) has been reported to occur in up to 69.3% of participants and persist throughout adulthood (53). The prevalence of moderate to severe OSA was reported as 38.4% compared to 5%, 22%, and 17% in average stature children, men, and women respectively (54). It is postulated that thoracic cage hypoplasia, upper airway obstruction from midface hypoplasia, and relative adenoid hypertrophy result in OSA, and compression in the cervicomedullary transition results in central sleep apnea (CSA) (61). In many cases, the resultant hypoxemia is so severe that surgical intervention is required, including cervicomedullary decompression, adenotonsillectomies, or midface advancement surgeries, all of which are associated with risk of operative complications (62). Some participants have also required burdensome tracheostomies or nightly noninvasive ventilatory support (63). Moreover, this chronic hypoventilation may also contribute to a few cases of life-threatening pulmonary hypertension and cor pulmonale in infants (64, 65).

The general consensus among experts is that SDB is due in part to foramen magnum stenosis and sleep apnea severity is an indication for decompression surgery (66, 67). Results of the CLARITY study revealed that 20.5% of participants required some form of surgery involving the foramen magnum (54). Additionally, cord compression at the cervicomedullary junction has been linked to neurologic complications, specifically ventriculomegaly and hydrocephalus resulting in increased intracranial pressure and necessitating surgical intervention. Ventriculomegaly has been reported in up to 32.9% of patients and hydrocephalus in 17.3%, the majority of which were present in childhood (53). In one study, 13.3% of infants within the first 2 years of life required cervicomedullary decompression as a result of such complications (68). Ventriculoperitoneal shunts are also sometimes required and associated with morbid complications such as infections or seizures. Approximately 10% of patients studied require ventriculoperitoneal shunt placement or ventriculostomy (54).

Neurologic complications associated with spinal stenosis also persist throughout life. Lumbosacral spine stenosis with resulting intermittent spinal claudication or overt stenosis (with asymmetric lower extremity strength, gait changes, and bladder or bowel incontinence) has been found to develop in older children and adults (48). Approximately 36% of patients with lumbar stenosis require decompression surgery (53).

Musculoskeletal impairments arising from disproportionate limb-to-trunk ratios result in limited reach and range of motion, mobility, and impaired independent self-care. A mixed joint contracture and/or joint hypermobility, including hip flexion contractures, can result in exaggerated lumbosacral lordosis with subsequent back pain and muscle fatigue (61). Tibial bowing, which is associated with knee and leg pain, altered gait, earlier onset osteoarthritis, and need for orthopedic corrective surgeries, has been noted in greater than 40% of children and adults with ACH (69). The majority of such patients requires long-term physical or occupational health therapies.

Otolaryngology complications are also frequently present. Midface hypoplasia, plus relative enlargement of tonsils and adenoids characteristic of ACH, have been linked to recurrent otitis media and subsequent hearing loss as well as to delayed speech and language development. Such

conditions persist into adulthood, if not treated early and aggressively with adenotonsillectomy and insertion of grommets in young children (47). Approximately 53% of individuals with ACH required an adenotonsillectomy by the age of 15 compared to 0.7% to 2% of the average stature population (54). Recurrent middle ear infections have been reported in up to 73% of patients and account for hearing loss requiring pressure equalization tube placement in 56.1% of patients by 3 years of age, compared with only 6.8% of patients in the average stature population (54). Unfortunately, this procedure resolves hearing loss in only about half of patients with ACH (59%), while 66.7% of patients must use hearing aids and 47.1% of patients require speech therapy (70).

These multiple complications significantly decrease functional status and quality of life (QoL). High rates of chronic problems such as allergies or sinus problems, arthritis, and sleeping difficulty along with surgical burden throughout life result in lower scores on physical and mental health surveys. Patients also struggle with chronic pain which worsens with age (71, 72).

Achondroplasia is also associated with long-term psychosocial consequences. Individuals with ACH have been found to have lower income, lower self-esteem, less education, and were less likely to be married. Quality of life indices in health and functioning, social and economic, psychological and spiritual, and family domains were also lower (73).

Current clinical practice guidelines for ACH focus on treating its complications. Vosoritide (Voxzogo), a modified C-type natriuretic peptide, was approved by the European Commission on August 26, 2021, for treating ACH in patients aged 2 years and older whose bones are still growing. The effect of this treatment on decreasing the burden of complications has not yet been established. In a randomized, double-blind, placebo-controlled Phase 3 trial, after 52 weeks of treatment, there was an increase in AGV in patients treated with vosoritide versus placebo of 1.57 cm/year (74). The least-squares mean difference in height Z-score (derived using age-sex specific reference data for average stature children) between vosoritide and placebo at Week 52 was +0.28 in favor of vosoritide (74). There were no significant improvements in upper to lower body segment proportionality in children receiving vosoritide during this 52-week study (74).

Off-label use of growth hormone therapy has shown only limited efficacy in increasing height in this patient population. Daily injections of recombinant growth hormone result in an increase in growth velocity by 1.9 to 3.6 cm/year and an increase in height standard deviation (SD) score by 1 to 1.6 in patients with ACH compared to those in healthy individuals during the first year of treatment. However, this effect wanes after the first year of treatment; during the second year of treatment, growth velocity increases by only 0.5 to 1.5 cm/year and the height SD score increases by only 0.2 in patients with ACH compared to those in controls (72). In addition to growth hormone therapy, patients sometimes undergo limb lengthening surgeries to increase their final height. Tibial and femoral lengthening surgeries result in a significant total length gain of up to 20 cm but require multiple procedures and are associated with significant pain and prolonged recovery times (73). These surgeries have also not been found to consistently improve physical and functional mobility scores (72).

Foramen magnum decompression is recommended for managing spinal cord compression due to foramen magnum stenosis associated with neurological symptoms and sleep apnea, and ventriculoperitoneal shunt placement is recommended for ventriculomegaly management. However, these are high-risk interventional procedures.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected AEs of SAR442501 may be found in the Investigator's brochure (IB), participant information leaflet, package insert or summary of product characteristics and/or investigational directions for use for a device product.

Preclinical data of [redacted] in a mouse model of ACH supports expectations of improvement in growth velocity, limb proportionality, and increases in foramen magnum size with this mechanism of action (MOA). Inhibition of the[redacted]with SAR442501 and [redacted], mouse model of ACH, resulted in increased chondrocyte proliferation and differentiation in the growth plate and improvement in skeletal parameters in ACH mice. In studies RDVV0014 and RDVV0026, treatment at [redacted] from Day 3 to 20 by subcutaneous administration showed improvement in skeletal parameters including increased growth plate volume, growth plate thickness and increased bone length in the skull, foramen magnum (perimeter and area), vertebral column (L4-L6, L5 pedicle length), and long bones (femur and tibia). Additionally, SAR442501 treatment significantly increased measurement of whole body bone mineral density. Secondary to skeletal improvements, SAR442501 treatment showed an increase in respiratory function, measurement of whole body of plethysmography showed significant increase in peak inspiratory flow and trends toward improvement in breathing frequency, peak expiratory flow, and enhanced pause (Penh) in ACH mice (RDVV0026).

Inhibition of the [redacted] with SAR442501 resulted in increased chondrocyte proliferation and differentiation in the growth plate of healthy juvenile NHP that resulted in increased skeletal bone growth. Subcutaneous administration of SAR442501 at [redacted] every 3 days for 12 weeks significantly increased tibial growth plate volume, growth velocity, bone length (tibia and femur), vertebrae and femur trabecular number, bone volume/total volume %, and bone density (RDVV0016).

- SAR442501 [redacted] addresses the underlying pathophysiology which could potentially lead to increase in growth velocity towards normalization to address short stature
- SAR442501 is expected to increase foramen magnum size, which may ameliorate both obstructive and CSA and decrease risk of morbidity (frequent ear infections and sleep related breathing disorders) and mortality (especially in children ≤5 years)
- Other potential benefits of SAR442501 include improvement in body proportionality, and QoL

2.3.1 Risk assessment

Currently, there are no important identified risks for SAR442501. The important potential risks are ocular toxicities, hyperphosphatemia, injection site reactions, immunogenicity, and embryo-fetal toxicities. Hyperphosphatemia (a potential risk) was seen in the completed FIH (TDU16639 SAD + TDR16640 MAD) and in the NHP studies.

- TDU16639/TDR16640: 18 cases in SAR442501-treated and 1 case in placebo-treated participants;

- Increases were ≤0.7 mmol/L (≤2.17 mg/dL) above upper limit of normal (ULN), except one outlier (about 2 mmol/L increase);
- Only 2 of 19 cases consisted of absolute phosphate levels of ≥1.78 mmol/L (5.5 mg/dL), which is the typical threshold where treatment with phosphate binders might be considered;
- In all cases hyperphosphatemia ultimately resolved either shortly after the end of dosing (after Day 14) in the daily dosing cohorts of [redacted] or resolved within few days from the IMP initiation in the [redacted] cohort with BIW IMP administration (lasting 32 days);
- An increase of dosing (from [redacted] once a day [QD] and to [redacted] BIW did not increase hyperphosphatemia occurrences (in a higher dosing cohort): most of occurrences reported in [redacted].

It is unknown whether the potential risks of ocular toxicity (not seen in the adult population of the FIH studies nor in preclinical SAR442501 studies), and hyperphosphatemia will manifest in the pediatric population of Phase 2. However, all hyperphosphatemia events were mild (Grade 1) and asymptomatic, did not require treatment, resolved spontaneously, and did not result in study intervention discontinuations (see above). Blood phosphate concentrations for the pediatric age groups are different (higher) from adult ULN. In the case of hyperphosphatemia occurrences (above pediatric ULNs) in Phase 2, the extent of clinical impact on overall growth and development is uncertain and will depend on such parameters as degree of elevation (different from ULN or "degree of elevation [>ULN]"), duration (days, weeks, months), character (continuous, intermittent, sporadic, or single increase), individual bone metabolism and personal diet specifics.

Investigational intervention

The following important potential risks are based on the observation in the studies of the pan-FGFR inhibitors and other monoclonal antibody drugs and the findings in the non-clinical studies of SAR442501.

Ocular toxicity: Ocular toxicity has been reported in clinical studies of the pan-FGFR inhibitors, erdafitinib and pemigatinib, that inhibit FGFR1-4 (75, 76, 77). The ocular toxicity induced by these molecules includes central serous retinopathy ([CSR]/RPED) and dry eye symptoms. The CSR/RPED may cause visual field defect or symptoms such as blurred vision, visual floaters, or photopsia, and were apparent in trials with erdafitinib and pemigatinib after a median time of 50 or 62 days, respectively (76, 77). The role of FGFR3 inhibition in the ocular toxicity is unknown at present. Nevertheless, a potential role of FGFR3 in the retinal toxicity observed with less specific FGFR inhibitors cannot be entirely excluded based on currently available data, as all 4 FGFR genes have been reported to be expressed in the lens and the expression of FGFR3 in retina has been observed in zebrafish and monkey (78, 79). Therefore, subjects with preexisting retinal or corneal disease will be excluded from the study. In Phase 1 FIH TDU16639/TDR16640 studies in healthy adults, no ocular findings were reported. No SAR442501-related ophthalmic findings were noted in the 6-month juvenile toxicity study in monkeys, including at the Spectral Domain Optical Coherence Tomography examination. Additionally, no SAR442501-related

microscopic findings were observed in the eyes from mice and monkeys in the repeat dose and juvenile toxicity studies. Corneal opacity/keratopathy associated with mineralization in the corneal epithelium have been described in rats treated with erdafitinib or pemigatinib.

Guidance for the Investigator

Minimization measures: patients with retinal disorders should be excluded from the studies.

Assessment measures: at-visit ophthalmological examination should be performed in the clinical studies. Visual acuity and/or Amsler grid assessment to be considered in participants who are capable of complying with the assessments, ocular coherence tomography (OCT) exam in ages ≥5; Dilated retinal exam in ages 0-5.

Hyperphosphatemia:

Hyperphosphatemia has been observed in both nonclinical and clinical studies with the recently approved pan-FGFR inhibitors, erdafitinib and pemigatinib.

In nonclinical SAR442501 program, increased phosphorus levels were not observed in toxicology 1-month studies (mouse and monkey). However, in the Good Laboratory Practice (GLP) subcutaneous 6-month toxicity study in juvenile monkeys, transient non dose-dependent increases in phosphorus were apparent in males at [redacted] on Week 13 only.

In both FIH Phase 1 TDU16639/TDR16640 studies we observed a total of 19 AESIs for hyperphosphatemia, including 1 AESI in a placebo subject and 18 in subjects who received SAR442501 (TDU16639: 4 events in subjects receiving SAR442501 and 1 in placebo; TDR16640: 14 events in subjects receiving SAR442501 and none in placebo). All events of hyperphosphatemia resolved spontaneously, and no subject needed to withdraw from the study due to high phosphate levels. We did not observe a dependency between the phosphate level increases and the doses administered, nor between the number of AESI occurrences and the dosing cohorts.

Guidance for the Investigator

Normal serum phosphate is an inclusion criterion and is monitored throughout the studies to further exclude the possibility of hyperphosphatemia caused by SAR442501.

At screening: subjects with serum phosphate above normal level for an age group should not be enrolled.

During the study: subjects with serum phosphate increase above managed level (for an age group) should temporarily discontinue SAR442501 and their biological parameters should be observed. Restarting at a lower dose is permitted depending on the judgement of the Investigator.

Normal serum phosphate is an inclusion criterion and is monitored throughout the study to further exclude the possibility of hyperphosphatemia caused by SAR442501.

Embryo-fetal toxicity: Based on findings in animal studies and mechanism of action, embryo fetal toxicity was labeled in Warnings and Precautions of the prescribing information of erdafitinib and pemigatinib. Oral administration of erdafitinib or pemigatinib to pregnant rats during the period of organogenesis caused malformations and embryo fetal death at maternal exposures that were less than the human exposures at the maximum human recommended dose based on area under curve (AUC) (76, 77). However, no SAR442501 related adverse changes were observed in in the definitive embryo-fetal toxicity studies in mice and rabbits up to the highest doses tested, [redacted] in mice and [redacted] in rabbits.

Guidance for the Investigator

A close monitoring is to be performed in case of an on-treatment pregnancy event (AESI) and a follow-up on the pregnancy outcome and on the child health status.

Immunogenicity: Systemic administration of monoclonal antibodies can be associated with production of ADA which can predispose patients to administration-related reactions and even alter the PK and/or activity of the molecule in cases where the ADA are Nab.

Guidance for the Investigator

Clinical laboratory monitoring (anti-drug antibodies) is a planned monitoring activity in this study.

[redacted]

Guidance for the Investigator

Clinical examination including visual body examination and AE recording are planned to be performed in this study.

Study Procedures

Blood draws and/or study drug injections carry the risk of bleeding, infection, and discomfort. The mitigation strategy includes the use of pressure dressing to decrease the risk of bleeding, cleaning of the procedure site and aseptic technique to reduce the risk of infection, and administration of anesthetics and analgesics to minimize the discomfort of the procedure.

Other

This study includes various imaging studies and associated potential risks.

X-rays and DXA scan carry the risk of radiation. As part of the risk mitigation strategy, radiation doses used will be as low as reasonably achievable without compromising the quality of patient care and study. A protective shield should be used when possible, including a lead apron or other shield.

MRI carries the risk of discomfort, claustrophobia and sedation. As part of the risk mitigation strategy, anesthetics may be required to help the participants relax or sleep during the procedure. While the participant is sedated and the MRI is taking place, he or she will be monitored constantly. Breathing, heart rate, blood-oxygen level, and blood pressure will be tracked. The staff will report any concerns to the doctor, in which case additional sedation may be needed or the test can be aborted and rescheduled.

2.3.2 Benefit assessment

The efficacy of SAR442501 has been evaluated in mice and juvenile monkeys in the preclinical setting. [redacted] of SAR442501 administered SC [redacted] resulted in a significant improvement in growth plate volume paired with trends toward increasing growth plate thickness and increased bone length in the skull, vertebral column, and long bones. Administration of [redacted] of SAR442501 [redacted] SC to juvenile cynomolgus monkeys [redacted] resulted in significant increases in tibia growth and growth rate at 84 days compared to those administered vehicle. These preclinical studies suggest SAR442501 has the ability to significantly improve the growth abnormalities that characterize ACH and therefore serve a therapeutic benefit to pediatric participants with ACH.

2.3.3 Overall benefit/risk conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with SAR442501 are justified by the anticipated benefits that may be afforded to pediatric participants with ACH.

Pediatric participants will be age stratified and assigned to [redacted]. The safety data obtained from [redacted] serves as a way to minimize potential risks to all study participants. This leads to a manageable profile on the risk side. Additionally, those who were enrolled to receive the [redacted] will have an opportunity to cross over to a [redacted] dose in later studies. This [redacted], selected based on efficacy data from this trial, should improve growth parameters and disease complications discussed in Section 2.3.2 and in the endpoints in Section 3 Objectives and Endpoints.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 4 - Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of SAR442501 administered SC twice weekly for 52 weeks in participants from birth to <12 years of age with ACH	The occurrence of AEs, SAEs, and AESIs during the TE period
Secondary	
To evaluate changes in growth parameters following twice weekly SC injections of SAR442501	Change from baseline to Week 26 and Week 52 in AGV Z-score Change from baseline to Week 26 and Week 52 in AGV (cm/year) Change from baseline to Week 26 and Week 52 in height Z-score
To evaluate changes in body proportionality following twice weekly SC injections of SAR442501 for 52 weeks	Change from baseline to Week 26 and Week 52 in the following calculated ratios: - Upper to lower body segment ratio - Upper to lower extremity ratio - Sitting to standing height ratio (crown-to-rump length to total length for infants) - Arm span to height ratio - Upper arm to forearm length ratio - Upper leg to lower leg ratio - Head circumference to height ratio
To evaluate changes in foramen magnum parameter via magnetic resonance imaging (MRI) following twice weekly SC injections of SAR442501 (Stage 2 only)	Change from baseline to Week 52 in brainstem, skull, and spine morphometric and volumetric parameters in participants birth to age <3 years (Stage 2 only)
To evaluate changes in health-related QoL as measured by the PedsQL Inventory Generic Core Scale	Change from baseline to Week 26 and Week 52 in social, emotional, and school functioning scores as well as the Psychosocial Health Summary Score, Physical Health Summary Score, and Total Score pooled across instrument versions by age
To evaluate changes in fatigue as measured by the PedsQL Multidimensional Fatigue Scale	Change from baseline to Week 26 and Week 52 in general fatigue, sleep/rest fatigue and cognitive fatigue scores and Total Score
To evaluate changes in pain as measured by the PedsQL Pediatric Pain Questionnaire	Change from baseline to Week 26 and Week 52 in PPQ score pooled across instrument versions by age

To evaluate changes in fatigue as measured by the PedsQL Multidimensional Fatigue Scale	Change from baseline to Week 26 and Week 52 (those ages ≥5 at enrollment) in mobility and symptom rating (STEMS) score
To evaluate changes in pain as measured by the PedsQL Pediatric Pain Questionnaire	
To collect developmental milestone data as measured by the Achondroplasia Developmental Recording Form	Change from baseline to Week 52 (those ages birth to <3 years at enrollment) in achievement of gross motor, fine motor, communication, and feeding milestones
To evaluate the pharmacokinetic profile of SAR442501 following twice weekly SC injections	Plasma concentration and parameters of SAR442501
To characterize changes from baseline in bone/collagen biomarkers following twice weekly SC injections of SAR442501	Change from baseline to Week 26 and Week 52 in CXM, osteocalcin, bone-specific alkaline phosphatase, P1NP, CTX levels
To evaluate the immunogenicity of SAR442501 administered as twice weekly SC injections	Number of participants with TE anti-drug antibodies (ADA), number of treatment-induced ADAs, number of treatment-boosted ADAs from baseline to Week 26 and Week 52, ADA status at each visit, ADA titer at each visit
To evaluate clinical signs and symptoms of foramen magnum stenosis following twice weekly injections of SAR442501 (Stage 2)	Number and percentages of participants with changes in neurological examination findings from baseline to Week 26 and Week 52 (Stage 2 only)
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: ACH = Achondroplasia; ADA = Anti-drug antibody; AEs= adverse events; AESIs = adverse events of special interest; AGV = Annualized growth velocity; CTX = collagen-Type 1 C-Telopeptide; CXM = collagen X biomarker; P1NP = procollagen type 1 N-terminal propeptide; PedsQL = Pediatric Quality of Life; [redacted]; PPQ= present pain and worst pain rating; MRI= magnetic resonance imaging; QoL = Quality of life; SAEs= serious adverse events; SC = subcutaneous; STEMS = Screening Tool for Everyday Mobility and Symptoms; TE = Treatment-emergent.

For China, please see Section 10.8 for details.

More details are provided in Section 9.2.

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the safety and efficacy assessments chosen for use in this study are considered well established and relevant in ACH. In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy to minimize risks to participant safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2 open-label, multicenter, 2-stage sequential cohort dose escalation study to evaluate the safety, tolerability, PK, PD, and efficacy of SAR442501 in pediatric participants with genetically confirmed ACH.

Participants who have completed at least 24 weeks (or 12 weeks for those younger than age 6 months at the time of OBS16647 enrollment) of data collection in the OBS16647, a longitudinal study to evaluate growth measurements and digital biomarkers in pediatric participants with ACH, will be eligible to enroll in this DRI16646 study (see inclusion/ exclusion criteria in Section 5).

The study will have two stages:

- In Stage 1 pediatric participants between the ages ≥3 to <12 years will enroll in a 52-week sequential cohort dose escalation period (primary treatment period) followed by an extended treatment period.
- In Stage 2 pediatric participants between the ages birth to <3 years will enroll in a 52-week sequential cohort dose escalation period (primary treatment period) followed by an extended treatment period.

In both stages, after the Week 52 visit, participants will enter the extended treatment period. During the extended treatment period, each participant will return for on-site visits every 12 weeks until the last participant enrolled in the study completes 52 weeks of the extended treatment period. Therefore, the duration of the extended treatment period will vary per participant. It will last between approximately 52 and 216 weeks.

In Stage 1, the participants will be divided into 2 age cohorts based on the ages of participants at the time of enrollment (date of first dose of IMP), and each age cohort will be divided into [redacted] subgroups [redacted]. Cohort 1 will include children with ACH between the ages of ≥6 to <12 years, and Cohort 2 will include children with ACH between the ages of ≥3 to <6 years.

In Stage 2 the participants (Cohort 3) will be between birth and age <3 years at the time of enrollment (date of first dose of IMP). These participants will be divided into [redacted] subgroups [redacted]

Enrollment will proceed as follows (see Figure 1):

Stage 1:

Initial dosing with [redacted] will occur in Cohort 1A, comprising the oldest participants (ie, between ≥6 and <12 years). Two participants in Cohort 1A will be enrolled and monitored. The accumulated safety data, including TEAEs will be reviewed by the DMC after both participants have completed at least 8 weeks of treatment. After review and approval by the DMC, then the following cohorts/ subgroups may open for enrollment in the manner detailed below:

- Cohort 1B: 2 participants between the ages ≥6 and <12 years will be enrolled to receive the dose of [redacted].
- Cohort 1C: After the 2 participants have been enrolled in Cohort 1B, then the next 12 eligible participants between the ages of ≥6 and <12 years will be randomized in a [redacted] manner into Cohort 1C to receive [redacted] of study intervention. No additional DMC meeting is required between the opening of Cohorts 1B and 1C.
- Cohort 2A: In parallel with Cohort 1B enrollment, Cohort 2A enrollment will start: 2 participants between the ages ≥3 and <6 years will be enrolled to receive the dose of [redacted].

The accumulated safety data available from all these cohorts (Cohorts 1A, 1B, 1C, and 2A), including TEAEs, will be reviewed by the DMC after both participants in Cohorts 1B and 2A have completed at least 8 weeks of treatment. If the stopping criteria are not met, and after review and approval by the DMC (see Section 10.1.5.2 Study stopping criteria), the following may occur:

- Cohort 2B: 2 participants between the ages of ≥3 and <6 years will be enrolled to receive the dose of [redacted].
- Cohort 2C: After the 2 participants have been enrolled in Cohort 2B as above, then the next 4 participants eligible between the ages of ≥3 and <6 years will be randomized in a [redacted] manner into Cohort 2C to receive [redacted] the dose of [redacted]. No additional DMC meeting is required between the opening of Cohorts 2B and 2C.

The accumulated safety data available from all cohorts (Cohorts 1A, 1B, 1C, 2A, 2B, and 2C) including TEAEs, will be reviewed by the DMC after all participants in Cohorts 1A, 1B, 1C, 2A, 2B, and 2C have completed at least 26 weeks of treatment. [redacted]

Stage 2:

Initial dosing with [redacted] will occur in Cohort 3A, comprising participants between birth and age <3 years. Two participants in Cohort 3A will be enrolled and monitored. The accumulated safety data, including TEAEs will be reviewed by the DMC after both participants have completed at least 8 weeks of treatment. If the stopping criteria are not met, and after review and approval by the DMC (see Section 10.1.5.2 Study stopping criteria), then the following cohorts/ subgroups may open for enrollment in the manner detailed below:

- Cohort 3B: 2 participants between birth and age <3 years will be enrolled to receive the dose of [redacted].
- Cohort 3C: After the 2 participants have been enrolled in Cohort 3B as above, then the next 8 participants eligible between birth and age <3 years will be randomized in a [redacted] manner into Cohort 3C to receive [redacted] the dose of [redacted]. No additional DMC meeting is required between the opening of Cohorts 3B and 3C.

Extended Treatment Period:

After the second interim analysis (Section 9.3), the investigator will be permitted to discuss the option of treatment discontinuation or a dose change (depending on the results of prior interim analyses) if the participant has experienced lack of improvement on the originally assigned dose. "Lack of improvement" will be defined as no change or a decrease from baseline AGV Z-score as established by data collected in the study. If the investigator wishes to discontinue the IMP or change the participant's dose due to suspected "lack of improvement," the investigator should inform the Sponsor so that the Sponsor biostatistical team may calculate the individual change in AGV Z-score for the participant to confirm whether "lack of improvement" is valid per the definition above. Otherwise, the participant will remain on the dose assigned at enrollment throughout the entire study including the extended treatment period.

Safety monitoring:

Comprehensive safety monitoring will be conducted for all participants throughout the duration of the study. Safety monitoring includes vital signs, laboratory assessments, ophthalmological testing, bone age X-ray, lower extremity X-ray, spine X-rays, DXA scan (Stage 1 only), and AE collection at the frequency specified in the SoA (Section 1.3). Laboratory and ophthalmological assessment safety data will be performed both as scheduled and as needed throughout the treatment period. Participants may be observed for a longer duration and/or additional visits may be added for further safety assessment at the discretion of the Investigator and in consultation with the Sanofi Medical Monitor.

Study intervention administration:

The first [redacted] administrations of study intervention will be done at the study site. Each time the medication is administered on site, the participant will be monitored for 30 minutes after the injection by study staff trained in recognizing acute hypersensitivity reactions. Medication and equipment to treat such reactions must be readily available at the study site. In the judgment of the Investigator, [redacted]. In case of any [redacted] or other AEs, the participant must contact the site as soon as possible for reporting, timely monitoring of any worsening of the events, and decision for best evaluation/treatment by the Investigator (including on-site visit if needed). The Investigator may also proactively contact the participant the day of [redacted] to assure absence of any events or to assure their best management if such occur. Phone/telemedicine calls may be performed between study site visits to assess AEs, record concomitant medications, confirm drug compliance, and to answer questions throughout the duration of the study when needed. Please refer to the SoA (Section 1.3) for additional details.

Efficacy assessments:

There will be a total of at least 11 required on study site visits throughout the study. **Visit 1/Screening, Visit 2/Week 0/Days 1 to 4, Visit 3/Week 8/Day 57, Visit 4/ Week 13/ Day 92, Visit 5/Week 26/Day 183, Visit 6/ Week 39/ Day 274, and Visit 7/Week 52/ Day 365** will take place during the primary treatment period. After the Week 52 visit, participants will enter the extended treatment period. During this, each participant will return for on-site visits every 12 weeks until the last participant enrolled completes 52 weeks of the extended treatment period. Therefore, the duration and number of visits during the extended treatment period will vary per participant. After the final visit during the extended treatment period, participants will enter a 4 week post-treatment observation phase, after which the end-of-study visit or phone call will take place. To reduce their burden, participants will have the option to have several visits replaced by decentralized visits, if permitted by the local regulations and based on study site/participant's decision as per SoAs in Section 1.3. All procedures planned in-between the on-site visits may be performed remotely. Please see the SoA (Section 1.3) for details.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.2.1 Participant input into design

In order to evaluate the attractivity and barriers to clinical trial of ACH, 6 advisory panels were conducted, in which 25 caregivers of individuals with ACH or adults living with ACH globally participated. The Sponsor provided an overview of the proposed clinical study design, and the following points were shared: eligibility criteria, study visits, and assessments. The panel participants did not raise any major concerns. The panel participants appreciated that this study was linked to a prior non-interventional study. The feedback from the advisory panel has been factored into the current clinical study design.

4.3 JUSTIFICATION FOR DOSE

[redacted]

[redacted]

4.4 END-OF-STUDY DEFINITION

The end of the study is defined as the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

Age

I 01. At the time of signing the ICF, participants must be aged birth to <12 years.

Type of participant and disease characteristics

I 02. Participants must have ACH with a confirmed mutation in the FGFR3 gene as confirmed in the OBS16647 study.

I 03. Participants must have completed at least 24 weeks (or at least 12 weeks for those age <6 months of age at the time of OBS16647 enrollment) of OBS16647 pretreatment growth assessment before Week 0/ Day 1/ Visit 2.

I 04. Participants must have at least 1 documented height (sitting or standing) or total length from OBS16647 at least 24 weeks (or 12 weeks for those age <6 months at the time of OBS16647 enrollment), but no greater than 52 weeks, prior to Week 0/Day 1/ Visit 2.

I 05. Participants and/or parent(s) or legal representative(s) must be willing and able to perform all the study procedures to the best of their physical ability.

Weight

Not applicable.

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

I 06. All

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

- If sexually active, participant is willing to use a condom when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant during the study intervention period and for at least 2 months after the last administration of study intervention)

b) Female participants with childbearing potential (ie, postmenarchal females)

- A postmenarchal female participant that is heterosexually active is eligible to participate:
  - If she agrees to use a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the study intervention period (to be effective before starting the intervention) and for at least 2 months after the last administration of study intervention.
  - If she is not pregnant or breastfeeding.
- A postmenarchal female participant that is heterosexually active must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) during screening before the first administration of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

  Note:

  For a female participant if the childbearing potential changes after start of the study (eg, a premenarchal female participant experiences menarche) or the risk of pregnancy changes (eg, a female participant who is not heterosexually active becomes active),

  OR

  - For a male participant who becomes heterosexually active after start of the study, the participant must discuss this with the Investigator, who should determine if a female participant must begin a highly effective method of contraception or a male participant must use a condom.

Informed consent

I 07. Parent(s) or legal representative(s) capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) of the protocol which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Have hypochondroplasia (or the N540K mutation) or short stature condition other than ACH (eg, trisomy 21, pseudochondroplasia)

E 02. Long bone fracture within 3 months of enrollment (Week 0/Day 1/Visit 2)

[redacted]

[redacted]

E 05. Current evidence of corneal or retinal disorder/keratopathy.

[redacted]

E 08. Participants have had a previous surgical intervention involving the foramen magnum (Stage 2 only).

[redacted]

E 11. Hyperphosphatemia (>1.3 ULN for age).

[redacted]

E 13. Have a history of growth plate closure.

Prior/concomitant therapy

E 14. Participants have received any dose of medications or investigational product, including human growth hormone, IGF-1, intended to affect participants' stature or body proportions between the completion of OBS16647 and start of enrollment (Week 0/Day 1/Visit 2).

[redacted]

Other exclusions

Additional exclusion criteria as per Amended protocol 02:

Medical Conditions

E 22. Have an existing diagnosis of any of the following which would in the opinion of the investigator significantly impact longitudinal growth:

- Celiac disease
- Insulin-requiring diabetes
- Inflammatory bowel disease
- Cystic fibrosis
- Severe cardiovascular disease
- Any other condition that may in the opinion of the investigator significantly impact longitudinal growth

5.3 LIFESTYLE CONSIDERATIONS

No lifestyle modifications are required for this study:

5.3.1 Meals and dietary restrictions

Not applicable.

5.3.2 Caffeine, alcohol, and tobacco

Not applicable.

5.3.3 Activity

Participants should abstain from strenuous exercise for 12 hours before each blood collection for clinical laboratory tests.

5.3.4 Other restrictions

Not applicable.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

In cases where original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment, the participant can be rescreened one time for this study. Participants who are rescreened are required to sign a new ICF, and should be assigned a new study participant number. In these cases, participants may need to repeat some of the screening procedures based on the Sponsor's judgment.

5.5 CRITERIA FOR TEMPORARILY DELAYING

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9) should be considered for screening, enrollment, or administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

After confirmation of eligibility to participate in the study, participants will receive SAR442501.

A complete description of IMP, including preparation for SC administration will be provided in the pharmacy manual available to the clinical site.

Table 5 - Study interventions(s) administered

Intervention label	**SAR442501**	**SAR442501**	**SAR442501**
Intervention name	SAR442501	SAR442501	SAR442501
Intervention description	[redacted]		
Drug	Drug	Drug	Drug
Dose formulation	[redacted]		
Unit dose strength Participant weight range			
Dosage level(s)	[redacted] BIW	[redacted] BIW	[redacted] BIW
Route of administration	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
Experimental	Experimental	Experimental	Experimental
IMP	IMP	IMP	IMP
Packaging and labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement
NA	NA	NA	NA

Abbreviations: AxMP= auxilliary medicinal product; BIW= twice weekly; IMP= investigational medicinal product; NA= not applicable; [redacted]

* Additional formulations of [redacted] (once available) would be used as defined in the Pharmacy Manual. Note that the doses obtained would be the same across all formulations. Concentration is achieved by the mixture of SAR442501 and [redacted] and matching placebo, for specific dilution.

Table 6 - Study arm(s

Arm title	SAR442501 (active)
Arm type	Experimental
Arm description	Participants will receive one of the following [redacted] for 52 weeks.
Associated intervention labels	Not applicable

The investigational product may be supplied at the site or from the Principal Investigator/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.1.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

6.1.1 Devices

Not applicable.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

1. The Investigator/designee, or healthcare professional/parent/legal representative/caregiver for remote dosing must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized individuals, including trained caregivers (after training and approval by the Investigator and Sponsor) and home nurses as per local regulations may supply, prepare, or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. Study intervention shipment and storage for participants who will have remote injections are provided in the pharmacy manual.
4. The Investigator, institution, or the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the study intervention/ device (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.4.10).

A potential defect in the quality of study intervention may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the study intervention and eliminate potential hazards.

Under no circumstances will the Investigator supply study intervention to a third party (except for direct to participant [DTP] shipment, for which a courier company has been approved by the Sponsor), allow the study intervention to be used other than as directed by this clinical trial protocol, or dispose of study intervention in any other manner.

6.3 ASSIGNMENT TO STUDY INTERVENTION

If more than one dose cohort within a participant's age range is open for enrollment at the time the participant signs the ICF (eg, in Stage 1, after 2 participants between ages ≥6 and <12 years have been enrolled, both dose cohorts in Cohort 1C will open for enrollment), then the participant will be randomized into one of the 2 available dose cohorts in a [redacted] manner. Please see Figure 1 for details.

- The randomized intervention kit number list is generated centrally by Sanofi.
- The IMPs are packaged in accordance with this list.
- The randomization and intervention allocation will be performed centrally by an interactive response technology (IRT). The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it.
- The randomization is conducted for three age groups separately (see Section 4.1): In Stage 1, ages ≥6 to <12 years, ≥3 to <6 years, and for Stage 2, birth to <3 years.
- A randomized participant is one from the screened population who has been allocated to a randomized dose regardless of whether the intervention dose was received or not.
- For these age groups, randomization will occur at the following times (see Section 4.1):

  In Stage 1:

  - Cohort 1C (ages ≥6 to <12 years): after both participants in Cohort 1B (ages ≥6 to <12 years, [redacted]) have enrolled, Cohort 1C will open and all 12 participants in Cohort 1C will be randomized in a [redacted] manner to receive either [redacted] of study intervention.
  - Cohort 2C (ages ≥3 to <6 years): after both participants in Cohort 2B (ages ≥3 to <6 years, [redacted]) have enrolled, Cohort 2C will open and all 4 participants in Cohort 2C will be randomized in a [redacted] manner to receive [redacted] of study intervention.
  - In Stage 2:

    Cohort 3C (birth to age <3 years): after both participants in Cohort 3B (birth to ages <3 years, [redacted]) have enrolled, Cohort 3C will open and all 8 participants in Cohort 3C will be randomized in a [redacted] manner to receive [redacted] of study intervention.
- A participant cannot be randomized more than once in the study.

6.4 BLINDING

Blinding is not applicable to this study.

6.5 STUDY INTERVENTION COMPLIANCE

- The following describes methods used by the Investigator or his/her delegate to ensure that the IMP was administered:
  - IMP compliance:
  - Intervention units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract)
  - The Investigator counts the number of vials, etc, remaining in the returned packs, and fills in the Intervention Log Form
  - The Investigator records the dosing information on the appropriate page(s) of the case report form (CRF)
  - The monitor in charge of the study then checks the CRF data by comparing them with the study intervention which he/she has retrieved and intervention log forms.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the study site will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

After proper training and approval from authorized study staff and Sponsor, the participant's caregiver or authorized home health nurse may administer the study intervention(s) at home as per local regulations. When participants or caregivers administer study intervention(s) at home, or a nurse administers the study intervention(s) remotely, compliance with study intervention will be assessed at each visit. Compliance will be assessed by diary record completed by the caregiver at home and direct questioning, counting returned vials, etc during the site visits, and documented in the source documents and relevant form. Deviations from the prescribed dosage regimen have to be recorded.

A record of the quantity of SAR442501 dispensed to and administered to each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

No doses should be missed. Noncompliance is defined as missing 4 consecutive doses (not for cause, such as when the missed doses are required by the protocol due to an AE or SAE) or 13 total doses during the 52-week treatment period. As they are identified, the Investigator should discuss noncompliant participants on a case by case basis with the Sponsor.

6.6 DOSE MODIFICATION

Dose modification will be performed in cases of reinitiation of treatment (See Section 7.1.5 Rechallenge) after temporary treatment discontinuation.

See Section 7.1.4 Temporary discontinuation for details regarding reasons for temporary treatment discontinuation. If the treatment administration was held due to an abnormal scheduled or unscheduled visual acuity or ophthalmological clinical examination assessment result:

If intervention was held due to hyperphosphatemia (or other relevant bone metabolism ion imbalance) either as judged to be clinically significant by the Investigator or ≥1.3 × ULN:

6.6.1 Retreatment criteria

Not applicable to this study.

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

6.8 TREATMENT OF OVERDOSE

Symptomatic overdose with IMP:

- An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the

intended dose within the intended therapeutic interval, adjusted according to the tested drug, OR any [redacted] separated by <1 day.

There is no specific treatment available for an overdose of SAR442501.

In the event of an overdose, the Investigator should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Evaluate the participant to determine, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Obtain a plasma sample for PK analysis as soon as possible.
- Document appropriately in the CRF.

6.9 PRIOR AND CONCOMITANT THERAPY

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

The following medications are to be excluded in the following timeframe before enrollment and during the course of the study:

- Daily therapy for at least 2 weeks of hydrocortisone (>10 mg/m^2/day), prednisone/prednisolone/methylprednisolone (any dose), or dexamethasone (any dose) within 6 months of enrollment (week (W)0/Day (D)1) or at any point during the study
- Any dose of medications or investigational product, including human growth hormone, IGF-1, intended to affect participants' stature or body proportions within 52 weeks of enrollment (W0/D1) or at any point during the study

- Any investigational product or investigational medical device within 30 days of enrollment (W0/D1) or at any point during the study.

The following medications excluding vaccines can be allowed between screening and enrollment and during the course of the study at the discretion of the Investigator:

- If serum 25-hydroxy-vitamin D (25(OH)D) levels fall below 20 ng/mL, oral supplementation with vitamin D formulations may be provided.
- Calcium replacement therapy in those participants with evidence of secondary hyperparathyroidism (defined as PTH above the normal range).

6.9.1 Rescue medicine

Not applicable to this study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1).

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the participant not to re-expose the participant to the study intervention at any time.

The study intervention should be continued whenever possible. In case the study intervention is stopped, it should be determined whether the stop can be made temporarily; permanent study intervention discontinuation should be a last resort. Any study intervention discontinuation should be fully documented in the CRF.

Stopping rules described in Section 10.1.6 should be applied.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for the early treatment discontinuation visit and follow-up visits 4 weeks after the last study intervention administration. In addition, if those participants discontinued treatment prior to the Week 26 visit, growth parameters (including height, weight, and body proportionality measurements) should be collected at additional follow-up visits at Weeks 26 and 52. If the participant discontinued treatment after the Week 26 visit but before the Week 52 visit, growth parameters should be collected at an additional follow-up visit at Week 52. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The participants may withdraw from treatment with the study intervention if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation, and this should be documented in the CRF or e-CRF.
Study-specific reasons for permanent treatment discontinuation and study termination:

- Growth plate closure (epiphyseal fusion).
- Clinically significant and persistent central serous retinopathy (CSCR) defined as: CSCR demonstrated on ophthalmological assessment (OCT and/or dilated retinal examination) that persists despite holding study intervention for at least 4 weeks.
- Significant and persistent hyperphosphatemia defined as either phosphorous level ≥1.3 × ULN or any other clinically significant level of hyperphosphatemia per the Investigator's judgment, that persists after holding study intervention for 2 weeks (at least 4 doses), and after rechallenging at the next lowest dose (see Section 7.1.5).

Other reasons for permanent treatment discontinuation and study termination may include:

- If noncompliance is identified, the Investigator should discuss noncompliant participants on a case by case basis with the Sponsor prior to permanent treatment discontinuation or study termination;
- Participant becomes pregnant during study;
- Participant develops exclusion criterion/concurrent disease that, in the opinion of the Investigator or the Sponsor, justifies removal of the participant from the study to ensure participant's safety or maintain the quality of the study;
- Participant needs to receive other study intervention;
- Participant develops an anaphylactic or other severe hypersensitivity reaction
- Participant develops a severe injection site reaction
- Participant experiences an AE considered intolerable by participant or Investigator;
- Sponsor terminates the study.

Any abnormal laboratory value will be rechecked for confirmation before making a decision of permanent discontinuation of the study intervention for the concerned participant.

Handling of participants after permanent intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the study intervention including a PK sample, if appropriate.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Refer to Appendix 6 (Section 10.6) for suggested actions and follow-up assessments related to liver abnormalities and other safety parameters.

7.1.3 QTc stopping criteria

Not applicable.

7.1.4 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency [Appendix 9 (Section 10.9: Contingency measures for a regional or

national emergency that is declared by a governmental agency)]. For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

Temporary discontinuation of study intervention should be considered in case of but not limited to the following (see Section 7.1.1):

- The participant develops any ocular finding such as strabismus or subjective change in visual acuity that could be in relationship to the study treatment as judged by the Investigator.
- CSCR as confirmed by an ophthalmologist on either OCT or dilated retinal exam.
- The participant develops significant and persistent hyperphosphatemia defined as either phosphorous level ≥1.3 × ULN or any other clinically significant level of hyperphosphatemia per the Investigator's judgment.

Temporary intervention discontinuation decided by the Investigator corresponds to more than 1 dose not administered to the participant.

7.1.5 Rechallenge

Reinitiation of intervention with the study intervention will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the study intervention in the occurrence of the concerned AE was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2).

If the treatment administration was held due to an abnormal scheduled or unscheduled visual acuity or ophthalmological clinical examination assessment result, reinitiation of intervention can be done as described in Section 6.6 Dose modification.

If intervention was held due to hyperphosphatemia (or other relevant bone metabolism ion imbalance) either as judged to be clinically significant by the Investigator or ≥1.3 × ULN, reinitiation of treatment can be done according to Section 6.6 Dose modification.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected

at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- If the participant withdraws consent from the study, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent, as per applicable clinical regulation(s).
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the study intervention, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized or reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls, and, if necessary, a certified letter to the participant's last known mailing address or local

equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA Section 1.3. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local Health Authority/ethics requirements (see Appendix 9 [Section 10.9]).
- The maximum amount of blood collected from each participant in an 8 week period, including any extra assessments that may be required, will not exceed 3 mL per kg.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

8.1 ADMINISTRATIVE PROCEDURES

Not applicable.

8.2 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy and/or immunogenicity assessments are provided in the SoA Section 1.3.

8.2.1 Efficacy assessments

8.2.1.1 Growth measurements

Each measurement (excluding weight) will be taken twice. If measurements are within 1 cm of one another, the average will be utilized. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated until they are within 1 cm. All measurements should be recorded, but only the 2 measurements within 1 cm should be entered into the electronic case report form (eCRF). Measurements not taken in the midsagittal plane should be taken on the right side of the body when possible. Growth measurements will include the following:

- Height (sitting and standing height will be measured for children who are 2 years of age or older and can stand independently; for infants and children who are unable to stand, these measurements will be crown-to-rump length and total length)
- Arm span
- Weight
- Circumference (head, waist)
- Length (head, upper arm, forearm, hand, palm, middle finger, upper leg, lower leg, foot)
- Width (palm and foot)
- Length from the sole of the foot to the symphysis pubis (lower body segment)

Body mass index (BMI) and body ratios (upper-to-lower body segment ratio, upper-to-lower extremity ratio, sitting-to-standing height ratio [crown-to-rump length to total length for infants], arm span to height ratio, upper arm to forearm length ratio, upper leg to lower leg length ratio, and head circumference to height ratio) will be calculated by the Sponsor.

8.2.1.2 MRI

Magnetic resonance imaging (MRI) will be collected to measure foramen magnum and other brainstem, skull, and spine morphometric parameters in participants birth to age <3 years (Stage 2 only). Images will be reviewed and reported by a central reader.

8.2.1.3 Clinical outcome assessments (COAs)

Clinical outcome assessments have been included to measure signs, symptoms, and impacts associated with ACH from the perspective of study participants, caregivers, and clinicians. The COAs should be completed before dosing, before completing any other health data forms, and before participating in any clinical assessments by the study Investigator or other healthcare provider(s). Each COA is described in further detail below.

8.2.1.3.1 Pediatric Quality of Life (PedsQL)

The PedsQL core scale is a brief, standardized, generic instrument that is used to measure HRQOL in various pediatric conditions (82). This scale consists of 23 items across the domains of physical, social, emotional, and school functioning. The standard version of this instrument uses a recall period of the past month, and responses range from “Never” to “Almost Always” on a 5-point verbal rating scale. Higher scores indicate better HRQOL and lower symptoms/problems (83). The PedsQL has been evaluated in qualitative and quantitative research with caregivers and individuals with ACH (84, 85) and has been used in ACH clinical trials (74). Mean social, emotional, and school functioning scores as well as the Psychosocial Health Summary Score, Physical Health Summary Score, and Total Score will be calculated.

Caregivers will complete the PedsQL Core Scale and Multidimensional Fatigue Scale parent proxy report for participants 2 years of age and older and the Pediatric Pain Questionnaire for participants 5 years of age and older. In addition, participants 8 years of age and older will

complete the PedsQL child self-report for all PedsQL scales. PedsQL scales will be completed as summarized by the age ranges in the table below (Table 7).

Table 7 - PedsQL assessments by age range

Version	Reporter
Child report (8 to12 years of age)	Child
Teen report (13 to 18 years of age)	Chlid
Parent report for toddlers (2 to 4 years of age)*	Parent
Parent report for young children (5 to 7 years of age)	Parent
Parent report for children (8 to 12 years of age)	Parent
Parent report for teens (13 to 18 years of age)	Parent

*Core Scale and Multidimensional Fatigue Scale only

8.2.1.3.2 PedsQL Multidimensional Fatigue Scale

The PedsQL Multidimensional Fatigue Scale consists of 18 items across three domains: general fatigue, sleep/rest fatigue and cognitive fatigue (comprised of 6 items each) (86). The standard version of this instrument uses a recall period of the past month, and responses range from "Never" to "Almost Always" on a 5-point verbal rating scale. Higher scores indicate lower symptoms/problems (83). Mean scale scores for each domain as well as the Total Score will be calculated.

8.2.1.3.3 PedsQL Pediatric Pain Questionnaire

The PedsQL Pediatric Pain Questionnaire assesses current pain and worst pain intensity in the last week using a Visual Analog Scale as well as pain location using a body map (87). Current and worst pain are scored separately, and scoring is based on the line length to the nearest 0.5 cm (5 mm). Higher scores indicate greater levels of pain intensity. The pain location item is not scored. The PedsQL Pediatric Pain Questionnaire will only be administered in participants ages 5 years of age and older using both self-report (ages 8 and older) and parent proxy report (ages 5 and older) forms in all countries. The toddler version (2 to 4 years, parent proxy report form) will not be administered in any country due to:

1. Literature indicating low relevance of pain in this age group (88),
2. Potential for increased challenges for accurate parent proxy reports of pain in this age group relative to older children, and
3. Lack of available translations in target countries.

8.2.1.3.4 Achondroplasia Developmental Recording Form

For participants <3 years of age, achievement of developmental milestones will be assessed using the ACH developmental recording form. The ACH developmental recording form was developed to aid clinicians in monitoring the development of young children with ACH over time across multiple skill areas (89). This form allows developmental milestones to be recorded and is not a formalized screening tool or assessment. The form measures the domains of gross motor function,

fine motor function, communication, and feeding via participant reports to the Investigator. The form depicts the cumulative percentage distributions for children with ACH for each item as well as norms for reference based on the Denver II test, where available. Data collected via this form will be evaluated descriptively to explore the age at which participants in this study achieve developmental milestones.

8.2.1.3.5 Screening Tool for Everyday Mobility and Symptoms (STEMS)

The STEMS will be completed by clinicians for participants 5 years of age and older. The STEMS captures mobility, use of mobility aides, and impact of pain and/or fatigue at the end of the day across three environments: home, school/work, and community (90). Mobility aides are recorded using numeric five-point rating scale where 1 = independent on all surfaces including stairs, 2 = use of sticks, 3 = use of crutches, 4 = use of wheeled walking device, and 5 = use of wheelchair or mobility scooter. Patient reported symptoms are recorded using letters where A = no pain or fatigue, B1= pain only, B2 = fatigue, and C = pain and fatigue. This is completed for each of the three environments resulting in three scores, whereby the numeric rating reflects the use of mobility aides, and the letter reflects the symptoms. eg, 1A, 1B1, 1C.

8.2.1.3.6 [redacted]

[redacted]

8.2.1.3.7 [redacted]

[redacted]

8.3 SAFETY ASSESSMENTS

This section presents safety assessments other than AEs which are presented in Section 8.4.

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Physical examinations

Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; and the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. Other body systems may be examined.

8.3.2 Neurological examination

A complete neurological examination will include assessment of mental status, motor function and balance, sensory exam, newborn and infant reflexes, muscle stretch reflexes in the older children and evaluation of the cranial nerves.

8.3.3 Electrocardiogram

Standard 12-lead ECGs will be recorded using an electrocardiographic device at the visits and timepoints specified in the SoA.

This printout will be retained at the site.

The study site Investigator or cardiologist should review the ECGs in a timely manner to determine if there are any safety concerns and for clinical management of the participant. In the event of any abnormal findings that meet the definition of an AE (see Section 8.4 for definitions and reporting), the Investigator will continue to monitor the participant with additional ECGs until the ECG returns to baseline or the Investigator determines that follow-up is no longer necessary. The Investigator's or cardiologist's assessments are to be captured in the e-CRF.

8.3.4 Vital signs

Vital signs, including blood pressure, heart rate, and respiratory rate, will be collected at each visit. These should be measured at least once at each visit but and can be measured in more than once if abnormal per the Investigator's judgment. Blood pressure will be obtained using a cuff appropriate for children with ACH. The method and site of blood pressure measurement will be recorded and will be utilized consistently throughout the remainder of the study (eg, left arm brachial, left arm radial, lower extremity tibial or popliteal, etc).

8.3.5 Collection of ACH-related events of interest

Occurrence of bone fractures, ear infections, tonsillectomies, adenoidectomies, cervical medullary decompression surgeries, any orthopedic surgeries, sleep apnea diagnosis, and other events the Investigator deems relevant to the disease course will be recorded at the time points specified in the SoA Section 1.3.

8.3.6 Chest circumference

Chest circumference will be measured mid-expiration and, optionally if possible, during maximum expiration and maximum inspiration; infants should be supine and at mid-expiration.

The measurements will be taken as described under “Growth measures” above.

8.3.7 Tanner stage of pubertal development

Tanner stage of pubertal development will be assessed for participants aged 5 years and older to determine whether the participant has progressed to puberty (precocious or normally timed). Tanner staging, also known as sexual maturity rating, is an objective classification system that providers use to document and track the development of secondary sex characteristics of children during puberty. A trained study staff member will compare participant’s development to the clinical references provided for Tanner stages (see Appendix 4 in Section 10.4). Tanner stage assessment will occur at the time points described in Section 1.3.

8.3.8 DXA scans

Dual energy X-ray absorptiometry scan will be performed on those participants in Stage 1 from sites capable of performing the assessment at the frequency described in the SoA.

8.3.9 Ocular assessments

Visual acuity, OCT, and dilated retinal examination will be performed at the frequency described in the SoA. These assessments should be carried out and results interpreted by a trained ophthalmologist per institutional guidelines. Referral to an ophthalmologist for additional ocular assessments not defined in the SoA may be performed at the judgment of the Investigator.

8.3.10 X-ray assessment Procedures

- Posterior-anterior (PA) X-rays of the hand and wrist to assess bone age, growth plates, hand length, and cortical thickness.
- Anterior-posterior (AP) lower extremity X-ray to assess growth plates, tibial length, cortical thickness, and bowing.
- Lumbar imaging X-rays to measure changes from baseline in bone morphology and pathology.

8.3.11 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- Routine safety labs including long and short chemistry panel (Table 9), and complete blood count (CBC) and differential will be collected at regular intervals indicated in the SoA (Section 1.3). Given the potential for FGFR inhibition to be associated with hyperphosphatemia, and the few cases of mild hyperphosphatemia observed the Phase 1

TDU16639/TDR16640 trial, serum phosphorous will be monitored regularly in participants as a part of the long or short chemistry panels. In cases of hyperphosphatemia, FGF23 level may be assessed to help determine the etiology of hyperphosphatemia.

- Given the potential for calcium homeostasis to impact growth in children, 25-hydroxyvitamin D, 1,25-hydroxyvitamin D, PTH, and calcitonin levels will be assessed regularly.
- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents. See Appendix 3 (Section 10.3) for abnormal laboratory results reporting. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.3.12 Concomitant medications

All medications (prescription, over-the-counter, and herbal) and nutritional supplements taken by participants within 6 months of screening and during the course of the study will be recorded on the designated e-CRF. In the event of an emergency, any needed medications may be prescribed without prior approval, but the Sponsor Medical Officer must be notified of the use of any excluded medications immediately thereafter. Any concomitant medications added or discontinued during the study should be recorded on the appropriate e-CRF. Concomitant medication information will be collected at the time points indicated in Section 1.3.

8.3.13 Medical history

A detailed medical history, including growth history, will be obtained. The medical history will include specific information concerning any prior or existing medical conditions and ACH-related symptoms (both significant previous symptoms as well as current symptoms) and should elicit all major illnesses, diagnosis, and surgeries that the participant has ever had. Additionally, the medical history will include any ACH-related assessments or interventions, such as pulmonary

function tests, neurologic evaluations, audiometry examinations, orthodontia, sleep apnea interventions (eg, continuous positive airway pressure), and use of supplemental oxygen and radiologic assessment findings, when available.

8.3.14 Suicidal ideation and behavior risk monitoring

Not applicable.

8.4 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.4.8.

[The definitions of unsolicited and solicited AEs can be found in Appendix 3 (Section 10.3)].

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.4.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the follow-up visit at the timepoints specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

8.4.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant or a caregiver, surrogate, or the participant's legally authorized representative, is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end-date, all SAEs and AEs of special interest (as defined in Section 8.4.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.4.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committee (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information (RSI).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 8 weeks after the last dose of study intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy from the pregnant pediatric participant's parent/legal representative or the female partner (parent/legal representative as applicable) of a male participant (after obtaining the necessary signed informed consent from the female partner, parent/legal representative, as applicable).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former participant/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.4.6 Cardiovascular and death events

No cardiovascular events are considered as AESI, therefore no other provisions apply to these events than those for reporting of fatal events and SAEs as appropriate/usual.

8.4.7 Disease-related events and/or disease-related outcomes not qualifying as AEs

The list of events not reportable as AEs is described in Section 10.3.1 Events NOT meeting the AE definition.

8.4.8 Adverse events of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Section 8.4.5).
- Symptomatic overdose (serious or nonserious) with IMP (see definition of an overdose in Section 6.8)
- ALT increase ≥2 x ULN (refer to related decision chart in Section 10.6)
- Central serous chorioretinopathy/retinal pigment epithelia detachment (CSCR/RPED)
- Hyperphosphatemia (>1.3 ULN for age)

- AEs that are known to be related to acceleration of growth induced by growth-promoting therapies, including slipped capital femoral epiphysis, avascular necrosis, and osteonecrosis.

8.4.9 Overdose, medication errors, misuses or abuses of medicinal product

All reports of overdose, medication error, misuse, or abuse in relation to the IMP with or without an AE must be recorded on the corresponding page(s) of the CRF and transmitted to the Sponsor's representative following standard processes. The Investigator will assess whether or not the overdose, medication error, misuse, or abuse event has to be reported together with an AE or SAE.

An overdose definition is given in Section 6.8.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, ie, intentional non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, "getting high" (euphoria).

This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not. Of note, if a medication error or misuse meets the protocol definition of an overdose, it will be recorded in the overdose page of the CRF.

8.4.10 Guidelines for reporting product complaints

Any defect in the study intervention must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.5 PHARMACOKINETICS

- Whole blood samples will be collected for measurement of plasma concentrations of SAR442501 as specified in the (PK flowchart or SoA [Section 1.3])

- Unscheduled samples may be collected at additional timepoints during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations or to reduce PK timepoints during the course of the study based on the updated knowledge of drug behavior) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate document. The actual date and time of each sample will be recorded. Pharmacokinetic samples will be tested by the Sponsor or Sponsor's designee.
- Samples collected for analyses of SAR442501 (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- If samples remaining after the PK analysis may be used for future exploratory research not included in the protocol (See Section 8.11).

Pharmacokinetic samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility and [redacted]

The PK parameters will be calculated using non-compartmental methods or other applicable PK analysis methods (ie, population PK (PopPK) models) from plasma SAR442501 concentrations obtained after subcutaneous administration. If feasible, the parameters will include, but may not be limited to, maximum concentrations observed (C_{max}), time to reach C_{max} (T_{max}), and AUC calculated using the trapezoidal method during a dose interval ($AUC_{0-\tau}$), and concentration observed before treatment administration during repeated dosing (C_{trough}).

A PopPK model of pooled data may be developed using nonlinear mixed effect modeling to describe the PK profile of SAR442501. If done, the data generated will be reported separately in standalone reports(s)

For China, please see Section 10.8 for details.

8.6 PHARMACODYNAMICS

Not applicable.

8.7 GENETICS

Genetics are not evaluated in this study.

8.8 BIOMARKERS

Serum samples will be collected to assess the change in PD markers with treatment. Biomarkers will include CXM, osteocalcin, bone alkaline phosphatase, collagen-Type I C-telopeptide (CTX),

and procollagen 1 intact N-terminal peptide (P1NP). Samples will be collected according to the schedule described in the SoA and as detailed in a separate document.

Collagen X biomarker is also named PRO-C10 because the biomarker assay which will be used is aiming to target the recognition of the C terminus of the NC1 domain of type X collagen.

For China, please see Section 10.8 for details.

8.9 IMMUNOGENICITY ASSESSMENTS

Antibodies to SAR442501 will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Instructions for the collection and handling of these samples will be provided by the Sponsor in a separate document. These samples will be tested by the Sponsor or Sponsor's designee using a qualified/validated assay method.

A 3-tiered approach will be employed to assess the immunogenicity of SAR442501 when applicable: Samples will be screened and then confirmed for antibodies binding to SAR442501 and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of SAR442501.

Samples may be used to perform genetic analysis for further research if consent is provided (see Section 8.11).

For China, please see Section 10.8 for details.

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable.

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of new medicines. Reuse of coded data and biological samples (leftover and additional) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing, or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study intervention to the Sponsor or which is co-developing the study intervention with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research

has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

Data protection – Processing of coded clinical data

The study participant will be provided will all mandatory details of the data processing in the core ICF.

The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Use of leftover samples and additional samples for future research

Remaining leftover samples will be used only after the study ends, ie, end-of-study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in the Core ICF.

Relating data will be stored for up to 25 years for regulatory purposes and future research. Biological samples for future use will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed, and related coded data will be anonymized unless otherwise required by applicable laws.

8.12 SAMPLED BLOOD VOLUME

The maximum amount of blood collected from each participant over the duration of the study and at each visit, including any extra assessments that may be required, must not exceed the body weight-specific allowable volumes as specified in the EMA guidance (92). The maximum amount of blood collected over 4 weeks will not exceed 3% of a participant's total blood volume, and the maximum amount of blood collected a single time will not exceed 1% of a participant's total blood volume. If the allowable volume would be exceeded, the Investigator should consult the Medical Monitoring team for guidance on prioritization of required samples.

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to database lock (DBL), and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined.

Table 8 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Enrolled/randomized	All participants from screened population who have been allocated to an intervention regardless of whether the intervention was received or not, and regardless of replacement
Intent-to-treat (ITT)	All enrolled/randomized participants. Participants will be analyzed according to the intervention allocated.
Safety	All enrolled/randomized participants who have taken at least 1 dose of study intervention, regardless of the amount of intervention administered. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All participants from the safety population with at least 1 postbaseline PK result with adequate documentation of dosing and sampling dates and times. Participants will be analyzed according to the intervention they actually received.
Pharmacodynamics (PD)	All participants from the safety population with at least one postbaseline PD parameter assessed. Participants will be analyzed according to the intervention they actually received.
ADA	All participants from the safety population treated with SAR442501 with at least one postbaseline ADA result (positive, negative, or inconclusive). Participants will be analyzed according to the intervention they actually received.

Abbreviations: ADA= anti-drug antibody; ICF= informed consent form; ITT= Intent-to-treat; PD= Pharmacodynamics; PK= Pharmacokinetic.

Participants exposed to study intervention before or without being enrolled/randomized will not be considered enrolled/randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Enrolled/randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as enrolled/randomized.

For any participant enrolled/randomized more than once, only the data associated with the first enrollment/randomization will be used in any analysis population. The safety experience associated with any later enrollment/randomization will be reported separately.

9.2 STATISTICAL ANALYSES

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section.

9.2.1 General considerations

The baseline value is defined as the last available value before the first dose of study intervention. For participants enrolled/randomized but not treated, the baseline value is defined as the last available value before enrollment/randomization.

Unless otherwise specified, analyses will be performed by dose level and overall for Stage 1 and Stage 2, and pooled at the time of final DBL.

Descriptive analyses will include summary statistics (using n, mean, SD, interquartile range, median, minimum, and maximum) for quantitative variables or number and percentage of participants in each category for qualitative data.

The observation period will be divided into 3 segments:

- The **pretreatment** period is defined as the period from the date the ICF is signed to first study intervention administration.
- The **treatment-emergent (TE)/ on-treatment period** is defined as the period from the first study intervention administration to the last study intervention administration + 5 days.
- The **post-treatment period** is defined as the period from the end of the TE period to end-of-study for a participant which is defined as the date of the end-of-study phone call or visit, or the early termination/phone call/visit.

9.2.2 Primary endpoint(s) analyses

The primary endpoint analyses will be evaluating the safety and tolerability of SAR442501 administered SC BIW at Weeks 26 and 52 in children ages ≥3 to <12 years and for 52 weeks in children ages birth to <3 years with a genetically confirmed diagnosis of ACH.

Safety will be evaluated according to the incidence of AEs, SAEs, TEAEs and AESIs during the treatment period.

The primary endpoint analyses will be descriptive and performed on the safety population.

The AEs are defined in the following 3 categories:

- Pretreatment AEs: That developed, worsened, or became serious during the pretreatment period.
- TEAEs: That developed, worsened, or became serious during the TE period.
- Post-treatment AEs: That developed, worsened, or became serious during the post-treatment period.

The analysis will focus on TEAEs although pretreatment AEs and post-treatment AEs may also be analyzed.

Any deaths that happen in the study, including during the Pretreatment, TE period, and post-treatment periods, will be analyzed.

Adverse event incidence table will be provided for all types of TEAEs: all TEAEs, all treatment-emergent AESI (defined with a preferred term (PT) or a prespecified grouping), all TE SAEs and all TEAEs leading to permanent treatment discontinuation.

The AE summaries will be generated with number (%) of participants experiencing at least one event.

- Deaths will also be summarized.

9.2.3 Secondary endpoint(s) analyses

The secondary endpoints detailed in this section are the secondary efficacy endpoints evaluating changes in growth and body proportionality. Other secondary endpoints analyses will be defined in the SAP.

Secondary efficacy endpoints will be summarized in the intent-to-treat (ITT) population for participants from stage 1 and stage 2 separately, as well as combined using descriptive statistics.

The AGV will be calculated from height measurements collected during the study. The baseline AGV will also be established using height measurements assessed in the longitudinal study OBS16647, before entry in study DRI16646.

For a given time interval [Date1, Date2], the AGV (cm/year) will be defined as follows:

$$\text{AGV} = \frac{\text{Height at Date2} - \text{Height at Date1}}{\text{Interval length in days}} \times 365.25$$

where the interval length in days is calculated as Date2 – Date1 + 1 day. AGV will be calculated for the following visits:

- At baseline, using the following interval: [Date of last height measurement in study OBS16647 at least 6 months prior to Date of Week 0/Day 1 (or at least 12 weeks prior to Date of Week 0/Day 1 for participants who were under 3 years of age at the time of OBS16647 enrollment), Date of Week 0/Day 1]
- At Week 13, using the following interval: [Date of Week 0/Day 1, Date of Week 13]
- At Week 26, using the following interval: [Date of Week 0/Day 1, Date of Week 26]
- At Week 39, using the following interval: [Date of Week 0/Day 1, Date of Week 39]
- At Week 52, using the following interval: [Date of Week 0/Day 1, Date of Week 52]

In order to take into account the natural growth history in children and assess the treatment effect in the absence of a placebo arm, AGV values (as calculated above) will be converted into Z-scores corrected for age and sex, using reference data. The reference data may be taken from an untreated ACH population and/or healthy population.

Values of AGV and AGV Z-score at baseline, Week 13, 26, 39 and 52, as well as change from baseline to Week 13, 26, 39 and 52 will be described in summary tables.

All available data regardless of intercurrent events (such as premature intervention discontinuation or intake of prohibited medications that may impact growth) will be used in the analysis, using a treatment policy strategy. Missing data will be imputed by assuming the AGV z-score at the time interval of missing is the same as the AGV z-score at baseline. Detailed missing data imputation method will be described in the statistical analysis plan.

Sensitivity and supportive analyses may be defined in the statistical analysis plan to assess the impact of missing data or intercurrent events.

Similar analyses will be performed for height Z-score (depending on the reference data availability, may be calculated both from reference data in an untreated ACH population and/or in average stature children) and calculated body ratios (as defined in the Table 4). For these endpoints, summary tables will include values at baseline, Week 13, Week 26, Week 39, Week 52, and the changes from baseline at each visit.

For the above growth-related measures including AGV, AGV Z-score, and height Z-score, the test of null hypothesis of no change from baseline will be conducted via analysis of covariance (ANCOVA) adjusting for baseline age and baseline value. 95% confidence intervals and nominal p-value for each dose group as well as comparisons between two dose groups will be provided for descriptive purpose. Change from baseline in calculated body ratios will be analyzed by mixed model of repeated measure (MMRM).

For participants from Stage 2 (age birth to <3 years) with measurement of foramen magnum, the change from baseline at Week 52 in Bony Foramen Magnum Cross-sectional Area will be summarized separately for each dose group, as well as pooled. Depending on the reference data availability, the Bony Foramen Magnum Cross-sectional Area Z-score may be calculated from reference data in an untreated ACH population and/or in average stature children. If Z-score was calculated, then change from baseline in Bony Foramen Magnum Cross-sectional Area Z-score will also be summarized separately for each dose group and pooled.

9.2.4 Tertiary/exploratory endpoint(s) analyses

[redacted]

9.2.5 Multiplicity adjustment

As the primary endpoint is for safety assessment, the sample size is determined based on empirical consideration, and interim analyses were not planned for any potential early stop for efficacy, no adjustment for multiplicity will be conducted.

9.2.6 Other safety analyses

The safety analyses include in this section are AEs, laboratory variables and vital signs. Other safety analyses will be defined in SAP.

9.2.6.1 Adverse events

Please refer to Section 9.2.2.

9.2.6.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

When relevant, for laboratory variables, vital signs, descriptive statistics for results and changes from baseline will be provided for each planned visit, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the TE period. These analyses will be performed using central measurements for laboratory variables.

Analyses according to potentially clinically significant abnormalities

The potentially clinically significant abnormalities analyses (PCSA) will be performed based on the PCSA list currently in effect at Sanofi at the time of the DBL.

Analyses according to PCSA will be performed based on the worst value during the TE period, using all measurements either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, and vital signs, the incidence of participants with at least one PCSA during the TE period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

9.2.7 Other analyses

PK, ADA, and bone/collagen biomarker analyses are briefly discussed as below. However, they will be described in greater detail in the statistical analysis plan before DBL.

Measured plasma concentrations and PK parameters for SAR442501 will be summarized using descriptive statistics [eg, mean, SD, median, min-max, and coefficient of variation (%CV)]. In addition, further PK analysis may be conducted later using a PopPK approach. The details of the

analysis will be presented in a separate PopPK analysis plan and the results will be presented in a separate PopPK report.

The incidence and titer of ADA will be provided by dose level and pooled.

Serum concentrations of PD biomarkers (ie, CXM, osteocalcin, bone alkaline phosphatase, CTX, etc) will be descriptively summarized and tabulated. In addition, potential correlations between the PK exposure of SAR442401 and changes in secondary efficacy endpoints (ie, AGV) and PD biomarkers from baseline to Week 26 and Week 52 will be explored using graphic method or regression analysis if applicable.

9.3 INTERIM ANALYSES

The accumulated safety data will be reviewed by the DMC on a regular basis (will be outlined in DMC Charter).

9.4 SAMPLE SIZE DETERMINATION

Approximately 36 participants will be enrolled to study intervention with two stages:

- Approximately 24 participants ages ≥3 to <12 years old will be enrolled in Stage 1. Of these, approximately 12 will be enrolled in the [redacted] dose cohort and 12 in the [redacted] cohort.
- Approximately 12 participants between ages birth to <3 years old will be enrolled in Stage 2. Of these, approximately 6 will be enrolled in the [redacted] dose cohort and 6 in the [redacted] dose cohorts.

The sample size was defined based on empirical considerations. No formal determination was performed. It is considered sufficient for the descriptive nature of the study regarding safety and efficacy evaluation for dose selection. Participants who discontinue study treatment or withdraw from the study may be replaced.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH-GCP guidelines
  - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use, as applicable
  - The General Data Protection Regulation (GDPR) and any other applicable data protection laws
  - Any other applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned

(an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:

- The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
- The finding reveals a substantial risk of a serious health condition or has concerned reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

As applicable, according to requirements of the Regulation No536/2014 of the European Parliament and the Council of the European Union, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as “substantial” (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EEA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48 hours after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the parent(s), participant, or legal representative(s)of the participants ,and answer all questions regarding the study, including what happens to the participant when his/her participation ends (posttrial access strategy for the study).
- Parent(s), participant, or legal representative(s) of the participants must be informed that their participation is voluntary. Parents of the participants, participant, or their legally authorized representative will be required to sign a statement of informed consent or assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent/ assent was obtained. The authorized person obtaining the informed consent/ assent must also sign the ICF/ assent form.
- In case of ICF/ assent form amendment while the participants are still included in the study, they must be re-consented/ re-assented to the most current version of the ICF(s)/assent form(s).Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent/ re-assent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).
- A copy of the ICF(s) or assent form must be provided to the parents of the participant or participant or their legally authorized representative, where applicable.
- Participants who can read the assent form will do so before writing their name and dating or signing and dating the form.
- Participants who can write but cannot read will have the assent form read to them before writing their name on the form.
- Participants who can understand but who can neither write nor read will have the assent form read to them in the presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

For participants who are rescreened, the participant, parent of participant or participant’s legal representative are required to sign a new ICF or assent form, The participant should be assigned a new study participant number, and all the screening procedures should be repeated and entered in the screening visit pages.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Parents or legal representatives of participants will be told that they are free to refuse to permit their child to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including trial participants, Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant personal data

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

"Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)". They will not be collected in the countries where this is prohibited by local regulation. Additionally, a participant's full date of birth (those age <2 years), or age in month and year (those age ≥2 years) may be collected.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.

- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc.), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of personal data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or precontractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com). In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the

framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up to date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by e-mail, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committee's structure

10.1.5.1 Data monitoring committee

An independent DMC appointed by the Sponsor will review the protocol and will thereafter provide medical and ethical guidance related to the conduct of this study. The DMC will be composed of 3 external members, 2 of whom will have clinical expertise in achondroplasia and 1 who will be a biostatistician. The DMC will review safety information as outlined in the DMC charter, which is maintained separately from the study protocol.

A formal safety review will be performed by the DMC:

- Prior to dose escalation steps as detailed in Section 4.1

- At a frequency throughout the study as predefined by the DMC Charter. This frequency can be adapted.
- With all relevant data at the end of the study.

Relevant data for DMC reviews will be, at a minimum, AEs including injection associated reaction (IARs), clinical laboratory results including, but not limited to, hematology and clinical chemistry, Vitamin D, PTH, calcitonin, and thyroid stimulating hormone (TSH) values, ECG, vitals, and any available immunology results as applicable.

The DMC has the possibility to request ad-hoc meetings (teleconferences), clearly identifying the safety-related reason for such an additional meeting and taking account of then current recruitment status and recruitment rate. At each DMC meeting during the conduct of the trial, the DMC makes a recommendation to the Sponsor to continue the trial as planned, or with an amendment, or to terminate the trial. Details regarding the DMC are included in the DMC charter.

An ad-hoc DMC meeting will be held to review the safety data and provide its recommendations to the Sponsor regarding further treatment if any of the following criteria are met:

- Any fatal or life-threatening TEAE.
- Any TE SAE assessed by Investigator, or the Sponsor as related to study intervention.
- Any other safety-related issues identified by the Sponsor's Medical Monitor or Global Safety Officer that pose a medical concern.
- After consideration of DMC recommendations, final decisions regarding discontinuation of study intervention for all or selected participants will be made by the Sponsor.
- Participant safety will be continuously monitored by the Sponsor's internal safety review team, which includes safety signal detection at any time during the study.
- All safety data collected will be summarized and reviewed by the Sponsor's safety team for agreement of next steps.

10.1.5.2 Study stopping criteria

- In particular, data will be reviewed by the Sponsor for identification of the following events that would potentially contribute to a requirement to pause/stop the study.

  - Two patients develop the same severe AE that is not related to their underlying condition
  - Any deaths, regardless of causality
  - Any cases of CSCR or RPED as diagnosed by an ophthalmologist
  - Any cases of persistent, clinically significant hyperphosphatemia
- After consideration of DMC recommendations from the ad-hoc meetings, final decisions regarding discontinuation of study drug for all or selected clinical trial participants will be made by the Sponsor.

- In the event a significant safety concern arises, not necessarily limited to the ones listed above, the Sponsor may immediately decide to discontinue study intervention dosing in all participants prior to receipt of the DMC recommendation.
- If the study is temporarily or permanently halted, the Sponsor will notify the health authorities of the halt by a substantial amendment in regions where this applies.

10.1.6 Dissemination of clinical study data

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual anonymized participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Drug Clinical Trial Registration and Information Disclosure Management Practice (Trial Implementation)", requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF Completion guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.
- Data reported on the CRF or entered in the e-CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in training materials or study manuals.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site termination

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

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

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

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 9, SoA will be performed by a central laboratory, unless local laboratory use for assessment of the short chemistry panel is specified.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 9 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry – long panel[a]	
	Bicarbonate
	Blood urea nitrogen (BUN)
	Calcium
	Creatinine
	Glucose [non-fasting]
	Potassium
	Sodium
	Chloride
	Magnesium
	Phosphorous
	Albumin
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase[b]
	Total, direct, and indirect bilirubin
Clinical chemistry – short panel	
	Calcium
	Magnesium
	Phosphorous
	Albumin
Endocrine panel	
	25-hydroxy-vitamin D
	1,25-dihydroxy-vitamin D
	Calcitonin
	FGF23
	Parathyroid hormone level
	TSH with reflex[d]
Pregnancy testing	[Serum or highly sensitive urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for participants of childbearing potential)[c]

Laboratory tests	Parameters
Pharmacodynamic (PD) parameters	
	CXM
	Osteocalcin
	Bone alkaline phosphatase
	CTX
	P1NP
Immunogenicity	
	ADA levels
Other screening tests	All study-required laboratory tests will be performed by a central laboratory

Abbreviations: ADA = Anti-drug antibodies; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; CTX = collagen-type 1 C-Telopeptide; CXM = collagen X biomarker; FGF23=fibroblast growth factor 23; hCG = human chorionic gonadotropin; INR= international normalized ratio; IRB= institutional review board; IEC= independent ethics committees; MCH = Mean corpuscular hemoglobin; MCV= Mean corpuscular volume; PD= pharmacodynamics; P1NP = procollagen 1 intact N-terminal peptide; RBC = Red blood cell; SGPT = Serum glutamic-pyruvic transaminase; SGOT = Serum glutamic-oxaloacetic transaminase; T3 = triiodothyronine; T4= thyroxine; TSH=thyroid stimulating hormone; WBC = White blood cell.

NOTES:

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 (Liver Chemistry Stopping Criteria) and Appendix 6 (Section 10.6) [Liver and other safety. Suggested actions and follow-up assessments [and study intervention rechallenge guidelines]]. All events of [insert criteria related to ALT, bilirubin, INR etc] which may indicate severe liver injury (possible Hy's Law) must be reported to [Sponsor] in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

b If alkaline phosphatase is elevated, consider fractionating.

c Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

d Any TSH value outside the standard reference range will prompt a free T3 and T4 test.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant/participant's parent(s)/legally authorized representative (LAR)(s) who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.

- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The participants/participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/participant's parent(s)/LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's parent(s)/LAR(s) will be collected during an interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.
- Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), or more severe than expected for the participant's condition), eg:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to study intervention discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- Signs, symptoms, or the clinical sequelae of any medication errors, misuse, and abuse with the IMP.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a) Results in death

b) Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

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

d) Results in persistent or significant disability/incapacity

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

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse
- ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

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

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

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

Assessment of causality

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

Follow-up of AEs and SAEs

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

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in site initiation training slides.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in site initiation training slides.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal unless permanently sterile (see below).

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent afertility due to an alternate medical cause other than the above (eg Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry eligibility.

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

If fertility is unclear (eg, amenorrhea in athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

Contraceptives[a] allowed during the study include:

Highly effective methods[b] that have low user dependency Failure rate of <1% per year when used consistently and correctly.
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS) [c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a medical cause). Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly effective methods[b] that are user dependent Failure rate of <1% per year when used consistently and correctly
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] - Oral - intravaginal - transdermal - injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] - Oral - injectable
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c Male condoms must be used in addition to hormonal contraception

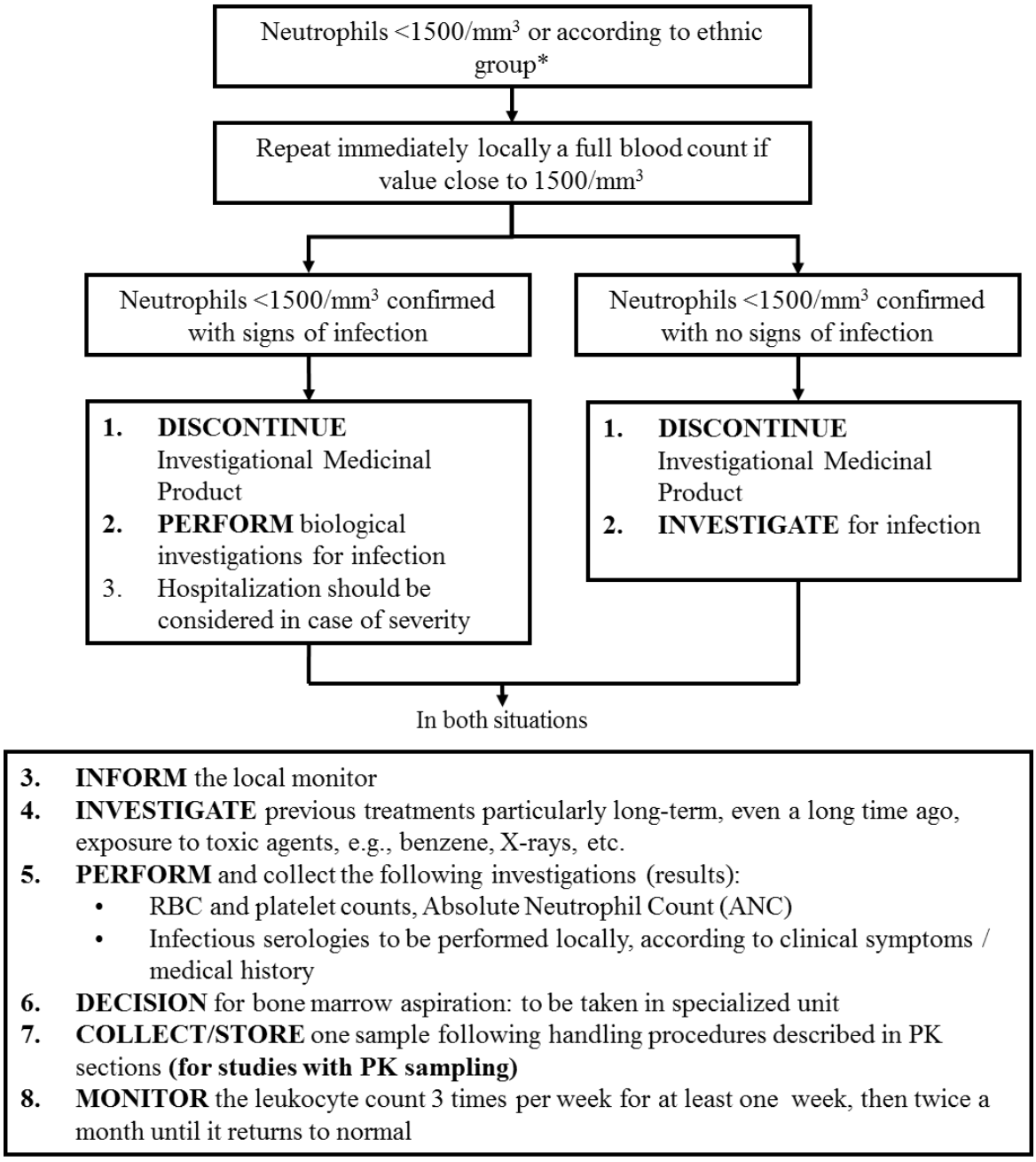
Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 APPENDIX 5: GENETICS

Not applicable.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

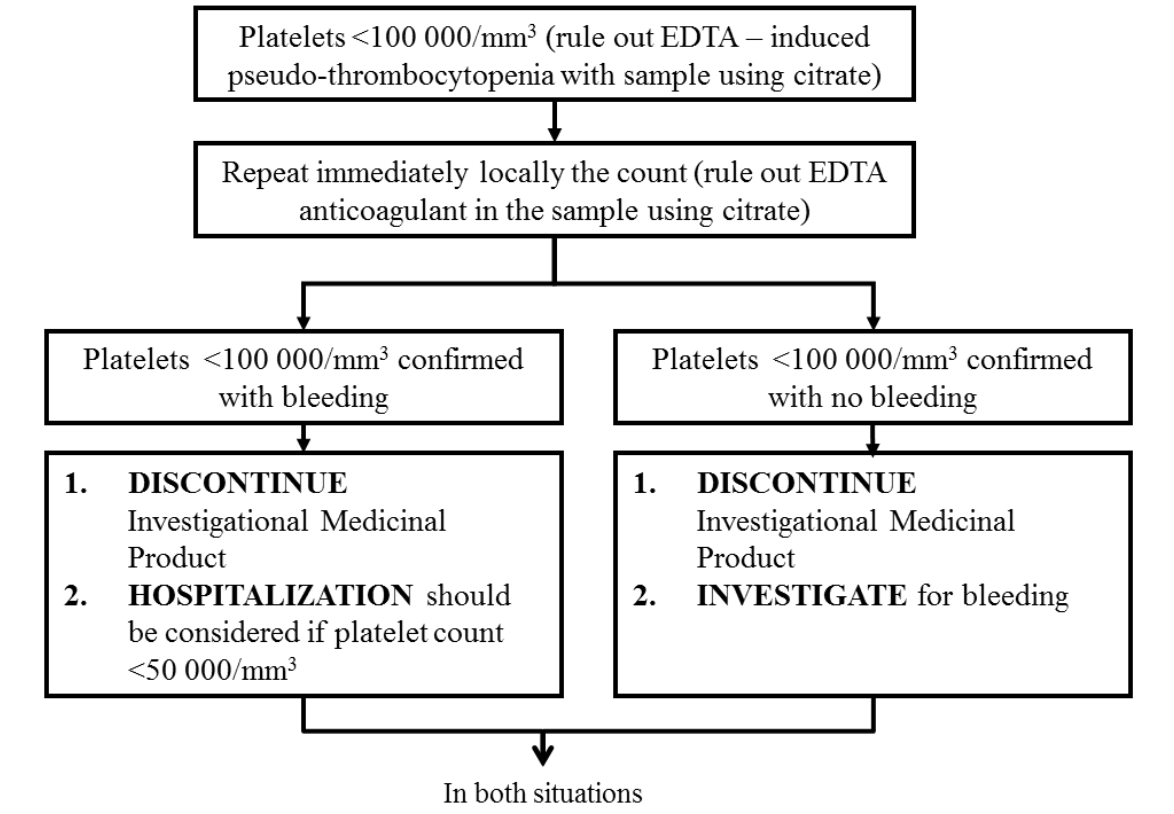
NEUTROPENIA



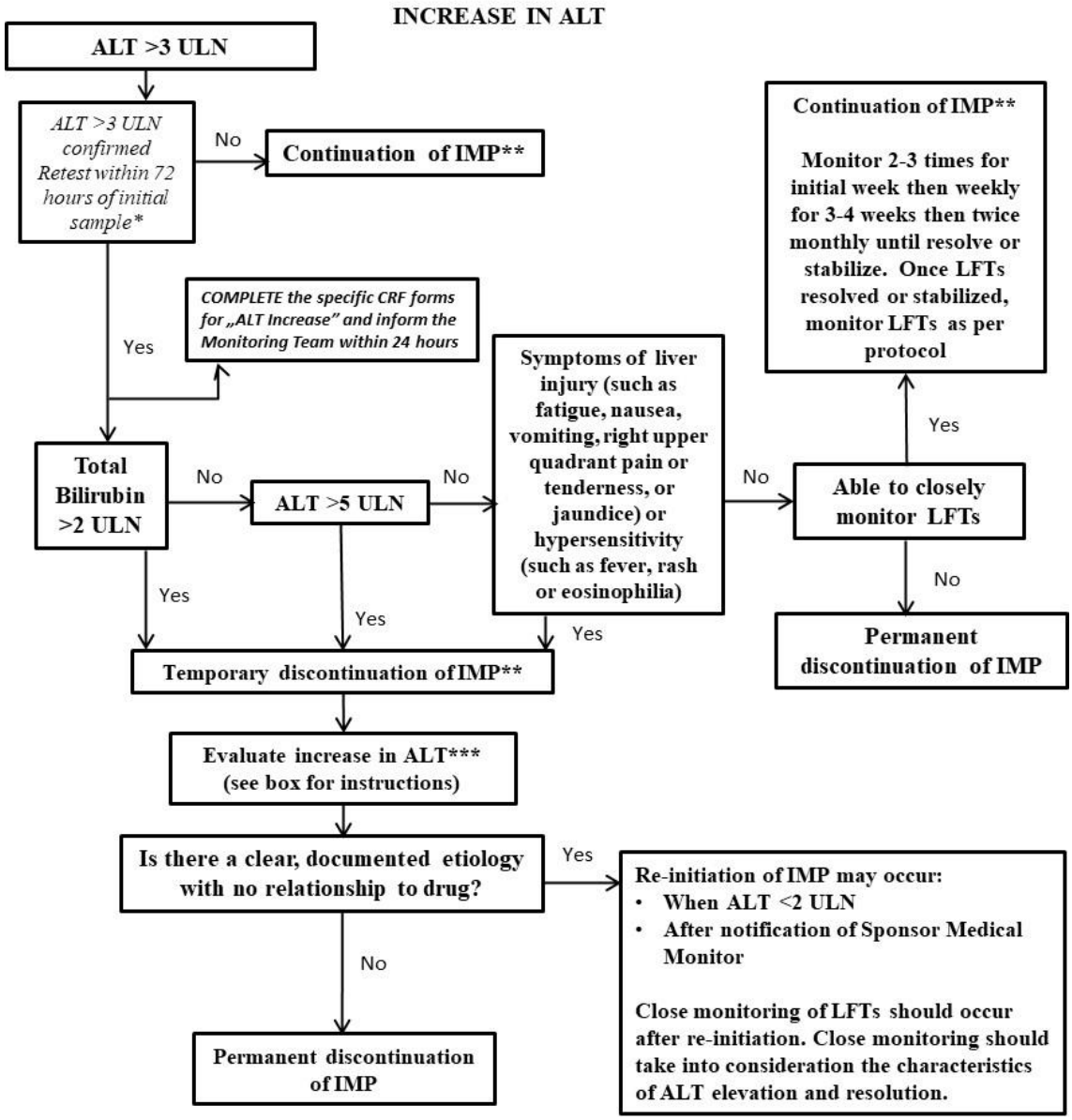
* For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 8.4 is met.

THROMBOCYTOPENIA



Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 8.4 is met.

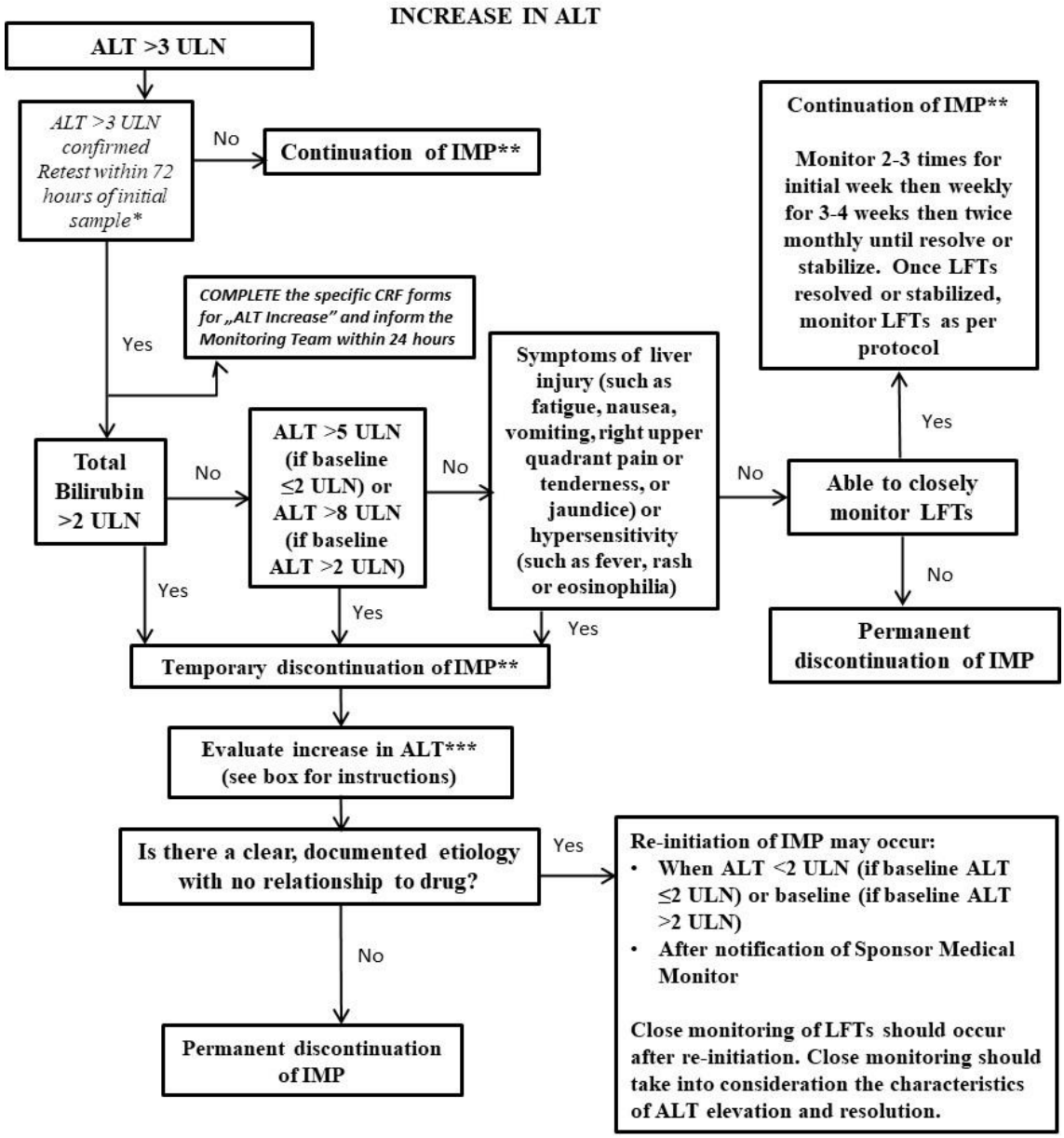


*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
** Unless a protocol-defined criterion for permanent discontinuation is met
*** See box below
Note:

- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 8.4 for guidance on safety reporting.

Evaluate Increase in ALT***

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **INVESTIGATE** if any recent alcohol use or travel
4. **INVESTIGATE** if any use of non-prescription medications including herbal or dietary supplements
5. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, GGT, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** iron, ferritin and transferrin
6. **CONSIDER** biomarkers for alcohol use (eg, urine ethyl glucuronide (EtG)]
7. **CONSIDER** consulting with hepatologist
8. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
9. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to ≤ULN, baseline value (if baseline >ULN) or clinical resolution.
10. **FREEZE** serum sample (5ml x 2)
11. **In case of suspicion of GILBERT Syndrome**, a DNA diagnostic test should be done



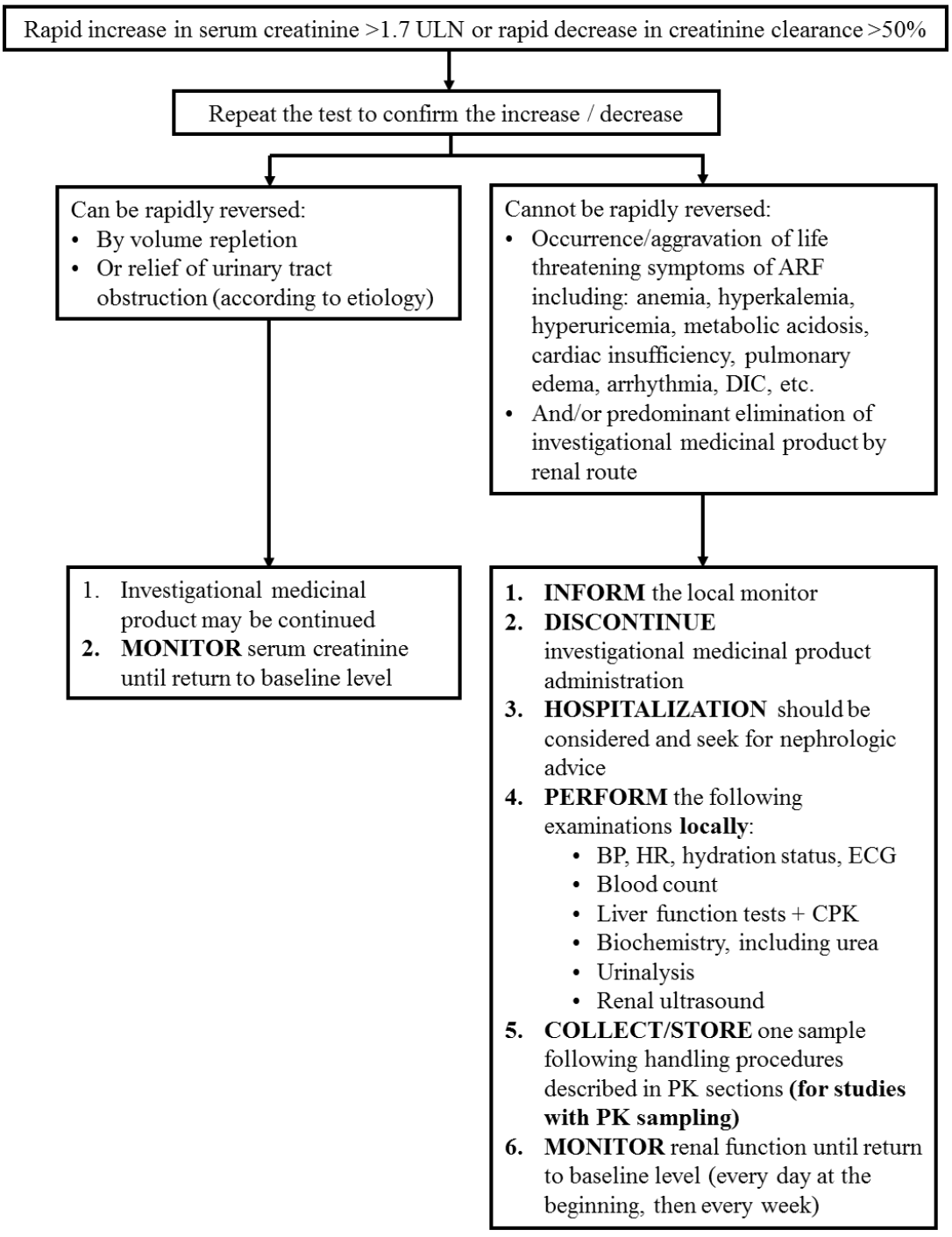
*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
** Unless a protocol-defined criterion for permanent discontinuation is met.
*** See box below
Note:

- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 8.4 for guidance on safety reporting.

Evaluate Increase in ALT***

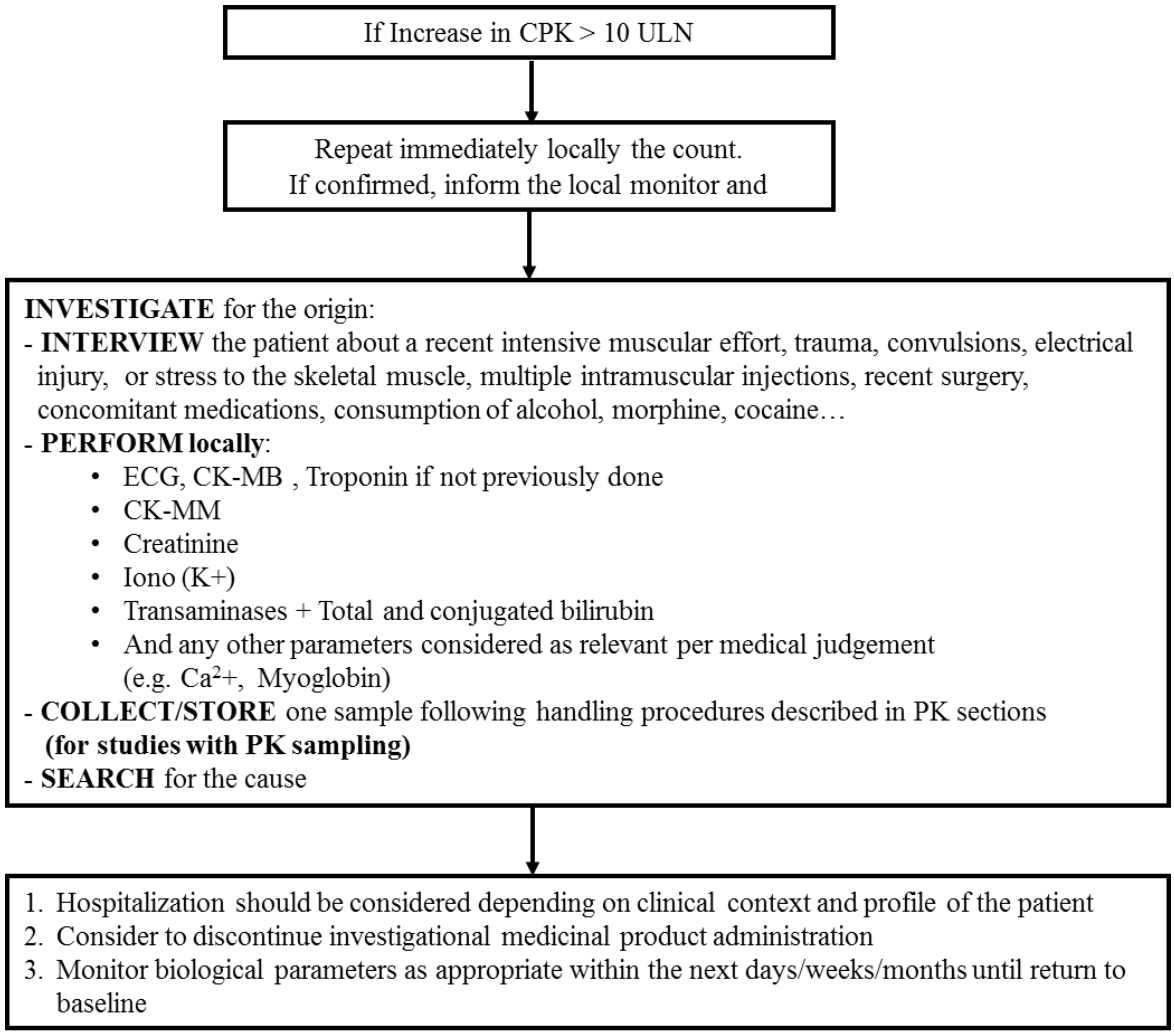
1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **INVESTIGATE** if any recent alcohol use or travel
4. **INVESTIGATE** if any use of non-prescription medications including herbal or dietary supplements
5. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, GGT, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** iron, ferritin and transferrin
6. **CONSIDER** biomarkers for alcohol use (eg, urine ethyl glucuronide (EtG)]
7. **CONSIDER** consulting with hepatologist
8. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
9. **MONITOR LFTs after discontinuation of IMP:**
   - A*s closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to ≤ULN, baseline value (if baseline >ULN) or clinical resolution.
10. **FREEZE** serum sample (5ml x 2)
11. **In case of suspicion of GILBERT Syndrome**, a DNA diagnostic test should be done

INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 8.4 is met.

INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Section 8.4 is met.

10.7 APPENDIX 7: MEDICAL DEVICES AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).

10.7.1 Definition of medical device AE and ADE

Not applicable.

10.7.2 Definition of medical device SAE, SADE and USADE

Not applicable.

10.7.3 Definition of device deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.7.4 Recording and follow-up of AE and/or SAE and device deficiencies

Not applicable.

10.7.5 Reporting of SAEs

Not applicable.

10.7.6 Reporting of SADEs

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.8.1 China-specific requirements

The below mentioned criteria are to align with the requirements of health authority. The contents in this section supersede the preceding sections correspondingly for study conduct in China.

All samples from Chinese participants will be disposed of following completion of the Clinical Study Report.
For whole blood (hematology, blood smears): The testing and analysis laboratory is designated as Labcorp Pharmaceutical Research and Development (Shanghai) Co. Ltd. The sample destruction company is designated as Shanghai Solid Waste Disposal Co. Limited.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

For European countries contingency measures are currently only applicable for the COVID-19 pandemic.

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, screening and enrollment may be temporarily delayed/halted. Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If on-site visits are not possible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely. Possibility of visit extension must be discussed on a case by case basis with the Sponsor considering first of all subject's safety and best interests.
- If on-site visits or alternative location (out of participant's home) are not possible, visits will have be performed at home by a trained healthcare professional and if allowed by local competent authorities for the following but not limited to:
- Monitoring of injection site reactions, AEs and SAEs.
- Collect study samples for safety, and pregnancy test (if applicable).
- Perform study examinations (eg, Measuring vital signs).
- IMP Injection Training: In case of emergency (eg, natural disaster, pandemic) different training ways (eg, training remotely with instruction provided by phone) can be performed (and will be documented in the participant's study file).
- After Sponsor agreement is obtained, the IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participants.
- Use of local clinic or laboratory locations may be allowed for safety follow-up in case the central lab cannot be used.

If on-site visit and home visit are not possible, the Investigator or delegate will perform a phone call visit at each on-site planned visit to collect safety data and concomitant treatment. All data collected remotely will be properly documented in the participant's medical record and the study CRF.

If on-site visits are possible and there is a need to reduce the time spent on-site to a minimum, the focus should be on IMP administration, collection of safety information (vital signs, AEs) and safety blood collection (mainly biochemistry, hematology, and ADA, if planned for the visit).

Contingencies implemented due to emergency will be documented.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participants or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg. study visit delays/treatment extension, use of local labs).

10.10 APPENDIX 10: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

A form compliant with EU Regulation No 536/2014 may be prepared separately to provide additional information regarding the collection, storage, and future use of human biological samples in this study.

10.10.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

This appendix is provided separately.

10.10.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (article 7 (1 d) of EU Regulation 536/2014

This appendix is provided separately.

10.11 APPENDIX 11: ADDITIONAL APPENDICES

10.11.1 Caregiver Acceptability Questionnaire

INSTRUCTION:

Please think about the study medication YOUR CHILD has received in the **past 7 days** when answering the questions.

For this set of questions, consider how YOU feel about your child's medicine.

Please select one answer for each question.

1. In the **past 7 days**, how happy were **you** with the number of times your child had to take the medicine?

Not at all happy
Very happy

1	2	3	4	5
☐	☐	☐	☐	☐

2. In the **past 7 days**, how happy were **you** with the time it takes to administer your child's medicine?

Not at all happy
Very happy

1	2	3	4	5
☐	☐	☐	☐	☐

3. Overall, how happy were **you** with the preparation required for your child's medicine before it is administered to your child?

Not at all happy
Very happy

1	2	3	4	5
☐	☐	☐	☐	☐

4. In the **past 7 days**, how happy were **you** with the use of a needle to administer your child's medicine?

Not at all happy
Very happy

1	2	3	4	5
☐	☐	☐	☐	☐

5. Overall, how acceptable is your child's medicine to **you**?

Not at all acceptable Very acceptable

1	2	3	4	5
☐	☐	☐	☐	☐

6. Overall, how happy are **you** with your child's medicine?

Not at all happy
Very happy

1	2	3	4	5
☐	☐	☐	☐	☐

7. Overall, how much do **you** think the medicine helps your child?
Does not help at all very much — Helps

1	2	3	4	5
☐	☐	☐	☐	☐

8. Overall, how important do **you** think it is for your child to take the medicine?
Not at all important — Very important

1	2	3	4	5
☐	☐	☐	☐	☐

9. Overall, how willing are **you** to have your child continue to use the medicine?
Not at all willing
Very willing

1	2	3	4	5
☐	☐	☐	☐	☐

INSTRUCTION:

Please think about the study medication YOUR CHILD has received in the **past 7 days** when answering the questions.

For this set of questions, consider ONLY what you have directly observed (e.g., seen or heard) when your child has taken the medicine or what your child has told you. Do NOT answer by making a judgment about how you think your child may feel about the medicine.

Please select one answer for each question.

10. In the **past 7 days**, how happy was **your child** with the number of times he/she has had to take the medicine?
Not at all happy
Very happy

1	2	3	4	5
☐	☐	☐	☐	☐

11. In the **past 7 days**, how happy was **your child** with the time it takes to administer the medicine?
Not at all happy
Very happy

1	2	3	4	5
☐	☐	☐	☐	☐

12. Overall, how happy was **your child** with the use of a needle to administer the medicine?
Not at all acceptable — Very acceptable

1	2	3	4	5
☐	☐	☐	☐	☐

13. Overall, how acceptable is the medicine to **your child**?
Not at all acceptable — Very acceptable

1	2	3	4	5
☐	☐	☐	☐	☐

14. Overall, how happy is **your child** with the medicine?
Not at all happy
Very happy

1	2	3	4	5
☐	☐	☐	☐	☐

15. Overall, how willing is **your child** to continue to use the medicine?
Not at all willing
Very willing

1	2	3	4	5
☐	☐	☐	☐	☐

16. How often does **your child** take the medicine exactly the way he/she has been told to?
Never
Always

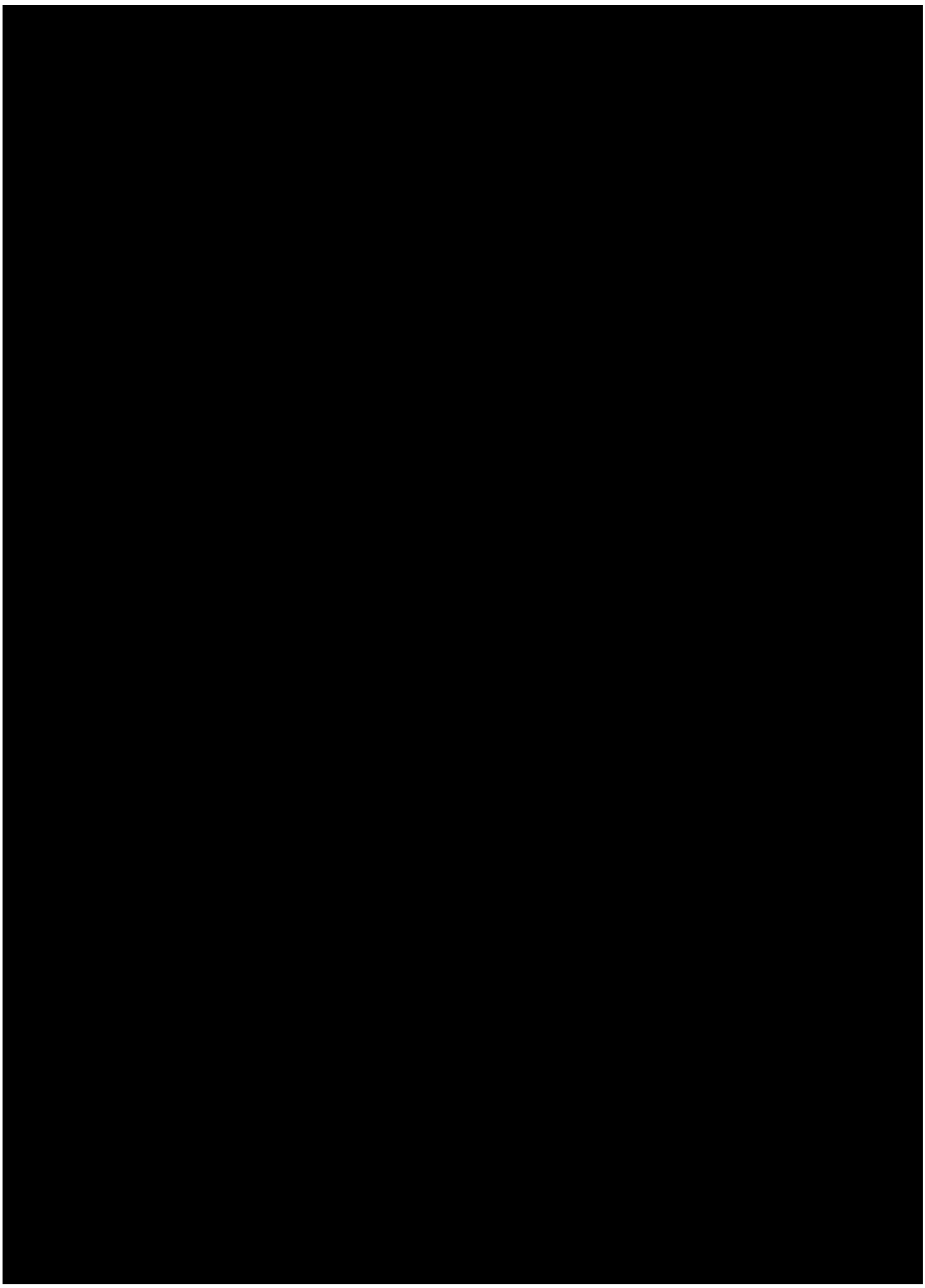
1	2	3	4	5
☐	☐	☐	☐	☐

10.11.2 Screening tool for everyday mobility and symptoms (STEMS)

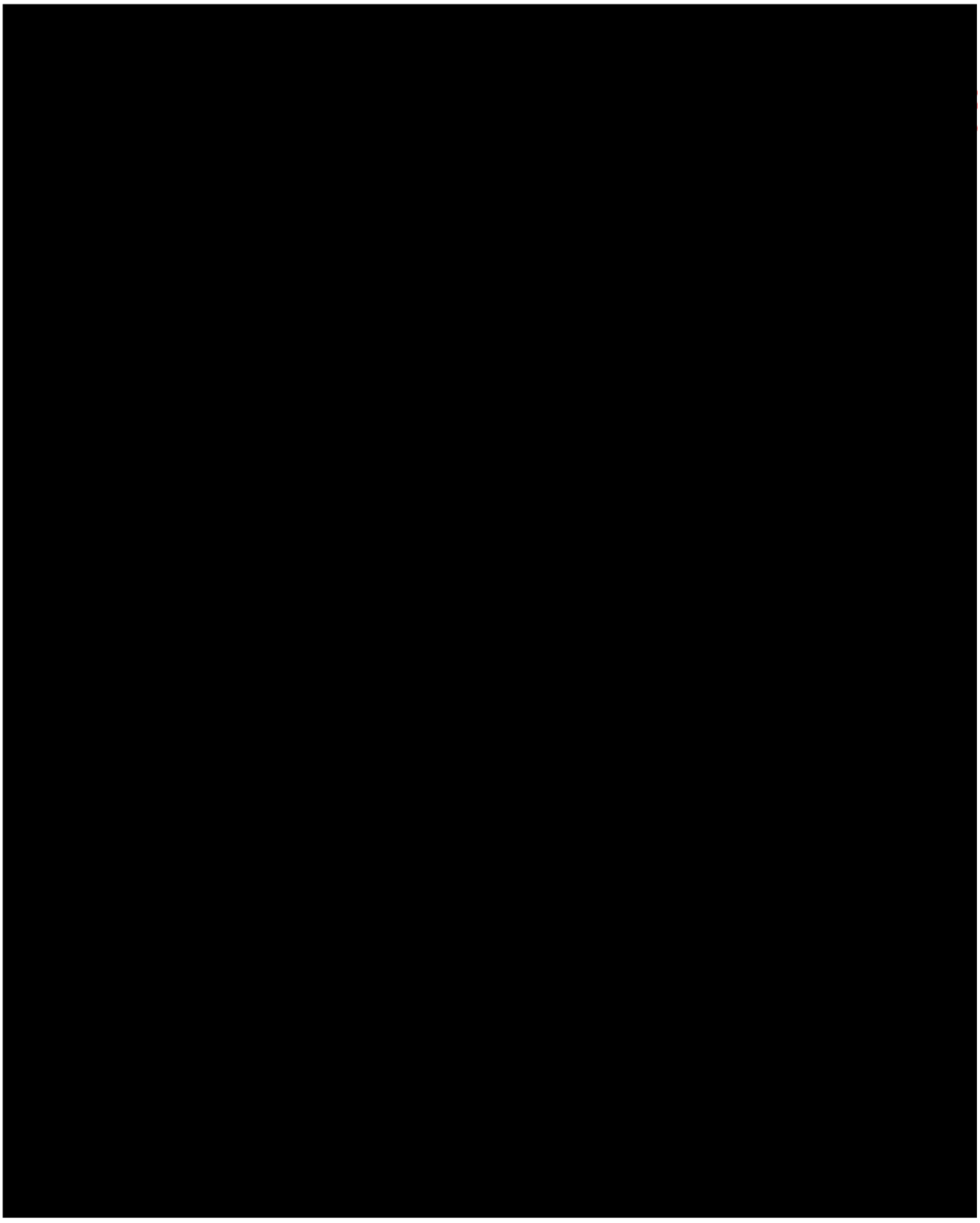
Score 1	A	Mobilises independently around this environment without requiring mobility aide. No activity limiting pain or fatigue reported.
	B1	Mobilises independently around this environment without requiring mobility aide. Reports pain that alters activity levels at end of day.
	B2	Mobilises independently around this environment without requiring mobility aide. Reports fatigue that alters activity levels at end of day.
	C	Mobilises independently around this environment without requiring mobility aide. Reports both pain and fatigue that alters activity levels at end of day.
Score 2	A	Mobilises around this environment using stick(s). No additional activity limiting pain or fatigue reported.
	B1	Mobilises around this environment using stick(s). Reports pain that alters activity levels at end of day.
	B2	Mobilises around this environment using stick(s). Reports fatigue that alters activity levels at end of day.
	C	Mobilises around this environment using stick(s). Reports both pain and fatigue that alters activity levels at end of day.
Score 3	A	Mobilises around this environment using crutch(es). No additional activity limiting pain or fatigue reported.
	B1	Mobilises around this environment using crutch(es). Reports pain that alters activity levels at end of day.
	B2	Mobilises around this environment using crutch(es). Reports fatigue that alters activity levels at end of day.
	C	Mobilises around this environment using crutch(es). Reports both pain and fatigue that alters activity levels at end of day.
Score 4	A	Mobilises around this environment using wheeled walking device. No additional activity limiting pain or fatigue reported.
	B1	Mobilises around this environment using wheeled walking device. Reports pain that alters activity levels at end of day.
	B2	Mobilises around this environment using wheeled walking device. Reports fatigue that alters activity levels at end of day.

	C	Mobilises around this environment using wheeled walking device. Reports both pain and fatigue that alters activity levels at end of day.
Score 5	A	Mobilises around this environment using wheelchair or power mobility scooter. No additional activity limiting pain or fatigue reported.
	B1	Mobilises around this environment using wheelchair or power mobility scooter. Reports pain that alters activity levels at end of day.
	B2	Mobilises around this environment using wheelchair or power mobility scooter. Reports fatigue that alters activity levels at end of day.
	C	Mobilises around this environment using wheelchair or power mobility scooter. Reports both pain and fatigue that alters activity levels at end of day.

10.11.3 Achondroplasia developmental recording form

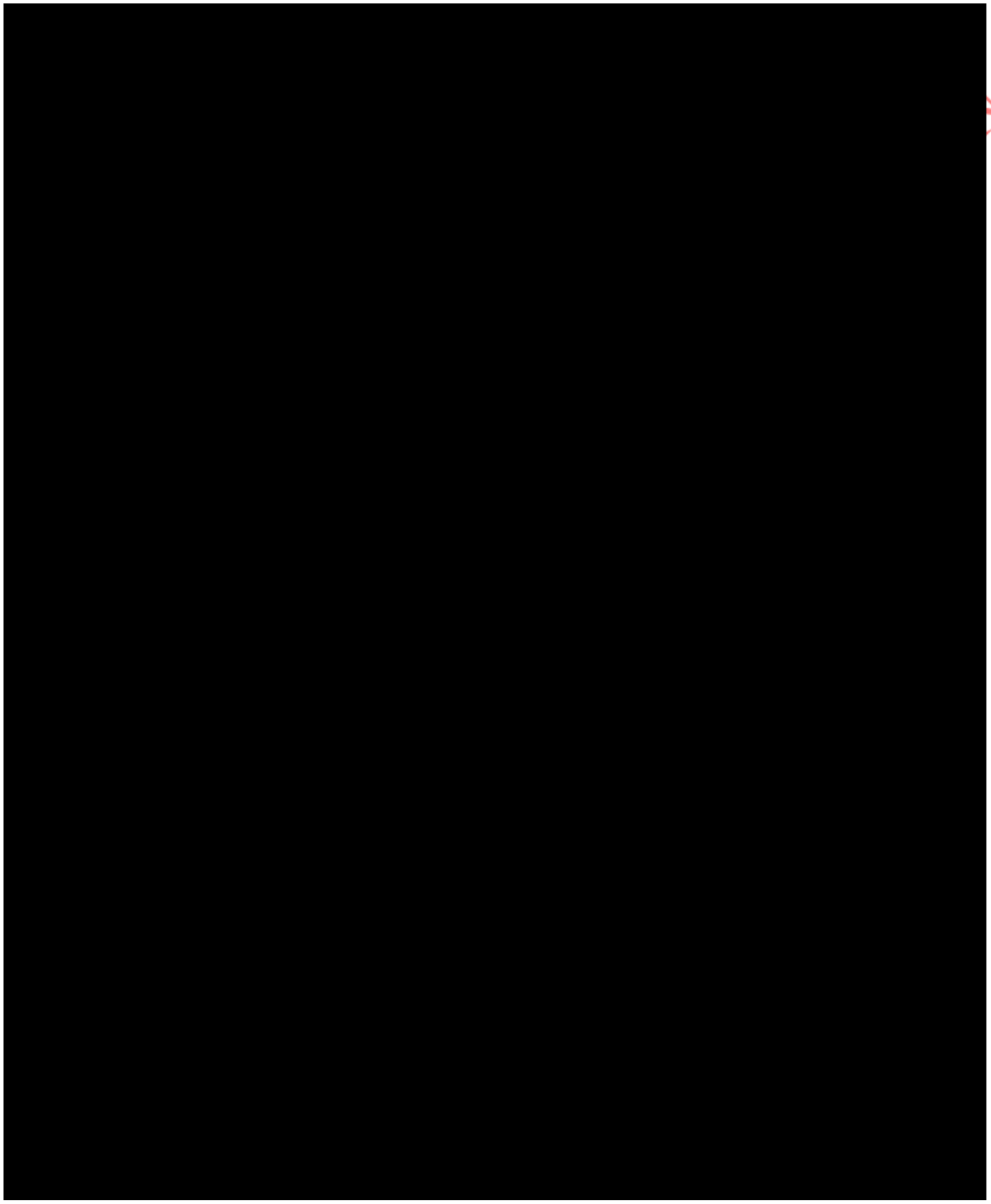


10.11.4 PedsQL™ Multidimensional Fatigue Scale

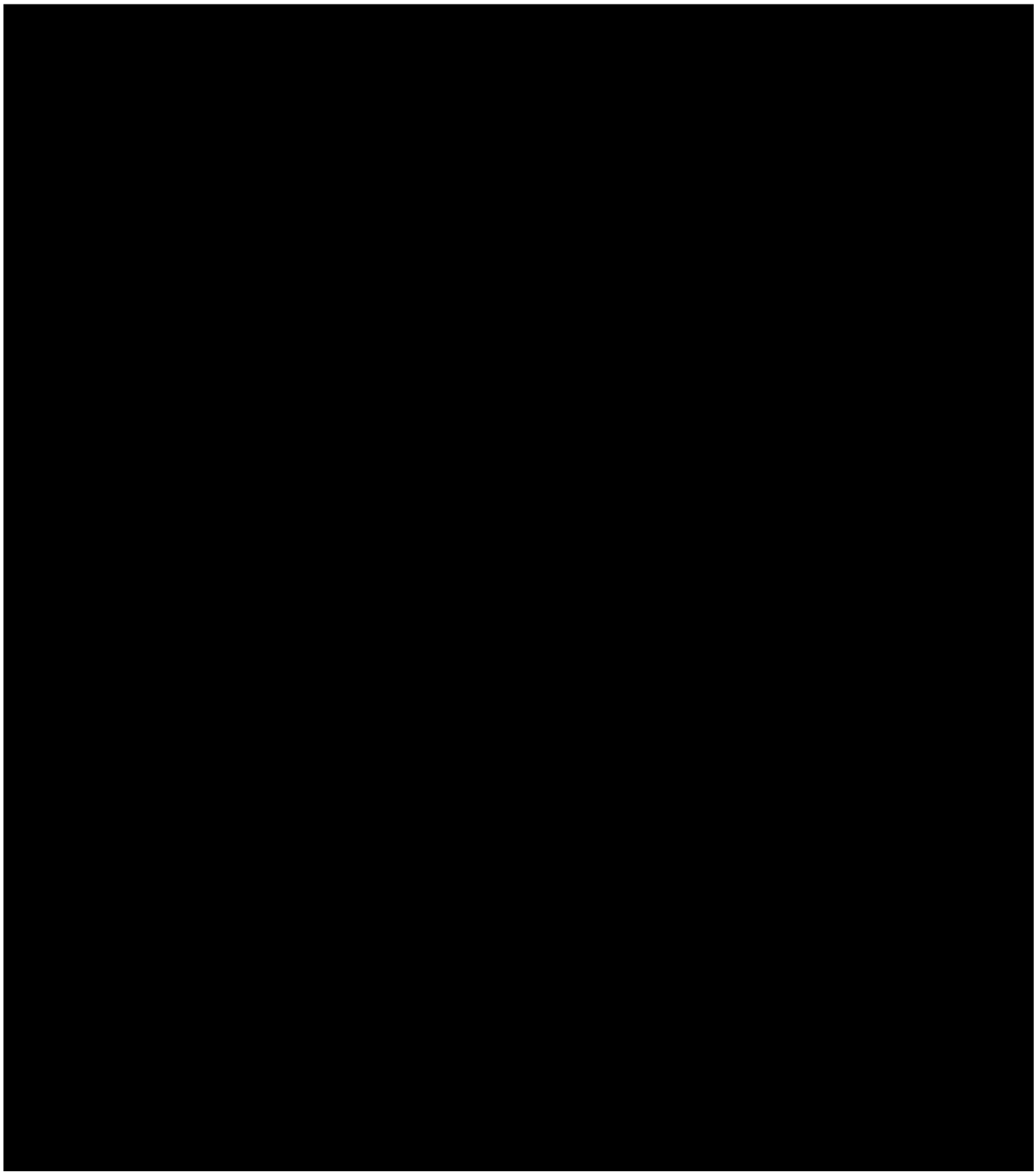


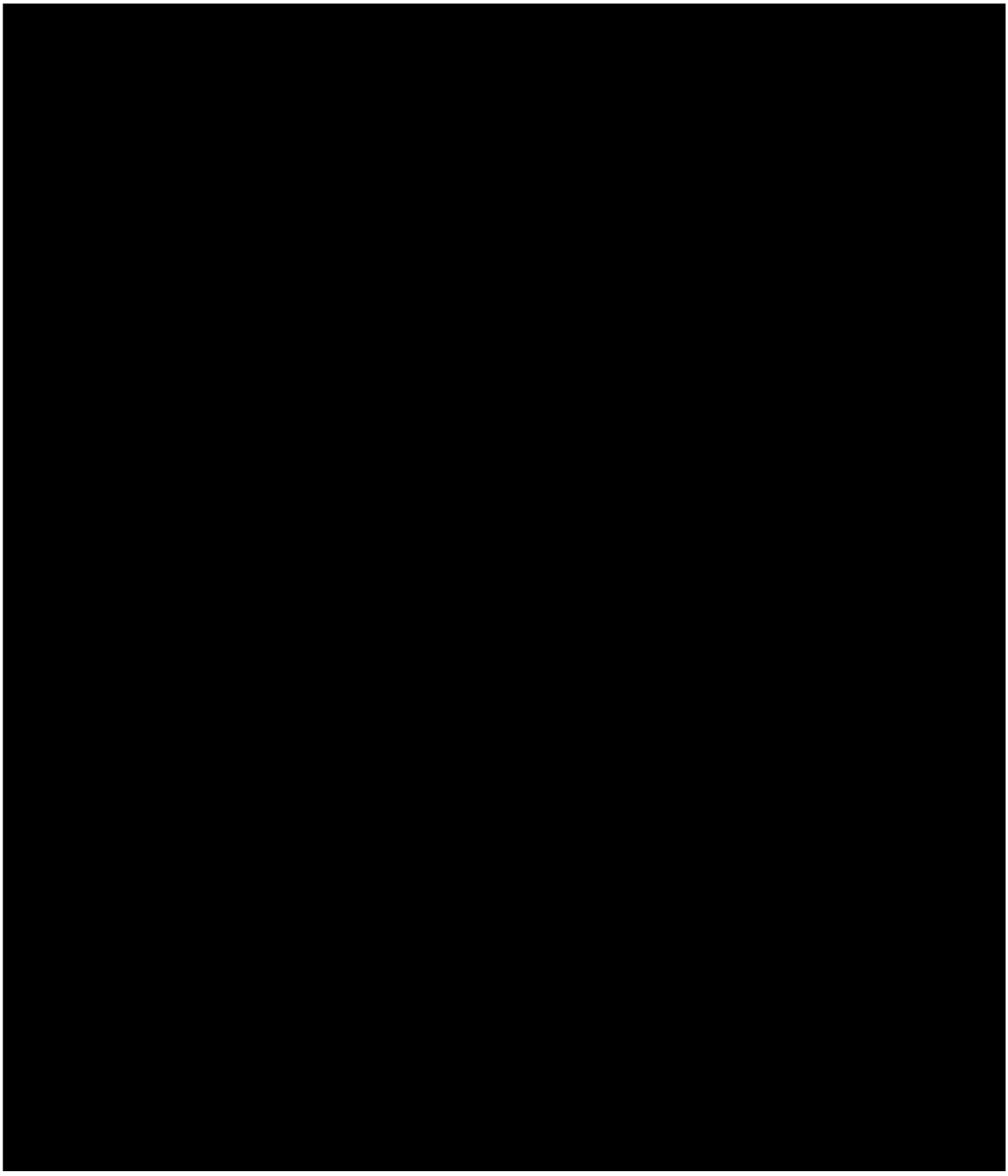
PedsQL 2

[redacted]



PedsQL 2





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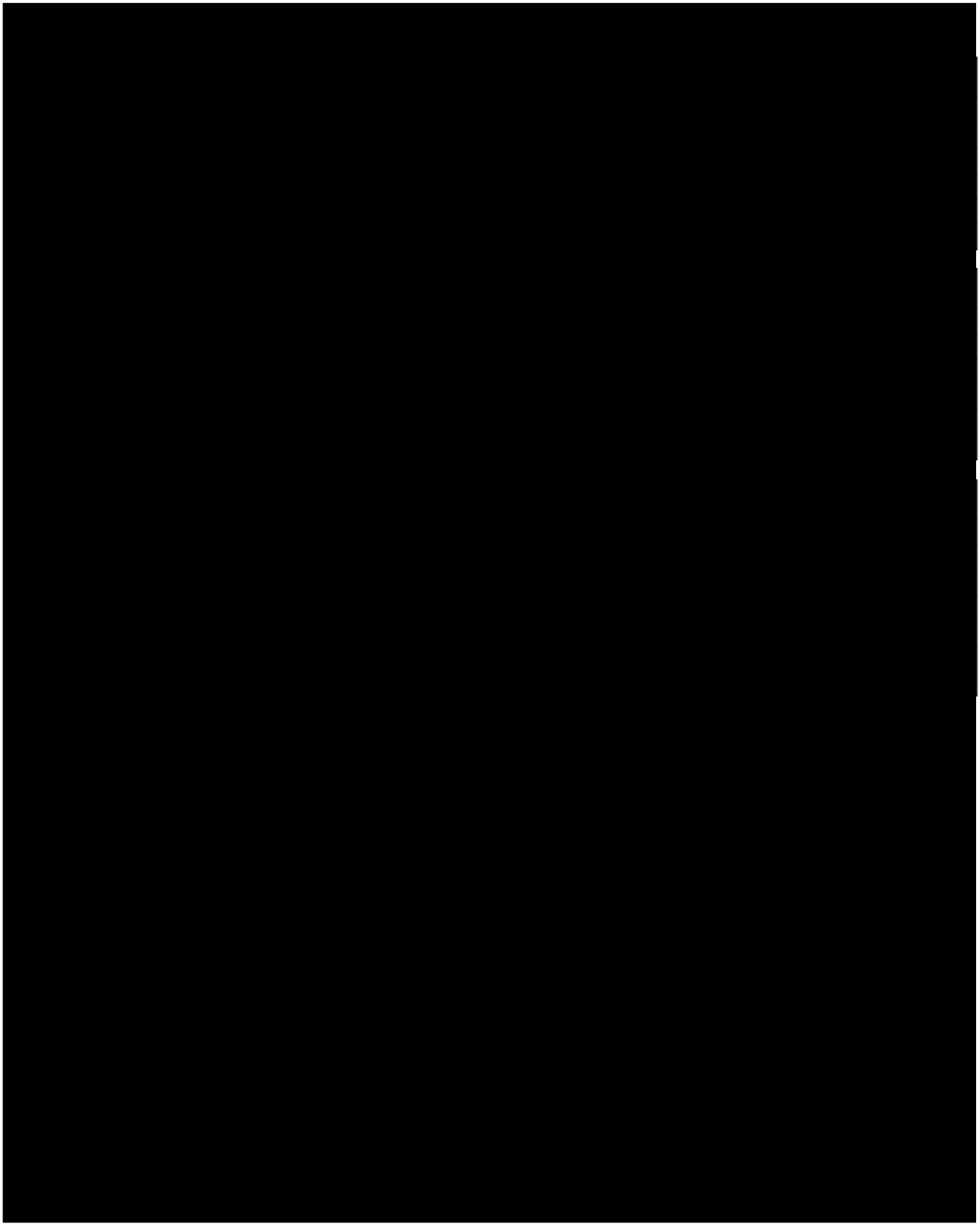

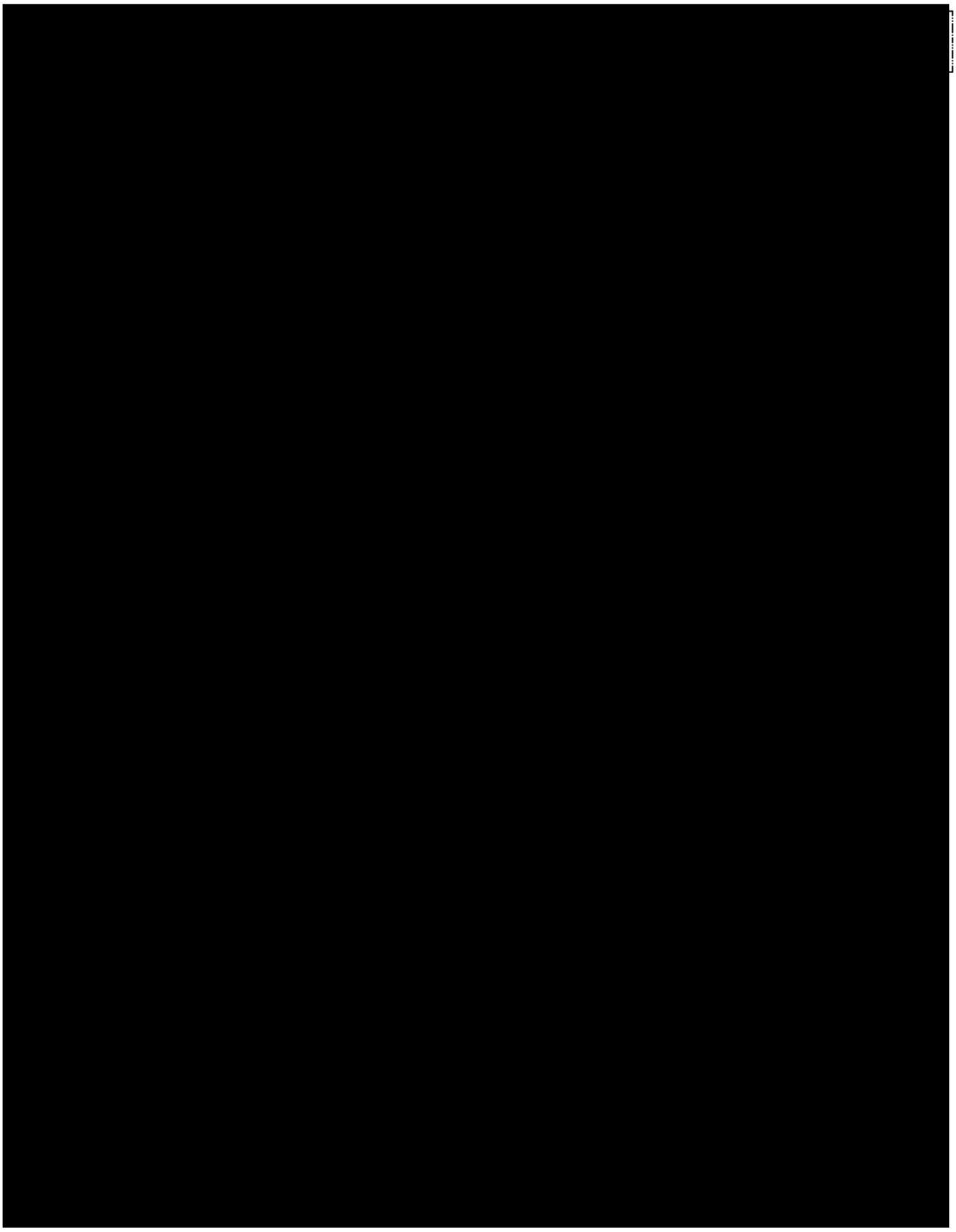

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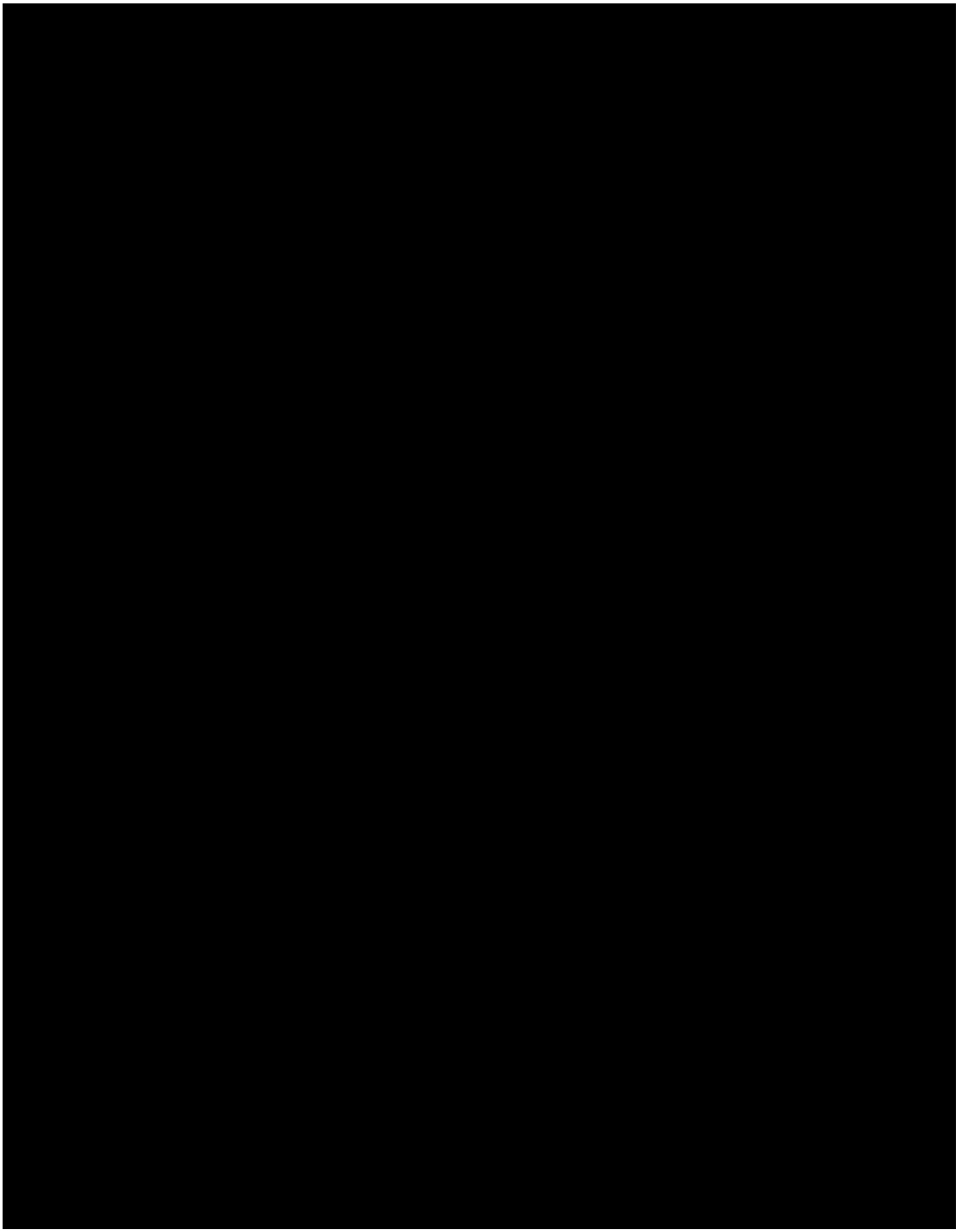

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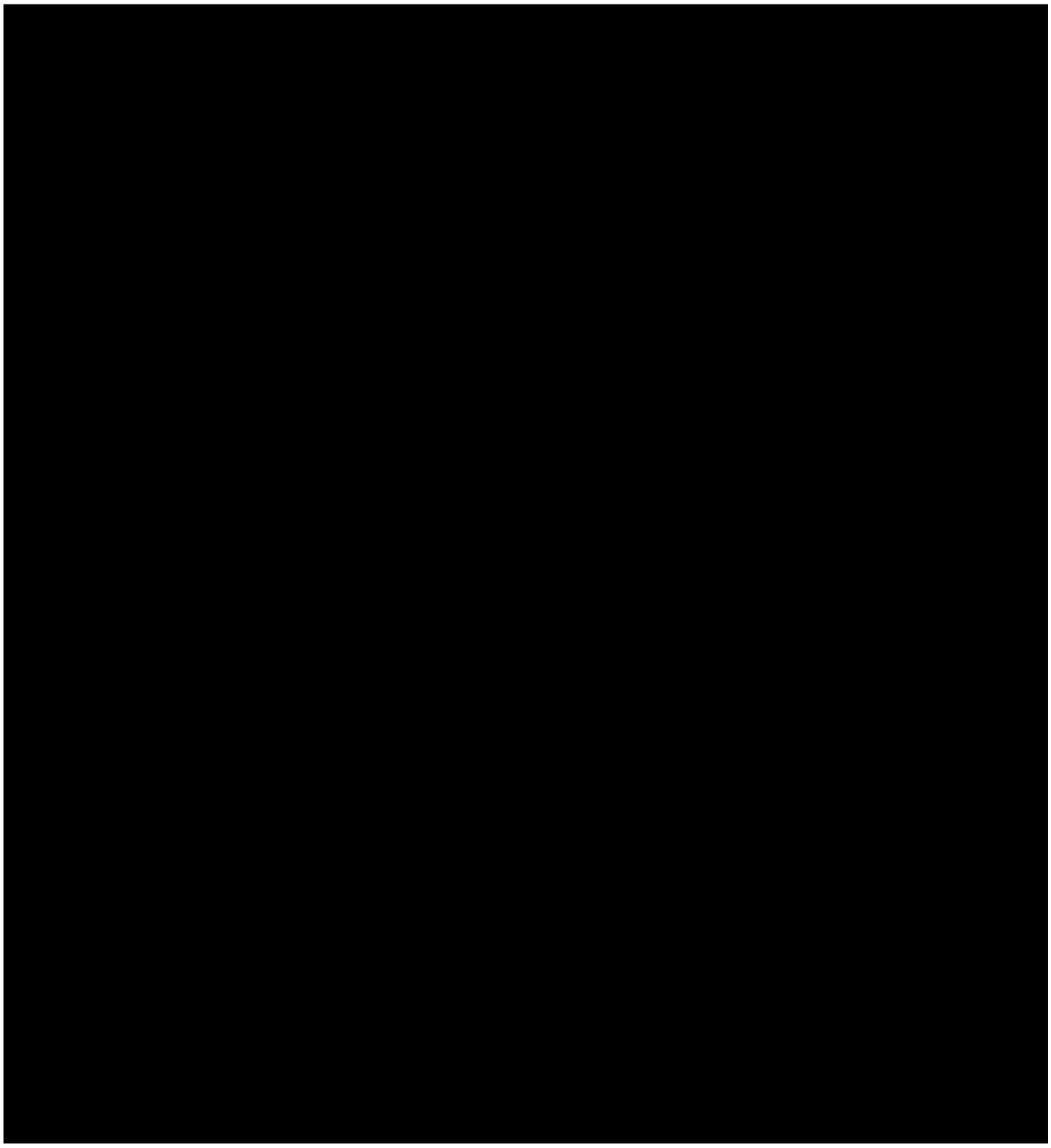
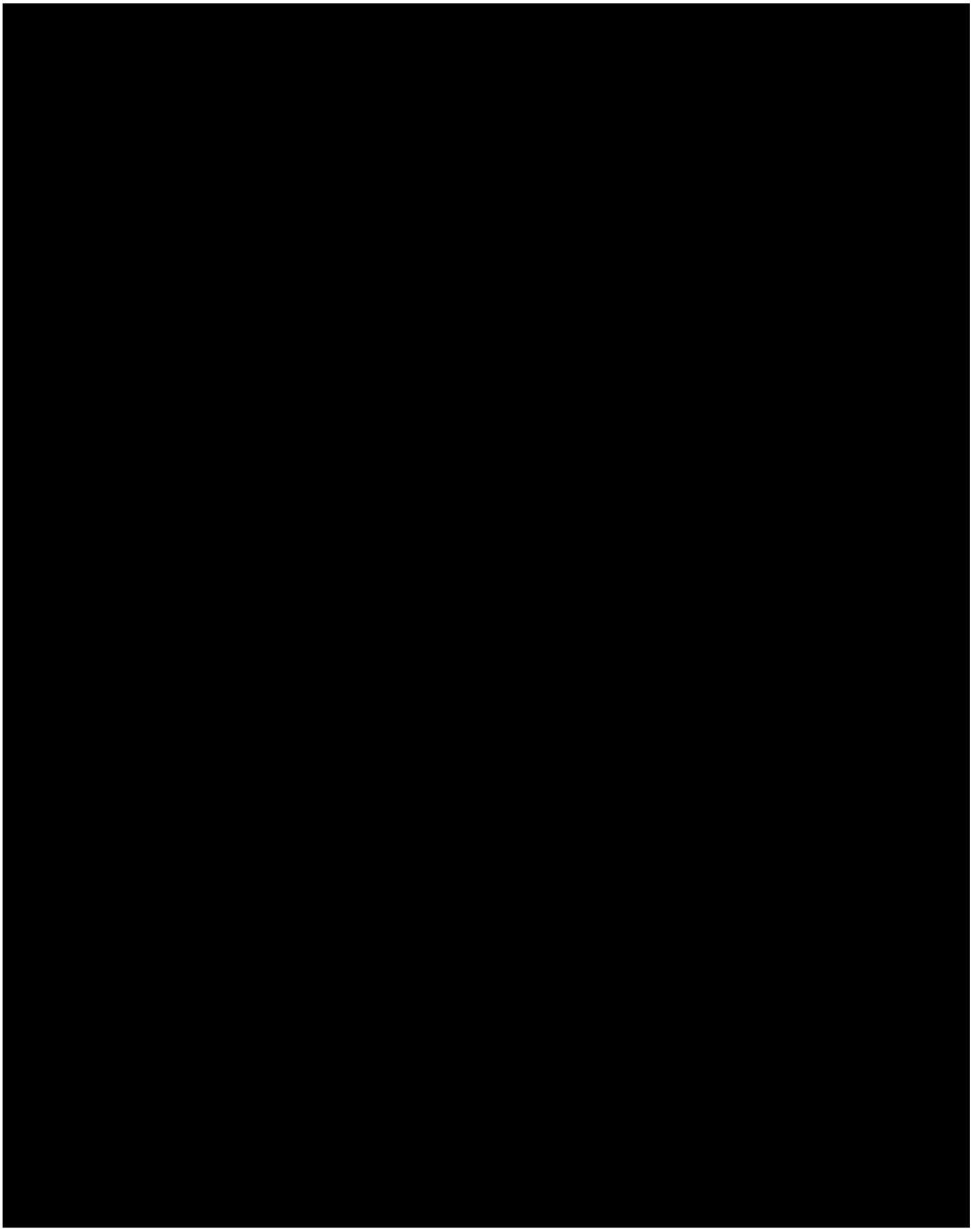
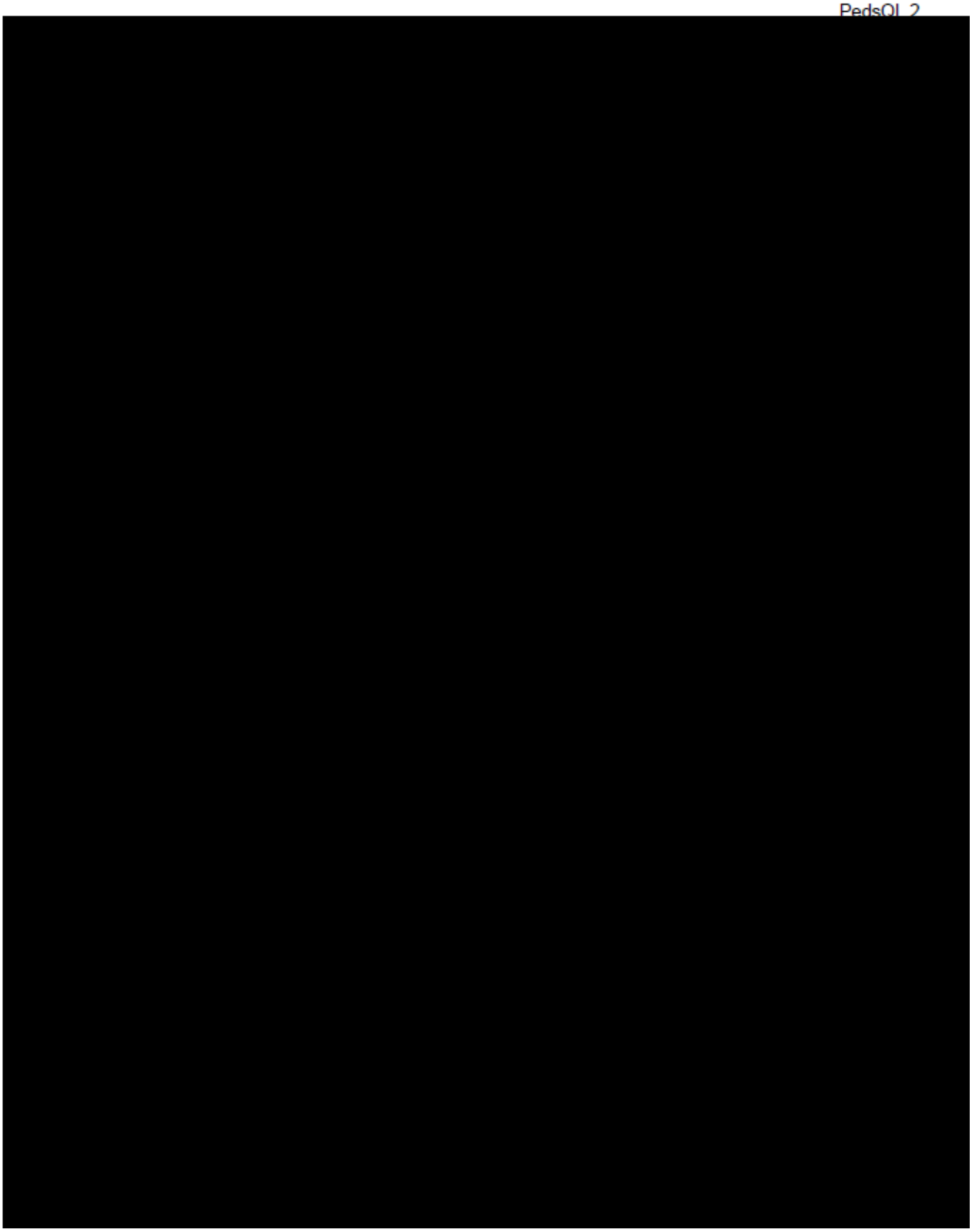
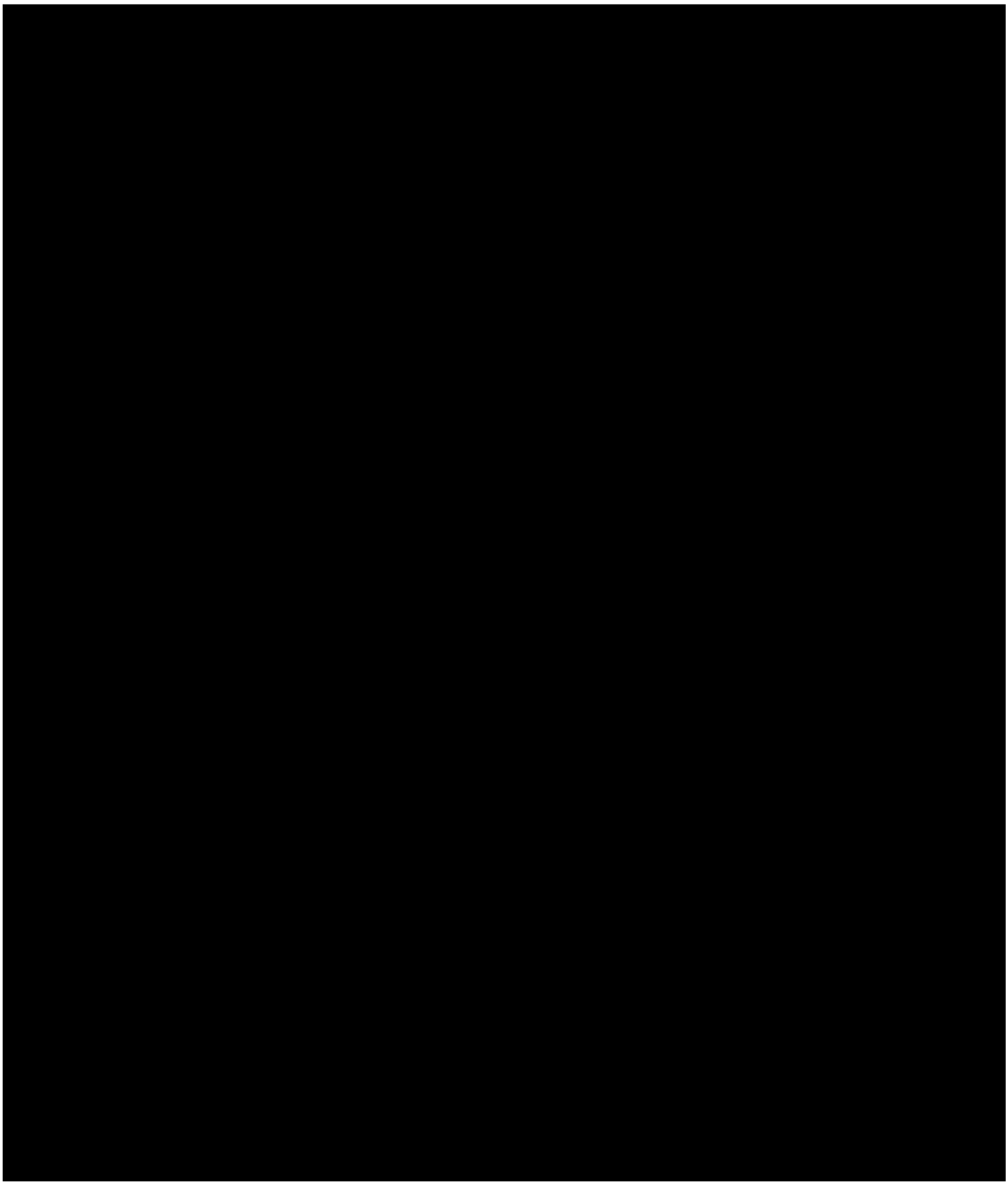


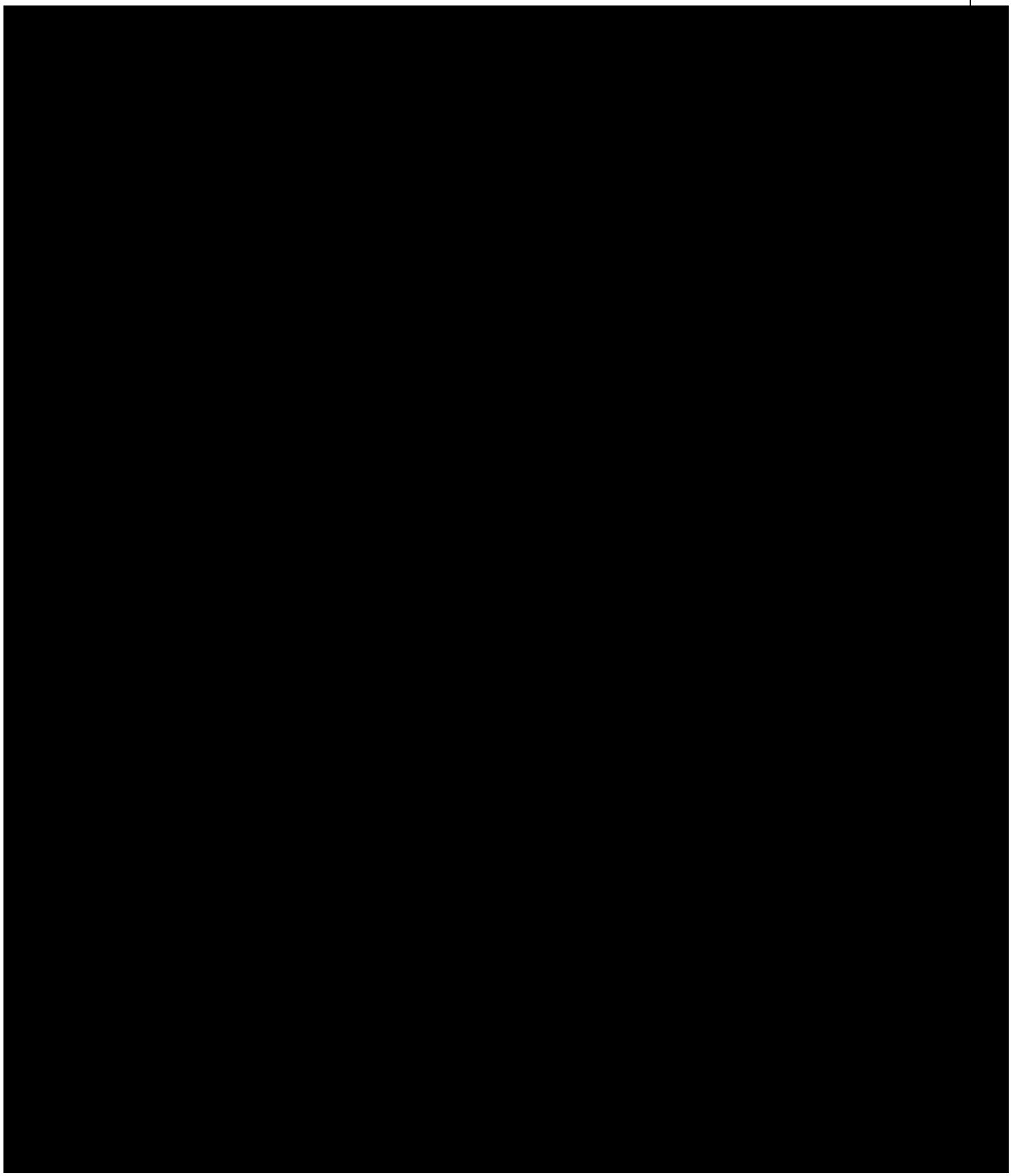


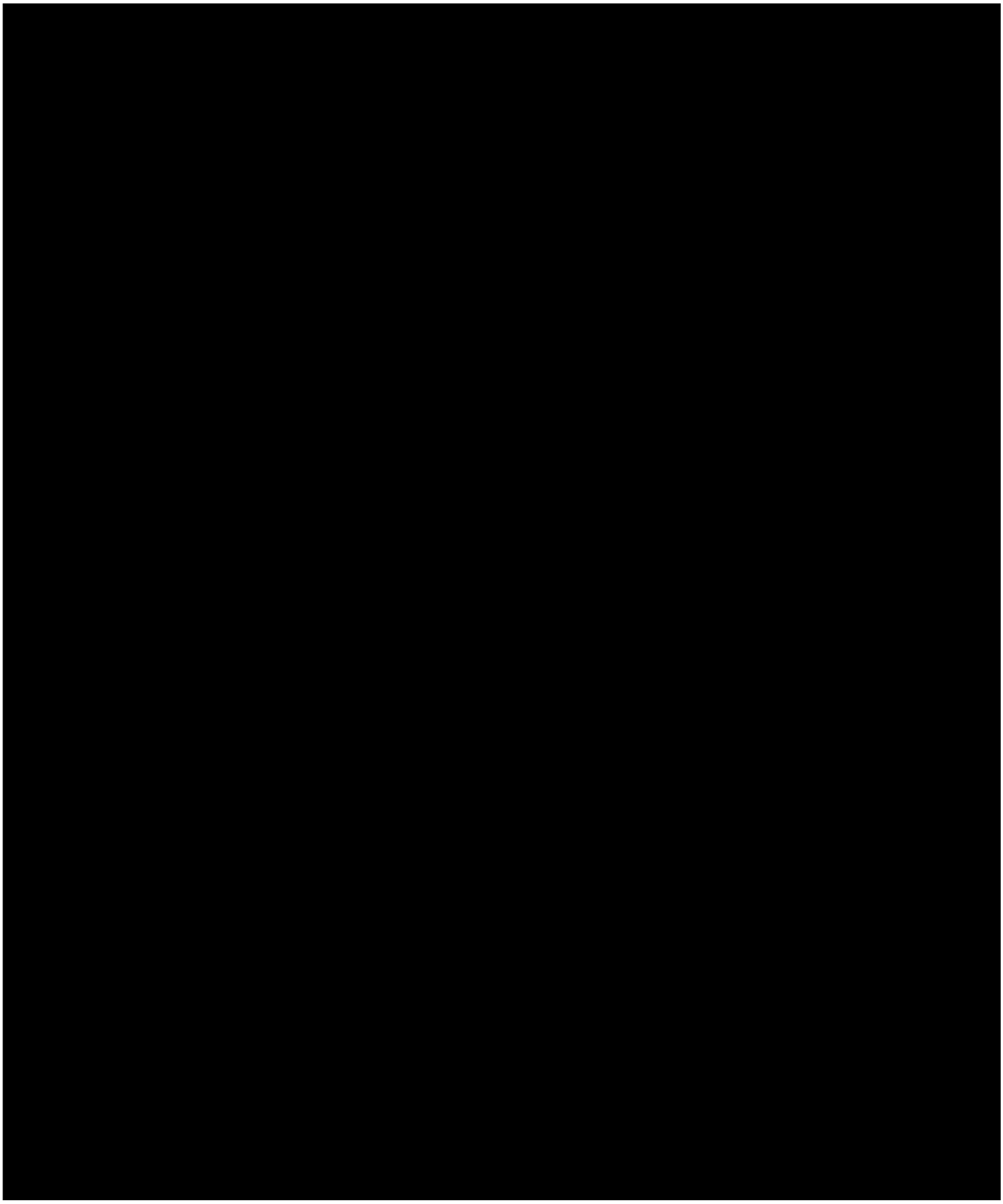
PedsQL 2

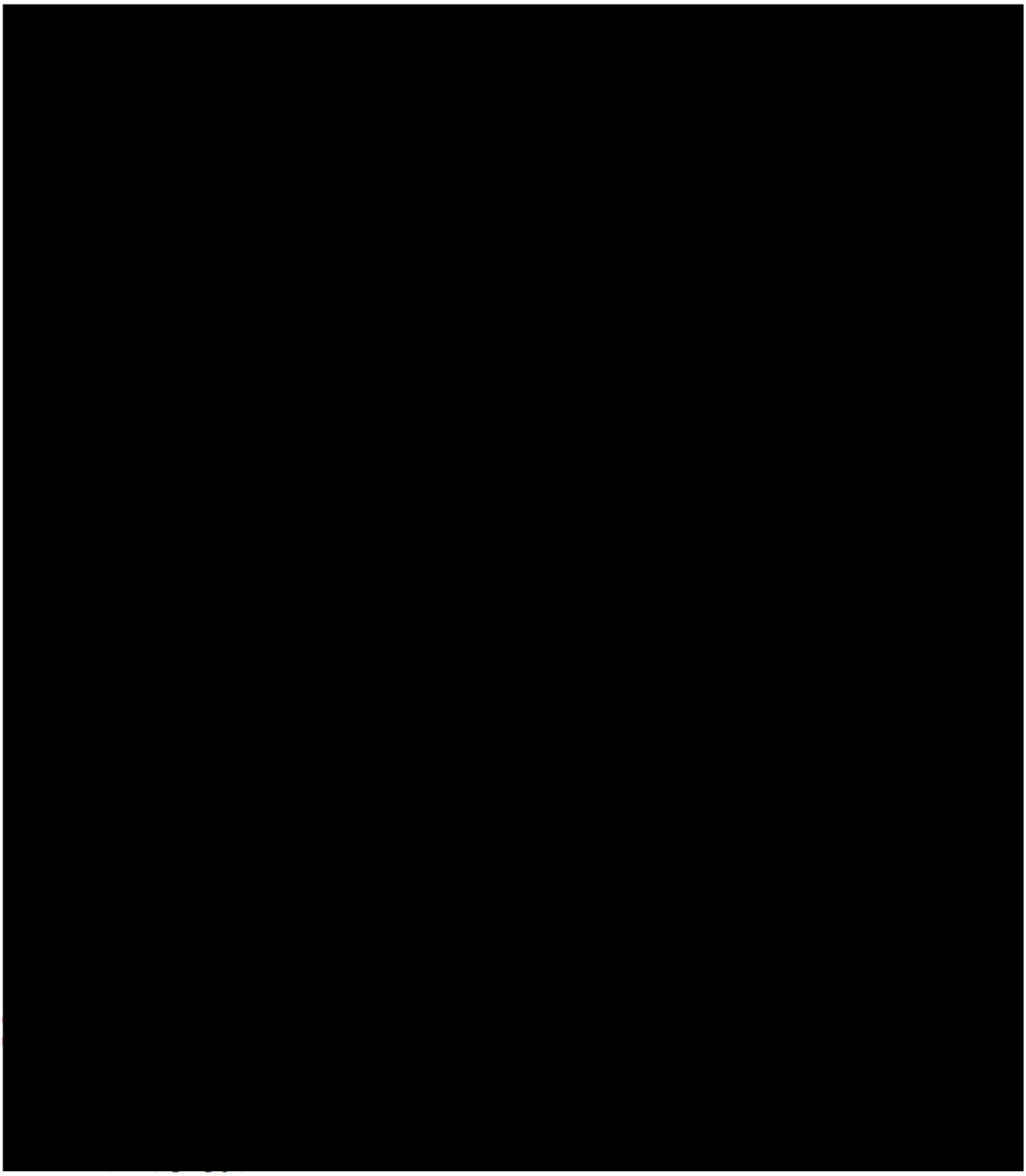


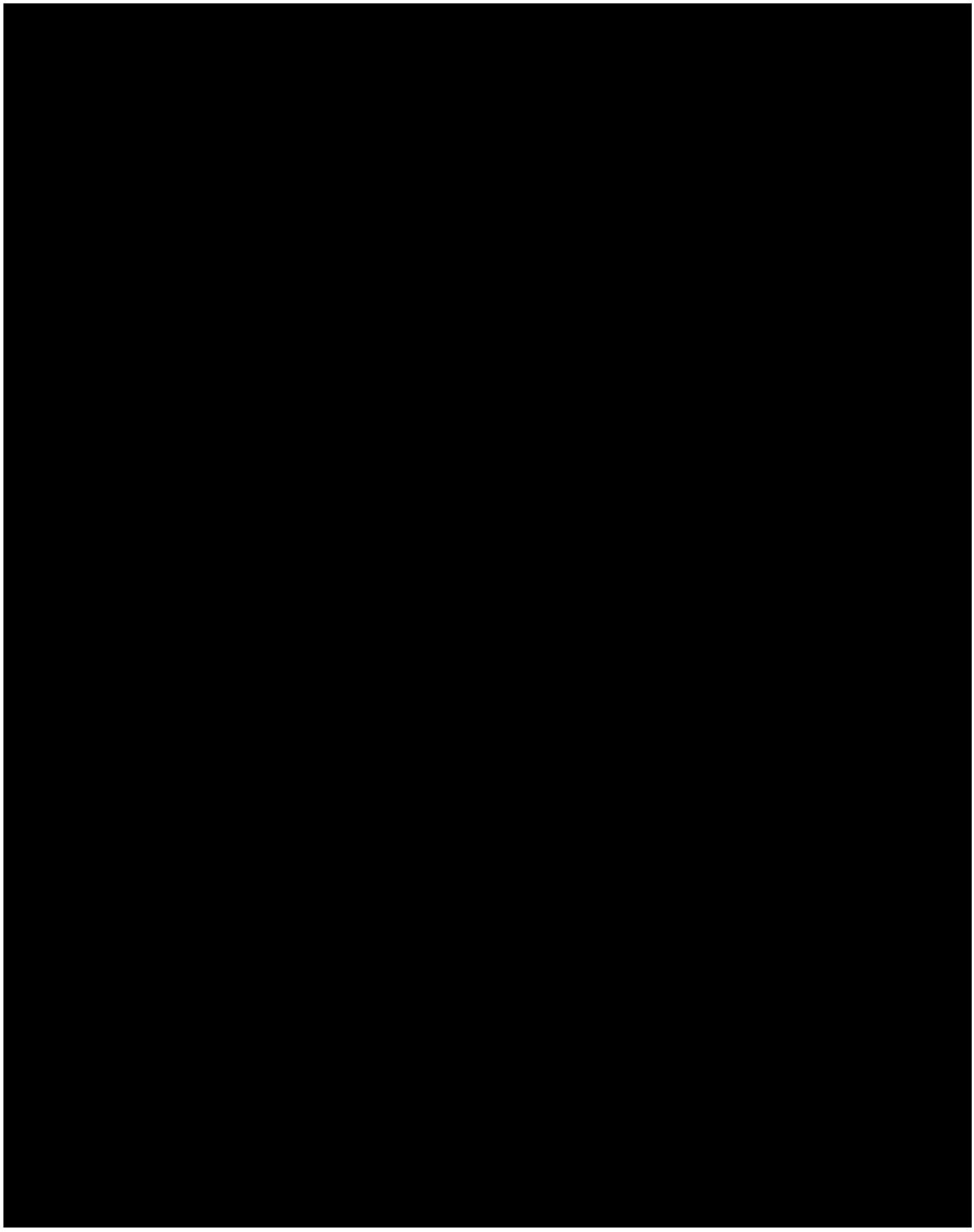
10.11.5 PedsQLTM Pediatric Pain QuestionnaireTM

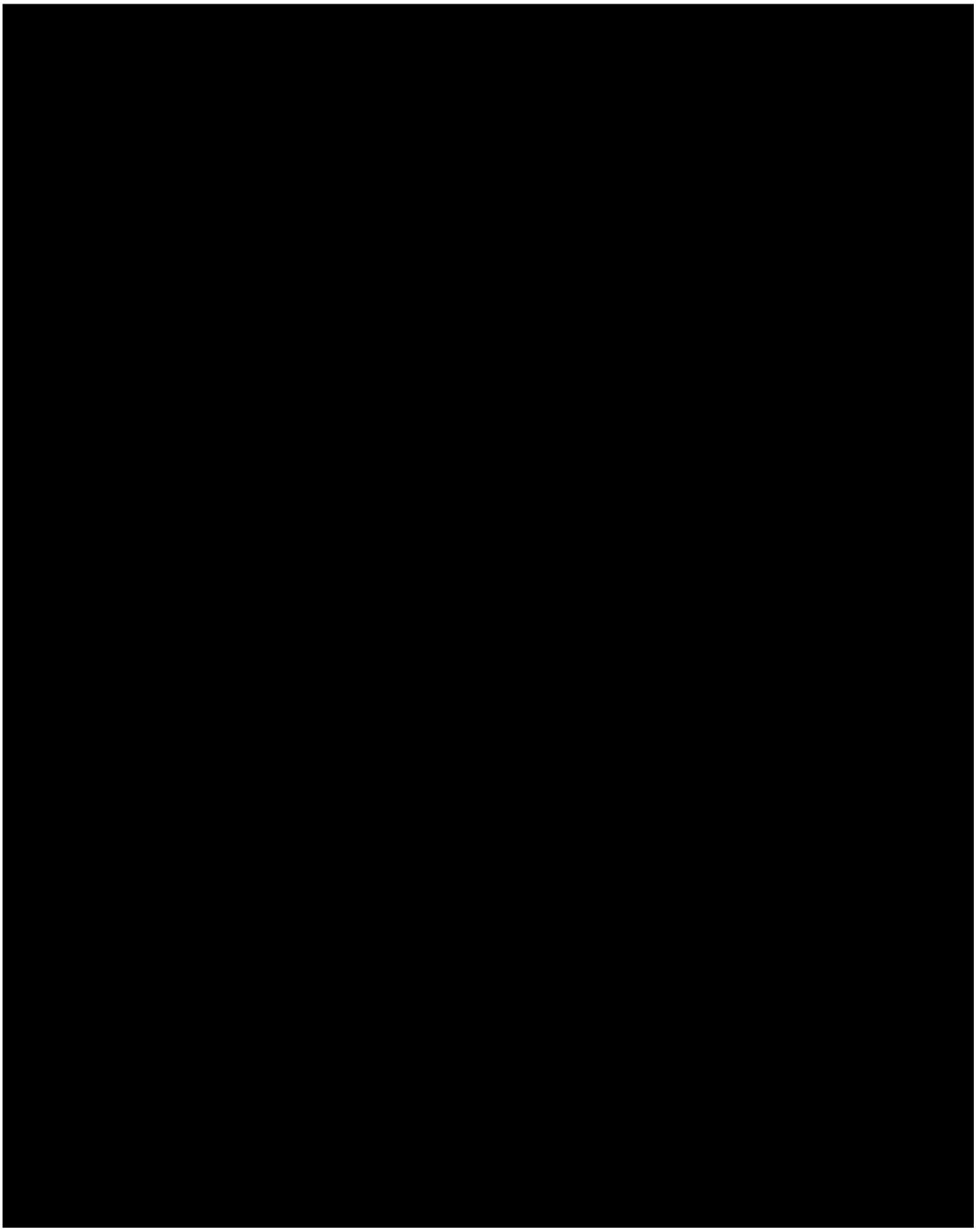


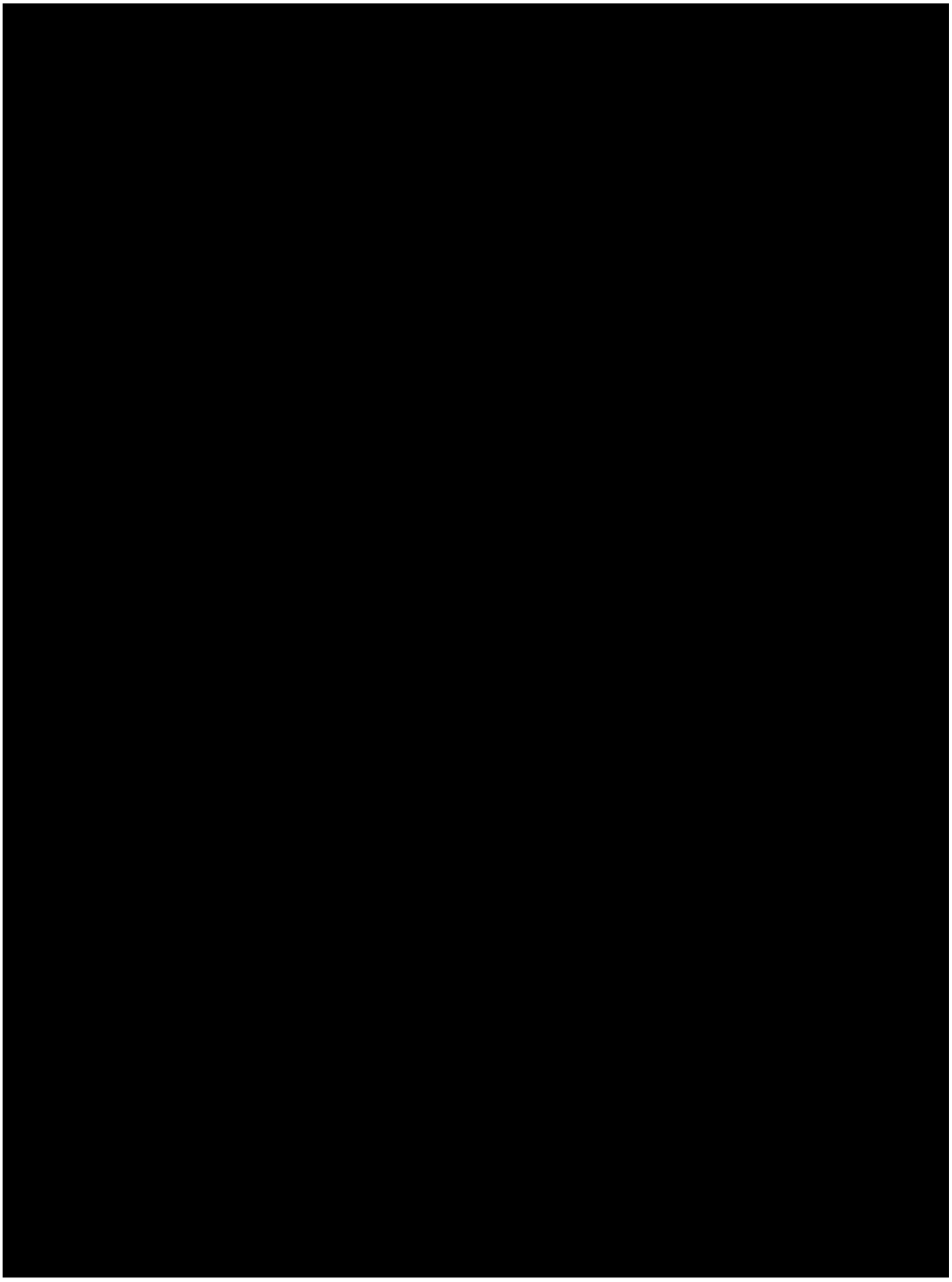


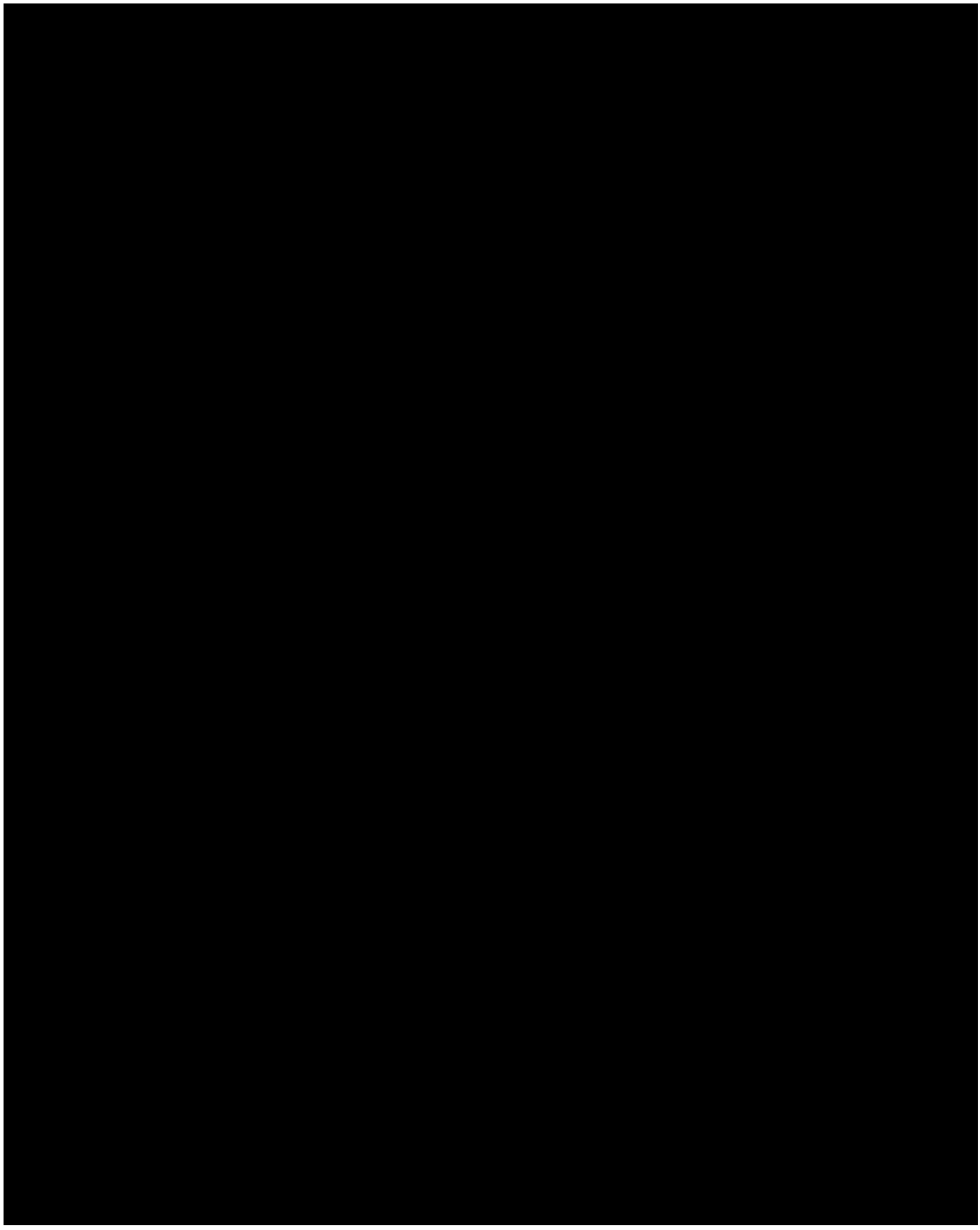


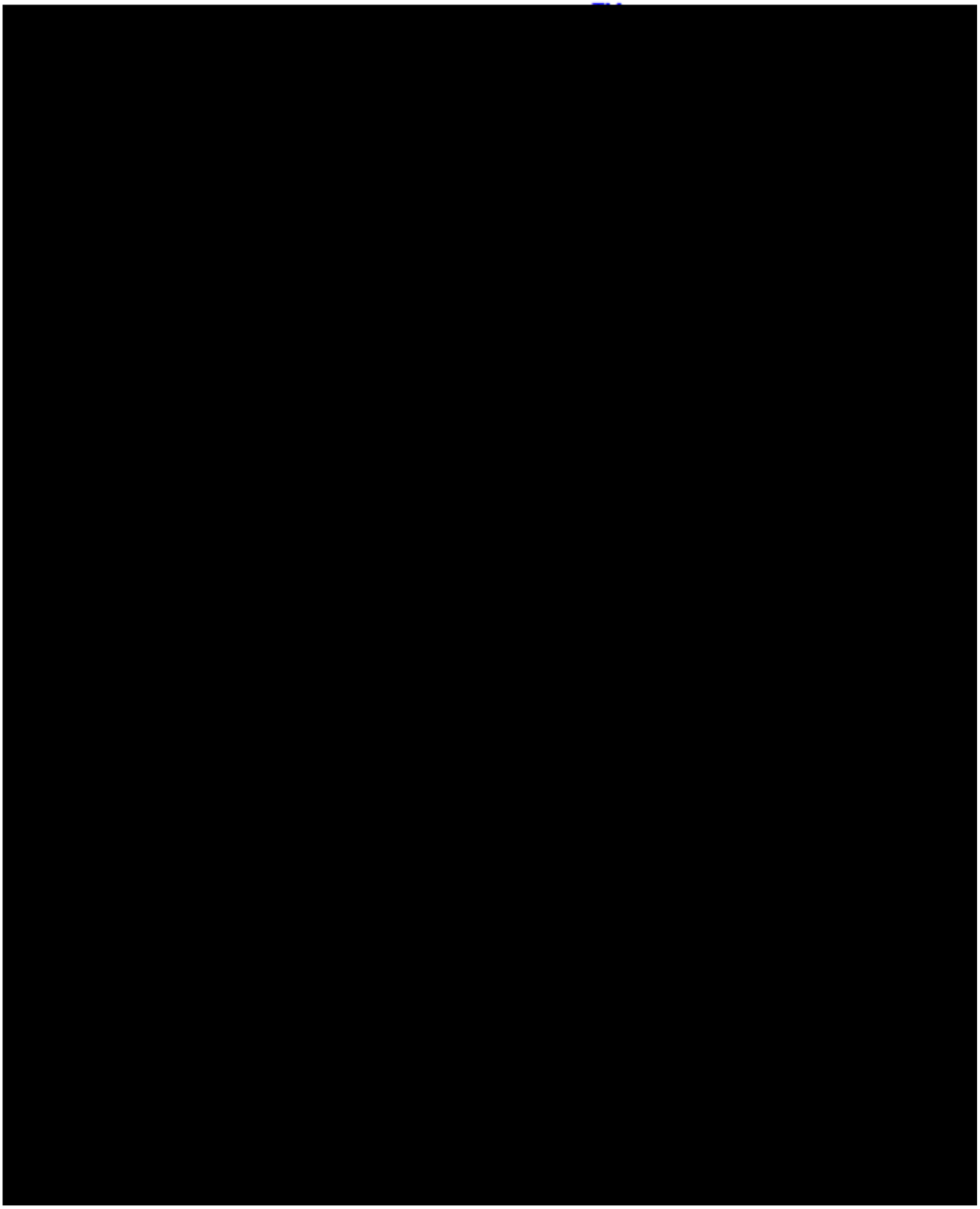


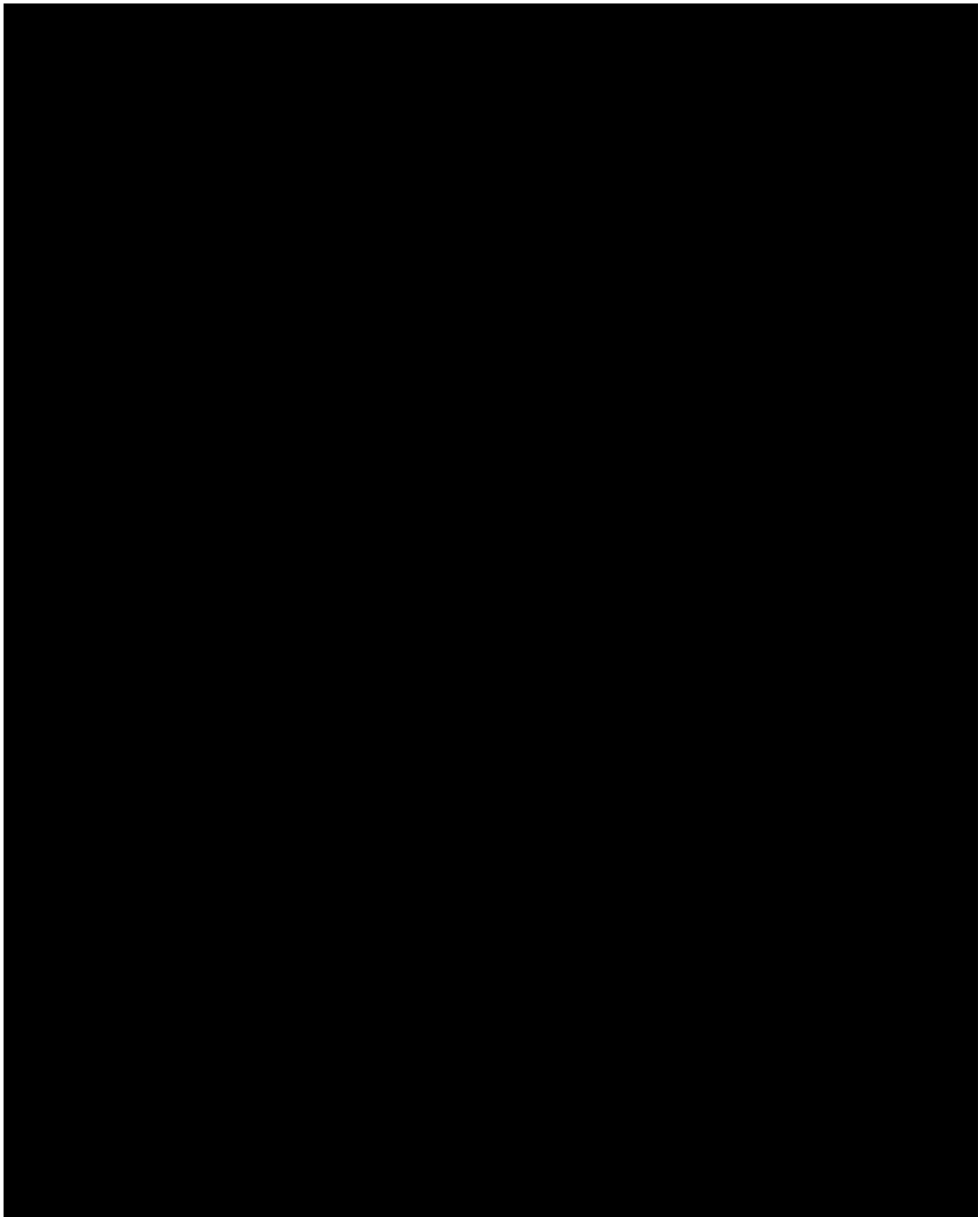




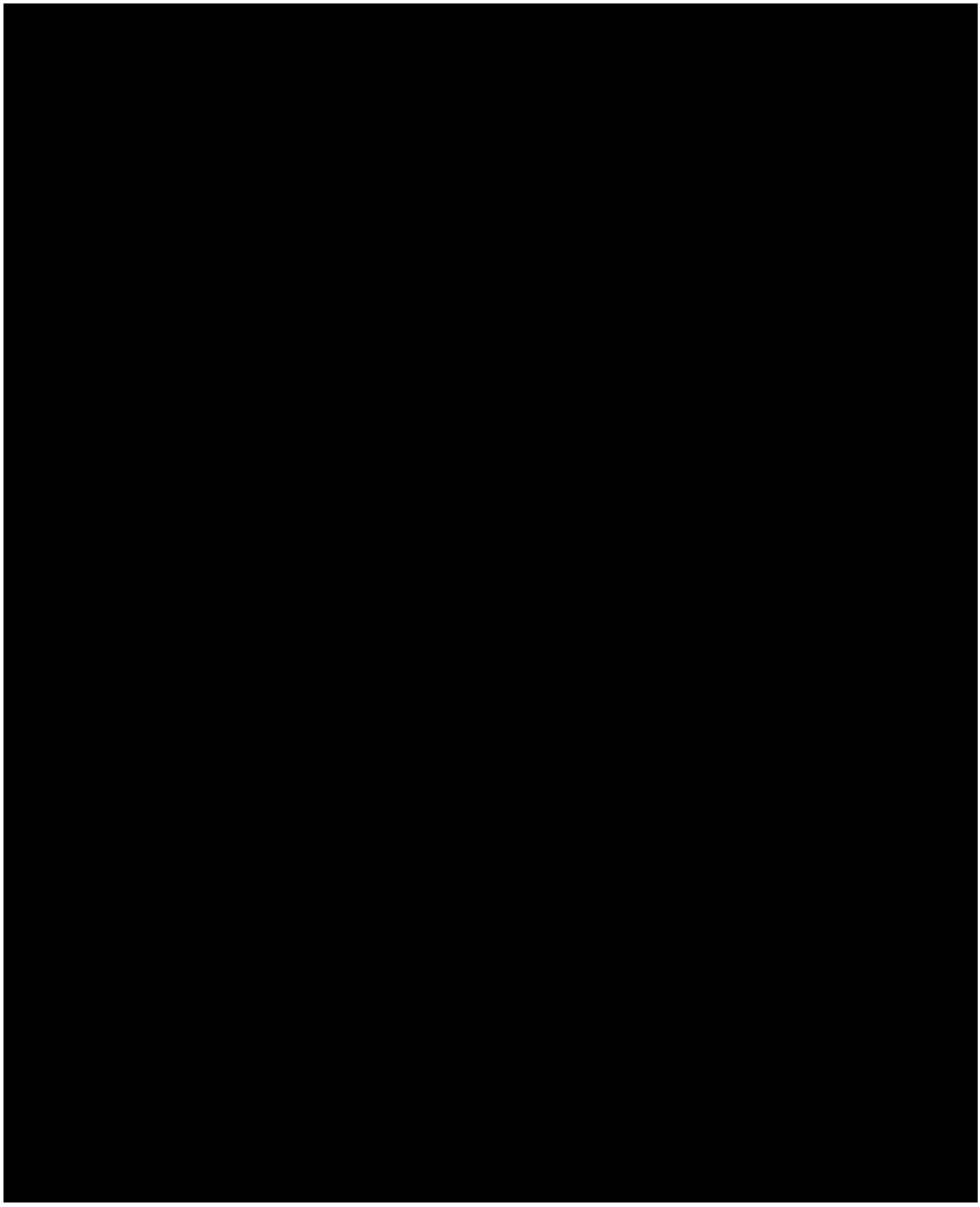








10.11.6 PedsQL Adult Quality of Life Inventory



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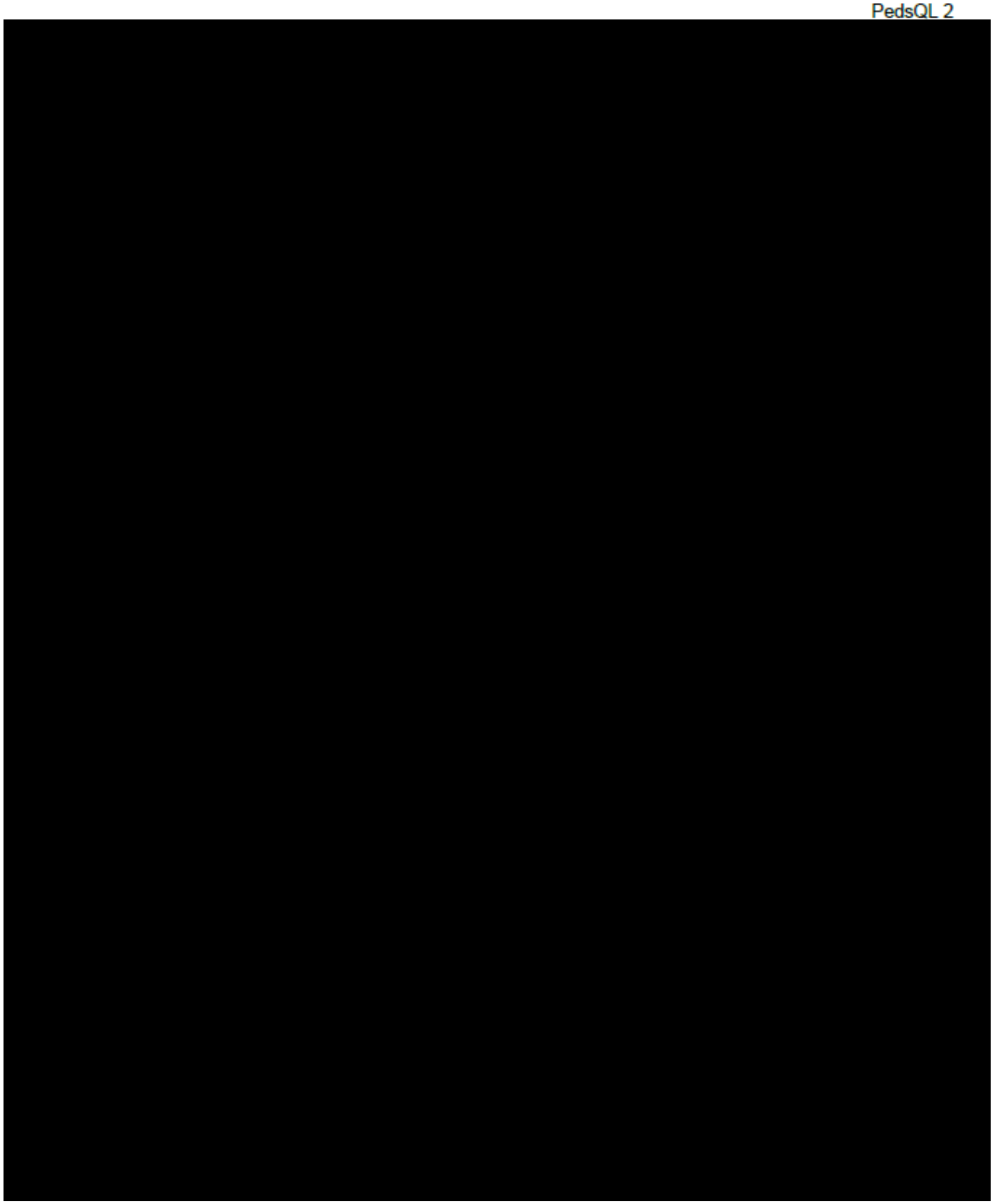

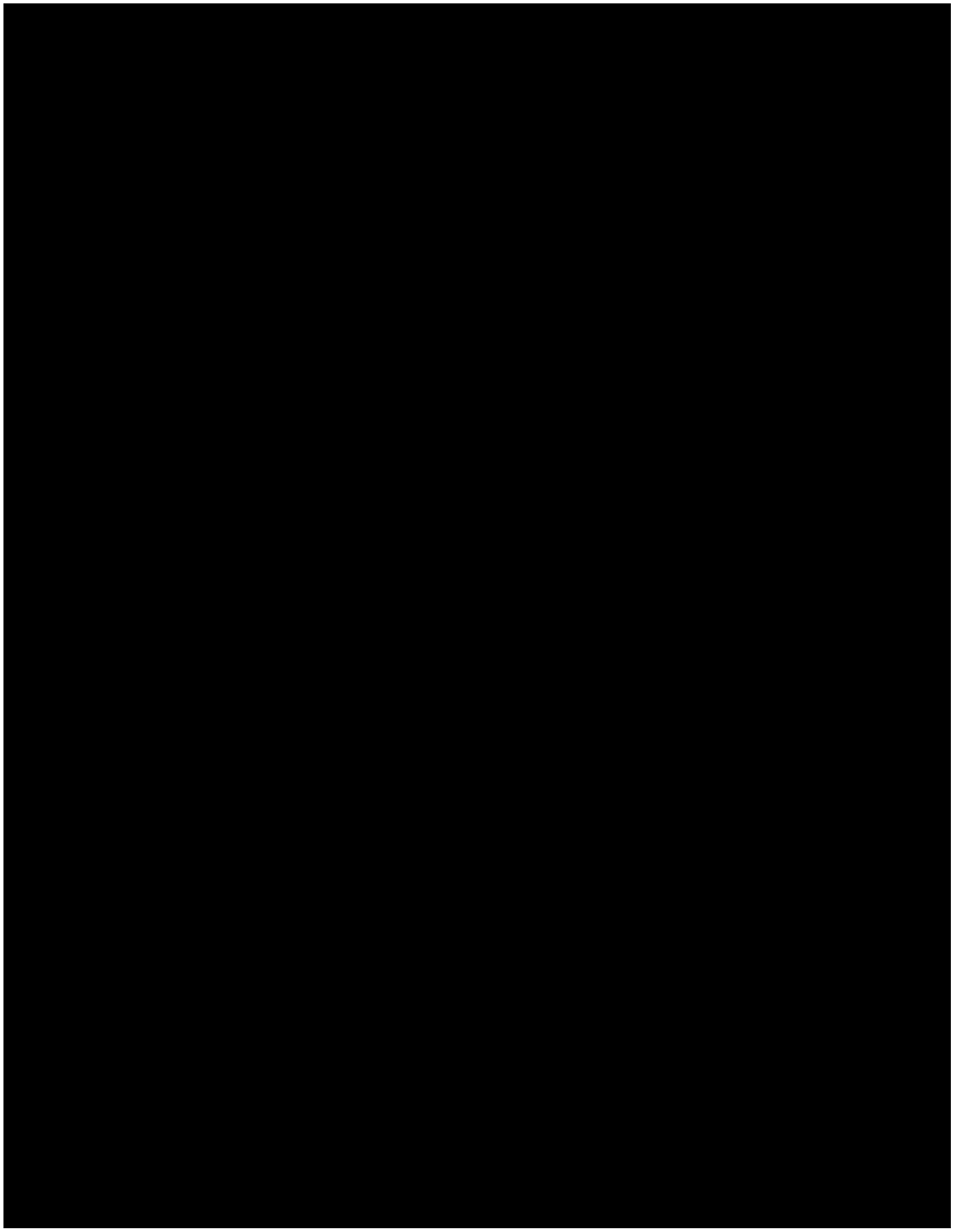

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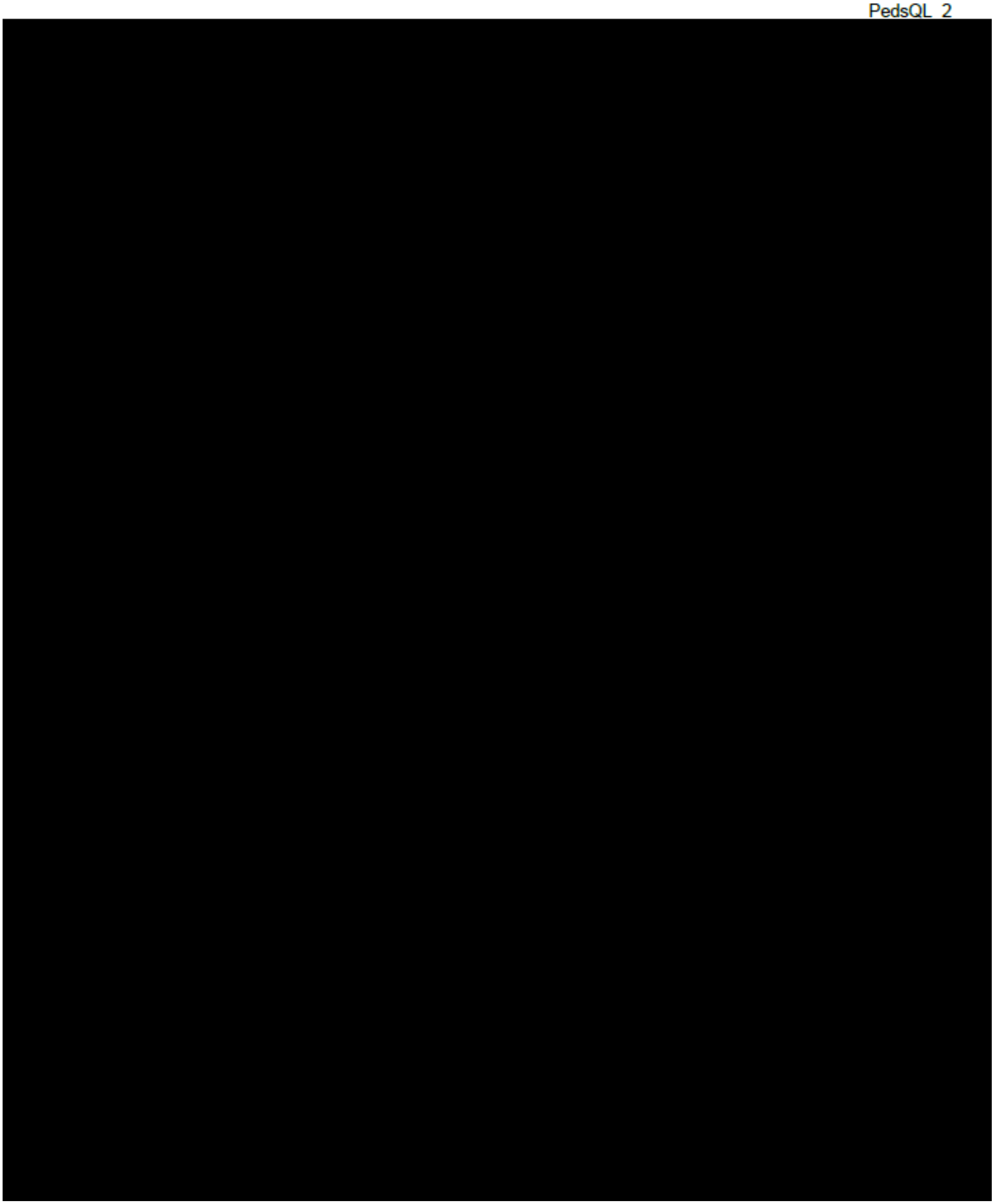

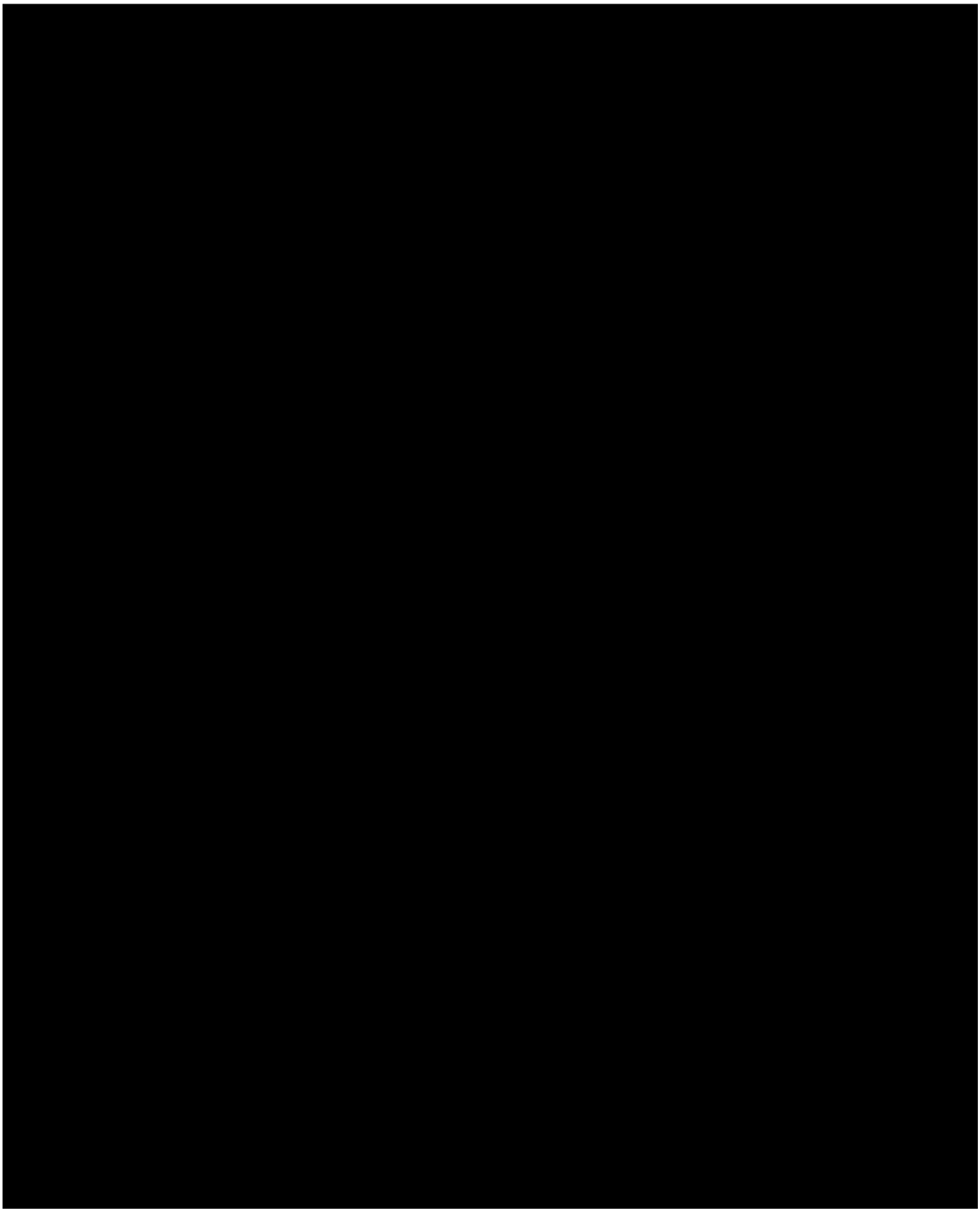

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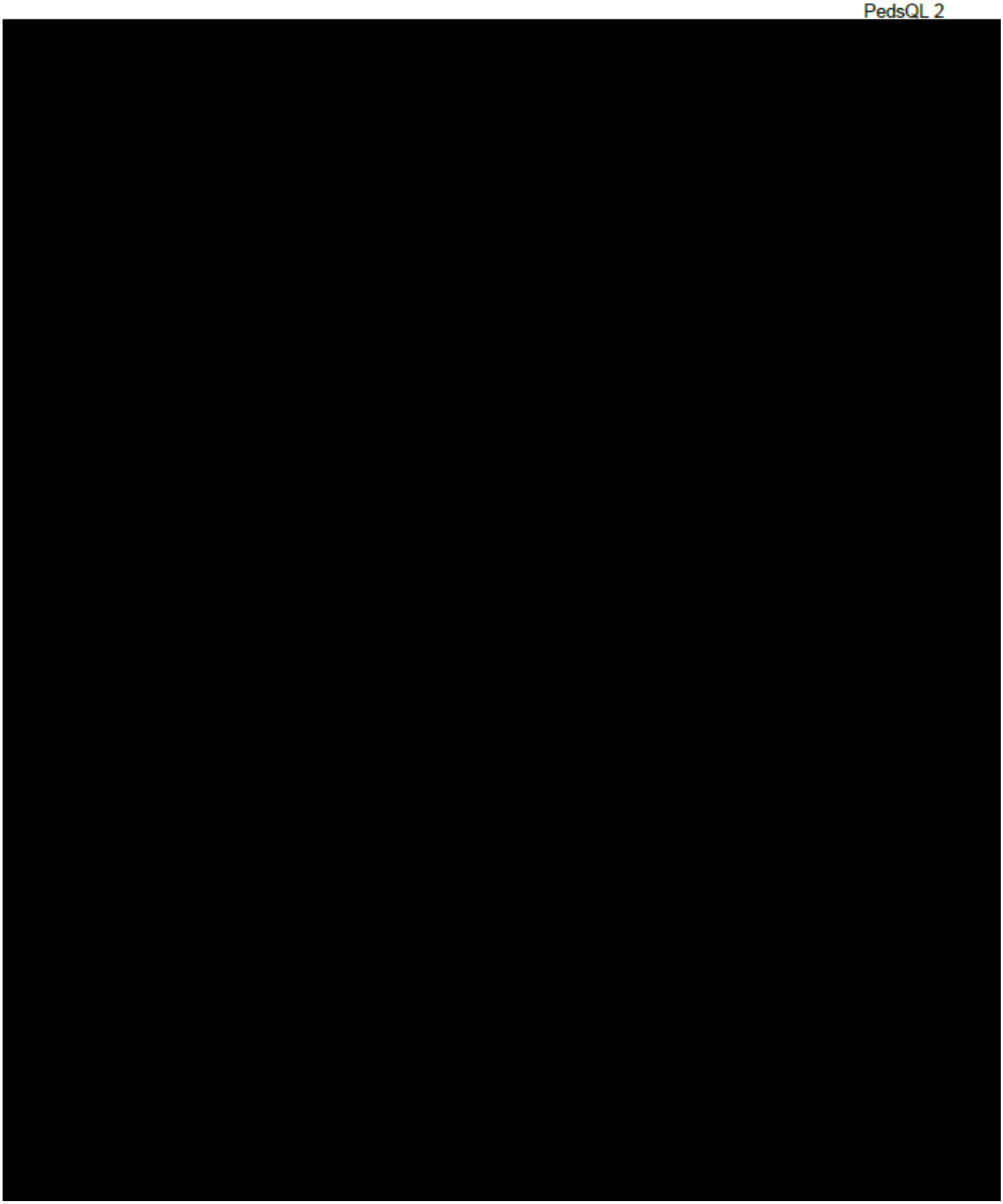

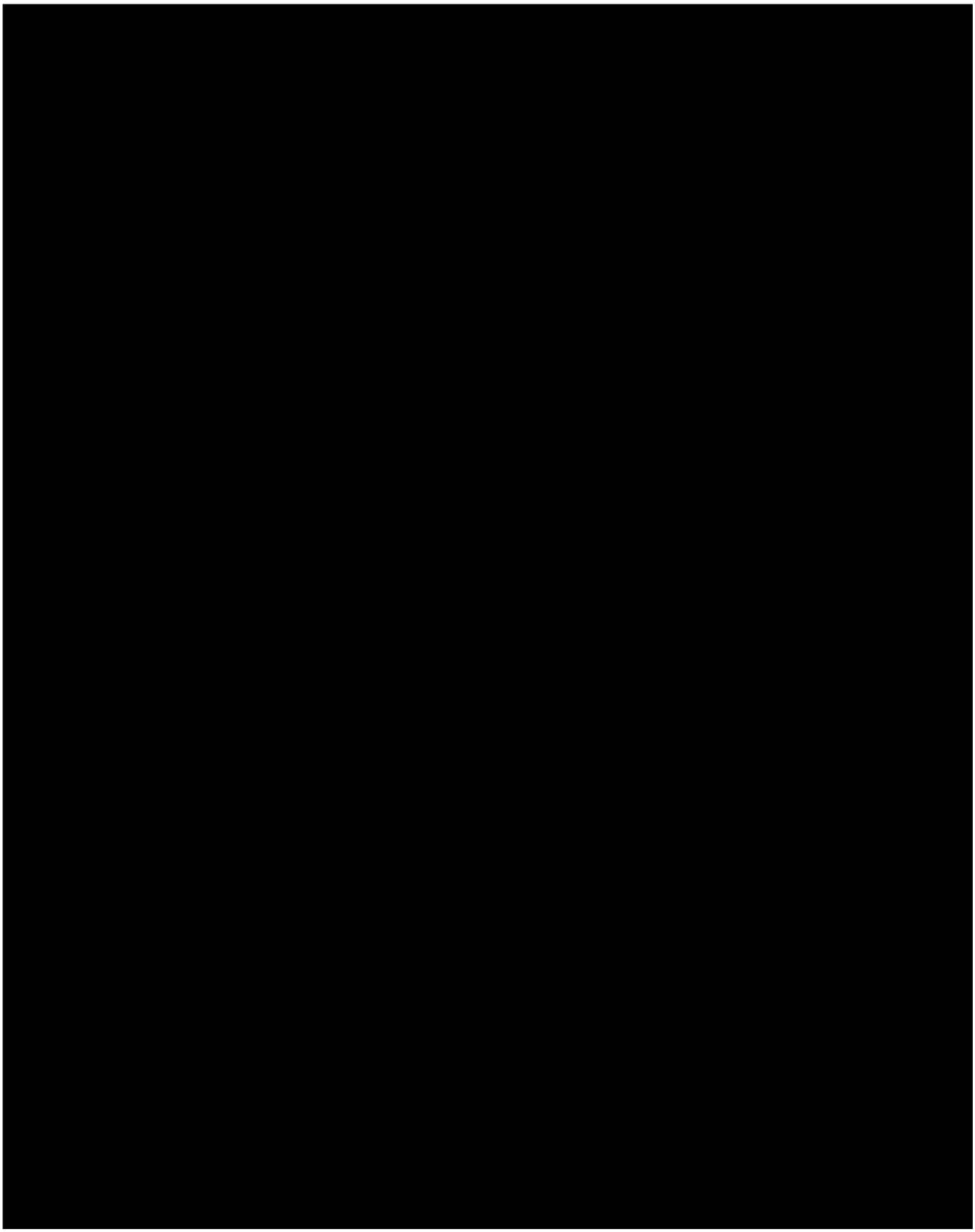

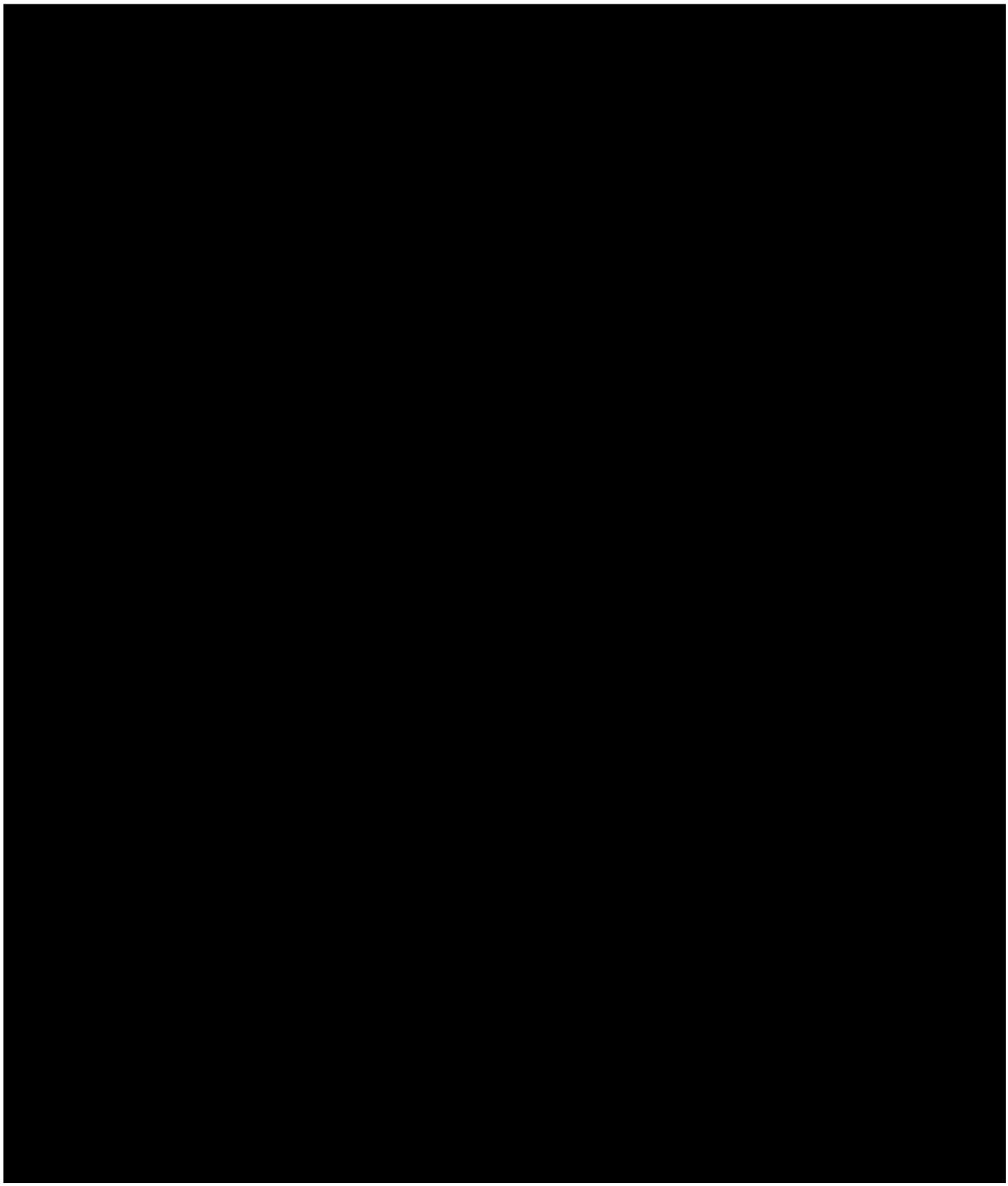

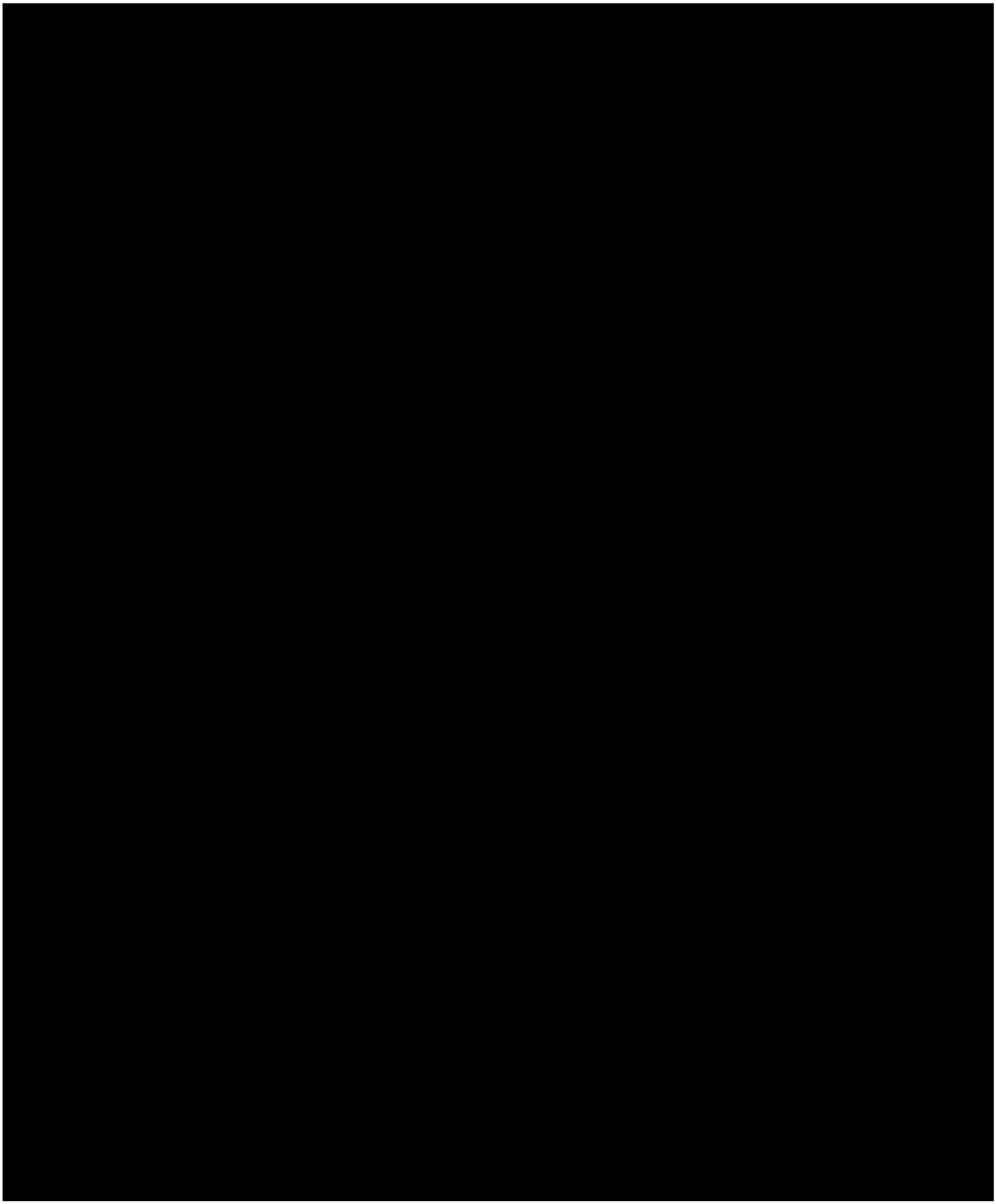

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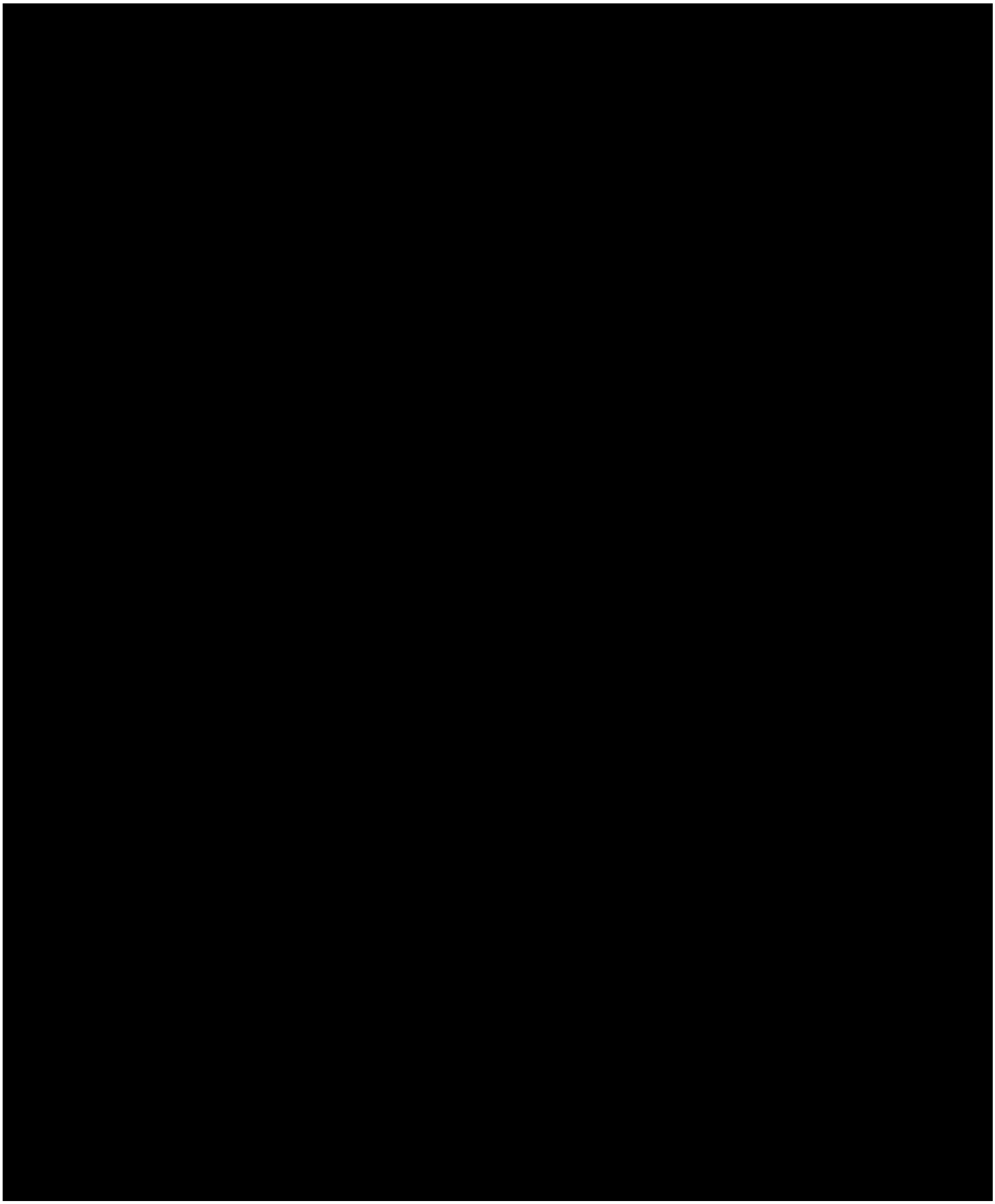

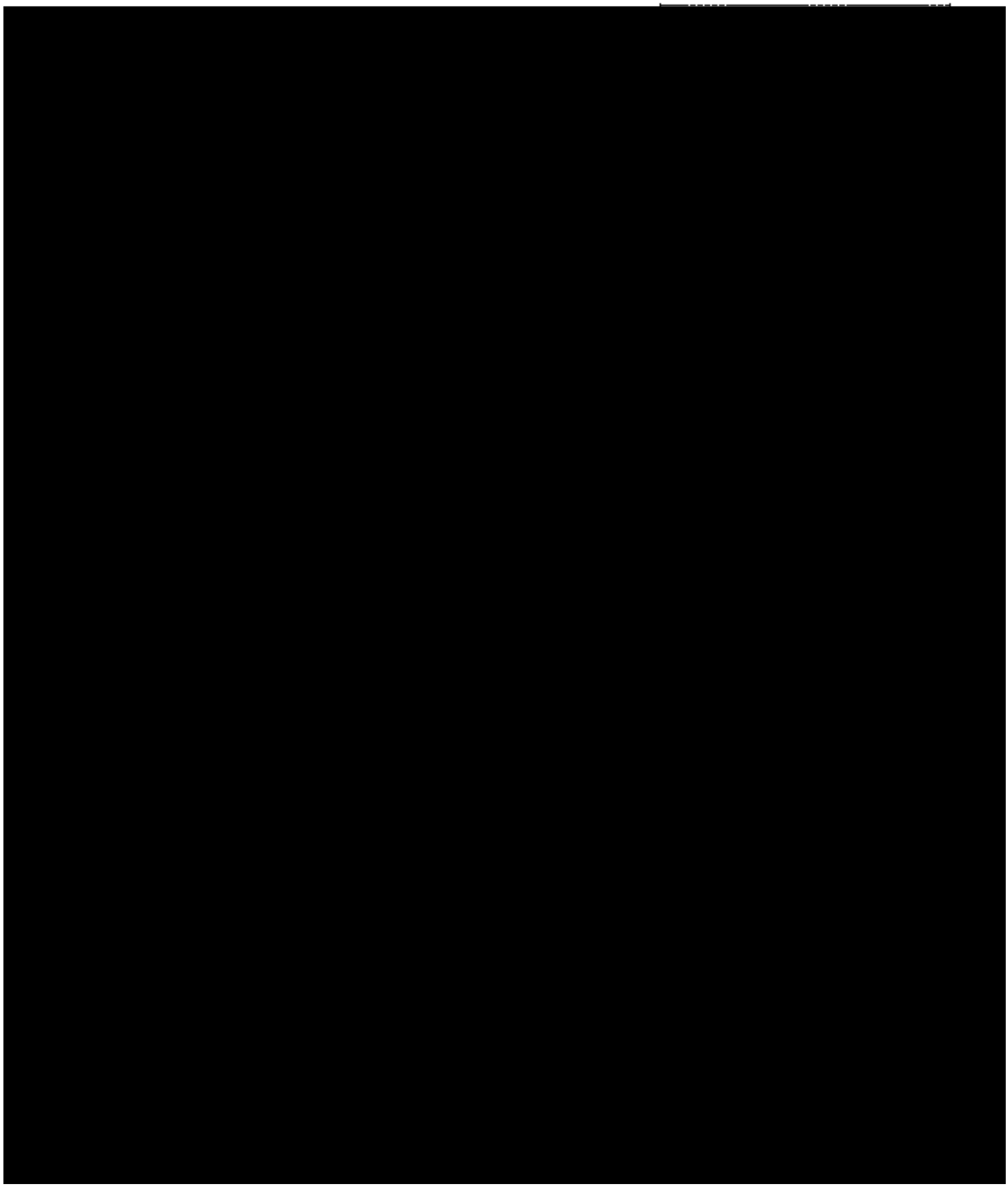

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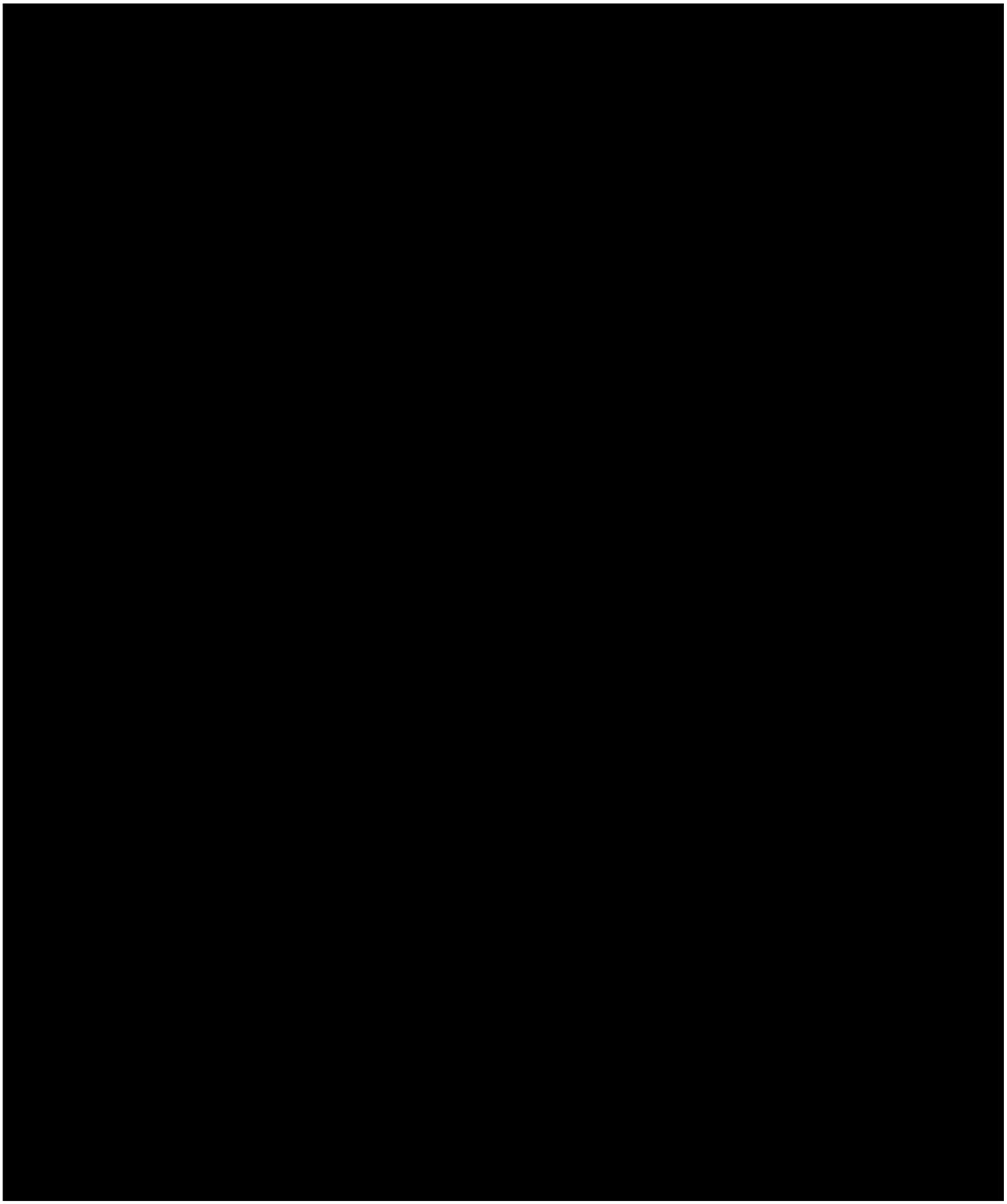

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

Amended protocol 02 (01 December 2023)

This Amended protocol 02 (Amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it may significantly impact the safety or rights of the participants and/or the reliability and robustness of the data generated in the clinical trial.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to align with feedback received from health authorities (FDA, PDCO, MFDS), correct typographical errors, and provide clarity on specific issues.

Protocol amendment summary of changes

Section # and Name	Description of Change	Brief rationale
Cover page	Addition of NCT number	NCT made available after listing published on clinicaltrials.gov
Rationale	Addition of explanation of the study OBS16647	To provide context by explaining the OBS16647 study from which baseline AGV will be derived.
Section 1.1 Synopsis Objectives and Endpoints, and Section 3 Objectives endpoints, and estimands, Table 4.	Primary objective: In the text, removal of "2 doses of" and addition of "for 52 weeks" after "administered SC twice weekly"	For clarification that objective is to assess safety and tolerability of SAR442501 administered for 52 weeks.
	Defining the change in number and percentage of participants with changes in neurological examination findings from baseline to Week 26 and Week 52 (Stage 2 only)" as the endpoint for evaluating the clinical signs and symptoms of foramen magnum stenosis	More specifically define how clinical impact of altering foramen magnum growth will be measured.
	Addition of "pooled across instrument versions by age" to secondary endpoints describing change in PRO Scores	Clarification that the endpoint will measure the change in scores pooled by age.
	The objectives and corresponding endpoints for ".. the PedsQL Multidimensional Fatigue Scale" and "PedsQL Pediatric Pain Questionnaire" have been demoted to below the "…STEMS" objective/ endpoint	In response to health authority concerns regarding the validity of observer-reported outcomes, these observer-reported outcome scales have been d [redacted]
	[redacted]	[redacted]

Section # and Name	Description of Change	Brief rationale
	[redacted]	[redacted]
Overall design synopsis, and Section 4.1	Moving paragraph explaining the population that will be eligible for the study earlier in the section	Editorial change so reader can understand immediately these participants will come from the OBS16647 study.
	Duration of the extended treatment period corrected: to 52 ~~104~~ and 216 weeks	Correction
	Clarification that those who are younger than 6 months (not 3 years) at the time of OBS16647 enrollment will be permitted to join DRI16646 after completing at least 12 weeks of data collection in OBS16647.	This is in response to health authority feedback that full 24 weeks of baseline data should be collected on those between 6 months and 3 years of age.
	Addition of sentences explaining when enrollment in Cohorts 1C, 2C, and 3C, begin	Per health authority feedback, clarification of how long after the enrollment of two subjects in cohorts 1B, 2B and 3B, will the enrollment in Cohorts 1C, 2C and 3C, begin
	Removal of sentence listing the assessments that will take place during the study.	Remove redundancy
	Addition of section “Extended treatment period”	In response to health authority feedback to provide all participants a chance to benefit from IMP administration. This section explains when during the study a participant may either discontinue the IMP for lack of improvement or transition to a different dose.
Overall design synopsis	Addition of sentence “participants who discontinue study treatment or withdraw from the study may be replaced.”	Clarification that participants may be replaced
	Study intervention, Investigational medicinal product: “when available” deleted	The formulations described here are available.
Table 1. Laboratory sampling schedule	Removal of “x” from ‘screening” for “25 hydroxyvitamin D and 1,25 dihydroxy vitamin D levels,” removal of these tests and PTH and calcitonin from Week 43, addition to Week 39 instead	Correction. This does not have to be performed at screening. For feasibility, should be performed at Week 39 rather than Week 43 so it is in line with an on-site visit.
	“Week 65” label corrected to “Week 64”	Correction; consistency throughout document.
		Clarification

Section # and Name	Description of Change	Brief rationale
	Labeling “PK” and “ADA” rows with “See PK and ADA sample collection schedule	
Table 3. PK and ADA sample collection schedule	Addition of column “Early treatment discontinuation visit” and PK sample/ADA collection time point at this visit	Correction that PK/ADA sample will need to be collected during the early treatment discontinuation visit.
	Addition of “ADA sample” row in table.	To indicate when ADA samples will be collected in relation to PK samples
	Addition of ADA sample at Day 8	To detect early immunogenicity response
	“Week 52” column split to indicate “Pre-dose” and “0 hr” IM administration points”	Consistency throughout table,to indicate PK/ ADA should be collected pre-dose at this visit.
Section 2.3.1 Risk assessment, Investigational intervention ocular toxicity	Sentence modified to indicate that visual acuity and amsler grid assessments are to be considered in participants who are capable of complying with the assessments, not those of a certain age.	Clarification that these assessments should be performed in all who are capable of completing them and are not restricted to age.
	“SAR” corrected to “SAR442501”	Correction of typo
Section 4.3 Justification for dose	Second paragraph: revision of the 2nd sentence to "In heathy adult subjects, PK exposure of SAR442501 exhibited increase in a near dose proportional manner after repeated daily SC administration."	Correction of grammatical error
	Last paragraph: “low dose” and “high dose” listed as bullets	Stylistic for presentation clarity
Section 5.1 Inclusion criteria	I03 amended to "Participants must have completed at least 24 weeks (or at least 12 weeks for those under ~~3 years~~ 6 months of age at the time of OBS16647 enrollment) of OBS16647.”	In response to health authorities that 12 weeks of baseline growth data is insufficient for those between 6 months and 3 years of age. At least 24 weeks of baseline growth data should be collected on those over 6 months of age.
	I04 amended to “Participants must have at least one documented height (sitting or standing) or total length from OBS16647 at least 24 ~~12~~ **weeks (or 12 weeks for those age <6 months at the time of OBS16647 enrollment)**, but no greater than 52 weeks **prior to** ~~apart from~~ Week 0/Day 1/Visit 2.”	Correction that the last growth measurement prior to Week 0/Day 1 should be at least 24 weeks for those ≥ 6 months of age, 12 weeks for those <6 months of age for reasons descried for “I03” above. Language clarified.
Section 5.2 Exclusion criteria	E06. Amended to indicate that 8-plate epiphysiodesis is allowed only under specific circumstances.	Per health authority feedback that 8-plate epiphysiodesis may confound growth measurement. Therefore, only those who have had plates removed and sufficient time for proper healing may be included.

Section # and Name	Description of Change	Brief rationale
	E10. Corrected to specify when participants who have had a history of hypothyroidism or hyperthyroidism may be eligible.	Per health authority feedback to further specify thresholds of hyperthyroidism and hypothyroidism. Only those with active untreated hypothyroidism or hyperthyroidism should be excluded as these conditions may confound growth measurements.
	E14. IGF-1 added among those products that are intended to affect participants' stature or body proportions. Additionally, E14 edited to "Participants who have received… between completion of OBS16647 and start of enrollment ~~6 months~~…" This is also corrected in Section 6.9 Prior and concomitant therapy.	Per health authority feedback that it should be clarified that those who have received IGF-1 should be excluded. Also to indicate that participants are not permitted to receive any of such agents between two studies.
	Addition of exclusion criterion 22. "Have an existing diagnosis of any of the following which would in the opinion of the Investigator significantly impact longitudinal growth: …"	Per health authority feedback that those with pre-existing conditions that may impact growth assessment should be excluded.
Table 5. Study intervention(s) administered	Updated with details of higher concentration formulation	Update.
Section 6.2 Preparation, handling, storage, and accountability, throughout document	Clarified that in addition to site staff, trained caregivers and home nurses may prepare and administer study intervention per local regulation	Clarification
Section 7.1.1 Permanent discontinuation	Addition of subject-level stopping criteria: Participant develops anaphylactic or other severe hypersensitivity reaction" and "participant develops severe injection site reaction"	Per health authority feedback suggesting subject level stopping criteria should address hypersensitivity reactions and injection site reactions.
Section 8.2.1 Efficacy assessments	Addition of Section 8.2.1.1 Growth measurements.	Explanation of how growth measurements, which is an efficacy endpoint, will be collected.
	Addition of Section 8.2.1.2 MRI	Explanation of how magnetic resonance imaging (MRI), which is an efficacy endpoint in Stage 2, will be collected.
	Renumbering of subsequent efficacy assessment headings	Editorial
Section 8.2.1.3 Clinical outcome assessments	[redacted]	
Data protection – processing of coded clinical data	Removal of reference to "section 2" of core ICF	Specific section of the ICF may change, but the reference to the ICF in general remains
Section 8.5 Pharmacokinetics	"If feasible, the parameters will include maximum ~~serum~~ concentrations …"	Correction. C_{max} corresponds to maximum concentration, not maximum serum concentration.

Section # and Name	Description of Change	Brief rationale
Section 8.9 Immunogenicity assessments	Sentence “all samples collected… may also be evaluated for SAR442501 serum concentration...” deleted.	Correction. These samples will not be used to evaluate serum concentration of SAR442501.
Section 8.11 Use of biological samples and data for future research	Data protection – processing of coded clinical data: “… ~~section 2 of~~ the core ICF”	These details will be provided in the core ICF and may not be limited to one specific section of the core ICF.
Section 9.1 Populations for analyses	All participants from the safety (not ITT) population… at least one postbaseline PD parameter will be assessed. Addition of sentence “participants will be analyzed according to the intervention they actually received.”	Clarification
	Table 9 – “enrolled/ randomized” in row description, phrase “… and regardless of replacement..” added	Clarification
	Table 9 – “pharmacodynamics” description modified to indicate this includes all participants from the safety population not ITT population, and that participants will be analyzed according to the intervention they actually received.	The enrolled/ randomized population analyzed will include those who were replaced. Correction. Also to clarify that the participants will be analyzed according to the intervention they actually received.
Section 9.2.3 Secondary endpoint(s) analyses	AGV time interval length in days is calculated as Date2-Date1 +1 day.	Clarification
	Removal of “calculated body ratios” from description of growth-related measures for which test of null hypothesis will be conducted via ANCOVA.	Correction
	Addition of sentence “change from baseline in calculated body ratios will be analyzed by…MMRM.”	Clarification
Section 9.2.4 Tertiary/ exploratory endpoint(s) analyses	[redacted]	[redacted]
Section 9.3 Interim analyses	Addition of primary completion analysis when all Stages 1 and 2 participants completed Week 52 or discontinued early.	Added as this analysis is needed for timely evaluation of primary and secondary objectives.
Section 10.2 Appendix 2: clinical laboratory tests	Addition of unless local laboratory use for assessment of the short chemistry panel is specified.	Accommodate sites for which Sponsor has previously agreed to permit local laboratory testing.
Appendix 10.8.1 China-specific requirements	Addition of specification “For whole blood. Labcorp pharmaceutical research and development (Shanghai) Co. Ltd…”	To specify which facility certain blood tests in China will be analyzed
Appendix 10.11– scales used	[redacted]	[redacted]

Section # and Name	Description of Change	Brief rationale
Section 10.12 Appendix 12: Protocol amendment history	Protocol amendment history for Amended protocol 01 moved to Section 10.12	To document history of protocol amendments
Miscellaneous		
Administrative changes	Changes from protocol amendment 01 to amendment 02 documented in Summary of Changes table.	To document changes in this amendment 02
Figure 1 Dose escalation schematic "Interim Analyses"	Figure replaced to reflect the primary completion analysis that will take place after all in Stage 1 and 2 have completed at least 52 weeks of treatment. Explanation of the primary completion analysis added to "interim analyses" section.	Clarification of when each of the interim analyses will take place during the study.
Section 1.3 Schedule of Activities, and relevant sections throughout document	Addition of window "+/- 3 days" to Week 8/ Visit 3,Week 52/Day 365, all Extended Treatment period visits, and End of study phone call or visit	To provide flexibility to participants when scheduling visits.
	Label "see Table 1. Laboratory sampling schedule" extended to cover "Screening"	This reference applies to Screening lab assessments as well.
	Addition of "FGF23" in activities with reference to Table 1, Laboratory sampling schedule.	Ensure everything in lab sampling table is included in schedule of activities
	Indication that MRI (Stage 2 only), DXA (Stage 1 only), and all X-rays will be performed every 48 weeks during the extended treatment period; also in footnote.	To ensure long term changes in foramen magnum growth and bone density are captured. Every 48 weeks rather than every 52 weeks chosen so assessment can fall on visit days. X-ray frequency decreased to limit the amount of radiation exposure.
	[redacted]	[redacted]
	Addition of "per local regulations" and "in the judgement of the .. **and Sponsor**" to footnote a. This is updated throughout document as well.	
	Removal of footnote "~~The final visit treatment after the last dose of study intervention administration should take place 3 to 5 days after the last dose of study intervention administration~~."	Correction. The final visit during the treatment period does not have to take place 3 to 5 days after the last dose of study intervention. Correction

Section # and Name	Description of Change	Brief rationale
	Correction in footnote e and throughout document: visit or phone call will be conducted approximately 4 weeks rather than 30 days after the last dose of study intervention.	Clarification of which components of the neurological examination must be performed.
	Addition of footnote f explaining a full neurological exam must be performed	Correction .
	Correction in footnote j: Amsler grid and visual acuity test assessments have no age requirement. All those who are capable of completing will complete.	Correction
	Footnote l: addition of “starting at Week 78”	Correction
	Footnote n: removal of requirement for “25-hydroxy-vitamin D, 1,25 dihydroxyvitamin D, calcitonin, and parathyroid hormone” from list of required results that must return prior to enrollment Addition of “long chemistry panel and TSH” to this list.	Clarification
	Footnotes y and gg: corrected to explain that if study intervention is discontinued between the Week 26 and Week 52 visit, the Week 52 visit should occur, along with the early treatment discontinuation and 4-week follow-up visit. If it is discontinued before Week 26, the follow-up visits at Weeks 26 and 52 should occur in addition to the Early treatment discontinuation visit and 4-week follow-up visit.	Permit investigators to conduct additional imaging assessments per clinical judgement.
	Addition of footnote q, “should subjects’ imaging assessment yield any concerns…”	Last visit may or may not be during the extended treatment period.
	[redacted]	[redacted] Editorial
	Footnote dd clarified to state that historical aBMD results collected per standard of care within 3 months… are acceptable	
	Addition of footnote “jj” concerning timing of IRT allocations	To specify timing of IRT allocations and dispensing of IMP with regard to DTP authorization
	Footnotes renumbered sequentially	

Amended protocol 01 (28 August 2023)

This Amended protocol 01 (Amendment 01) is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to align with feedback received from health authorities.

protocol amendment summary of changes

Section # and Name	Description of Change	Brief rationale
Throughout	Word "guardian" or "legal guardian" will be replaced by "legal representative"	Clarification
Throughout	Assent form, in addition to consent, is going to be explicitly mentioned in the protocol.	Clarification
	Minor editorial and grammatical changes	Consistency
Section 1.1 Synopsis, Overall design synopsis	Addition of sentence "Study will take place across approximately 15 sites, subject to change based on recruitment and enrollment."	Addition of information
	Reference to Section 10.1.5.1 Data monitoring committee for description of instances in which Sponsor may decide to stop recruitment	Clarification
Section 1.1 Synopsis, Overall design synopsis, Step 2	Addition of reference to "study stopping criteria" section and reference to Section 10.1.5.2 for criteria when Sponsor may stop dosing	Clarification
Section 1.3 Schedule of activities, all other relevant sections	Addition of language that all participants will be monitored for a certain period of time after each injection administered on-site, and that site personnel must include individuals trained in diagnosing and treating acute hypersensitivity reactions and medication and equipment to treat such reactions must be available.	For safety purposes, ensure all participants are properly monitored while on site.
Section 8	Addition of detailed description of blood sampling volumes, assays, and investigations related to the trial.	Addition of information on maximum blood volumes permitted to be sampled
Section 9.2 Statistical analyses	Include explanation of how missing data will be imputed	Explain how missing data will be imputed
Section 9.2.1 General Considerations	Clarification that the observation period will be divided into 3 rather than 4 segments: pre-treatment, treatment-emergent/ on-treatment, and post-treatment	Clarification
Section 9.2.5 Statistical Consideration	Provided the rationale as to why no multiplicity adjustment will be conducted in this study.	Clarification

Section # and Name	Description of Change	Brief rationale
Appendix 10	Addition of “COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES” information	Clarification

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