CLINICAL TRIAL PROTOCOL

COMPOUND: Toujeo®/insulin glargine 300 U/mL/HOE901-U300

Evaluation of virtual versus traditional study conduct in a 6-month, multicenter, randomized, open-label, 2-parallel group pilot study in adult patients with Type 1 diabetes mellitus

STUDY NUMBER: MSC15146

STUDY NAME: eStudy

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: Toujeo®/Insulin Glargine 300 U/mL/HOE901-U300	**STUDY No.: MSC15146** **STUDY NAME: eStudy**
TITLE	Evaluation of virtual versus traditional study conduct in a 6 month, multicenter, randomized, open-label, 2-parallel group pilot study in adult patients with Type 1 diabetes mellitus (T1DM)
INVESTIGATOR/TRIAL LOCATION	The United States of America, Canada
PHASE OF DEVELOPMENT	Phase 4
STUDY OBJECTIVE(S)	**Primary objective:** To evaluate the effect of virtual approach via novel technologies versus traditional study conduct on glycemic control in terms of glycated hemoglobin A1c (HbA1c). **Secondary objectives:** To evaluate the appropriate utilization of virtual approach via novel technologies during the study and to assess the effect of the virtual versus traditional study conduct on multiple outcomes in terms of study methodology and diabetes control. • Study methodology with the two approaches: - Patient satisfaction with the trial experience via a patient reported outcome (PRO) - Impact of clinical trial participation via a PRO - Patient burden with the clinical trial experience via a PRO - Resource use via a PRO - Medication and key study activity compliance - Patient retention • Diabetes control with the two approaches: - Diabetes related PROs - Glycemic control (HbA1c, fasting plasma glucose [FPG], self-monitoring of plasma glucose [SMPG]) • Patient care with the two approaches: - Doctor/site-patient relationship - Site satisfaction with provisioned care - Patient experience in the clinical trial via a qualitative exit interview • Safety assessment managed by the two approaches including: - Hypoglycemic events - Adverse events (AEs)
STUDY DESIGN	A 28-week, randomized, open-label, 2 approach groups, multicenter, pilot study The study consists of 3 periods:

	An up-to-3-week **screening period**, which includes 2 steps to complete the consent in person, the eligibility assessment and the shipment of study material. Patients with T1DM currently treated with insulin glargine 100 U/mL (eg, Lantus or Basaglar) plus rapid-acting analog insulin and with internet access will eSign the consent on the study website. Screening procedures will be performed in person by medical professionals provided by Homecare services (via The Medical Research Network [MRN]) in collaboration with the investigators. The investigators will then complete the eligibility assessments at the end of screening, the randomization, and the shipment of study material. Eligible patients will be randomized 1:1 (virtual:traditional) into 2 study groups to receive the same investigational medicinal product (IMP, Toujeo) but follow either a traditional trial approach or a remote, virtual approach for completion of all study procedures. Stratification factors for randomization include study site and HbA1c <7.6% or ≥7.6%. Thus, patients randomized to the virtual group will not visit the study sites during the entire study course, except for a physical examination before IMP initiation. All other study assessments, including vital signs, weight, lab variables, etc, will be completed via Bluetooth devices that instantly transfer the digital data, available for investigators' view. Video chat between the patients and investigators/designees may occur for safety reason in addition to the planned study visits. A 24-week **treatment period**. Patients in both groups will receive the same study treatment with Toujeo as the basal insulin plus their existing rapid-acting insulin analogs (Humalog, Novolog, or Apidra) to manage their diabetes. Toujeo dose will be titrated to target the fasting SMPG between 80 and 130 mg/dL; meal-time insulin analogs will be adjusted following investigators' instructions to maintain postprandial SMPG within a range of 130 to 180 mg/dL. All patients will monitor their plasma glucose via the study-provided glucose meter. The SMPG values will be used to guide the insulin dose adjustment and document the hyper- or hypoglycemic events. A 1-week **posttreatment period** to collect any posttreatment safety information.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Patients with T1DM diagnosed at least one year before the screening visit. • Patients who are treated with multi-dose insulin using insulin glargine 100 U/mL (eg, Lantus or Basaglar) as basal insulin and rapid acting insulin analogues as bolus insulin • Patient with access to or experience with mobile technology (eg, tablet or smartphone) • eSign the consent on the study web portal

	Exclusion criteria: • Age <18 years at screening (Visit 1 – Step 1) • Type 2 diabetes mellitus • HbA1c <5.4% or ≥9.0% at screening (Visit 1-Step 2) • Patients who received less than 6 months treatment with any basal plus mealtime insulin • Use of any basal insulins other than insulin glargine 100 U/mL (eg, Lantus or Basaglar) within 3 months before screening • Use of an insulin pump within 6 months before screening • Use of meal-time insulin other than rapid-acting insulin analogs (Humalog, Novolog, or Apidra), eg, human regular insulin, within 30 days before screening • Use of systemic glucocorticoids (excluding topical application or inhaled forms) for one week or more within 3 months before screening • Patients experienced with any severe hypoglycemic episode resulting in seizure, unconsciousness, or coma, and/or leading to hospitalization during the past 6 months before screening • Patients with insufficient smartphone skills or unwilling to properly use the virtual tools deemed by the investigator based on the observation over the digital screening procedure • Mental disorders or any neurologic disorder that would affect patient's ability to meet the study requirements, or patients deemed unlikely to safely manage insulin dosage by the Investigators • Known hypersensitivity/intolerance to insulin glargine, rapid-acting insulin analogs or any of their excipients • Pregnant or breast-feeding women, or women who intend to become pregnant during the study period
Total expected number of patients	150 randomized patients (75 patients in virtual group, 75 patients in traditional group)
STUDY TREATMENTs **Investigational medicinal product** **Formulation:** **Route of administration:**	 Toujeo (insulin glargine 300 U/mL, HOE901-U300) Toujeo (insulin glargine-U300) will be supplied as a sterile, nonpyrogenic, clear, colorless solution in the Toujeo SoloStar® prefilled (disposable) pen (insulin glargine 300 units/mL solution for subcutaneous [SC] injection). Each Toujeo SoloStar contains in total 450 units of insulin glargine (1.5 mL of 300 units/mL insulin glargine solution). This pen allows dose setting in the range of 1 to 80 units with a minimum of 1 unit increment. Dilution or mixing of Toujeo with other insulin products is not allowed. Subcutaneous injection once daily (self-administration)

Dose regimen:	Starting dose of Toujeo is the patient's existing insulin glargine 100 U/mL dose prior to Day 1. Toujeo will be titrated based on self-measured, fasting (prebreakfast/preinjection) plasma glucose levels (target range 80 to 130 mg/dL; 4.4 to 7.2 mmol/L) while avoiding hypoglycemia.
Noninvestigational medicinal products	Patients in both treatment groups will continue with their existing rapid-acting mealtime insulin analogs (Humalog, Novolog, or Apidra) during the study.
Formulation:	Solution for SC injection
Route(s) of administration:	Subcutaneous injection
Dose regimen:	Dosing of the rapid-acting mealtime insulin will be adjusted based on the pattern of mean postmeal SMPG level or based on the carbohydrate content of the meal (carb counting) as per instruction of the investigator; target range for 2-hour postprandial plasma glucose is 130 to 180 mg/dL (7.2 to 10.0 mmol/L).
ENDPOINT(S)	**Primary endpoint:** Changes in HbA1c from baseline to Week 24 **Secondary endpoints:** Study methodology assessment with the two approaches: • Patient satisfaction with trial experience PRO: Was it Worth It (WIWI) Questionnaire at Week 24 • The effect of the trial on a patients' ability to work and perform regular activities PRO: Work Productivity and Impairment-study participation (WPAI-SP), change from baseline to Week 24 • Patient burden with the trial participation: (PRO: Overall Study Experience-Participation [OSEP]), change from baseline to Week 24 (OSEP part 1-diabetes appraisal)/at Week 24 (OSEP part 2-study appraisal) • Patient-reported healthcare resource utilization: resource use questionnaire (RUQ) over the 24 week treatment period • Medication and key study activity compliance from baseline to Week 24: - The exposure time to basal insulin (Toujeo) and percentage of actual dose over the prescribed dose - The number of times the patient used the Bluetooth devices, in accordance with the study instructions - The number of times the patient completed the blood draw visit, in accordance with the study instructions - Patient withdrawal from baseline to Week 24 Diabetes control with the two approaches: • Diabetes related PROs, changes from baseline to Week 24 in: - Diabetes Treatment Satisfaction Questionnaire status (DTSQs)

	- Diabetes Treatment Satisfaction Questionnaire change (DTSQc), administered on Week 24 only - Hypoglycemia Fear Survey-II (HFS-II) - Diabetes Distress Scale (DDS) • HbA1c: change from baseline to Week 16 • FPG: change from baseline to Week 16 and Week 24 • Change in 7-point SMPG profiles, mean and per time-point from baseline to Week 16 and Week 24, • Insulin doses Patient care with the two approaches: • Study-specific resource requirements: Overall Study Experience-Sites (OSES) questionnaire part 1 (resource requirements) over the 24 week treatment period • Site-perceived patient relationship and satisfaction: OSES questionnaire part 2 at Week 24 • Patient interview in a subset of patients at Week 24 Safety assessment managed by the two approaches: • Hypoglycemic events and incidence rate (as per the American Diabetes Association (ADA) classification) during the 24-week period in each group • Adverse events (including Injection site reactions and hypersensitivity), Serious AEs (SAEs) and Product Technical Complaints (PTCs)
ASSESSMENT SCHEDULE	See study flowchart in Section 1.2.
STATISTICAL CONSIDERATIONS	**Sample size determination:** This is a pilot study, consequently no formal sample size calculation was done. The sample size was not powered for confirmatory testing, only descriptive statistics will be provided. Number of patients per trial approach group: randomization using a ratio 1 (virtual):1 (traditional). Nevertheless, a precision calculation based on the 2-sided 95% confidence interval (CI) shows that the change in HbA1c from baseline in virtual approach, the change in HbA1c from baseline in traditional approach and the difference in HbA1c change between the two approaches will be estimated with a precision of approximately 0.37%, using a standard deviation (SD) of 1.1 and taking into account an up to 10% rate of non-evaluable patients for HbA1c. **General aspects of the analyses:** Except if defined below, the baseline value will be the last available value prior to the first injection of IMP. **Analysis population:** The primary population for all non-safety endpoints will be the Intent-To-Treat (ITT) population, which will comprise all randomized

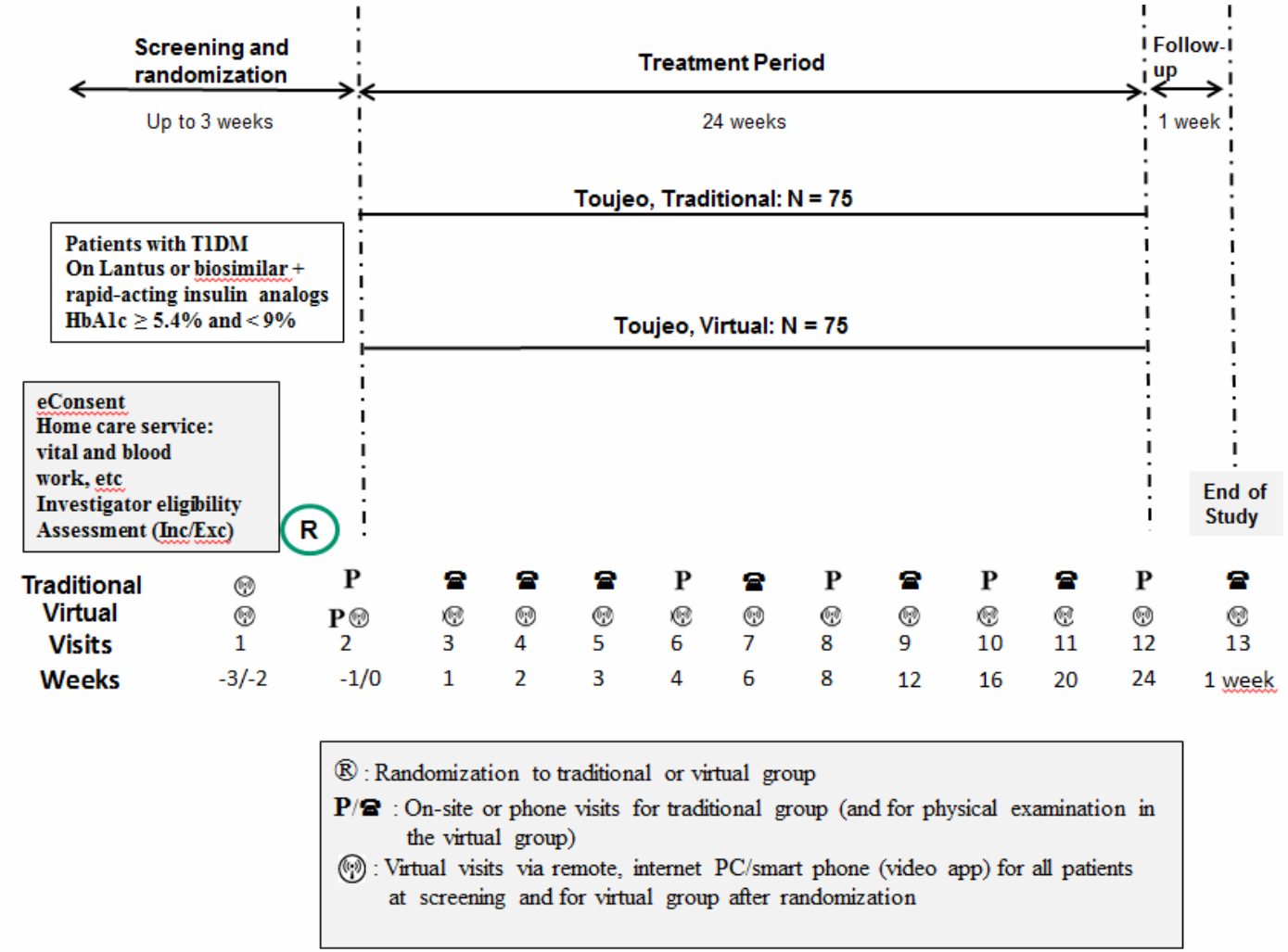
	patients, irrespective of the trial approach group being used, analyzed according to the approach group allocated by randomization. The safety population is defined as all randomized patients who did actually receive at least one dose of Toujeo, regardless of the amount of Toujeo administered. **Primary analysis:** The primary efficacy endpoint (change in HbA1c from baseline to Week 24) will be analyzed using a mixed-effect model with repeated measures (MMRM) approach, using the missing at random framework carried out via SAS PROC MIXED using adequate contrasts. The model will include fixed categorical effects of trial approach group, visit, trial approach-by-visit interaction, randomization stratum of site; and the continuous fixed covariates of baseline HbA1c value and baseline HbA1c value-by-visit interaction. **Analysis of secondary endpoints:** A descriptive summary will be provided for each endpoint per approach group. Additional statistical analyses are summarized below. **Analysis of study methodology** The change in WPAI-SP and OSEP part 1 scores from baseline to Week 24 will be analyzed using an analysis of covariance (ANCOVA). WIWI and OSEP part 2 scores will be compared at Week 24 between approach groups using an analysis of variance (ANOVA). The total and average resource utilization per patient will be calculated on all on-treatment questionnaires using the RUQ. Duration of IMP exposure will be summarized descriptively and categorically (by periods) by numbers and percentages. The number of times the patient used the Bluetooth devices and the number of times the patient completed the blood draw visit will be summarized only in the virtual approach group. Patient withdrawal from baseline to Week 24 will be analyzed descriptively and using a Kaplan-Meier plots/estimates of the cumulative incidence of study discontinuation. **Analysis of diabetes control** The change in DTSQs, HFS-II, and DDS scores from baseline to Week 24 will be analyzed using an ANCOVA. DTSQc scores at Week 24 will be compared between approach groups using an ANCOVA. The change in HbA1c from baseline to Week 16 will be described in each trial approach group and analyzed using the same model as done for primary endpoint The change in FPG, and 7-point SMPG from baseline to Week 24 will be described in each trial approach group and analyzed using an MMRM approach. **Analysis of patient care**

	Overall Study Experience-Sites (OSES) part 1 will be compared between approach groups using an ANCOVA; OSES part 2 will be compared between approach groups using an ANOVA. Patient experience via a qualitative exit interview will be analyzed via an expert qualitative research analysis group. **Safety analyses:** Safety analyses will be descriptive, based on the safety population. The baseline value for safety endpoints will be the last available value prior to the first injection of IMP. The following safety parameters will be analyzed: • Hypoglycemia - Hypoglycemia event (categories as defined by the ADA Workgroup on Hypoglycemia: severe, documented symptomatic, asymptomatic, probable symptomatic, relative, and nocturnal) - Number and percentage of patients experiencing at least one hypoglycemic events by categories (any, severe, documented symptomatic) - Number and rate per patient-year of hypoglycemic events by categories (any, severe, and documented symptomatic) Hypoglycemia analyses will be performed at any time, nocturnal (00:00-05:59) and daytime. • AEs • SAEs • Deaths • Adverse events of special interest (AESIs) • Injection site reaction and hypersensitivity reaction • PTCs • Vital signs The observation period of safety data will be divided into 3 segments: • The pre-treatment period is defined as the time between the date of the informed consent and the date of first injection of open-label IMP • The treatment-emergent AE (TEAE) period is defined as the time from the first injection of IMP up to 2 days after the last injection of IMP • The posttreatment period is defined as the time starting 3 days after the last injection of IMP
DURATION OF STUDY PERIOD (per patient)	The study consists of: • A 3-week screening period, including 1 week between randomization and first IMP administration due to shipment of IMP and the Bluetooth devices for virtual group and the appointment making with the site for the traditional group • A 24-week treatment period

	• A 1-week posttreatment safety follow-up period after treatment completion or premature discontinuation of study treatment In total the maximum study duration for one patient will be approximately 28 weeks.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

(📡 = virtual visits; ☎ = phone call visits; P = on-site in-person visits)

	Screening		Randomization		Treatment period										Follow-up
Visits	1 Step-1[a]	1 Step-2[b]	2 Step-1[c]	2 Step-2[d]	3	4	5	6	7	8	9	10	11	12 EOT[g]	13 EOS
Traditional group	📡 (Digital screening)		☎	P	☎	☎	☎	P	☎	P	☎	P	☎	P	☎
Virtual group			☎	P & 📡	📡	📡	📡	📡	📡	📡	📡	📡	📡	📡	📡
Weeks	-3	-2	-1	0	1	2	3	4	6	8	12	16	20	24	1 week
Window (day)			-/+ 4		-/+ 3	-/+ 3	-/+ 3	-/+ 4	-/+3	-/+ 4	-/+ 3	-/+ 4	-/+ 3	-/+ 3	+/-2
Informed Consent (eConsent)	X														
Schedule Homecare visit	X														
Interactive response technology (IRT) calls	X		X					X		X		X		X	
Inclusion	X	X													
Exclusion		X													
Demography	X	X													
Video chat with Investigator and site staff	X	X													
Medical and surgical history; diabetes history		X													
Concomitant medication(s)		X		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[d]				X											
Vital signs[h] and body weight		X		X				X		X		X		X	
Height		X													
Virtual material/device shipment (Bluetooth devices)[e]			X												
Dispensation/collection of e-diary				X	X	X	X	X	X	X	X	X	X	X	

	Screening		Randomization		Treatment period										Follow-up
Visits	1 Step-1[a]	1 Step-2[b]	2 Step-1[c]	2 Step-2[d]	3	4	5	6	7	8	9	10	11	12 EOT[g]	13 EOS
Traditional group	(Digital screening)		☎	P	☎	☎	☎	P	☎	P	☎	P	☎	P	☎
Virtual group			☎	P &											
Weeks	-3	-2	-1	0	1	2	3	4	6	8	12	16	20	24	1 week
Window (day)			-/+ 4		-/+ 3	-/+ 3	-/+ 3	-/+ 4	-/+3	-/+ 4	-/+ 3	-/+ 4	-/+ 3	-/+ 3	+/-2
Randomization via IRT call			X												
Video chat with investigator and site staff via the virtual device[e]				X	X	X	X	X	X	X	X	X	X	X	X
Allocation of study medication (IMP)				X				X		X		X			
First IMP (Toujeo) injection[e]				X											
Documentation and review of IMP and NIMP doses[f]				X	X	X	X	X	X	X	X	X	X	X	
IMP compliance check; collecting & counting used & unused pens								X		X		X		X	
Diet and lifestyle counselling		X		X	X	X	X	X	X	X	X	X	X		
Glucose meter shipment[c]			X												
7-Point SMPG[i]				X								X		X	
5-point SMPG[i]				X	X	X	X	X	X	X	X	X	X	X	
Upload SMPG to PC[j]				X				X		X		X		X	
AE/SAE		To be assessed and reported (if any) since consent throughout the study (report SAE to the sponsor within 24 hours)													
Hypoglycemia recording			To be assessed and reported (if any) since randomization throughout the study												
Injection site reactions, PTCs			To be assessed and reported (if any) since randomization throughout the study												
Central Laboratory[k,e]															
HbA1c, FPG		X										X		X	
Hematology, clinical biochemistry[l]		X													

	Screening		Randomization		Treatment period										Follow-up
Visits	1 Step-1[a]	1 Step-2[b]	2 Step-1[c]	2 Step-2[d]	3	4	5	6	7	8	9	10	11	12 EOT[g]	13 EOS
Traditional group	(Digital screening)		☎	P	☎	☎	☎	P	☎	P	☎	P	☎	P	☎
Virtual group			☎	P &											
Weeks	-3	-2	-1	0	1	2	3	4	6	8	12	16	20	24	1 week
Window (day)			-/+ 4		-/+ 3	-/+ 3	-/+ 3	-/+ 4	-/+3	-/+ 4	-/+ 3	-/+ 4	-/+ 3	-/+ 3	+/-2
Urine analysis[m]		X													
Pregnancy test (WOCBP only)[n]		X		X				X		X		X		X	
PROs and other questionnaires[o]															
Diabetes related PROs: DTSQs, DDS, HFS-II				X										X	
Diabetes related PRO: DTSQc														X	
Was it Worth It (WIWI) Questionnaire														X	
Work Productivity and Impairment Study Participation (WPAI-SP)				X										X	
Overall Study Experience - Participation (OSEP) part 1				X										X	
Overall Study Experience - Participation (OSEP) part 2														X	
Resource Use Questionnaire (RUQ)				X				X		X	X	X	X	X	
Overall Study Experience - Sites (OSES) – part 1 (resource requirements)				X	X	X	X	X	X	X	X	X	X	X	
Overall Study Experience – Sites (OSES) – part 2 (relationship, satisfaction)														X	
Qualitative exit interview[p]														X	

a Prior to Visit 1, patients will be contacted by the sites or guided by the multi-channel digital recruiters to the eConsent web portal (Parallel 6 Website). Informed consent process will be completed electronically by the candidate trial patients. During the eConsent process, the study purpose, virtual tools for participation, and other protocol requirements will be introduced and discussed with the patients in the text or audio/video manner. After eSigning and counter-eSigning by the patient and the investigator, the enrolment IRT call will be made and the patient ID assigned.

b Assessments at Visit 1- Step 2 will be performed in-person by Homecare health professional (The MRN) in corporation with the study investigators and designees. This visit can occur at the patient's home, at work, or at any location providing the adequate space and level of privacy. Patient identification will be further verified and confirmed.

c At the end of screening, investigators will determine the eligibility of the screened patients for participation. The randomization IRT call will be made at the Visit 2- Step 1. Patients will be informed by the study sites of their randomization group and Visit 2- Step 2 will be scheduled for the baseline assessments within 1 week (+/- 4 days).
Glucose meters with Bluetooth access and associated accessories (lancet, control solutions, test strips, etc), e-diaries features, and instructions will be shipped to all eligible patients. Patients will use the study provided glucose meters throughout the study.

d Physical examination will be performed at the in-person visit in the traditional group. In the virtual group, physical examination will be performed on-site, in-person, between randomization IRT call and the first IMP administration. All other assessments will occur remotely on the day of the first IMP administration (Day 1).

e Only for patients randomized in virtual group:

- They will receive the Bluetooth devices for their remote participation and the IMP (Toujeo®) before Visit 2-Step 2.
- Shortly after randomization (IRT call), they will be scheduled for an in-person visit to allow for the initiation physical examination performed by the investigator.
- They will be further trained on the Bluetooth devices utilization.
- The IMP starting date and dose will be instructed by the investigator at the time of Visit 2-Step 2. The first IMP (Day 1) data will be documented with the dose in the e-CRF.
- All study assessments, including vital signs and weight, will be done via the Bluetooth devices by the patients at home.
- Patients located in the United States (US) will receive a laboratory requisition and have their blood drawn at any local Quest®. For patients located in Canada, blood draw will be performed by the Homecare via The MRN.
- Unscheduled on-site visits or Homecare physician visits (depending on the patient's location) only for safety assessment could be scheduled as deemed necessary by the investigator (ie, performance of physical examinations is critical to determine a diagnosis or further evaluation procedure for an AE).

f IMP dose will be titrated at the investigator's discretion to achieve the fasting glycemic target while avoiding hypoglycemia

g EOT assessments will also be performed for any patients who prematurely discontinue the study treatment. Patients should continue the study procedure as planned up to the EOS after IMP discontinuation.

h Heart rate and blood pressure (sitting position)

i 7-point SMPG profile (before [preinjection after randomization] and 2 hours after breakfast, lunch and dinner, and at bedtime): at least ONE day during the weeks before Visit 2-Step 2 (Week 0), Visit 10 (Week 16), and Visit 12 (Week 24)
5-point SMPG profile (before breakfast, lunch and dinner; 2 hours after a main meal [or as per investigator's instruction] and at bedtime): at least 3 days during the week before each visit
The SMPG before breakfast should be measured in the fasting status, ie, after the patient wakes up, before breakfast, and before injection of any insulin; preferably no food should have been taken overnight. A note should be made in the diary if the SMPG is not tested in fasting status (eg, if food was taken to cope with a hypoglycemic episode)

j Only for patients randomized in the traditional group

k Blood samples will be sent to and analyzed by Quest® central lab

l Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes and platelets. Clinical chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), AST, ALT, ALP, plasma glucose, creatinine, estimated creatinine clearance, uric acid, sodium, and potassium

m Urine analysis by dipstick: pH, glucose, ketones, leucocytes, blood/hemoglobin, protein

n For women of child-bearing potential (WOCBP): serum pregnancy test for screening; urine pregnancy test for subsequent monitoring and it can be confirmed with a serum test if needed. For WOCBP in virtual group, the urine pregnancy test kit will be provided by the study.

o For patients randomized to the virtual group, all questionnaires will be performed remotely via the mobile technology at home. For patients randomized in the traditional group, the questionnaires will be completed electronically (via the mobile technology) at the study site (before visiting the study site for baseline assessment on Visit 2 Step 2).

p In a subset of patients (approximately 30) in the virtual approach group.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DDS = Diabetes Distress Scale; DTSQc = Diabetes Treatment Satisfaction Questionnaire change; DTSQs = Diabetes Treatment Satisfaction Questionnaire status; e-CRF = electronic case report form; EOS = end of study; EOT = end of treatment; FPG = Fasting plasma glucose; HbA1c = glycated hemoglobin A1c; HFS = Hypoglycemia Fear Survey; ID = identification; IMP = investigational medicinal product; IRT = interactive response technology; MRN = medical research network; NIMP = noninvestigational medicinal product; OSEP = overall study experience – participation; OSES = overall study experience – sites; PC = personal computer; PRO = patient reported outcome; PTC = product technical complaints; RUQ = resource use questionnaire; SAE = serious adverse event; SMPG = self-monitoring of plasma glucose; US = United States; WIWI = was it worth it; WPAI-SP = work productivity and impairment study participation; WOCBP = women of child-bearing potential;

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3 LIST OF ABBREVIATIONS

ADA:	American Diabetes Association
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine transaminase
ANCOVA:	analysis of covariance
ANOVA:	analysis of variance
BP:	blood pressure
CI:	confidence interval
CPMP:	Committee for Proprietary Medicinal Products
CRF:	case report form
CV:	curriculum vitae
CVD:	cardiovascular disease
DDS:	Diabetes Distress Scale
DRF:	discrepancy resolution form
DTP:	direct to patient
DTSQ:	diabetes treatment satisfaction questionnaire
DTSQc:	Diabetes Treatment Satisfaction Questionnaire change
DTSQs:	Diabetes Treatment Satisfaction Questionnaire status
ECG:	electrocardiogram
e-CRF:	electronic case report form
EOT:	end of treatment
FPG:	fasting plasma glucose
GCP:	good clinical practice
HbA1c:	glycated hemoglobin A1c
HFS-B:	hypoglycemia fear survey-behavior
HFS-II:	Hypoglycemia Fear Survey-II
HFS-W:	hypoglycemia fear survey-worry
HLGT:	high level group term
HLT:	high level term
ICH:	International Conference on Harmonisation
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	interactive response technology
ITT:	intent to treat
MedDRA:	medical dictionary for regulatory activities
MMRM:	mixed effect model with repeated measures
MRN:	Medical Research Network
NIMP:	noninvestigational medicinal product
NPH:	neutral protamine Hagedorn
OSEP:	overall study experience-participation

OSES:	overall study experience-sites
PCSA:	potentially clinically significant abnormality
PRE:	pen-related event
PRO:	patient reported outcome
PT:	preferred term
PTC:	product technical complaint
RUQ:	resource use questionnaire
SAE:	serious adverse event
SC:	subcutaneous
SD:	standard deviation
SMBG:	self-monitoring of blood glucose
SMPG:	self-monitoring of plasma glucose
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
T1DM:	Type 1 diabetes mellitus
TEAE:	treatment-emergent adverse event
ULN:	upper limit normal
US:	United States
USPI:	United States package insert
WIWI:	was it worth it
WOCBP:	woman of child-bearing potential
WPAI:	work productivity and impairment, work productivity and impairment-study participation
WPAI-SHP:	WPAI-specific health problem
WPAI-SP:	Work Productivity and Impairment-study participation

4 INTRODUCTION AND RATIONALE

Across the clinical landscape, there are an increasing number of clinical studies with increased study complexity. These traditional studies typically have several factors which contribute to recruitment and retention challenges, as well as reduced patient engagement, study compliance, and, ultimately, data quality issues. Common factors include the requirement for a patient to stay near the clinical site, affiliation with a physician in a pharmaceutical investigator network, ability to schedule life events around specific study requirements, or have medical insurance.

Traditional, complex studies increase patient burden with the often rigid study requirements. Additional frustration can occur when a patient does not receive their individual or study results. In addition, the increased study complexity and operational processes by many of the study sponsors place an additional burden on the clinical sites and increase the operational costs (1), which is a main driver of total study cost.

The strategic use of innovative methods and mobile health technologies in clinical studies may provide a true patient-centric operational model, improving both patient experience and study compliance. This innovative approach could facilitate patient participation beyond the established sponsor-investigator network, by allowing for recruitment of geographically remote patients. For the clinical site, this approach may provide processes equivalent with the current clinical practice, while allowing sites to be more efficient in the execution of clinical studies. These benefits extend to the sponsor: by eliminating geographical restrictions, a smaller number of sites may be needed per trial – thereby reducing monitoring efforts and saving costs.

With the impact of increasing smartphone use, decreasing age and socioeconomic barriers due to technology (2), and the increasing number of patients seeking disease specific online communities (3), creating an operational approach aligned with these trends can allow for a simple, cost effective, and more encompassing clinical trial approach.

The first industry sponsored virtual study was a Phase IV overactive bladder study in the United States (US), conducted by Pfizer in 2011. The study did not reach a successful conclusion, but there were many lessons learned (3). These lessons learned shared by Pfizer and the experiences gained from vendors who participated in the virtual study have benefited the larger pharma community. The integration of mobile health technology, telemedicine, and remote sensors into classic clinical studies has increased significantly over the past decade (4). Pfizer's first attempt at the virtual study was an evolution of this continued innovative clinical activity. Sanofi eStudy will be a compilation of collective experience and lessons learned to provide the best chance of success.

Diabetes (type 1 and type 2) affects 415 million people globally, approximately 22 million adults and 0.54 million children have Type 1diabetes (5). The effect of type 1 diabetes-related complications on patients and healthcare systems is significant, with reported incidences of proliferative retinopathy, nephropathy and cardiovascular disease of 47%, 17% and 14%, respectively, after 30 years of diabetes (6). There are a number of barriers to glycemic control in type 1 diabetes, including the occurrence and fear of hypoglycemia and the complexity and

demands of day-to-day management, in particular the need for frequent self-monitoring of blood glucose (SMBG) and regular adjustments in insulin dosing. These challenges have an enormous impact on patient quality of life and healthcare cost (7, 8). Utilizing mobile health technologies (eg, assisting in medication compliance, SMBG monitoring, reinforcing diabetes health, etc) could play an important role in reducing some of the common barriers, improving glycemic control, and increasing empowerment of the patients by supporting them in informed decision making.

MSC15146 (eStudy) is a pilot clinical study to evaluate the methodology of a virtual clinical trial conduct in patients with type 1 diabetes prior to performance of full-scale studies. The effect of the virtual versus traditional trial conduct on multiple outcomes including study activities, investigational medicinal product (IMP)/noninvestigational medicinal product (NIMP) compliance, patient retention, etc, will be analyzed to assess the usability and appropriateness of the virtual methodology. The virtual study conduct on glycemic control will be evaluated by the changes in glycated hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and self-monitoring of plasma glucose (SMPG) profile in the two groups that will receive the same basal plus insulin regimen during the study period. In addition to the glycemic parameters, the study introduced a number of patient reported outcomes (PROs), including the diabetes related questionnaires that assess glycemic control, fear of hypoglycemia, satisfaction of treatment from patients' perspective, and other questionnaires that assess the operational process, physician-patient relationship, trial time consumption, burdens to trial patients, etc.

For the first time in a Sanofi study, designated data (eg, SMPG, safety and central lab results, etc) will be available to patients in the virtual group, using a smartphone. This direct access to their data could support patients in diabetes management by helping them make better-informed decisions, which may have a positive impact on metabolic outcomes.

With the above study design the eStudy outcomes are expected to provide useful information for the future use of a virtual approach about the feasibility and appropriateness in both glycemic control and operational process, such as IMP adherence, barriers, burden to patients and sites, study complexity, patient compliance, data quality etc.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to evaluate the effect of virtual approach via novel technologies versus traditional study conduct on glycemic control in terms of HbA1c.

5.2 SECONDARY

The study secondary objective is to evaluate the appropriate utilization of virtual approach via novel technologies during the study and to assess the effect of the virtual versus traditional study conduct on multiple outcomes in terms of study methodology and diabetes control:

- Study methodology with the two approaches:
  - Patient satisfaction with the trial experience via a PRO
  - Impact of clinical trial participation via a PRO
  - Patient burden with the clinical trial experience via a PRO
  - Resource use via a PRO
  - Medication and key study activity compliance
  - Patient retention
- Diabetes control with the two approaches:
  - Diabetes related PROs
  - Glycemic control (HbA1c, FPG, SMPG)
- Patient care with the two approaches:
  - Doctor/site-patient relationship
  - Site satisfaction with provisioned care
  - Patient experience in the clinical trial via a qualitative exit interview
- Safety assessment managed by the two approaches including:
  - Hypoglycemic events
  - Adverse Events (AEs)

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

MSC15146 (eStudy) is a randomized, open label, 2 approach groups, multicenter pilot study. The study is a postmarketing Phase 4 trial which will recruit outpatients with Type 1 diabetes mellitus (T1DM) currently treated with insulin glargine 100 U/mL (eg, Lantus or Basaglar) plus rapid-acting insulin analogs. The patients must have access to mobile technology (eg, smartphone) and be digital-literate. They will eSign the consent on the study website.

The study will be conducted in the US and in Canada with at least 3 participating investigational centers. It is planned to recruit 150 patients.

Eligible patients will be randomized 1:1 (virtual : traditional) into 2 study groups to follow one of two approaches for completion of all study procedures:

- a remote, virtual approach (n = 75 patients); patients of this group will not visit the study sites during the entire study course, except for a physical examination before IMP initiation. All study assessments, including vital signs, weight, lab variables, etc, will be completed via the Bluetooth devices that instantly transfer the digital data, available for investigators' view. Video chat between the patients and investigators/designees may occur for safety reason in addition to the planned study visits.
- a traditional trial approach (n = 75 patients)

Stratification factors for randomization include study site and HbA1c <7.6% or ≥7.6%. The rationale for stratification by study site is the small number of sites and the fact that some assessments for patient care are done at site level. It is therefore deemed important to ensure balance at site level in number of patients randomized across the virtual and traditional approach groups. Patients of both groups will receive the same IMP: daily subcutaneous (SC) injection of Toujeo as the basal insulin. Protocol-mandated background therapy consists of the existing rapid acting insulin analogs (Humalog, Novolog, or Apidra) that have been used before the start of the study and will be continued throughout the study. This background treatment will not be supplied by the sponsor.

The study consists of 3 periods:

- an up-to-3 week screening period
- a 24-week treatment period
- a 1-week post-treatment period (follow-up)

The **screening period** includes 2 steps to complete the digital consent process via the study-specific webpage and the eligibility assessment by the study site. Screening procedures will be performed by Homecare services (via the Medical Research Network [MRN]) provided medical professional in collaboration with the investigators. The investigators will then complete the

eligibility assessments at the end of screening, the randomization, and the shipment of study material (Step 2).

During the 24-week **treatment period**, the patients in both groups will receive the same study treatment with Toujeo as the basal insulin plus their existing rapid-acting mealtime insulin analogs (Humalog, Novolog, or Apidra) to manage their diabetes. Toujeo dose will be titrated to target the fasting SMPG between 80 and 130 mg/dL; meal time insulin analogs will be adjusted following investigators' instructions to maintain postprandial SMPG within a range of 130 to 180 mg/dL.

All patients will monitor their plasma glucose via the study provided glucose meter. The SMPG values will be used to guide the insulin dose adjustment and document the hyper- or hypoglycemic events.

Any posttreatment safety information will be collected during the 1-week **posttreatment period**.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study duration consists of:

- An up-to-3 weeks screening period. The screening starts from signed consent form
- A 24-week treatment period
- A 1-week (+/-2 days) posttreatment safety follow-up after treatment completion or premature discontinuation of study treatment.

For an individual patient, the maximum study duration is about 28 weeks.

6.2.2 Determination of end of clinical trial (all patients)

End of clinical trial is defined as the last patient completes the last visit (Visit 13).

6.3 INTERIM ANALYSIS

No interim analysis

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patients with T1DM diagnosed at least one year before the screening visit

I 02. Patients who are treated with multi-dose insulin using insulin glargine 100 U/mL (eg, Lantus or Basaglar) as basal insulin and rapid- acting insulin analogues as bolus insulin

I 03. Patient with access to or experience with mobile technology (eg, tablet or smartphone)

I 04. eSign the consent on the study web portal

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 2 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Age <18 years at screening (Visit 1 – Step 1)

E 02. Type 2 diabetes mellitus

E 03. HbA1c <5.4% or ≥9.0% measured at screening (Visit 1- Step 2)

E 04. Patients who received less than 6 months treatment with any basal plus mealtime insulin

E 05. Use of any basal insulins other than insulin glargine 100 U/mL (eg, Lantus or Basaglar) within 3 months before screening

E 06. Use of an insulin pump within 6 month before screening

E 07. Use of meal-time insulin other than rapid-acting insulin analogs (Humalog, Novolog, or Apidra), eg, human regular insulin, within 30 days before screening

E 08. Use of any noninsulin injectable or oral antidiabetic medication within the past 3 months before screening

E 09. Use of systemic glucocorticoids (excluding topical application or inhaled forms) for one week or more within 3 months before screening

E 10. Use of any investigational drug(s) within 3 months, or 5 half-lives, whichever is longer, before screening (Visit 1)

E 11. Patients with severe systemic disease or with short life expectancy or any medical condition that might interfere with the evaluation of study medication according to investigator's medical judgment

E 12. Hemoglobinopathy resulting in undetectable HbA1c by the central laboratory, or hemolytic anemia requiring transfusion of blood or plasma products within 3 months before screening

E 13. Mental disorders or any neurologic disorder that would affect patient's ability to meet the study requirements, or patients deemed unlikely to safely manage insulin dosage by the investigator

E 14. Patients with insufficient smartphone skills or unwilling to properly use the virtual tools deemed by the investigator based on the observation over the digital screening procedure

E 15. Patients unable to speak, read, or write

E 16. Patient is the investigator or any subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

7.2.2 Exclusion criteria related to the current knowledge of Sanofi compound

E 17. Known hypersensitivity/intolerance to insulin glargine, rapid-acting insulin analogs, or any of their excipients

E 18. Patients experienced with any severe hypoglycemic episode resulting in seizure, unconsciousness, or coma, and/or leading to hospitalization during the past 6 months before screening

E 19. Documented (within 12 months) medical history of unstable proliferative diabetic retinopathy or or macular edema likely to require laser, surgical treatment during the study period

E 20. Pregnant or breast-feeding women or women who intend to become pregnant during the study period

E 21. Woman of child-bearing potential (WOCBP) not protected by highly-effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy (see contraceptive guidance in Appendix A).

E 22. Any country-related specific regulation that would prevent the subject from entering the study

Note: A patient should not be randomized more than once. One time re-screening is allowed at the Investigator’s medical judgment for any manageable reasons that cause the screening failure and the patient is likely to be eligible before the enrolment completion.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

The IMP is Toujeo (insulin glargine 300 U/mL, HOE901-U300).

Note: Dilution or mixing of Toujeo with other insulins is not allowed.

8.1.1 Formulation

Toujeo (HOE901-U300) is supplied for SC injection as a sterile, nonpyrogenic, clear, colorless solution in the Toujeo SoloSTAR® pen (a prefilled, disposable pen for insulin glargine 300 U/mL).

Each pen contains in total 450 units of insulin glargine (1.5 mL of 300 units/mL insulin glargine solution). This pen allows dose setting in the range of 1 to 80 units with a minimum of 1 unit increment.

8.1.2 Injection devices and training for injection devices

8.1.2.1 Injection devices

Patients will be provided with needles and the pen injection devices (prefilled study drug pens) specifically labeled for the use in the study.

The following commercial pen needles will be provided for use with the disposable injection pen devices:

- BD Ultra Fine Needles 31 G x 5 mm
- BD Ultra Fine Needles 31 G x 8 mm

Handling procedures of the pen and needles and administration technique is provided in specific manuals. The patients will be reminded of the IMP dosage at Visit 2-Step 2 before the IMP administration. For the duration of the treatment, the patients will be required to use the same type of study drug disposable pens and needles.

Pen device issues (malfunctions) should be reported to the sponsor by the means of a procedure on product technical complaint (PTC) forms (see details in Section 8.1.2.4).

Injection pens should never be shared with others.

8.1.2.2 Injection pen for Toujeo

All study patients will receive the appropriate number of disposable pens for Toujeo (insulin glargine 300 U/mL) and needles according to the dose range.

Each pen contains a cartridge with a total 450 units of insulin glargine. Doses can be set in steps of 1 unit. If a dose of Toujeo greater than 80 units is required, it will be given as two or more consecutive SC injections at the same time with the daily dose split in equal or close to equal doses. Splitting the doses into a morning and evening injection is not allowed.

8.1.2.3 Training on injection devices

Instructions for use will be provided, which explain how to use the disposable pen injectors. The injection device for the IMP is the same as or similar to the device that they have used for insulin glargine 100 U/mL. Therefore, no additional training on the devices is planned. The capability of self-injection with the SoloSTAR pen will be checked by the site staff in-person (traditional group) or via video technology (virtual group).

8.1.2.4 Pen-related events

A Pen-Related Event (PRE) includes any suspected problem with the injection device(s) used in the study which has or may lead to a health hazard (eg, AE). Typical problems include pen performance failure, patient (or caregiver) having difficulty understanding the instructions or using the pen, use error, etc.

Examples of PREs include but are not limited to:

- Dosing problems: jamming, inability to inject, partial injection, need to repeat injection, dosage knob stuck
- Needle issues: difficulty attaching the needle
- Breakage of the pen
- Difficulty to understand the instructions in the instructions for use
- Use error: Incorrect use of the pen by the patient/caregiver/healthcare provider

Pen-related events will be proactively monitored during the study by asking at each study visit whether the patient/caregiver experienced any PRE. If answer is yes, the specific electronic case report form (e-CRF) PRE Questionnaire will be completed.

If the PRE is associated with a symptomatic hypoglycemic event, a hyperglycemic AE or another AE, the corresponding symptomatic hypoglycemic forms or AE forms must also be completed. This associated AE will be qualified as a serious adverse event (SAE) only if it fulfills seriousness criteria, and in this case, the SAE reporting procedure (Section 10.4.3) should be followed.

As needed, further instruction and troubleshooting guidance should be provided to the patient by the study site according to the instructional materials/troubleshooting guide provided by the Sponsor.

For PREs that are not resolved by further guidance/review of instructions or troubleshooting with the pen during a visit, a PTC form must be completed, the pen associated with the event should be retrieved and both should be sent to the manufacturing site for technical investigation.

8.1.3 Provision of investigational medicinal product

Patients of the traditional group will be provided with the IMP by the site pharmacist or investigator during the on-site visits (Visit 2-Step 2, Visit 6, Visit 8, and Visit 10).

Patients of the virtual group will receive the IMP at home using the Direct-To-Patient (DTP) service. Patient identification remains confidential and will not be disclosed to study sponsor. For this reason, the IMP delivery will be managed by the Marken company (service provider). The clinical site will advise the patient as appropriate as to how the DTP process operates before the DTP process start.

- The clinical site investigator or pharmacist will have to inform Marken at least 72 hours before the pick-up time.
- Marken will send the shipping material to the site on the day before the pick-up time at the latest.
- Marken will deliver the IMP at patients' home at Visit 2, Visit 6, Visit 8, and Visit 10.

8.1.4 Route and method of investigational medicinal product administration

Toujeo will be self-administered once daily by SC injection, in the left or right anterolateral or left or right posterolateral abdominal wall or thighs or upper arms. Within a given area, location of the injection site of IMP should be changed (rotated) at each time to prevent injection site skin reactions.

The injection sites for IMP and NIMP should be different so that, if any, an injection site reactions can be attributed specifically either to IMP (Toujeo) or NIMP (mealtime insulin).

8.1.5 Starting dose of investigational medicinal product

After randomization, patients will follow the investigator's instruction to start the IMP (Toujeo) and the daily dose of Toujeo at Visit 2-Step 2.

Patients randomized in the virtual group will receive the IMP by DTP process (Section 8.1.3) while patients in the traditional group will receive their IMP at the site at Visit 2-Step 2. The IMP should **NOT** be started until the completion of all the baseline performances (see flowchart in Section 1.2) and discussed with the investigator at Visit 2-Step 2, which should occur 7 (± 4) days after the randomization interactive response technology (IRT) call.

The starting dose of IMP on Day 1 is the patient's current insulin glargine 100 U/mL dose, ie, the same dose used on the day before. Patient should administer Toujeo at the same time of the day as their previous insulin glargine 100 U/mL injection, which is usually in the morning or in the evening around the same time daily.

Patient should not change the injection time during the 24-week treatment period.

The date, time, and dose of Toujeo will be documented in the e-CRF.

8.1.6 Adjustment of investigational medicinal product

Investigators should follow Toujeo prescribing information to adjust Toujeo (9) dose. It is expected that a higher dose of Toujeo is needed to maintain the same level of glycemic control, when patients shift the basal insulin from insulin glargine 100 U/mL (eg, Lantus or Basaglar) to Toujeo. During the treatment period, Toujeo will be titrated at the investigator's discretion to achieve the fasting glycemic target while avoiding hypoglycemia.

The target range for fasting (prebreakfast/preinjection) plasma glucose is between 80 and 130 mg/dL (4.4 and 7.2 mmol/L).

The upward dose titration should continue until the patient reaches the target fasting (prebreakfast/preinjection) SMPG. All efforts should be made to reach the target ranges for plasma glucose by 6 to 8 weeks post randomization. Thereafter, the dose will be adjusted as necessary to maintain the glycemic control until the end of treatment (EOT) at Week 24.

Changes in the Toujeo dose are based on the average fasting pre-breakfast SMPG values of past 3 days measured by the patients. If the fasting SMPG is ≥130 mg (7.2 mmol/L), the Toujeo dose will be increased by 10%. Table 1 provides examples for the 10% titration rule. Other preprandial (prelunch, predinner) SMPG measurements may also be taken into account.

If considered helpful to achieve the fasting glycemic target by the investigator, the mealtime insulin (including bedtime) may be titrated before additional basal insulin titration to achieve a bedtime and prebreakfast glucose delta <50 mg/dL.

A dose increase may be split into 1-2 incremental dose steps rather than implementing the entire dose increase at once, if it is considered by the investigators or medically qualified designee to be in the best interest of the patient to do so. The dose of Toujeo should be titrated no more frequently than every 3 to 4 days.

Table 1 – Titration of investigational medicinal product dose

Toujeo daily dose	10% increase rules
Up to 21 u	2 u , or split into 2 x 1 u over 3 days apart
22 to 29 u	2 or 3 u , split into 2 or 3 x 1 u over 3 days apart
30 to 36 u	3 u, split into 3 x 1 u over 3 days apart
37 to 44	3 or 4 u, split into 2 x 2 u over 3-4 days apart
≥45 u	4 u , split into 2 x 2 u over 3-4 days apart

Good clinical judgment is to be exercised while titrating the basal insulin dose.

Regular SMPG is very important in order to achieve the blood glucose targets. It is recommended to perform daily fasting/prebreakfast SMPG and 5-point profiles to support the titration process. More frequent SMPG at other timepoints (eg, postbreakfast and postdinner) may be needed at the investigator's discretion.

Patients will be familiarized with the adjustment schedule so that they will be able to monitor the dose adjustment with the assistance of the investigator or medically qualified designee. During the first month of the treatment period, weekly contacts between the investigator and patient are scheduled to assess the response to treatment and to decide on dose adjustment. During these visits (phone or virtual), patients will report their SMPG data, insulin doses and hypoglycemia to the study site.

It is at the discretion of the investigator to allow well-trained patients to adjust their IMP insulin dose between the scheduled visits without prior consultation of the site personnel.

In cases of hypoglycemia, dose will be adjusted as follows:

- Upward titration is to be stopped for 1 week after a case of severe hypoglycemia (requiring assistance) or ≥2 episodes of documented symptomatic hypoglycemia within a week, unless there was a manageable factor (eg, omission of a meal or overdosed insulin) for the event
- Doses of basal insulin or meal-time insulin may be reduced or modified at any time for hypoglycemia during the study
- Patients who experience mild to moderate hypoglycemia as a result of a missed meal, unusual exercise, or alcohol use will be counseled on the correction of those behaviors and should not reduce their insulin dose

8.1.7 Evaluation of patients not meeting glycemic targets

In case the target fasting glycemic goal cannot be achieved in spite of successive IMP dose titration over 4-8 weeks, the investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in fasting condition (eg, before breakfast within 30 minutes window prior to injection)

- IMP and mealtime insulin are properly injected
- There is no intercurrent disease which may jeopardize glycemic control (eg, infectious disease)
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the investigator should take appropriate action, eg:

- Adjust the IMP dose and mealtime insulin dose
- Check the compliance of IMP and mealtime insulin injection
- Evaluate and treat any intercurrent disease (to be reported in the AE/SAE/concomitant medication parts of the e-CRF
- Organize a specific interview with a registered dietician or other medically qualified person to discuss with the patients on the absolute need to be compliant to diet and lifestyle recommendations

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

The noninvestigational medicinal products (NIMP) are the protocol-mandated mealtime insulins, ie, rapid insulin analogs (Humolog, Novolog, or Apidra), which have been used by the patient before the screening visit. This background treatment will not be supplied by the sponsor.

The patients in both study groups will continue with their existing mealtime insulin throughout the study. The type of mealtime rapid-insulin analog for each patient cannot be changed during the course of study. Any other types of meal-time insulin are prohibited for this study.

The injection sites should be different for the fast-acting mealtime insulin analogs from the IMP so that any injection site reactions can be attributed specifically either to the fast-acting insulin or to IMP. Changes in the body areas used for injection of either insulin should be avoided as far as possible during the study.

8.2.1 Adjustment of noninvestigational medicinal products

The dose of the mealtime insulin analogs (Humolog, Novolog, or Apidra) will be titrated to achieve a target of 2-hour postprandial plasma glucose. The dose adjustment is at the investigator's discretion in accordance with the national product label. Two recommended dose titration algorithms are based on a pattern of postprandial plasma glucose results of SMPG (simple titration) OR based on the carbohydrate content of the meal (carb counting).

- The **titration goal is a 2-hour postprandial SMPG in the range of 130 and 180 mg/dL (7.2-10.0 mmol/L)** while avoiding hypoglycemia. For the purpose of this protocol, 2-hour postprandial is defined as 2 hours after the start of the meal.
- While basal insulin doses are increased, mealtime insulin doses may be reduced to avoid daytime hypoglycemia as deemed appropriate by the investigator.

- Appropriate adjustment in mealtime insulin will continue throughout the entire treatment period (Week 0-24).

The two recommended regimens are described in Table 2 and Table 3.

Table 2 - Simple titration: Titration of mealtime insulin based on a pattern of post-meal glucose (median <130/>180 mg/dL in the prior 3 days)

Mealtime dose of Insulin	Pattern of postprandial BG values <130 mg/dL[a]	Postprandial BG values >180 mg/dL[a]
≤10 U	Decrease dose by 1 U	Increase dose by 1 U
11-19 U	Decrease dose by 2 U	Increase dose by 2 U
≥20 U	Decrease dose by 3 U	Increase dose by 3 U

a If more than 50% of the mealtime blood glucose (2-hour PPG) values for the week were above target.

Table 3 - Carbohydrate counting: Insulin-to-carbohydrate ratio group

Mealtime dose of Insulin	Pattern of postprandial BG values <130 mg/dL[a]	Postprandial BG values >180 mg/dL[a]
1 U/20 g	Decrease to 1 U/25 g	Increase to 1 U/15 g
1 U/15 g	Decrease to 1 U/20 g	Increase to 1 U/10 g
1 U/10 g	Decrease to 1 U/15 g	Increase to 2 U/15 g
2 U/15 g	Decrease to 1 U/10 g	Increase to 3 U/15 g
3 U/15 g	Decrease to 2U/15 g	Increase to 4 U/15 g

a If more than one-half of the mealtime blood glucose values for the prior 3 days were above target.

Starting recommendation 1 U to 15 grams carbs

Consider calculating insulin to carb (I:C) ratio = 500/total daily dose (TDD) of insulin.

Investigators will also be provided with an initial guideline of 1800/TDD as a correction factor to be used if applicable at the investigators' discretion.

The injection of the mealtime insulin analogs in relation to the meal intake will be done according to the individual habits of the patient prior to the study while following the instructions in the national product label.

Dietary modifications (eg, snacks) will be made by the Investigator, dietician, or other medically qualified person based on his/her best judgment.

8.3 BLINDING PROCEDURES

There will be no blinding procedures during the present study. All patients will self-inject themselves Toujeo (open label way) during the trial.

The study conduct approach (virtual or traditional) cannot be blinded to physicians or patients. As virtual and traditional approaches are distinguishable in terms of database source, it is also not possible to blind this information to the Data Management team.

Despite the open-label nature of study, assessment of outcomes will be based on objectively collected data, ie, assessments of HbA1c and FPG by central laboratories blinded to patients' study approach group. Also, the sponsor team will be provided blinded summary tables and listings to follow the study before database lock.

8.4 METHOD OF ASSIGNING PATIENTS TO GROUP

There is only one study medication provided in open-label boxes for all randomized patients. Boxes will be individually identified with treatment kit numbers. The nonrandomized sequential treatment kit number list will be generated centrally by Sanofi. The study medication will be packaged in accordance with this list.

The Study Biostatistician will provide the randomization scheme (including stratification) to the centralized randomization system (IRT). Then, the IRT generates the patient randomization list according to which it allocates study approach to the patients.

At screening (Visit 1 – Step 1), the investigator or designee will contact the IRT system to receive the patient number. The patient identification (patient number) is composed of 12-digits (3-digit country code, 4-digit center code, and 5-digit patient chronological number). If a patient who had previously failed screening is approached for rescreening, a new informed consent form must be signed. In such case, a new patient number will be assigned by IRT.

Patients will be randomized in a 1:1 ratio to either virtual or traditional study conduct approach.

Randomization will be stratified by HbA1c obtained at the screening visit (<7.6%; ≥7.6%) and study site (see rationale in Section 6.1).

On Visit 2-Step 1, the IRT will be contacted for randomization and for first treatment kit(s) allocation. The investigator or designee will have to call the IRT to provide some information (such as patient number provided by IRT at screening visit, date of birth, etc). Afterwards the IRT will be called again each time a new treatment kit(s) allocation is necessary, ie, the visits as indicated in the study flowchart (Section 1.2).

A randomized patient is a patient who has been allocated to a randomized trial approach by the IRT, regardless whether Toujeo treatment kit was provided and used or not.

A patient cannot be randomized more than once in the study.

8.5 PACKAGING AND LABELING

Toujeo (insulin glargine 300 U/mL solution) is supplied for SC injection as a sterile, nonpyrogenic, clear, colorless solution in a 1.5 mL Toujeo SoloStar disposable prefilled pen (450 Units/1.5 mL).

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements. Treatment labels will indicate the treatment number used for treatment allocation.

The respective number of the study treatment will be packaged under the responsibility of sanofi according to good manufacturing practice and local regulatory requirement. Toujeo will be supplied in boxes of 5 disposable pens for insulin glargine 300 U/mL.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

The expiry date is mentioned on the IMPs labels, and storage conditions are written on the IMP kits labels and in the instructions for use.

As for all medications and devices, the pens should be kept out of reach of children.

Instructions for use including storage conditions will be provided to all sites and patients for optimal home storage.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP 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 IMP and eliminate potential hazards.

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

8.7.1 Treatment accountability and compliance

At each contact with the patient, either by phone, by virtual contact (eg, video chat), or during on-site visit, the investigator or his/her delegate has to ask the patient about administered doses of IMP (Toujeo).

Returned and dispensed IMP pens and kits will be documented into the Treatment Log Form. Investigator or delegate has to visually check the filling status of the cartridges in the pens in the returned treatment kits and compare to dosing records documented in the patients' eDiaries. Discrepancies have to be addressed to the patient for clarification of real treatment administration.

The investigator completes the appropriate treatment log form based on the unused, used and in-use IMP (study drug pens) returned and records the dosing information on the appropriate page(s) of the e-CRF. However as type 1 diabetes patients are requiring insulin, the level of glycemia as reflected by SMPG and HbA1c is a sensitive marker of adherence to insulin treatment.

The monitor will check the e-CRF data by comparing them with patient's diary entries, treatment log forms and unused treatment kits.

8.7.2 Return and/or destruction of treatments

Patients of the traditional group will have to return all the used, in-use, and unused IMP (box[es] and pen[s]) at each on-site visit (or final assessment on treatment visit in case of permanent premature discontinuation).

In the virtual group, the used, in-use, and unused IMP (boxes and pens) will be retrieved by Marken's driver on Visit 6, Visit 8, Visit 10, and end of treatment (EOT) visit, and returned to the site.

For both groups, the site will be responsible for the IMP accountability, tracking, and destruction. The detailed instructions for handling will be provided by the sites.

8.7.2.1 Investigational medicinal product (Toujeo)

All partially-used or unused treatments (inject devices with inserted cartridges; disposable SoloSTAR pens) will be retrieved by the Sponsor. Pens and boxes will be retrieved for destruction according to local regulations. The investigator will not destroy any IMP unless the Sponsor provides written authorization. A detailed treatment log of the returned and destroyed IMP will be established with the investigator (or the pharmacist) and countersigned by the investigator and the monitoring team.

A potential defect in the quality of IMP may initiate 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 IMP and eliminate potential hazards.

8.7.2.2 Noninvestigational medicinal product (mealtime insulin analogs)

Since NIMPs are not provided by the sponsor, tracking and reconciliation has to be performed by the investigator (or pharmacist if appropriate) according to local procedures.

Patients have to record the administration of their mealtime insulin analog in the diary. All doses of mealtime insulin analogs during the day as taken for all meals and all snacks must be recorded. The sites have also to take care of source document of the NIMP in patient source documents and e-CRF (NIMP name, dosage, daily total dose, injection compliance and dose-titration recommendation, etc, as specified in Section 8.2).

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

The following drugs are not permitted during the study until the EOT visit (Visit 12, Week 24):

- Any antidiabetic agents other than the study medications (IMP and NIMP) including oral or injectable antihyperglycemic agents, other type of basal insulin (eg, neutral protamine Hagedorn [NPH], Detemir, premixed insulin), and human regular insulin
- Insulin pump therapy
- Systemic glucocorticoid use for more than 10 days at a dose >10 mg/day of prednisone or the equivalent. Topical or inhaled applications are allowed.

Note: After permanent IMP discontinuation (per protocol or premature), any treatment is permitted, as deemed necessary by the Investigator.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

All biological analysis (HbA1c and FPG) will be performed by a Central Laboratory. Detailed information on samples drawing, management and analysis will be provided in a specific manual.

Observation period for primary and secondary endpoints (glycemic and insulin dose)

The 24-week on-treatment period for primary and secondary endpoints (glycemic and insulin dose) is defined as displayed in Table 4.

Table 4 – 24-week on-treatment period for primary and secondary endpoints (glycemic and insulin dose)

Endpoint	Start of observation period	End of observation period
HbA1c	first injection of open-label IMP	7 days after date of last IMP administration
FPG	first injection of open-label IMP	1 day after date of last IMP administration
7-point SMPG	first injection of open-label IMP	date of last IMP administration
Insulin dose	first injection of open-label IMP	date of last IMP administration

HbA1c:glycated hemoglobin A1c; FPG: fasting plasma glucose; SMPG: self-monitoring of plasma glucose; IMP: investigational medicinal product

The randomized 24–week period for primary and secondary endpoints (glycemic and insulin dose) is defined from first dose of IMP up to Week 24, regardless of study treatment discontinuation.

9.1 PRIMARY ENDPOINT

- Change in HbA1c from baseline to Week 24.

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified level I "National Glycohemoglobin Standardization Program" (NGSP) central laboratory.

HbA1c is assayed at screening (Visit 1 – Step 2, Week -2); at Visit 10 (Week 16); Visit 12 (Week 24; final primary endpoint assessment visit).

9.2 SECONDARY ENDPOINTS

9.2.1 Study methodology endpoints

9.2.1.1 Patient satisfaction with trial experience

Patient satisfaction with trial experience will be measured using the Was It Worth It (WIWI) Questionnaire (10, 11), administered at Week 24 (Visit 12). The WIWI has 5 items, each with a 3-level categorical response scale. Each item is scored separately. The WIWI will be administered electronically using mobile technology. See questionnaire in Appendix B.

9.2.1.2 Impact of trial participation patient reported outcome

The effect of the trial on a patients' ability to work and perform regular activities will be measured using an adaptation of the Work Productivity and Impairment (WPAI) Questionnaire, administered at Week 0 (Visit 2-Step 2) and Week 24 (Visit 12). The WPAI used in this study has been adapted, with permission, from the WPAI-Specific Health Problem (WPAI-SHP) V2.0 (12), to provide information on the impact of study participation rather than on a health condition per se. The WPAI-SP has 6 items, and scoring follows that of the WPAI-SHP. As such, each item is presented separately, expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes. In addition, the following combined items will be reported:

- the percent work time missed due to study participation [Q2/(Q2 + Q4)]
- the percent impairment while working due to study participation [Q5/10]
- the percent overall work impairment due to study participation [Q2/(Q2 + Q4) + (1-(Q2/(Q2 + Q4)))x(Q5/10)]
- the percent activity impairment due to study participation [Q6/10]

The WPAI-SP will be administered electronically using mobile technology.

See questionnaire in Appendix B.

9.2.1.3 Patient burden with trial participation

Patient burden with trial participation will be measured using a new PRO: the Overall Study Experience-Participation (OSEP) Questionnaire. Each item will be scored separately. The OSEP has 2 parts:

- OSEP part 1 contains 4 items to examine perceptions of diabetes control; it will be administered at Week 0 (Visit 2-Step 2) and Week 24 (Visit 12)
- OSEP part 2 contains 9 items to examine perceptions of study participation; it will be administered only at Week 24 (Visit 12)

The OSEP will be administered electronically using mobile technology.

See questionnaire in Appendix B.

9.2.1.4 Resource use

Healthcare resource use will be measured using a new PRO: the resource use questionnaire (RUQ). The RUQ will be administered every 4 weeks from baseline to Week 24. The RUQ asks the patients to report the resources used (time and expenses) during the previous 4 weeks in terms of visits to healthcare professionals.

The RUQ will be administered electronically using mobile technology.

See questionnaire in Appendix B.

9.2.1.5 Other study methodology endpoints

The following additional endpoints will be considered:

- Compliance with medication during the treatment period (from Day 1 to Week 24), expressed in terms of IMP exposure time and the percentage of actual dose over the prescribed dose
- Compliance with key study activities during the treatment period (from Day 1 to Week 24), including:
  - Number of times the patient used the Bluetooth devices in accordance with the study instructions
  - Number of times the patient completed the blood draw visits (Visit 10 and Visit 12) in accordance with the study instructions
  - Patient withdrawal during the treatment period (from Day 1 to Week 24)

9.2.2 Diabetes control endpoints

9.2.2.1 Diabetes-related patient reported outcomes

Treatment satisfaction will be measured with the Diabetes Treatment Satisfaction Questionnaire (**DTSQ)**. The DTSQ is available in two versions:

- the DTSQ status (DTSQs) version (13) evaluates absolute treatment satisfaction in the "past few weeks" and will be administered at Week 0 (Visit 2-Step 2) and Week 24 (Visit 12)
- the DTSQ change (DTSQc) version (14) measures the relative change in treatment satisfaction from previous therapy and will be administered (after the DTSQs) at Week 24 (Visit 12) only

The DTSQs and DTSQc conceptually contain the same 8 items, each scored on a 7-point scale but with different response options. Six items are summed to produce a measure of treatment satisfaction, with total scores ranging from 0 (very dissatisfied) to 36 (very satisfied) for the

DTSQs and −18 (much less satisfied) to +18 (much more satisfied) on the DTSQc. The remaining 2 items, which measure perceived frequency of hyperglycemia and perceived frequency of hypoglycemia, are treated independently. These items are scored on a scale ranging from 0 (none of the time) to 6 (most of the time) on the DTSQs and −3 (much less of the time now) to +3 (much more of the time now) on the DTSQc.

The DTSQs and DTSQc will be administered electronically using mobile technology.

Fear of hypoglycemia will be measured with the Hypoglycemia Fear Survey-II (**HFS-II)** (15) on Week 0 (Visit 2-Step 2) and Week 24 (Visit 12). The HFS-II comprises 33 items:

- 15 items explore behaviors that patients may engage in to avoid low blood sugar and its negative consequences (the hypoglycemia fear survey-behavior subscale [HFS-B])
- 18 items relate to concerns that patients may have about their hypoglycemia (the hypoglycemia fear survey-worry subscale [HFS-W])

Responses are made on a 5-point Likert scale where 0 = “Never” and 4 = “Always” with a past 3 months recall period. Subscale scores (HFS-B, HFS-W) and a total score are calculated by summing item responses.

The HFS-II will be administered electronically using mobile technology.

Diabetes-related distress will be measured using the Diabetes Distress Scale (DDS) (16) at Week 0 (Visit 2-Step 2) and Week 24 (Visit 12). The DDS contains 17 items related to potential problem areas that people with diabetes may experience. Patients are asked to consider the degree to which each of the items may have distressed or bothered them during the past month, and respond between 1 (not a problem) and 6 (a very serious problem). The DDS yields a total diabetes distress score and 4 subscale scores, each addressing a different kind of distress (emotional burden, physician distress, regimen distress, interpersonal distress). Each score (total and subscales) are presented as an average, by summing the patient’s responses to the appropriate items and divide by the number of items in that scale. In addition, total and subscale scores will be categorized: a mean score 2.0 – 2.9 should be considered ‘moderate distress’ and a mean score >3.0 should be considered ‘high distress’ (17).

The DDS will be administered electronically using mobile technology.

See questionnaires in Appendix C.

9.2.2.2 Secondary glycemic endpoints

The baseline value for glycemic endpoints is the last available value prior to the first injection of open-label IMP.

List of secondary glycemic endpoints

- Central lab HbA1c: change from baseline (Visit 1 Step 2) to Week 16 (Visit 10)

- Central lab FPG: change from baseline (Visit 1-Step 2) to Week 16 (Visit 10) and Week 24 (Visit 12)
- Mean 7-point SMPG: change from baseline (Visit 2-Step 2) to Week 16 (Visit 10) and Week 24 (Visit 12)
- 7-point SMPG at each timepoint (preprandial and 2-hour postprandial plasma glucose at breakfast, lunch and dinner, and bedtime): change from baseline (Visit 2-Step 2) to Week 16 (Visit 10) and Week 24 (Visit 12)

9.2.2.2.1 Fasting Plasma Glucose

Fasting plasma glucose will be measured at a central laboratory.

Blood samples for FPG measurement will be taken at baseline (Visit 1-Step 2), at Week 16 (Visit 10) and at Week 24 (Visit 12, EOT).

9.2.2.2.2 Self-measured plasma glucose

Glucose meter, patient diary and training

Blood glucose values will be self-measured by the patients using the sponsor-provided **glucose meter** and associated accessories (lancet, control solutions, test strips etc). Note that this type of glucose meter does not measure glucose in plasma but in the blood of capillaries. A correction is applied to the result to express it as "plasma equivalent". In the present protocol, SMPG should thus be understood as "self-measured plasma-equivalent glucose".

After the randomization IRT call, eligible patients will receive the study glucose meter and associated accessories by mail. Patients should not use their personal glucose meter during the study.

The investigator or a member of the investigational staff will explain the importance to measure glucose appropriately via video chat to ensure the patient's commitment to SMPG performances. Training may be repeated as deemed necessary at the study visits and the investigational staff will review the patient's diary at each visit.

Self-monitoring of plasma glucose readings will be used to guide the basal and mealtime insulin titration to reach glucose targets. The investigators should review the SMPG records at each onsite visit and also ask the pattern of fasting and postprandial SMPG at the phone visits so that they can provide instruction to the patients for appropriate insulin dose adjustment. Investigators may request more frequent blood glucose test and/or at specific time, eg, midnight, if needed, to help the patients optimize insulin dosage.

The performance of SMPG is outlined in Table 5 and also specified also in Section 1.2 flow chart.

Table 5 – Instruction for SMPG performed during the study

SMPG	Definition	Frequency	
		Recommended	Mandatory
5-points	Before breakfast, lunch, and dinner, 2 hours post a main meal (or as per investigator's instruction) and at bedtime	5 days per week	3 days during the week prior to each visit
7-points	before and 2 hours after breakfast, lunch, and dinner, and at bedtime	As needed	1 day during Week -1, 15, and 23

SMPG: self-monitoring of plasma glucose

5-point SMPG profiles

Patients should measure a 5-point SMPG profile (before breakfast, lunch, and dinner [before insulin injection when applicable], 2 hours after the patient's main meal [eg, lunch or dinner] or as per investigator's instruction, and at bed time) for at least 3 days per week before each visit.

Before breakfast, SMPG should be measured after the patient wakes up, before breakfast, and before injection of any insulin (if applicable). Preferably, no food should have been taken overnight. The values will be used as fasting SMPG to guide the modification in insulin dose (Section 8.1.6).

7-point SMPG profiles

Seven-point blood glucose profiles should be measured at the following 7 time-points: before (preinjection after randomization) and 2 hours after breakfast; before and 2 hours after lunch; before and 2 hours after dinner; and at bedtime). Two hours post meal is defined as 2 hours after the start of the meal.

Patients are required to have 7-point SMPG profiles performed on at least 1 day in the week before the baseline visit and before the visits of Week 16 and Week 24 (EOT).

SMPG during episodes of symptomatic hypoglycemia

Whenever the patient feels hypoglycemic symptoms, plasma glucose should be measured by the patient (or others, if applicable), if possible. Patients should be instructed to measure plasma glucose levels prior to the administration of glucose or carbohydrate intake whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose/carbohydrate rescue prior to confirmation with the SMPG.

Patients have to document hypoglycemic events appropriately in their diaries and to contact the investigator as soon as possible following severe events for review and for decision on any necessary actions to be taken.

All hypoglycemia episodes will be documented on the "hypoglycemia specific form" in the e-CRF. This includes all symptomatic hypoglycemia events and asymptomatic hypoglycemia.

Hypoglycemia events fulfilling the criteria of a SAE will be documented on the SAE form in the e-CRF.

9.2.2.3 Dose of basal and mealtime insulin

Patients will record their basal insulin and mealtime insulin dosing data (time and dose), including corrective doses, in the eDiary daily during the following periods:

- the randomization period after receiving of glucose meter and the eDiary device
- the treatment period up to Visit 9 (Week 12)
- at least over one week before each visit during the remainder of the treatment period until the EOT visit (Visit 12 – Week 24 or early treatment discontinuation)
- During the week of the follow-up period

The following endpoints will be considered: total insulin dose, basal insulin dose, mealtime/bolus as daily dose and u/kg.

9.2.3 Patient care endpoints

9.2.3.1 Investigator questionnaires

Site investigators (one per site) will be asked to complete the Overall Study Experience-sites (OSES) questionnaire. The OSES has 2 parts:

- OSES part 1 contains 1 item to examine resource requirements: “Approximately how much time did you spend with this participant (in person or via phone) during this scheduled visit/communication?”. OSES part 1 will be administered following each study visit.
- OSES part 2 contains 2 items to examine relationship (“I had a good relationship with this patient during the study”) and satisfaction with care (“I am satisfied with the level of care I have provided for this participant in this study”). OSES part 2 will be administered at Week 24 (Visit 12) only.

Each item is scored separately.

See questionnaire in Appendix D.

9.2.3.2 Patient interviews

English-speaking patients of the virtual group who consent will be invited to participate in interviews following their Week 24 (Visit 12) study visit (ie, after completion of the trial). These qualitative exit interviews will be conducted one-on-one with up to 30 patients to:

- Examine patients’ experiences of trial participation, in their own words
- Explore the positive and negative aspects of trial participation
- Provide some context to responses given in the PRO questionnaires

Interviews will be held by trained site staff.

See interview guide in Appendix D.

9.2.4 Safety endpoints

Observation period for safety endpoints:

The observation period of safety data will be divided into 3 segments:

- The pre-treatment period is defined as the time between the date of the informed consent and the first injection of open-label IMP
- The treatment-emergent AE (TEAE) period is defined as the time from the first injection of open-label IMP up to 2 days after the last injection of IMP
- The post-treatment period is defined as the time starting 3 days after last injection of open-label IMP (after the TEAE period)

The baseline value for safety endpoints will be the last available value prior to the first injection of IMP.

9.2.4.1 Adverse events

Adverse events and SAEs, including injection site reactions. Refer to Section 10.4 to Section 10.6 for details.

9.2.4.2 Product technical complaints

Refer to Section 8.1.2.4 for details.

9.2.4.3 Laboratory safety variables

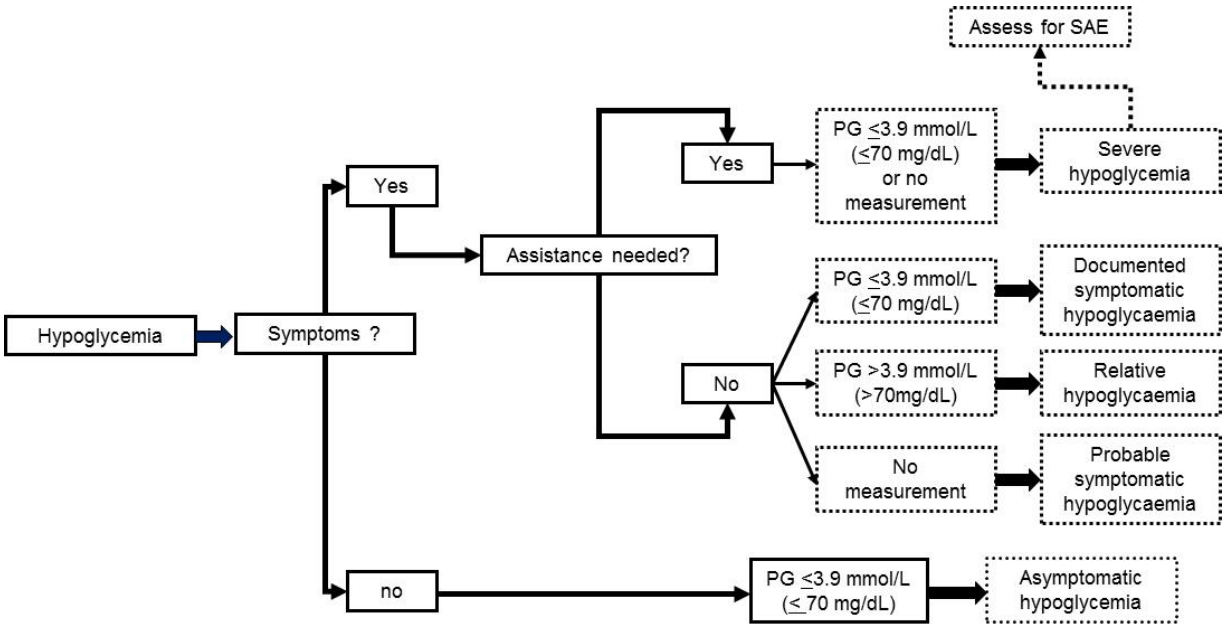
For WOCBP, urine pregnancy test will be performed at Week 4, Week 8, Week 16, and Week 24. It can be confirmed with a serum test if needed. No other laboratory safety variables will be measured after baseline.

9.2.4.4 Hypoglycemia

9.2.4.4.1 Definition of hypoglycemia

Hypoglycemia events will be categorized as follows (following the American Diabetes Association [ADA] Workgroup on Hypoglycemia) (18). Classification of hypoglycemia is summarized in Figure 1.

Figure 1 – Classification of hypoglycemia



- **Severe hypoglycemia**

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

The definition of severe hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others.

Note that “requires assistance” means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a “requires assistance” incident.

Severe hypoglycemia will be qualified as an SAE only if it fulfills SAE criteria. All events of seizure, unconsciousness or coma must be reported as SAEs.

- **Documented symptomatic hypoglycemia**

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L).

Clinical symptoms that are considered to result from a hypoglycemic episode can include (but are not necessarily limited to): increased sweating, nervousness, asthenia, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, and coma.

Patients will be instructed to measure finger stick plasma glucose levels prior to the administration of carbohydrates whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose rescue prior to confirmation, and then a glucose measurement should be performed as soon as safe, with appropriate diary documentation. Details on hypoglycemia episodes will be captured in the patient diaries, and patients will contact the sites as soon as possible following severe events to review the details and decide on any necessary measures to be taken.

- **Asymptomatic hypoglycemia**

Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L).

- **Probable symptomatic hypoglycemia**

Probable symptomatic hypoglycemia is an event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L); symptoms treated with oral carbohydrate without a test of plasma glucose.

- **Relative hypoglycemia**

Relative hypoglycemia recently termed “pseudo-hypoglycemia” (19) is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L) but approaching that level.

- **Nocturnal hypoglycemia**

Nocturnal hypoglycemia is any hypoglycemia of the above categories that occurs:

- Between 00:00 and 05:59, regardless whether patient was awake or work up because of the event
- Sleep status: patient was asleep between bedtime and before getting up in the morning, ie, before the morning determination of fasting pre-breakfast SMPG and patient woke up due to the hypoglycemia

9.2.4.4.2 Reporting hypoglycemia

All hypoglycemia episodes will be documented on the dedicated hypoglycemia event page in the e-CRF. The information about the hypoglycemic events including onset date/time, counter-measurements, whether the patient needed assistance from other to treat the hypoglycemic event, etc. will be collected to support hypoglycemia analyses.

Hypoglycemic events and the symptoms accompanying the events will not be reported as an AE. However, symptomatic hypoglycemia events fulfilling the criteria of an SAE will be documented

on SAE complementary forms in the e-CRF in addition to the hypoglycemic event form. All hypoglycemic events resulting in seizure, unconsciousness, or coma will be reported as SAEs.

For more details on the analysis of hypoglycemia, refer to Section 11.4.3.4.

9.3 FUTURE USE OF SAMPLES

Not applicable.

9.4 APPROPRIATENESS OF MEASUREMENTS

The purpose of the pilot study is to evaluate the methodology of a virtual clinical trial conduct in management of diabetes in the patients with T1DM. The primary endpoint (HbA1c) is well accepted by medical society and the health agencies as a stable indication for glycemic control. Secondary endpoints aim at measuring the appropriate utilization of virtual approach via new technologies during the study; therefore, multiple endpoints are chosen to assess the effect of the virtual versus traditional study conduct on a number of the study activities, including diabetes questionnaires, IMP/NIMP compliance, patient retention, protocol deviation, etc.

The usability and appropriateness of the virtual methodology will also be assessed by a battery of PRO questionnaires. The satisfaction questionnaires (WIWI) will reveal the patient experience of the trial participation from patient's perspective; the WPAI-SP questionnaire will assess the impact of trial participation on the patients' daily life and working hours; the OSEP questionnaire will measure the patient burden with trial participation; and the RUQ will evaluate the number of healthcare professional visits and the associated cost.

Patients in both virtual and traditional groups will receive the exactly same insulin regimen using Toujeo as the basal insulin plus rapid-acting insulin analogs to treat their T1DM during the treatment period. With the HbA1c stratification at the randomization, the baseline HbA1c is expected to be similar in the two groups. The 24-week treatment is considered sufficient for the purpose of the study: after switching from insulin glargine 100 U/mL (eg, Lantus or Basaglar) in a stable dose prior to the study entry, steady state is expected to be reached within 2 weeks of treatment start with Toujeo and the optimal dose of Toujeo is expected to be reached within 8 weeks following fasting SMPG-orientated dose titration regimen.

Thus, the operational effect of the study methodology on glycemic control will be well measured by the change in HbA1c from baseline to Week 24, which is a widely accepted standard endpoint for assessing the glycemic control. Other glycemic variables (FPG, SMPG) will also be assessed. In addition to the laboratory variables, diabetes control will be evaluated by 3 well established PRO questionnaires (DTSQ, HFS-II and DDS) to assess the treatment satisfaction, the hypoglycemia fear, and the diabetes related stress.

Safety will be evaluated by standard clinical measurements, including TEAE, SAE, adverse event of special interest (AESI), and AE leading to IMP discontinuation. Specific safety parameters of interest for a glucose lowering injectable peptide such as hypoglycemia and injection site reactions will also be assessed.

10 STUDY PROCEDURES

This is an approximately 28-week outpatient study. Screening procedures will be performed as a virtual visit followed by a Homecare in-person visit. Eligible and consenting patients will be randomized to an approach group at telephone Visit 2-Step 1, which will determine the way the next visits are organized:

- Traditional group: 5 onsite visits and 7 telephone visits
- Virtual group: 11 virtual visits and 1 mixed onsite-virtual visit (Visit 2-Step 2)

Additional, optional virtual or telephone visits (according to the approach group) will be scheduled to monitor and support the progress of insulin titration whenever considered necessary by the investigator. For both groups, unscheduled onsite visits or Homecare physician visits (depending on the patient's location) may be scheduled only for safety assessment if deemed necessary by the investigator (ie, performance of physical examinations is critical to determine a diagnosis or further evaluation procedure for an AE).

All onsite visits should take place in the morning at approximately the same time. On the day before each onsite visit, patients should be reminded to bring the medical devices (glucose meter), diaries and IMP (used, in-use or unused) to sites and to be in the fasted status if required at some visits.

The **fasting condition** is defined as an overnight fast no less than 8 hours that consisted of no food or liquid intake, other than water. IMP and noninsulin antidiabetic medication should be administered after the fasting blood sample is drawn for all laboratory tests.

Note: If the patient is not in fasting conditions at visits which required in fasting conditions, the blood sample is not collected and a new appointment should be given to the patient for the following day if possible, with instruction to be fasted.

For phone-call visits and virtual visits, the patient is called by the investigator or qualified designee at a scheduled time.

A visit window of ± 3 days using the day of Visit 2-Step 2 as reference is acceptable (4 days for Visit 6, Visit 8, and Visit 10).

If one visit date is changed, the next visit should take place according to the original schedule, ie, counting from Day 1 on Visit 2-Step 2.

Diet and lifestyle counseling including training in carbohydrate counting, if chosen to be used for the mealtime insulin titration, will be continued during the study. Dietary and lifestyle counseling should be given by a registered dietician or other medically qualified person (eg, diabetes educator, endocrinologist) and should be consistent with the recommendations of national or local guidelines (with regard to distribution of calories among carbohydrates, proteins, fats and to exercise) for individuals with type 1 diabetes.

Compliance with the diet and lifestyle recommendations will be discussed with the patients throughout the study, and more specifically in case of insufficient glucose control.

For a complete list of procedures scheduled for each study visit please refer to the study flowchart (Section 1.2). The aim of the following sections is to provide details on how some of the procedures have to be performed.

10.1 VISIT SCHEDULE

10.1.1 Screening Visit (Visit 1-Step1 and Step 2) Week -3 to Week -2

The screening will be done electronically in 2 steps:

- Step 1: electronic informed consent: patients will have been guided to the eConsent web portal by the sites or by multi-channel digital recruiters. The study will be presented to them before eConsent.
- Step 2: eligibility assessment: verification of patient identity, vital signs measurement, and blood draw for central laboratory tests will be done in-person by a Homecare health professional visit. This visit can occur at the patient's home, at work, or at any location providing the adequate space and level of privacy. Investigators will complete the determination of eligibility at the end of screening.

For a complete list of procedures scheduled for each study step please refer to the study flow chart (Section 1.2).

Demographic data and electronic **informed consent** must be obtained from the patient prior to any study-specific procedures. During the stepwise process on the study web portal for the e-consent, the patient will receive information concerning the aims and methods of the study, its constraints and risks and the study duration and will be provided with the written information. This will be done virtually through the study web portal through video conferencing with the investigator or designee, with the support of animations or text. The informed consent will be counter-eSigned by the investigator. Interactive response technology will be contacted for notification of screening and patient number allocation (Section 8.4). Please note that it is important to have the IRT contact before any blood sample is drawn because the patient number is given by IRT and it must be reported on the laboratory requisition forms. Homecare visit will be scheduled with the patient.

The following will be collected and assessed by the investigator and the site virtual team (designee and study coordinators):

- Collection of **diabetes history** will include documentation of duration of diabetes, history of microvascular [eye, kidney] and of neuropathic complications and their treatments. For patients with a documented medical history of proliferative retinopathy or macular edema, if the latest ophthalmologic investigation have been performed longer than 12 months prior to the planned randomization, the patient has to be referred to an ophthalmologist (or optometrist) prior to randomization. The previous experience with hypoglycemia during the past 12 months will be verified with the source document.

- **Medical/surgical history** may include macrovascular complications (heart, brain, legs) as well as all additional comorbidities. Alcohol and smoking habits are to be recorded.
- Check of **concomitant medication** refers to documentation of medication including over-the-counter medication taken/administered within the previous 3 months prior to this visit.
- Basal insulin analogs and mealtime insulin doses have to be recorded.
- Further discussion about the study and answering patient questions may occur between the investigator and patients via e-chat.

The following will be performed by the Homecare health professional:

- Verification of patient identity in person
- Determination of the **reference arm for blood pressure** (BP) measurements: after the patient has rested comfortably for at least 10 minutes, BP will be measured on both of the patient´s arms while the patient is in sitting position and then again on both arms after 2 minutes . The arm with the higher diastolic BP will be determined at this visit, identifying the reference arm for future measurements. The reference arm will be used for later BP measurements by **the patients themselves** in the virtual group or by the site staff for the traditional group. The average value of the 2 measurements (2 minutes apart) will be recorded in the e-CRF (all BP values are to be recorded in the source data).
- **Heart rate** will be measured at the time of the BP measurement.
- **Height** will be measured when patient´s shoes are off, feet together, and arms by the sides. Heels, buttocks, and upper back should also be in contact with the wall when the measurement is made.
- **Body weight** should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer. The weight is read and recorded in the e-CRF and source data.
- Blood will be drawn for all central **laboratory tests** needed for evaluation of the eligibility criteria (eg, HbA1c) of the patients. Patient has to provide a urine sample.
- In WOCBP, the **contraceptive methods**, if used, have to be documented. According to CPMP/ICH/286/95 (20), “Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly.” Refer to Appendix A for details. A serum pregnancy test will be performed.
- If needed, diet and lifestyle counseling should be provided.

At Visit 1-Step 2, the investigator will complete the eligibility assessment of the patients when the laboratory results become available.

As soon as a patient is found ineligible, the patient must not enter the randomized treatment phase and IRT has to be contacted in order to register the patient as a screening failure.

Patients can be rescreened one time before randomization in case of nonevaluable exclusion criteria (eg, not evaluable screening laboratory findings) or in case of manageable exclusion as deemed by the investigator. Rescreened patients will be subject to the screening visit procedures/assessments (see below) including new informed consent signed and allocation of a new patient number.

10.1.2 Randomization Visit (Visit 2)

10.1.2.1 Visit 2-Step 1 (Week -1)

Visit 2-Step 1 telephone call will occur about 1 week after Visit 1-Step 2 when the investigator has received laboratory reports for the screened patients in order to assess exclusion criteria E 03 and E 12 (Section 7.2). The eligible patients will be randomized to the study group through IRT.

Appropriate study materials will be shipped to eligible patients: Bluetooth blood glucose meter with associated accessories (lancets, control solutions, test strips etc.), e-diaries features, and instructions. Bluetooth devices (pulse oximeter, BP cuff, and scale) will be shipped to patients allocated to the virtual group. Bluetooth devices are listed in Appendix E.

Patients of the virtual group will record any symptoms in the eDiary so that the investigator is informed through the study website portal and will record the AE into the e-CRF.

An onsite visit will be scheduled within a week (+/- 4 days) for the traditional group.

Patient randomized in the virtual group will also be scheduled for an onsite visit, but for physical examination only. The virtual Visit 2-Step 2 visit will be scheduled within 1 week (+/- 4 days) of the Visit 2-Step 1 for the virtual group.

Patients should be reminded to perform at least one day of 7-point SMPG prior to the Visit 2-Step 2 visit. Patients of the traditional group will be reminded to bring the glucose meter to the study visit.

10.1.2.2 Visit 2-Step 2 (Week 0)

This is the baseline visit (onsite visit for the traditional group and mixed onsite-virtual visit for the virtual group). The full list of assessments is provided in the study flow chart (Section 1.2). Additional details are provided below for a number of assessments.

For the traditional group:

- During the week prior to the scheduled site visit:
  - patients should perform at least one day of 7-point SMPG
  - The baseline questionnaires (DTSQs, DDS, HFS, WPAI-SP, OSEP part 1, RUQ, and OSES part 1 resource requirements) should be administered by patient via parallel 6 portal
- Patients will bring the glucose meter to the site and SMPG data will be collected.

- Any AE/SAE, including hypoglycemia, that occurred since Visit 1 will be documented.
- A disease-focused initial physical examination will be performed by the investigators at the study site, including neck palpation of thyroid, screening for diabetic neuropathy (eg, assessment of appearance of feet and ankles, reflexes, and vibration perception at the great toes) and a check for injection site reactions.
- The IMP, Toujeo basal insulin, will be dispensed. The first dose of IMP may start on the day of this visit (ie, evening dosing) or the second day (ie, morning dosing). Patients will document the dose and date/time in the eDiary.

For the virtual group:

- Patients will receive the Bluetooth devices by mail and IMP by DTP before Visit 2-Step 2. Upon receipt, they will activate the devices (Bluetooth, e-diary, digital BP and pulse device, etc) and confirm to the study site the successful connection with the virtual platform.
- They will be scheduled within a week to visit study site in-person for the investigator to perform the physical examination. No other assessments will be done at this onsite visit.
- Patients will be guided for using the device to measure BP, heart rate, and weight appropriately.
- The 7-point SMPG will be performed for at least 1 day within the week prior to the first dose of the IMP and the data will be immediately available via the Bluetooth for investigator's review.
- Any AE/SAE, including hypoglycemia, that occurred since Visit 1 will be documented in the eDiary.
- Baseline PROs should be completed electronically independently from influence of the investigator and the site staff.
- After all baseline assessments have been completed, the investigator will instruct patients to initiate the first dose of the IMP, Toujeo basal insulin, and patients will document the dose and date/time in the eDiary.

All patients in both study groups will be reminded by the study staff to refer to the instructions for use to properly use the Toujeo pens. IMP administration will be explained to patients including reminding the IMP dose, time of the once daily administration, and dose titration requirements (Section 8.1).

The day of the first administration of IMP will be defined as Day 1.

All patients are asked to self-titrate their IMP according to the algorithm provided (Section 8.1). The short-acting insulin analog will be continued for mealtime insulin requirements and correction of SMPG according to recommendation (Section 8.2.1). Investigators and their study staff are required to offer adequate training, thus enabling patients to successfully self-titrate their insulins.

10.1.3 Phone call/Virtual Visits (V3-5, V7, V9 and V11)

During the study treatment period, 6 phone call/virtual visits are scheduled between the IMP dispensing visits. The purpose of the contact with the patients is to monitor the patients' compliance with SMPG and insulin titration and to collect injection information, AE/SAE, including hypoglycemia, any change in concomitant medications, and OSES part 1 questionnaire (resource requirement). Resource use questionnaire will be administered on Visits 9 and 11.

Patient of the traditional group will be called by the investigator or qualified designee at a scheduled time. If the call has been completed by site staff other than the investigator, the investigator has to be consulted if AE/SAE is suspected.

Patients of the virtual group will contact the sites and communicate via virtual chat. It can also occur ad-hoc as needed.

During the phone or video, the following will be checked and information collected accordingly:

- Injection of the IMP (Toujeo) and NIMP (the mealtime insulin analogs) as instructed by the investigators
- Occurrence of new medical events, diseases, or symptoms since the last visit
- Occurrence of hypoglycemic events or symptoms, or any injection site reaction
- Change or addition of any new medications since the last visit
- If the patient feels comfortable in handling e-diary, glucose meter and IMP injection device or he/she needs help

Further following procedures will be performed:

- Instruct patients on further insulin dose adjustment according to their SMPG values
- Remind the patients to measure required SMPG and complete the diary
- Remind patients to perform the 7-point SMPG before Visit 10 and Visit 12
- Document change of concomitant medication and actual basal and mealtime insulin doses in the e-CRF
- Report AE/SAE and hypoglycemia if any
- For patients of the traditional group, remind to be fasting prior to Visit 10 and Visit 12; remind and check with the patients of the virtual group to have their blood drawn at the local laboratory (US patients)
- For patients of the traditional group, remind to bring the glucose meter and IMP (used, in-use, or unused) at each onsite visit

For a complete list of procedures scheduled for each phone-call visit please refer to the study flowchart (Section 1.2).

10.1.4 Onsite/virtual visits (V6, 8, and V10) during treatment period

Three study visits will occur onsite before the EOT for the traditional approach group. Virtual approach group patients will have the corresponding visit as virtual visit.

During these visits, study material (eg, ancillaries and glucose meter accessories) and IMP will be dispensed or shipped, and the patients' progress, SMPG patterns, dose regimens and data collected during the study (eg, hypoglycemia, AE/SAE, average fasting and postprandial SMPGs over the past days) will be discussed. For patients of the traditional group, the IMP dispensation will be done on site by the investigator or pharmacist. For patients of the virtual group, the IMP will be shipped using the DTP service described in Section 8.1.3.

Patients of the traditional group will bring their glucose meter and IMP boxes to the study site at each onsite visit. For patients of the virtual group, the used and unused IMP will be returned to the sites by Marken driver.

Patients of the virtual group will perform all assessments via virtual device for vital signs (BP, HR) and weight measurements.

The investigators and study staff will check and document in the source data if the patient has reached the titration goal or not at each visit. Appropriate titration will be continued until target fasting SMPG without hypoglycemia has been reached.

Investigational medicinal product compliance (collecting and counting used and unused cartridges and syringes) will be checked and addressed with the patients. The IMP compliance will be checked by video chat between the patients of the virtual approach group and the site staff.

Consultation for diet and life-style modification should be provided during the visits if needed.

Overall Study Experience-Sites part 1 questionnaire (resource requirement) should be completed by the Investigator.

Within 1 week prior to Visit 10, patients should be reminded, if needed, to perform at least one day of 7-point SMPG.

Resource use questionnaire will be completed by the patients at Visits 6, 8, and 10.

Additionally, at Visit 10, patients should be fasted and blood will be drawn for measurements of HbA1c and FPG at central laboratory. The patients from the virtual approach group will attend the local Quest laboratory with the study requisition to complete the blood sampling (for patients located in Canada, phlebotomy may be done by the Homecare nurses at the patients' home or other suitable location).

For a complete list of procedures scheduled for each study visit please refer to the study flowchart (Section 1.2).

10.1.5 End of Treatment (EOT) visit (Visit 12, Week 24)

The EOT visit will occur onsite for the traditional approach group. Virtual approach group patients will have the corresponding visit as virtual visit.

Before the EOT visit, the patients will be reminded to:

- perform at least one day of 7-point SMPG during the week prior to the visit. The visit will be postponed if the patient has not done or missed data point(s) of the 7-point profile
- be fasted for about 8 hours prior to on-site visit (traditional group) or presentation to the local laboratory for blood draw (virtual group)
- bring the glucose meter and used and all unused IMP to the sites (traditional group) or as instructed by the study sites (virtual group)

The following will be performed at the EOT visit:

- Vital signs including BP and HR, body weight will be assessed and collected on site (traditional group) or via virtual device (virtual group)
- The questionnaires at the EOT will be performed electronically by the patients. The following questionnaires will be administered: DTSQs, DTSQc, DDS, HFS, WIWI, WPAI-SP, OSEP part 1 and 2 , and RUQ. Investigators will be asked to complete the OSES part 1 and 2 questionnaire. The PROs should be completed prior to any other procedure to ensure no impact of site-patient interaction on responses. A subset of patients will be interviewed (Section 9.2.3.2).
- Blood sampling for laboratory tests will be done at study site, local Quest laboratory, or by Homecare nurse (virtual group patients in Canada only)
- The last IMP must be injected no earlier than completion of all the EOT assessment. Patients of the traditional group will return all their used and unused IMP to the site for accountability and destruction at the EOT visit. For patients of the virtual group, Marken driver will retrieve all used and unused IMP at patients' home after the EOT visit and will return them to the site for accountability and destruction.
- IRT call will be made to register the EOT for the patient

For a complete list of procedures scheduled for this study visit please refer to the study flowchart (Section 1.2).

10.1.6 Follow-up Visit (Visit 13)

Following the last administration of IMP either as scheduled or prematurely, a post-treatment follow-up should be scheduled for all the patients in one week (+/- 2 days) after permanent discontinuation of the study treatment. This visit can be a virtual of phone call visit, or an on-site visit in case of ongoing or new AE during the post-treatment period, if needed. The patient is called by the investigator or qualified designee at scheduled time. If the call has not been performed by the investigator, the investigator has to be consulted if AE/SAE and hypoglycemic event are suspected.

During the phone call the same set of questions as listed for other telephone/virtual visits has to be asked (Section 10.1.3), except IMP-related questions.

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in patient´s file

For both patient groups, all evaluations recorded in the e-CRF must be supported by appropriately signed source documentation related but not limited to the following:

- Agreement and signature of informed consent form with the study identification; the signed electronic informed consent form will be printed from the study web portal
- Study identification (name)
- Patient number, confirmation of randomization, approach group, treatment batch number, dates and doses of study medication administration
- Medical, surgical, diabetes history, including information on :
  - Demography, inclusion and exclusion criteria
  - Last participation in a clinical trial
  - Contraception method for WOCBP
  - Previous and concomitant medication
- Dates and times of visits and assessments including examination results (vital signs, height, body weight, laboratory reports)
- For patients of the virtual group, the data transferred directly from Bluetooth devices to the study web portal will be considered as source data and will not have to be recorded in the patient file
- Insulin dose (both basal and mealtime) titration assessment and recommendation for insulin dose adjustment
- Investigator/physician notes, nursing notes, dietician’s notes
- AEs and AEs follow-up,
  - In case of SAE, the site should file in the source documents at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE
- Date of premature study discontinuation (if any) and reason.
- Patient eDiaries

A monitor will visit the sites to verify the accuracy of the source data listed above against patient’s files.

10.2.2 Source data verification requirements for screen failures

For screen failure patients, the following source data must be verified: patient's identification details, the informed consent signed by the patient, the study identification (name), dates of study visits, and the main reasons for screen failure.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the e-CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product

Temporary treatment discontinuation may be considered by the investigator because of suspected AEs. Reinitiation of treatment with the IMP 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 IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

Patients will have to document any temporary discontinuation of the IMP insulin in the diary (date/time of last injection of the IMP insulin; date/time of resuming IMP insulin injection). It is in the interest of the patient to monitor plasma glucose during the temporary discontinuation period, therefore SMPG or other regular determination of plasma glucose is to be performed and documented.

For all temporary treatment discontinuations, duration should be recorded by the investigator in the appropriate pages of the e-CRF.

Temporary treatment discontinuation decided by the investigator corresponds to more than 1 dose not administered to the patient.

10.3.2 Permanent treatment discontinuation with investigational medicinal product

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

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP 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 e-CRF.

Criteria for permanent treatment continuation include:

- At the patient's own request, eg, withdrawal of consent for treatment

- If, in the investigator's opinion, continuation with the administration of the study treatment would be detrimental to the patient's well-being, (eg, requiring treatment with insulin pump)
- Pregnancy
- Specific request of the sponsor.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients 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.

As far as possible, and after the permanent discontinuation of treatment, the patients will have a week-24 visit (on-site for traditional, remote for virtual approach group) with all assessments, except those related to IMP, performed as planned 24 weeks after randomization.

After permanent discontinuation of the IMP, patients will return to standard of care for T1DM management based on investigator and patient healthcare providers' clinical recommendation.

Since the IMP, insulin Toujeo is approved basal insulin available in the market. It can be prescribed by the physician if deemed by the Investigator as the best option to manage the diabetes.

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

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to attend the EOT visit, unless the patient withdraws consent for follow-up, the Investigator should make the best effort to recontact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited 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 patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered 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
- Alanine transaminase (ALT) >3 x upper limit normal (ULN) + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x 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

10.4.1.3 Adverse event 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. AEs of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy occurring in a female participant entered in the clinical trial.
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant is mandatory until the outcome has been determined (see Appendix A).
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic IMP count) and resulting in clinical symptoms and/or signs and considered a "significant overdose" by the Investigator.
- Reportable by Canadian sites – not applicable to other countries: unusual lack of efficacy for IMP (serious or nonserious)
  - An unusual lack of efficacy is when a health product fails to produce the expected pharmacological or therapeutic benefit and there may be an adverse outcome for the patient, including an exacerbation of the condition for which the medication is being taken. Since no health product can be expected to be effective in 100% of the patients, clinical judgment should be exercised by a qualified health care professional to determine if the problem reported is related to the product itself, rather than one of treatment selection or disease progression. One example of unusual failure in efficacy is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF (or the pre-screening log for the patients who will have consented to the study but will not be assigned a patient number, eg, because they are ineligible).
- For patients of the virtual group, any symptom will be entered by the patients in the eDiary. The investigator will be informed through the study web portal and will document the corresponding AEs in the e-CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms; if not possible, then each symptom must be reported separately as an AE (eg, nausea, headache). The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or electrocardiogram abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

Instructions for AE reporting are summarized in Table 6.

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's

identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper case report form [CRF] process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF.

For reporting unusual lack of efficacy for Canadian patients:

To be in line with Canadian Regulations, any AE that can be related to an unusual lack of efficacy (definition in Section 10.4.1.3) in the Investigator's judgment must be reported to the Sponsor in an expedited report even if a seriousness criterion hasn't been met. Consequently, as soon as the Investigator is informed by the patient of the occurrence of an AE that can be related to unusual lack of efficacy, he/she must immediately report this event on the AE page of the e-CRF. Even if the seriousness criterion has not been met, a paper copy of the SAE Complementary form and the Follow-up Information form (if needed) must still be completed:

- ENTER (within 1 working day) the information related to the unusual lack of efficacy in the appropriate screens of the e-CRF (AE screen);
- SEND (by fax) a printed copy of the AE form and a paper copy of the completed SAE Complimentary form to the representative of the Monitoring Team whose fax number appear on the Clinical Trial Protocol. Send also any photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

Instructions for AE reporting are summarized in Table 6.

Table 6 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Pregnancy	No	No	Yes
		Symptomatic overdose	Yes	No	Yes
Adverse Event of Special Interest (Canada only)		Unusual lack of efficacy of IMP, Canada only	Yes	Yes	No

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (suspected unexpected serious adverse reaction [SUSAR]), to the regulatory authorities, independent ethics committees (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.
- For Canada, Phase IV studies will follow post-marketing regulatory requirements. Reports of unusual lack of efficacy (serious or not), originating from Canada, will be submitted to the Canadian regulatory authority, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected (please refer to the "Adverse Reaction section" in the US Package Insert (USPI) for Toujeo (9). Any other AE not listed in the "Adverse Reaction" in the USPI will be considered as unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

Adverse events will be monitored until final outcome or return to patient's baseline as applicable. Follow-up information on SAEs ongoing after study completion and for which an outcome is unavailable must be reported to the Sponsor's Global Pharmacovigilance and Epidemiology department.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

A sample size of 150 patients (75 in virtual approach and 75 in traditional approach) will be randomized using a 1:1 ratio (virtual:traditional); this sample size was not powered for confirmatory testing, only descriptive statistics will be provided.

As this is a pilot study, no formal sample size calculation was performed.

Nevertheless, a precision calculation of the primary endpoint based on the 2-sided 95% confidence interval (CI) shows that the change in HbA1c from baseline in virtual approach, the change in HbA1c from baseline in traditional approach and the difference in HbA1c change between the two approaches will be estimated with a precision of approximately 0.37%, using a standard deviation (SD) of 1.1 and taking into account an up to 10% rate of non-evaluable patients for HbA1c. These calculations were made using nQuery Advisor 7.0.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all screened patients with a trial approach group allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

The total number of patients for each of the following categories will be presented.

- Screened patients
- Screen failure patients and reason for screen failure
- Randomized patients
- Safety population (Section 11.3.2) presented as treated
- The intent-to-treat (ITT) population (Section 11.3.1) analyzed as randomized
- The randomization strata (sites and screening HbA1c categories [<7.6%, ≥7.6%] assigned by IRT); the discrepancy between the strata assigned by IRT and the information reported on e-CRF will be listed for all randomized patients

- Patients who permanently discontinued the IMP, and the reasons for permanent treatment discontinuation
- Patients who completed the 24-week treatment period (patients who have attended Visit 12, who did not permanently discontinue treatment, and who did not take any rescue medication)
- Patients who did not complete the 24-week treatment period
- Patients who discontinued 24-week treatment by main reason for permanent treatment discontinuation
- Patients who completed the study (patients who have attended Visit 12, whichever the treatment duration)
- Patients who did not complete the study (patients who have not attended Visit 12)
- Patients who discontinued the study by main reason for study discontinuation

For all categories of patients except screened and screen failure patients, percentages will be calculated using the number of randomized patients as denominator for each approach group.

Patients with the following deviations will be identified and described in separate listings:

- Treated but not randomized
- Randomized but not treated
- Randomized but not treated as randomized

A list of patients prematurely discontinued from the treatment, along with reasons for discontinuation, will be provided.

11.3 ANALYSIS POPULATIONS

11.3.1 Intent-to-treat population

The ITT population will be used to analyze all non-safety endpoints. It consists of all randomized patients, irrespective of the trial approach group actually being used, analyzed according to the approach group allocated by randomization.

11.3.2 Safety population

The safety population is defined as all randomized patients who did actually receive at least one dose of IMP, regardless of the amount of IMP administered.

In the event of patients having followed a trial approach that differed from the one assigned according to the randomization schedule, the safety analyses will be conducted according to the trial approach group assigned by randomization.

Patients will not be considered exposed if there is documented evidence that patients have not taken the study drug:

- If a patient is dispensed IMP and is lost to follow-up without any documented evidence, the patient will be considered exposed and included in the safety population
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized

In addition:

- Non randomized but treated patients will not be part of the safety population, but their safety data will be presented separately

11.3.3 PRO population

The analysis of PROs will be conducted on the ITT population.

11.4 STATISTICAL METHODS

No multiplicity adjustment will be made on endpoints; 95% CIs presented for these endpoints will be calculated for descriptive purpose only.

Except if defined below, the baseline value will be the last available value prior to the first injection of IMP.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by randomized trial approach group within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

The duration of exposure during the study will be the total number of days of administration of IMP, regardless of unplanned intermittent discontinuations.

The duration of exposure to the open-label IMP during the study is defined as:

(Date of the last IMP administration – date of the first IMP administration) + 1 day.

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- up to 4 weeks
- >4 to 8 weeks
- >8 to 12 weeks
- >12 to 16 weeks
- >16 to 20 weeks

- >20 to 22 weeks
- >22 to 23 weeks
- >23 to 24 weeks
- >24 weeks

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Treatment compliance percentage will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance is <80% will be summarized.

11.4.2 Analysis of primary endpoint

Primary endpoint is described in Section 9.1.

11.4.2.1 Analysis of primary efficacy endpoint

11.4.2.1.1 Primary analysis

The change in HbA1c from baseline to Week 24 will be analyzed using available data during the 24-week randomized period. A mixed effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out via SAS PROC MIXED using an adequate contrast at Visit 12 (Week 24).

This model will be run with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least squares means estimates at Week 24 for both approach groups, as well as the differences of these estimates, with their corresponding standard errors and 95% CIs.

The model will include fixed categorical effects of trial approach group, visit, trial approach-by-visit interaction, randomization stratum of sites; and the continuous fixed covariates of baseline HbA1c value and baseline HbA1c value-by-visit interaction.

11.4.3 Analysis of secondary endpoints

11.4.3.1 Analyses of study methodology endpoints

The analysis of study methodology endpoints will be conducted on the ITT population, on the 24-week randomized period, ie, using all available post-baseline data, regardless of IMP discontinuation.

Study methodology endpoints are described in Section 9.2.1.

11.4.3.1.1 Analysis of study methodology questionnaires

For WIWI, WPAI-SP, and OSEP questionnaires a descriptive summary will be provided for each approach group at each applicable visit (baseline and/or Week 24) and, if applicable, change from baseline to Week 24, including:

- WIWI scores for each item
- WPAI-SP: item scores, and combined scores (Section 9.2.1.2)
- OSEP: each item score

For RUQ, descriptive summary will be provided for each approach group at baseline and for each applicable on-treatment visit on the following items:

- Total number of visits (overall and per healthcare professional type)
- Total money spent
- Total time spent

In addition, the total and average resource utilization per patient will be calculated on all on-treatment questionnaires. The change between baseline and this on-treatment average will be calculated.

The change in WPAI-SP and OSEP part 1 (perceptions of diabetes control) scores from baseline to Week 24 will be analyzed using an ANCOVA. This model will include fixed categorical effects of approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites as well as continuous fixed covariates of corresponding baseline score. WIWI and OSEP part 2 scores (measured only at Week 24) will be compared between approach groups using an ANOVA. This model will include fixed categorical effects of approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites.

11.4.3.1.2 Analysis of compliance with IMP

See Section 11.4.1.1.

11.4.3.1.3 Analysis of compliance with key study activities

For the **number of times the patient used the Bluetooth devices** and the **number of times the patient completed blood draw visit** in accordance with the study instructions from baseline to Week 24, only descriptive statistics will be calculated including the number of available data, mean, SD, median, minimum, and maximum. These endpoints will be calculated only for the virtual group.

For **patient withdrawal** from baseline to Week 24, Kaplan-Meier plots/estimates of the cumulative incidence of study discontinuation due to any reason will be provided. Time to study discontinuation is defined as the number of days from Day 1 until the day of study

discontinuation. All completers are considered as censored observations. The censoring time is the number of days from the randomization date until the last visit date.

11.4.3.2 Analyses of diabetes control endpoints

The analysis of diabetes control endpoints will be conducted on the ITT population on the 24-week randomized period, ie, using all available post-baseline data, regardless of IMP discontinuation.

Diabetes control endpoints are described in Section 9.2.2.

11.4.3.2.1 Analysis of diabetes control PROs

For each questionnaire a descriptive summary at each applicable visit (baseline and/or Week 24) and change from baseline to Week 24 will be provided, including:

- DTSQs and DTSQc subscale scores (total treatment satisfaction, perceived frequency of hyperglycemia, and perceived frequency of hypoglycemia, see Section 9.2.2.1)
- HFS-II total score and subscale scores (HFS-B and HFS-W)
- DDS: total score, subscales scores, distress category for total and subscales (Section 9.2.2.1)

The change in DTSQs, HFS-II, and DDS scores from baseline to Week 24 will be analyzed using an ANCOVA. This model will include fixed categorical effects of approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites as well as continuous fixed covariates of corresponding baseline score.

Average scores at Week 24 in total treatment satisfaction score, hyperglycemia perception, and hypoglycemia perception score from DTSQc will be analyzed using an ANCOVA model. This model will include fixed categorical effects of approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites as well as continuous fixed covariates of corresponding baseline score from DTSQs.

11.4.3.2.2 Analysis of glycemic endpoints

The following endpoints will be analyzed using available data during the 24-week treatment period. A mixed effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out via SAS PROC MIXED using an adequate contrast at Visit 12 (Week 24).

This model will be run with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least squares means estimates at Week 24 for both approach groups, as well as the differences of these estimates, with their corresponding standard errors and 95% CIs.

- HbA1c (%): change from baseline to Week 16
- FPG: change from baseline to Week 16 and Week 24
- Change in 7-point SMPG profiles per time-point from baseline to Week 16 and Week 24

For HbA1c endpoint, the model will include fixed categorical effects of trial approach group, visit, trial approach-by-visit interaction, randomization stratum of sites, as well as, the continuous fixed covariates of baseline HbA1c value and baseline HbA1c value-by-visit interaction.

For FPG and 7-Point SMPG endpoints, the model will include fixed categorical effects of trial approach group, visit, trial approach-by-visit interaction, randomization stratum of sites, randomization stratum of HbA1c (7.6 % and ≥7.6%), the continuous fixed covariates of the corresponding baseline value, and baseline value-by-visit interaction.

11.4.3.3 Analyses of patient care endpoints

The analysis of patient care endpoints will be conducted on the ITT population on the 24-week randomized period, ie, using all available post-baseline data, regardless of IMP discontinuation

Patient care endpoints are described in Section 9.2.3.

11.4.3.3.1 Analysis of investigator questionnaires

For OSES (Section 9.2.3.1) a descriptive summary will be provided for each approach group at each applicable visit.

For OSES part 1 (study-specific resource requirements), a descriptive summary will be provided for each approach group at each applicable visit, and a total time will be calculated for each patient and averaged within each approach group. Overall Study Experience-Sites part 1 scores will be compared between approach groups using an ANCOVA. This model will include fixed categorical effects of approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites as well as continuous fixed covariates of corresponding baseline score.

For OSES part 2 (relationship and satisfaction), a descriptive summary will be provided for each item for each approach group at Week 24. Item scores will be compared between approach groups using an ANOVA. This model will include fixed categorical effects of approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites.

11.4.3.3.2 Analysis of patient interviews

Exit interviews with a subset of patient from the virtual group is described in Section 9.2.3.2. Data will be analyzed via an expert qualitative research analysis group using standardized qualitative methods (eg, thematic analysis, grounded theory). A specific Statistical Analysis Plan and report will be developed for the exit interviews.

11.4.3.4 Analyses of safety endpoints

Safety endpoints are described in Section 9.2.4.

The summary of safety results will be presented by approach group.

All safety analyses will be performed on the safety population, on the on-treatment period, defined as the time from first IMP injection up to 2 days after the last IMP injection.

The baseline value for safety endpoints will be the last available value prior to the first injection of IMP.

11.4.3.4.1 Hypoglycemia

The number and incidence of patients experiencing at least 1 hypoglycemic event will be presented per trial approach group and type of hypoglycemic event (Section 9.2.4.4) according to time of occurrence (nocturnal [ie, 00:00 to 05:59, by sleep status], any time of the day) during the treatment period. The Odds Ratio and its corresponding 95% CI of virtual group over traditional group for each hypoglycemic event will be estimated by a logistic regression model adjusted on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites. This model will also estimate the Odds Ratio of virtual group and traditional group and its corresponding 95% CI.

The number and rate of hypoglycemic events (in patient-year of exposure) will be determined per trial approach group and type of hypoglycemic event (Section 9.2.4.4), according to time of occurrence (nocturnal [ie, 00:00 to 05:59, by sleep status], any time of the day) during the on treatment period. For each hypoglycemic event, the rate ratio, and its corresponding 95% CI, of virtual group over traditional group will be estimated using an over-dispersed Poisson regression model adjusted on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of site.

11.4.3.4.2 Adverse events

All AEs will be coded to a preferred term (PT), high level group term (HLGT), high level term (HLT), and associated primary system organ class (SOC) using the version of medical dictionary for regulatory activities (MedDRA) currently in use by the sponsor at the time of database lock.

Adverse event incidence tables will present by SOC (sorted by internationally agreed order), HLGT, HLT, and PT sorted in alphabetical order, and for each approach group, the number (n) and percentage (%) of patients experiencing at least one AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment period. The denominator for computation of percentages is the safety population within approach group.

Adverse event incidence table will be provided by study conduct approach group for all types of TEAEs: all TEAEs, all treatment emergent SAEs, all TEAEs leading to permanent treatment discontinuation and all TEAEs related to local tolerability at injection site and hypersensitivity.

Death

The following deaths summaries will be generated on the safety population:

- Number (%) of patients who died by study period (TEAE, on-study, poststudy) and reasons for death summarized by allocated approach group
- Death in nonrandomized patients or randomized and not treated patients
- TEAE leading to death by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT

Post-study deaths, if presented, will follow safety guideline instruction.

Injection site reaction and hypersensitivity reaction

Number (%) of patients with events related to injection site reactions or hypersensitivity reaction will be provided separately.

Adverse event of special interest

A listing of patients with symptomatic overdose with IMP/NIMP will be provided separately.

Patients with an SAE or AESI should be followed until resolution, stabilization, or death as appropriate.

Product technical complain

Information regarding PTC will be described.

11.4.3.4.3 Vital signs and physical examination

The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for vital signs

Potentially clinically significant abnormality criteria will determine which patients had at least one PCSA during the TEAE period, taking into account all evaluations performed during the on-treatment TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage during the TEAE on-treatment period

The incidence of PCSAs at any time during the TEAE period will be summarized by approach group whatever the baseline level and according to baseline status.

11.5 INTERIM ANALYSIS

Not applicable

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

Before accessing to the study web portal, potential participants to the study will have to agree with the General Terms of Use of the portal.

Electronic consent is described in Section 10.1.1.

The patients will be fully informed of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form should be electronically signed, name filled in and dated by the patient or by the patient's legally acceptable representative. A paper version of the signed electronic consent form will be printed twice for giving a copy to the patient and filing in the investigator study file. The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, labeling documents [summary of product

characteristics, package insert], Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the labeling information will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data. Source document requirements

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional

secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the CV describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database and the study web portal database, shall be treated in compliance with all applicable laws and regulations
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio
- Patient enrollment is unsatisfactory
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon
- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP
- The total number of patients are included earlier than expected

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be recollected if necessary.

16 BIBLIOGRAPHIC REFERENCES

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17 APPENDICES

Appendix A Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy.
2. Postmenopausal
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Since glycemic control may be unstable and insulin doses may be variable during the study, female patients must not be breast feeding or pregnant (as confirmed by serum pregnancy test) at the time of study entry and must agree to undergo urine pregnancy testing at onsite visits as indicated in the study flow chart (Section 1.2). All WOCBP must be fully informed about the requirement to prevent pregnancy while in this study. Sexually active WOCBP must agree to use a reliable medically accepted contraceptive method throughout the study.

Reliable contraception regimens are defined for this protocol as:

- True abstinence: when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, post ovulation methods] and withdrawal are not acceptable methods of contraception). Non-sexually active WOCBP participating to this study before becoming sexually active must also agree that they will use acceptable contraception method.

- Highly effective oral contraceptives, such as biphasic and triphasic oral contraceptives are considered adequate. Progestogen only pills or “mini pills” which have demonstrated high efficacy will be acceptable.
- Injectable hormones (ie, Depo-Provera), hormonal implants, transdermal patches, intrauterine devices, intrauterine systems, or an intravaginal ring (NuvaRing) which have demonstrated efficacy comparable to high efficacy oral contraceptives are adequate.
- Female patients having a sterilized permanent partner; before becoming sexually active with another partner, such patients must also agree to use an acceptable contraceptive method.

Local additional requirements must be followed.

If during the study, a female patient becomes pregnant (Section 10.4.1.3) or decides to attempt to become pregnant, then she must contact the Investigator immediately and the IMP will be withdrawn and exchanged by an approved basal insulin. The study IMP will also be withdrawn and exchanged by an approved basal insulin if a female patient undertakes behavior deemed by the investigator to be at risk of getting pregnant.

COLLECTION OF PREGNANCY INFORMATION

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- Pregnancy is considered to be an AESI. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Section 10.4.4. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Appendix B [redacted]

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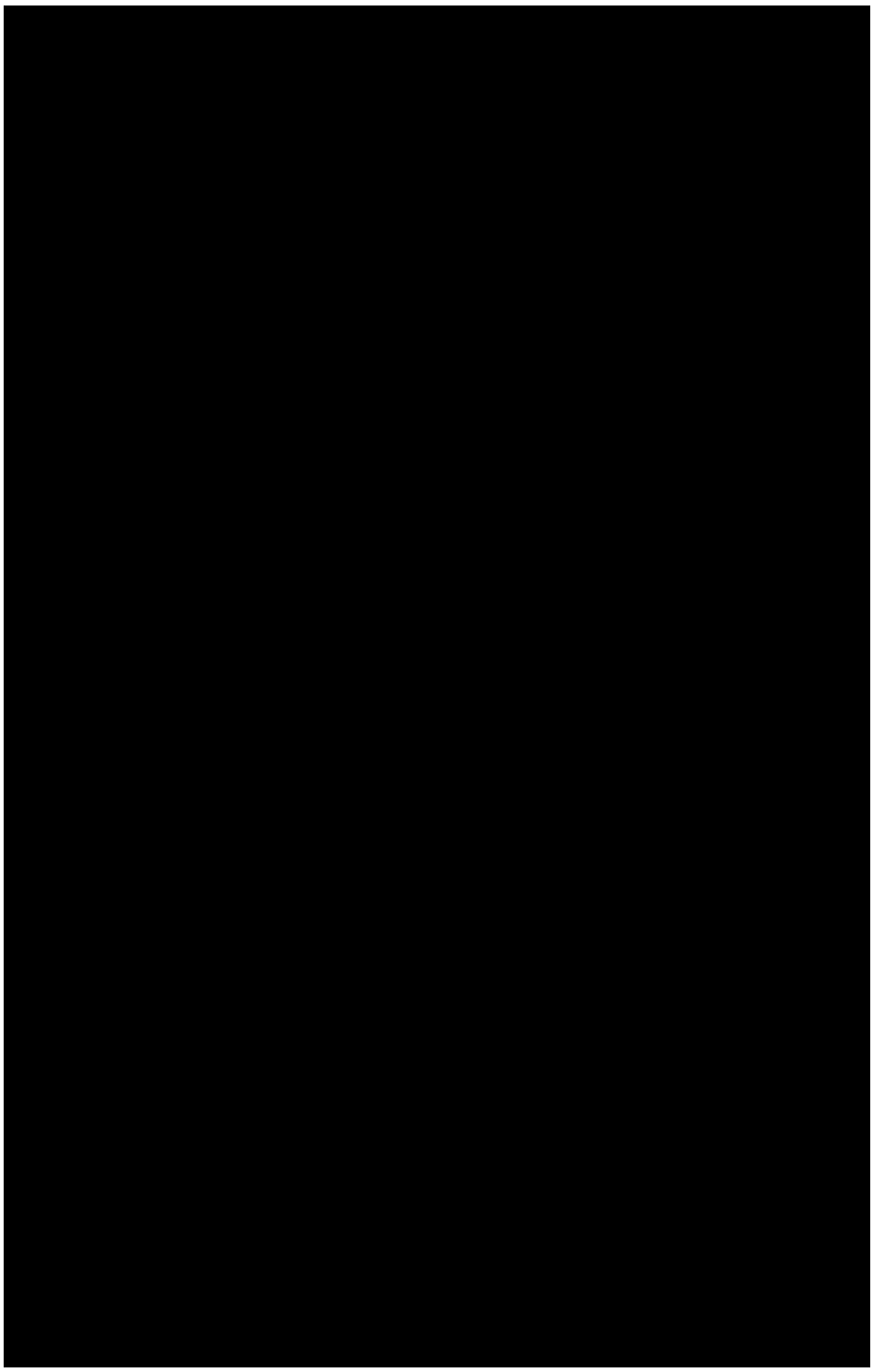

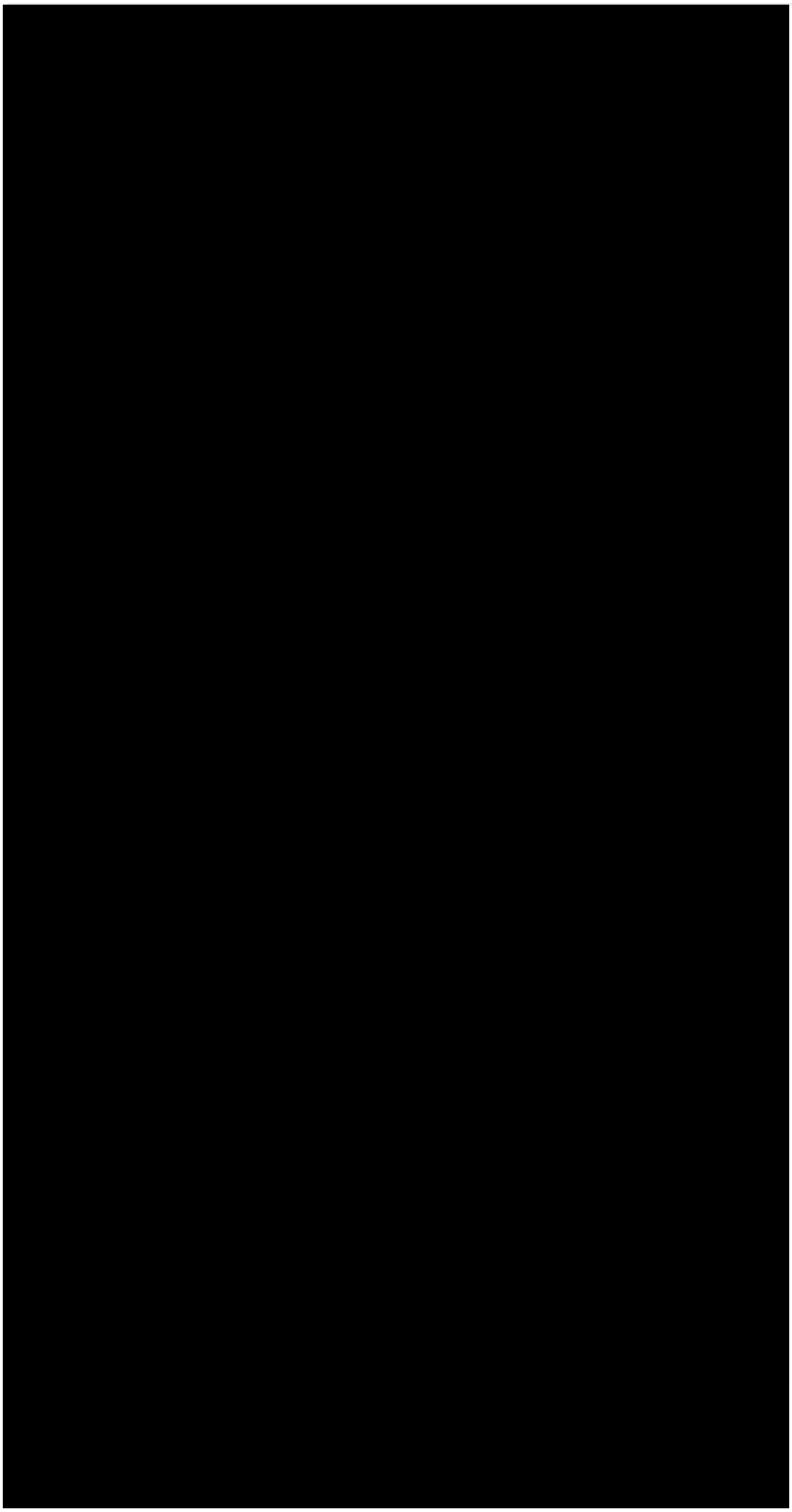

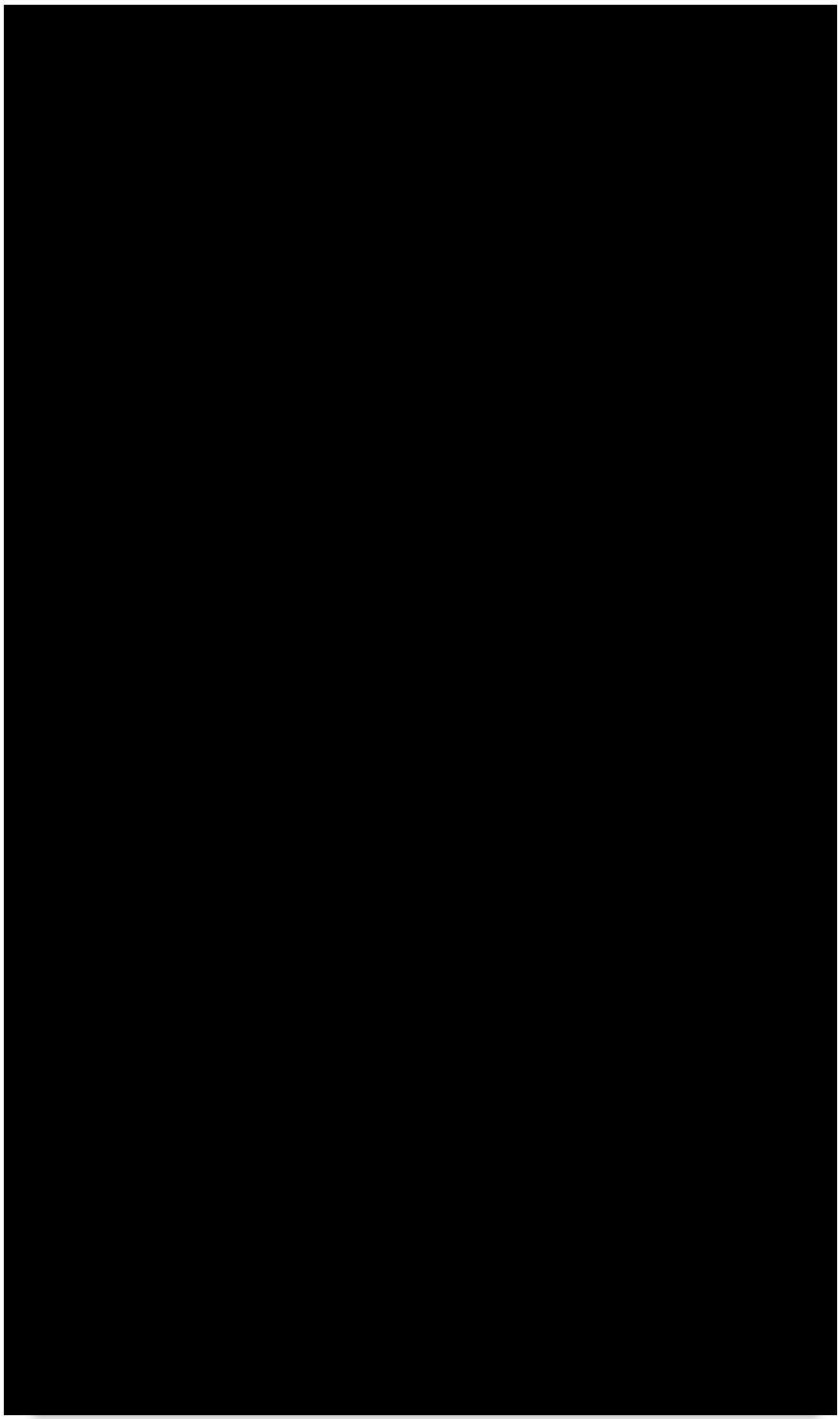

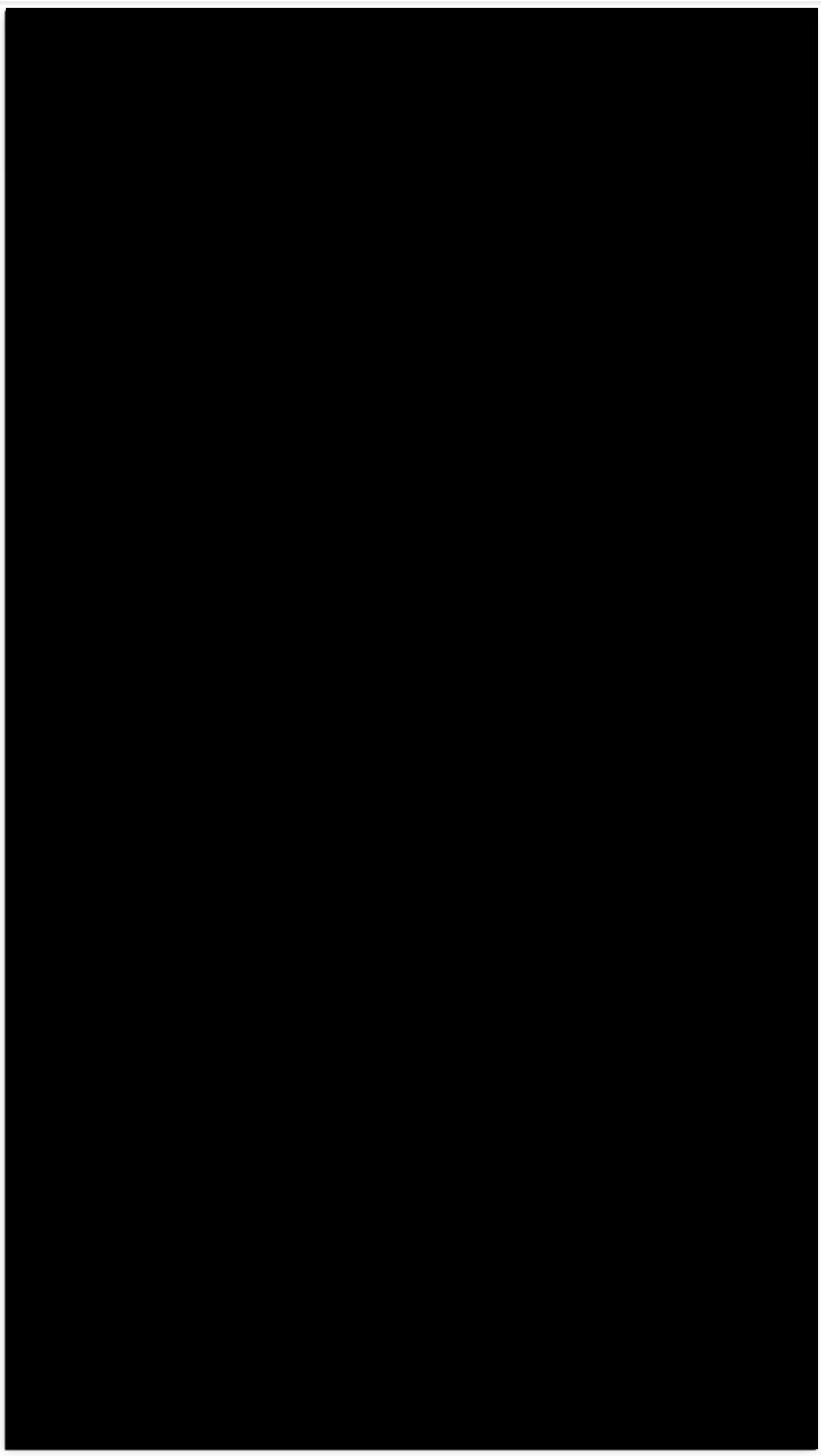

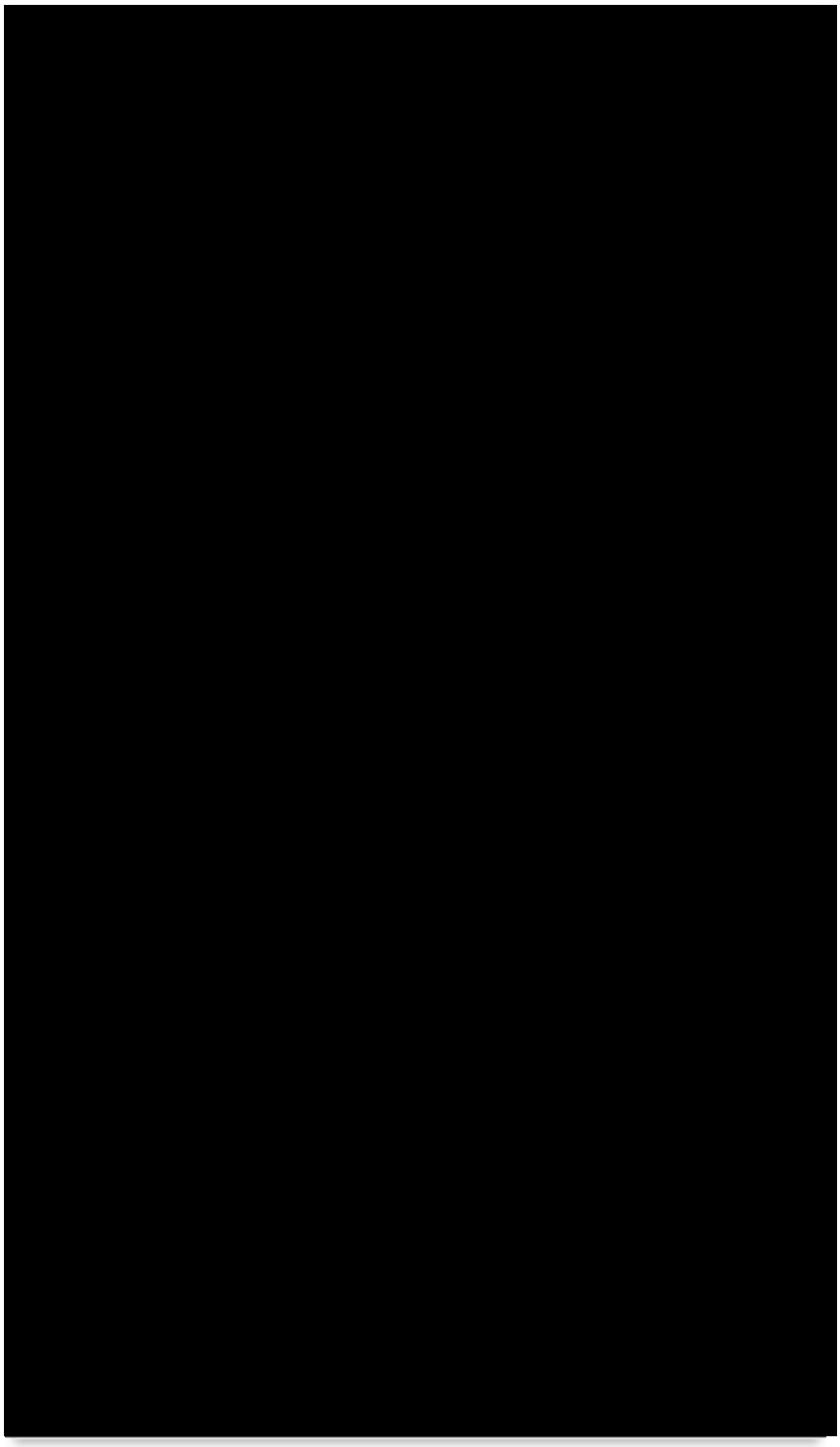

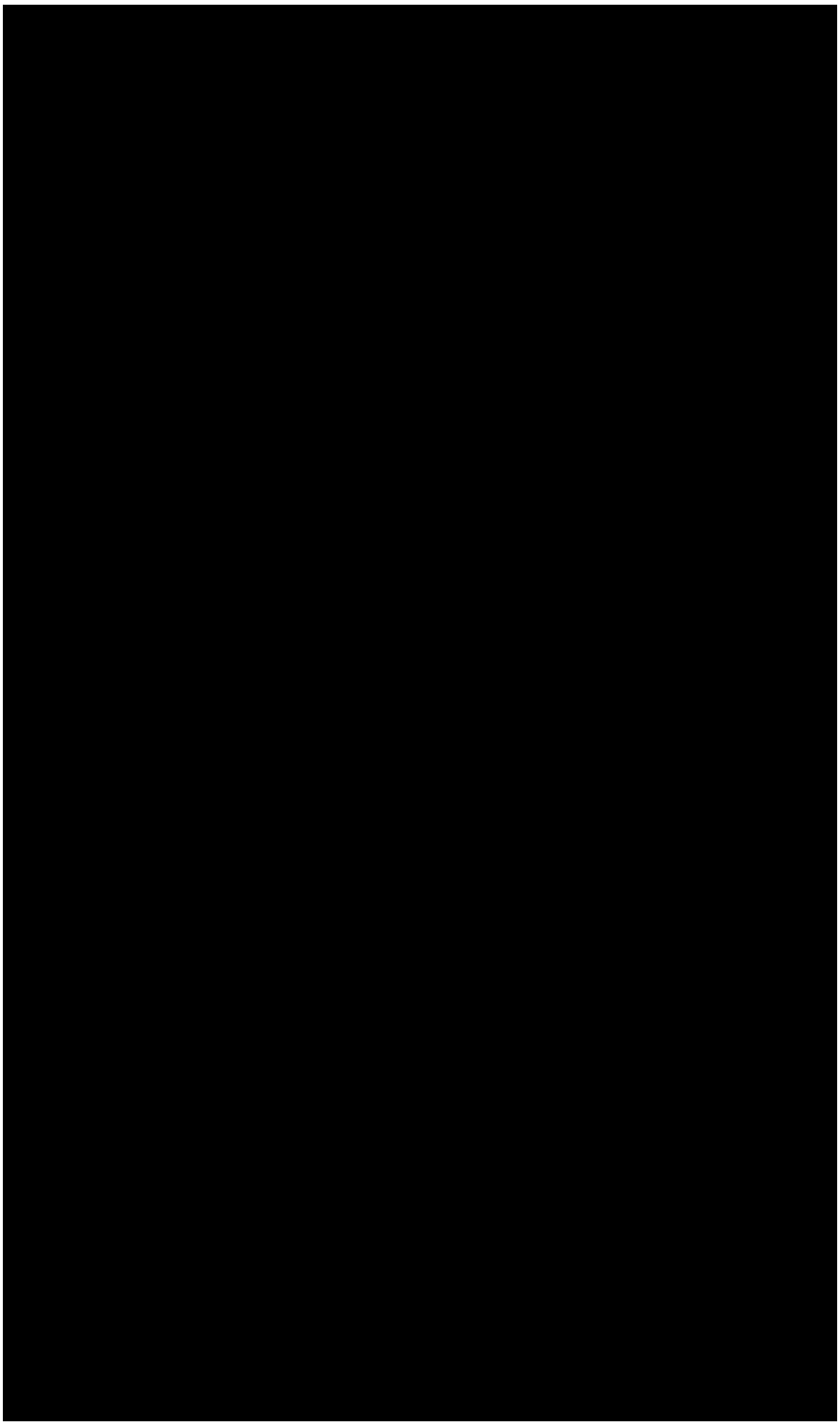

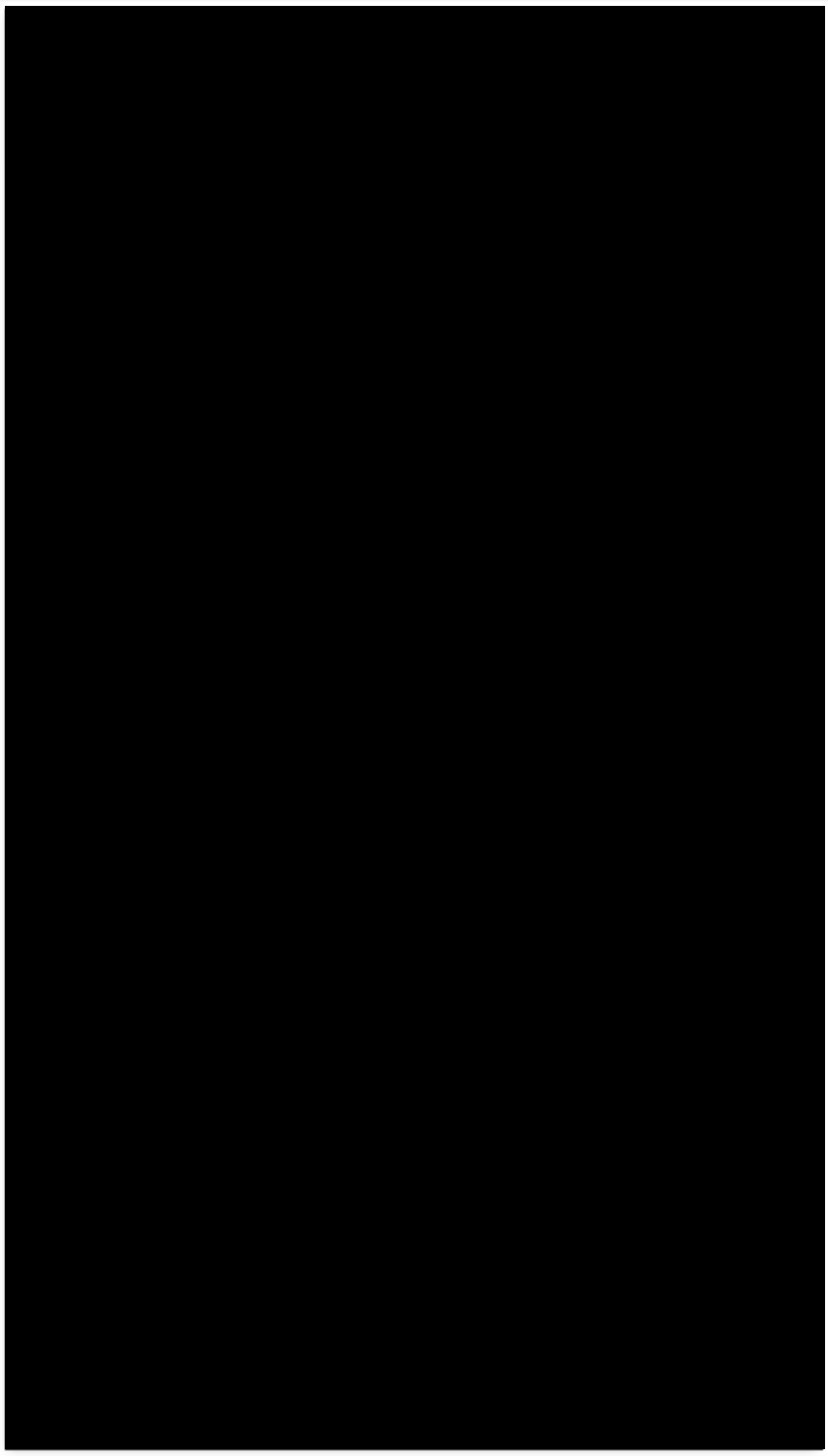

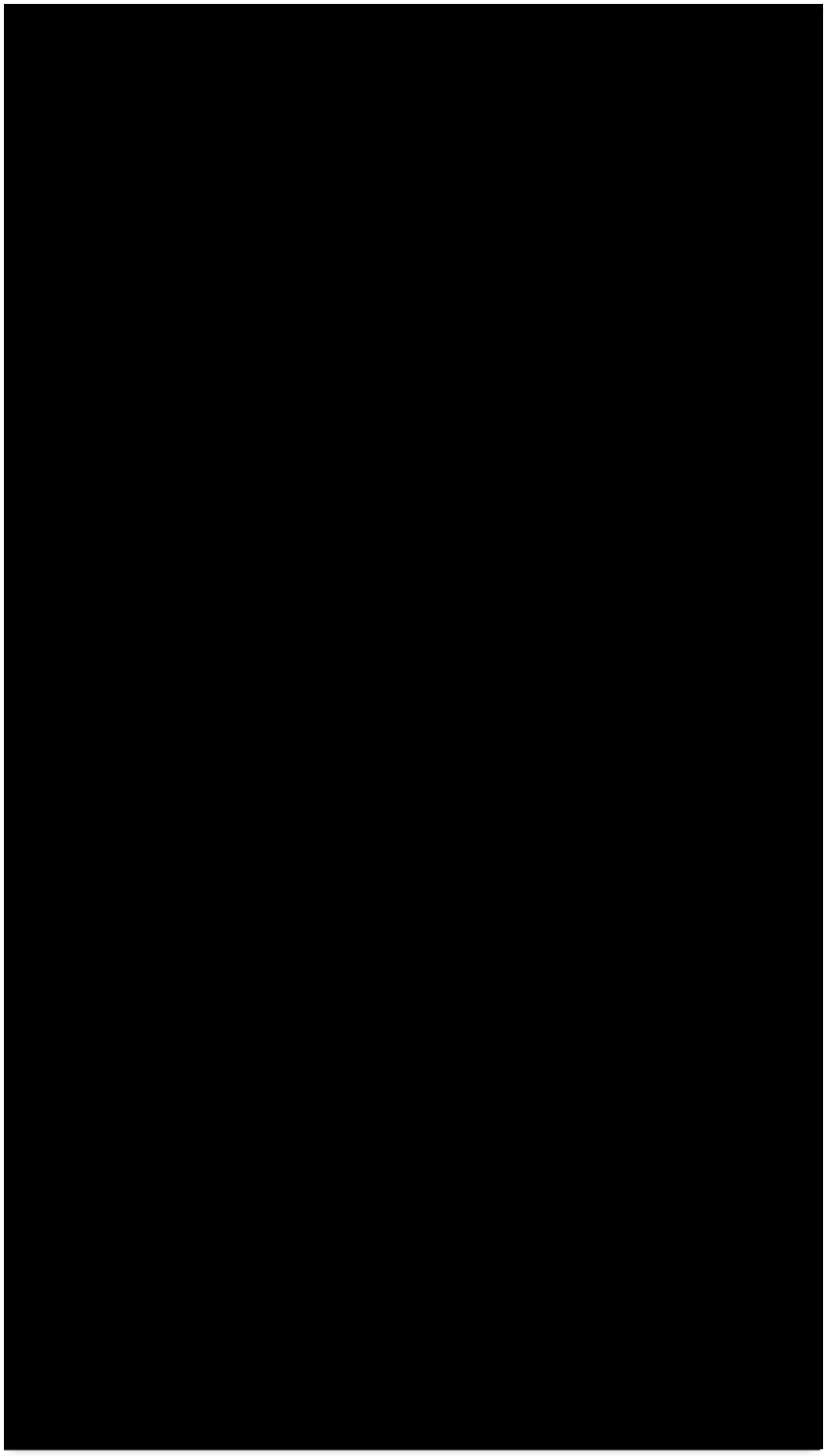

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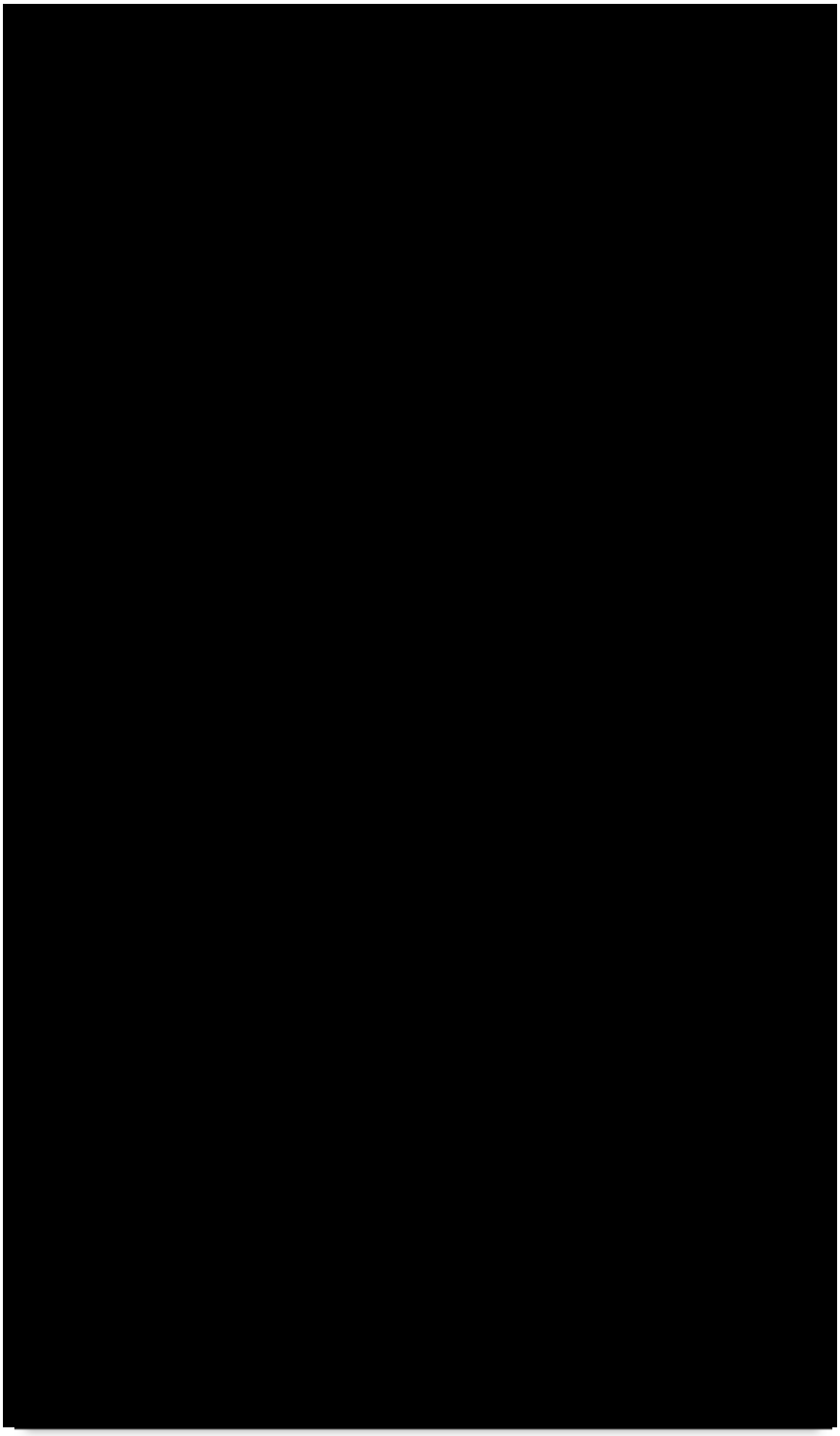

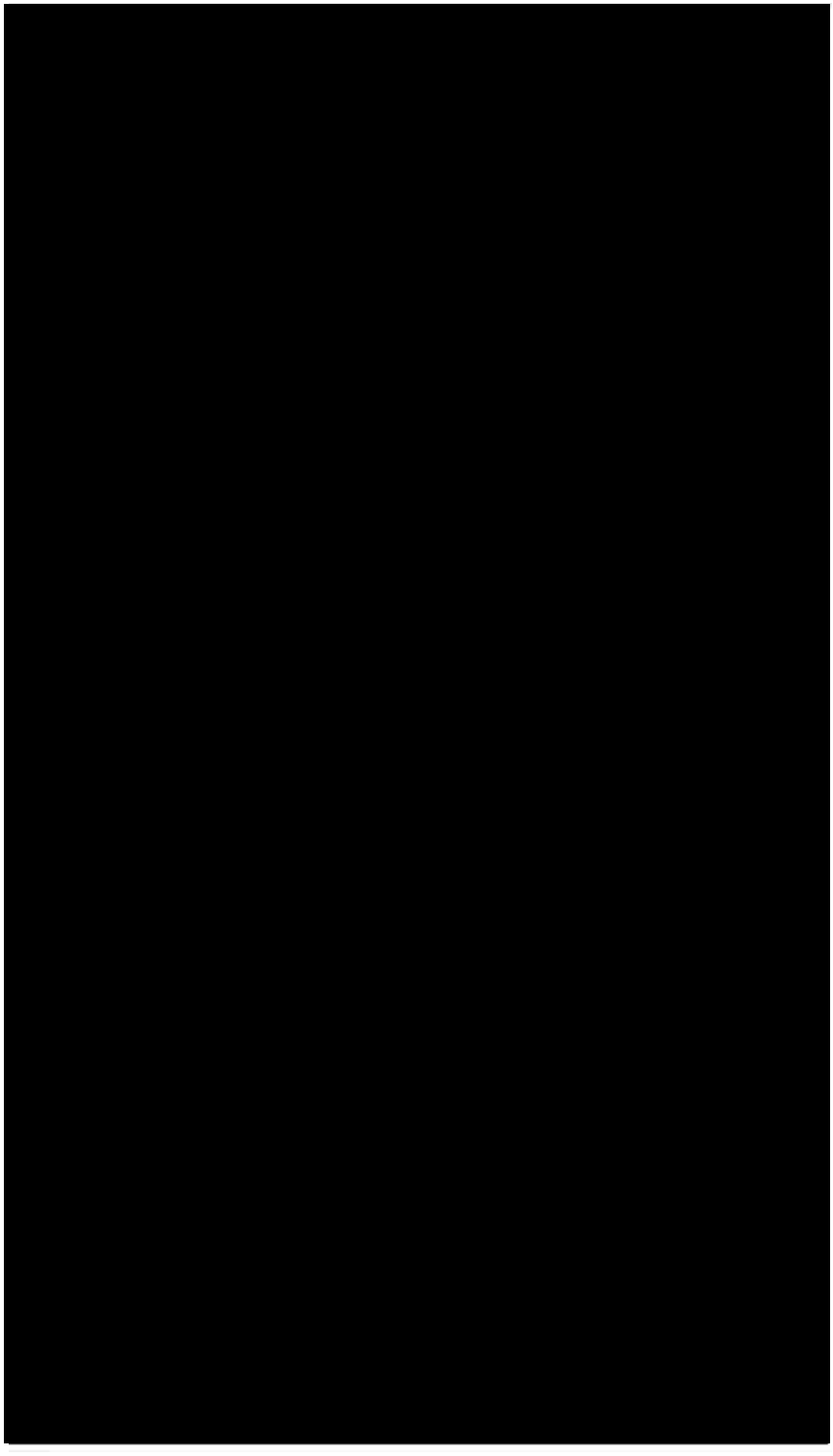

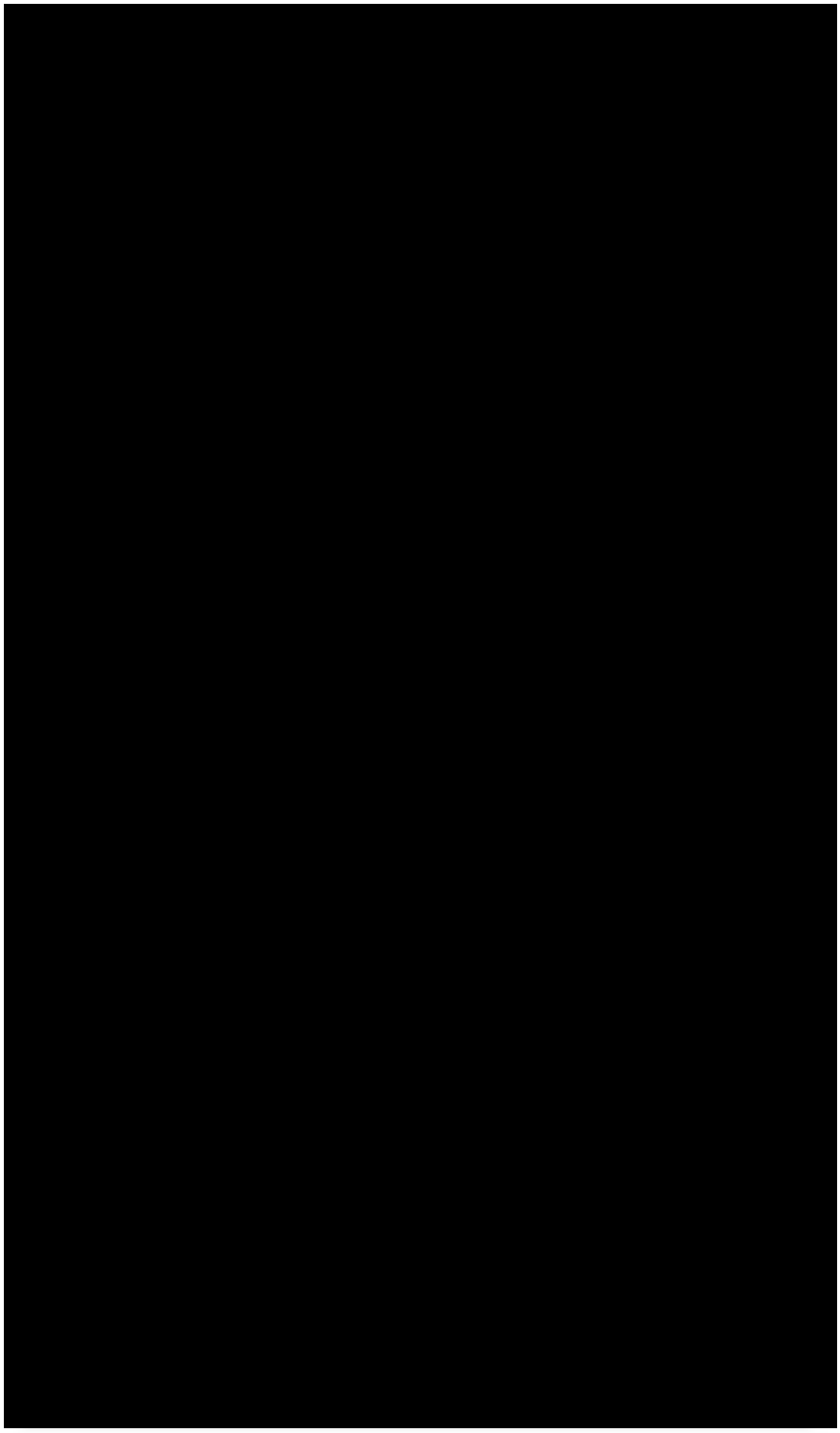

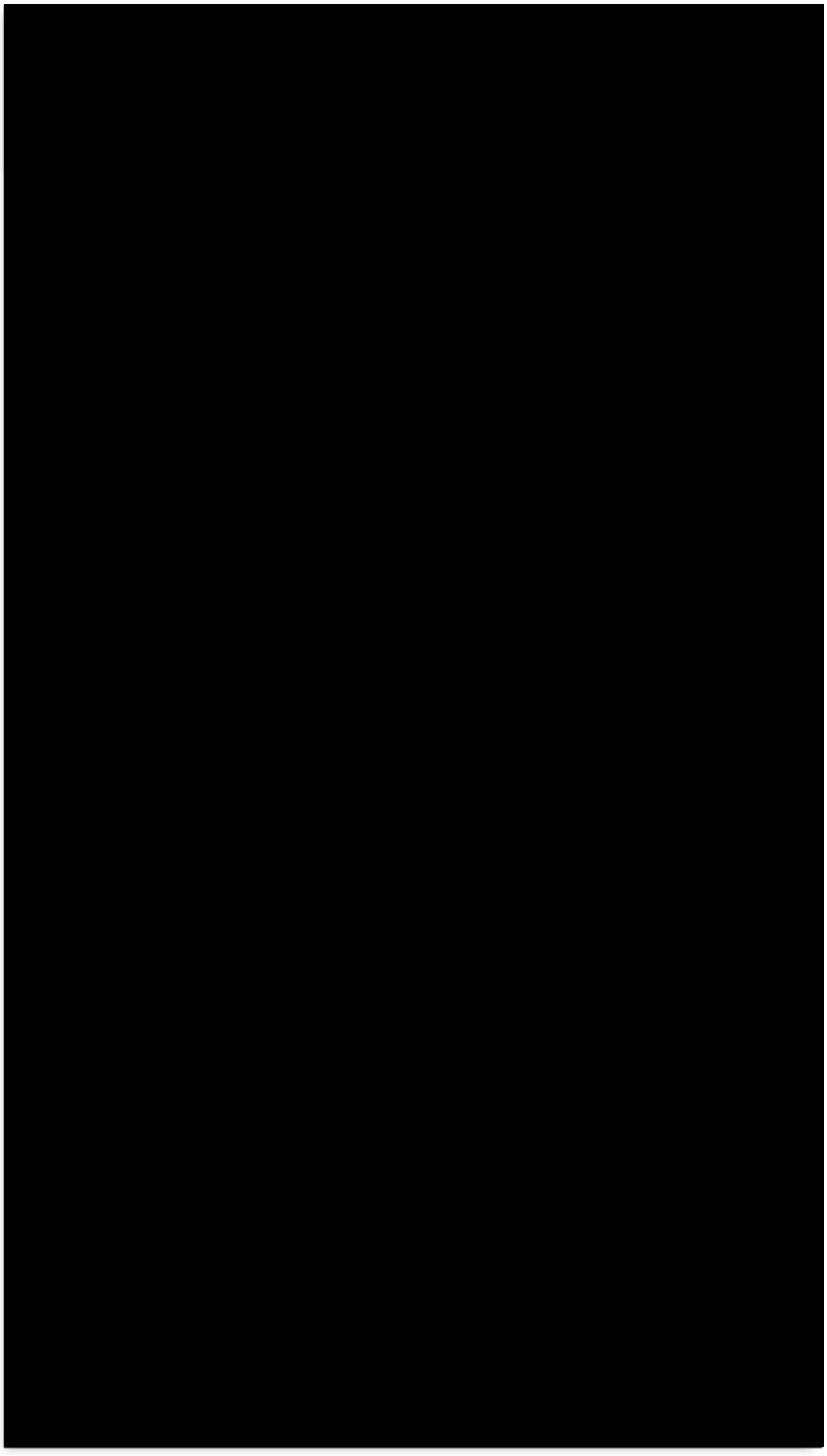

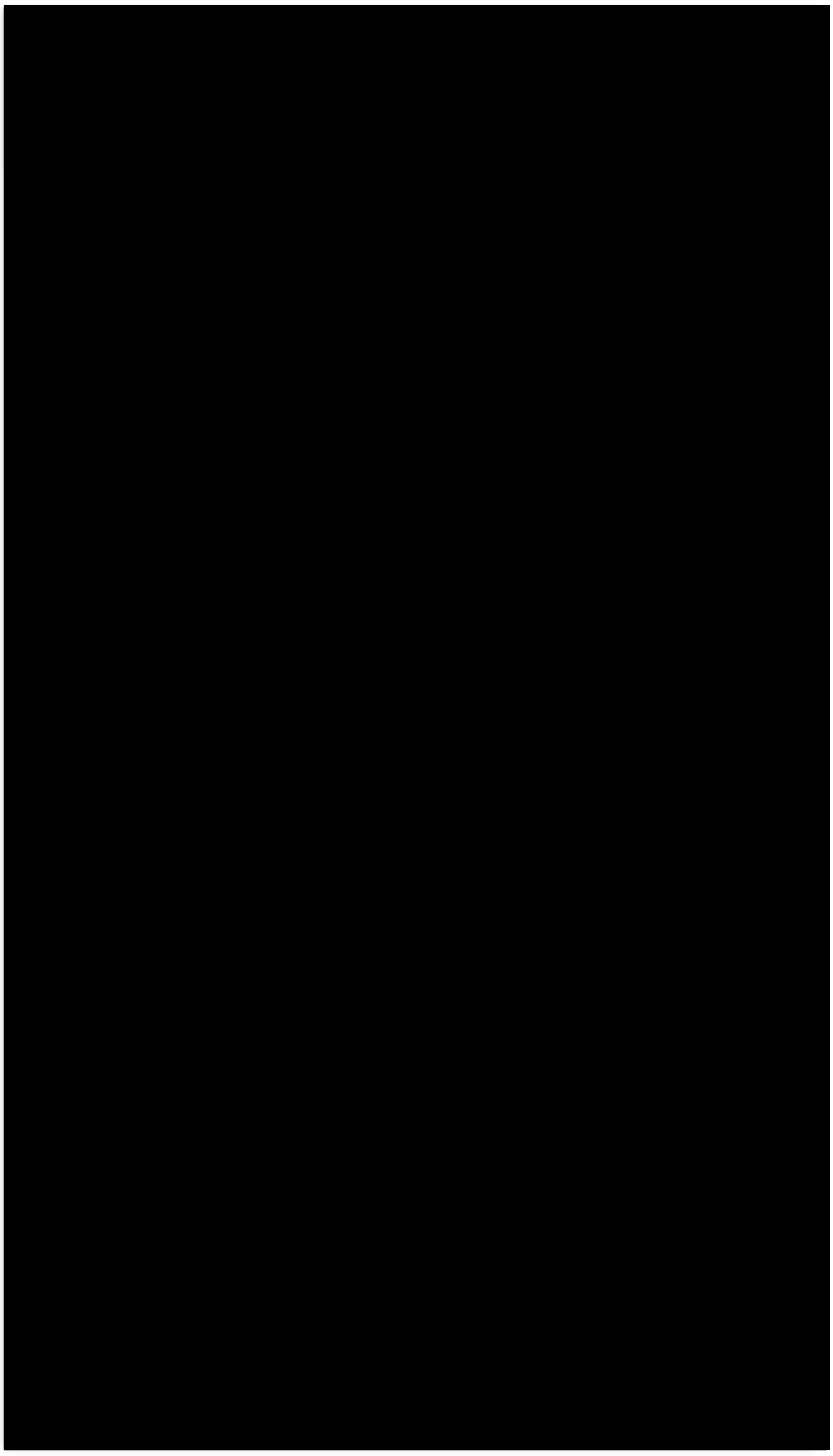

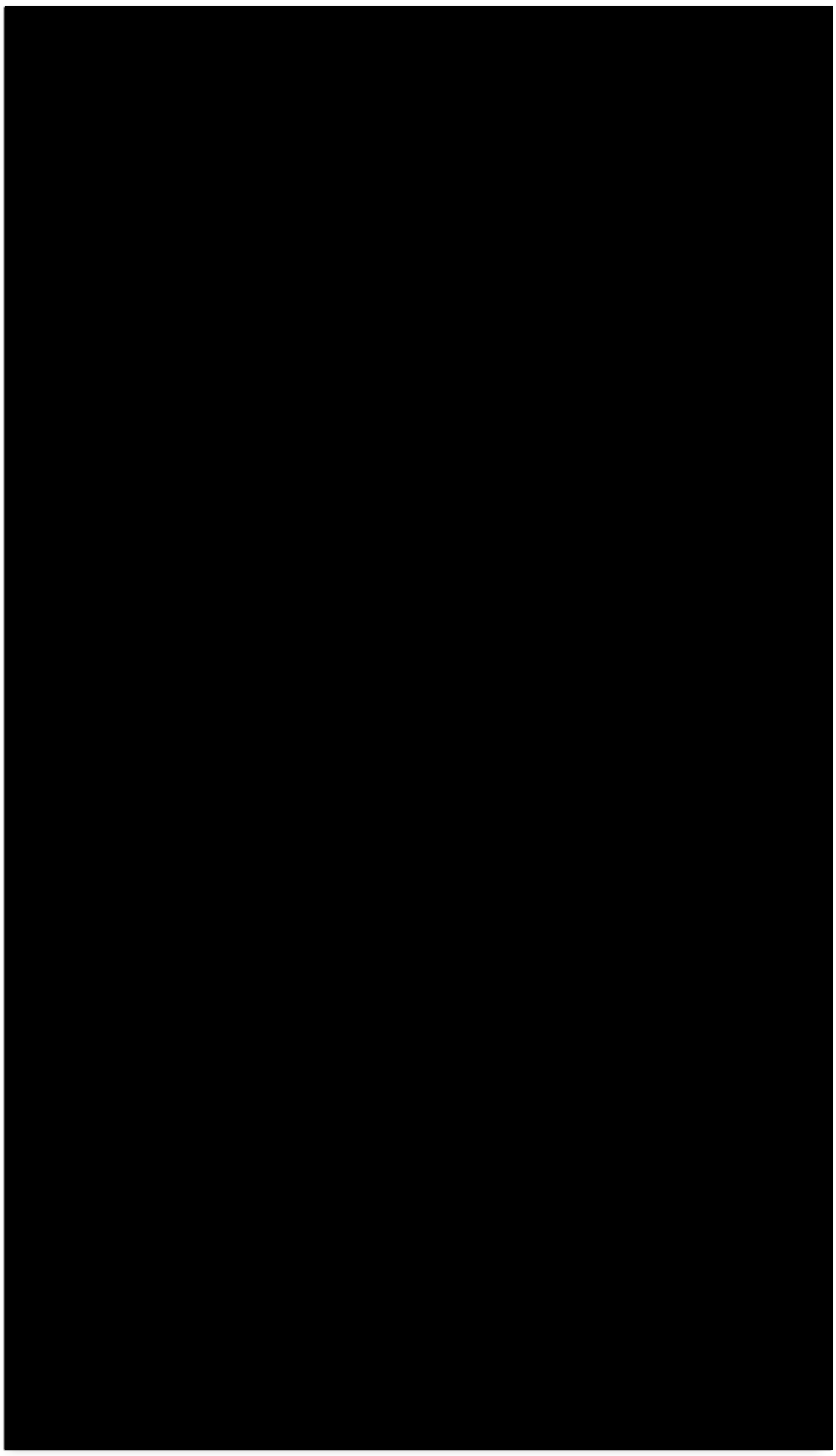

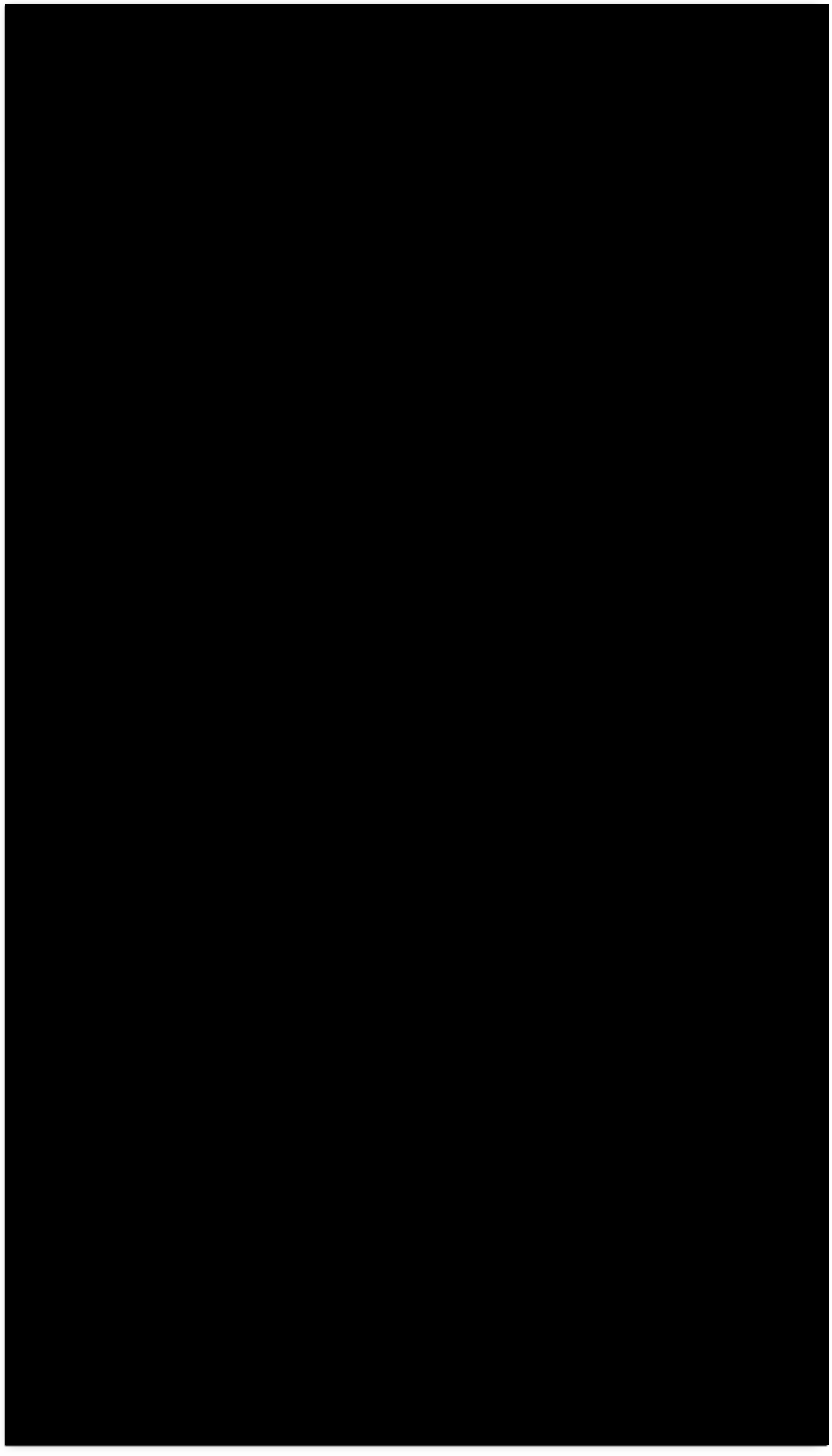

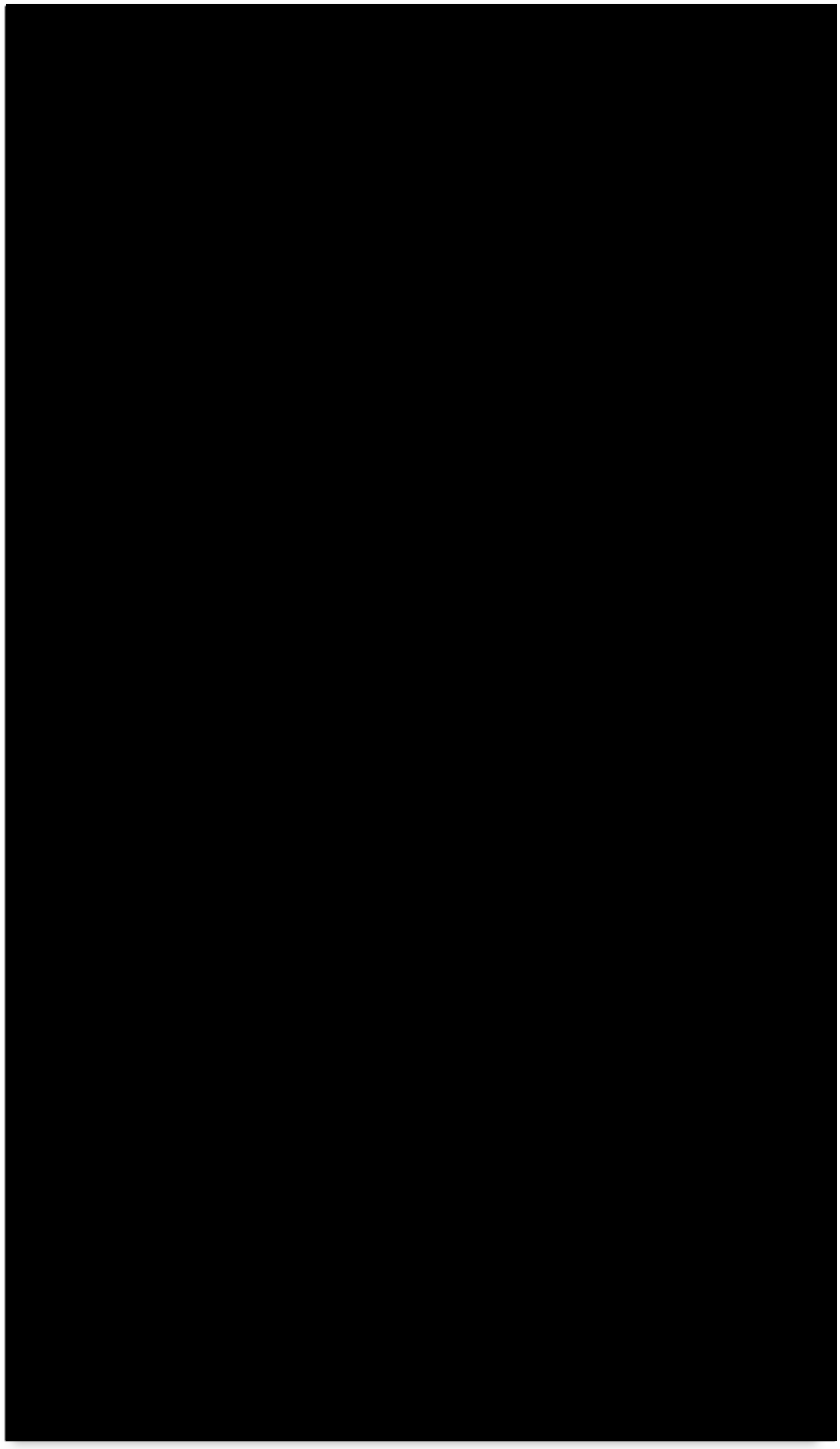

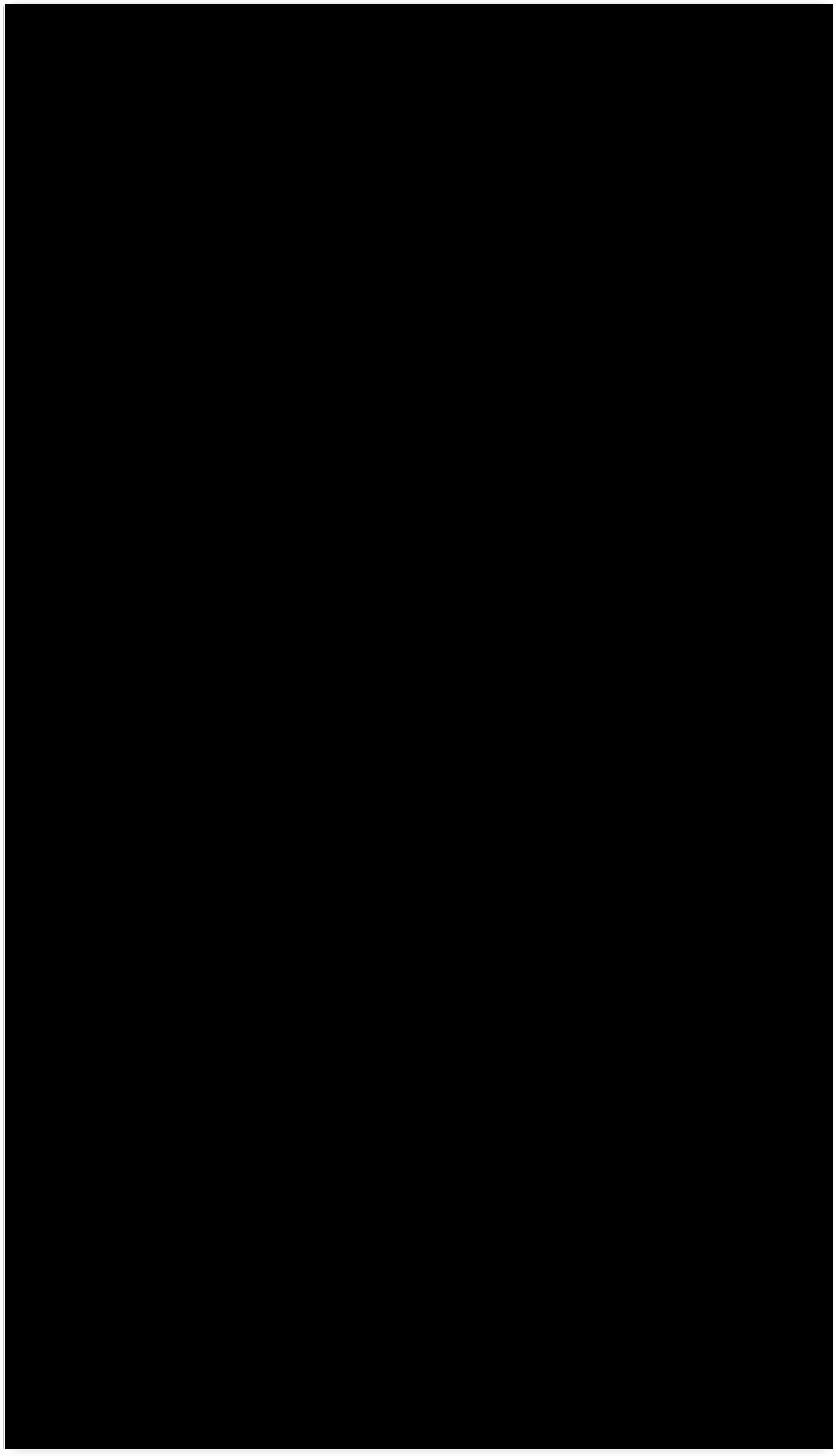

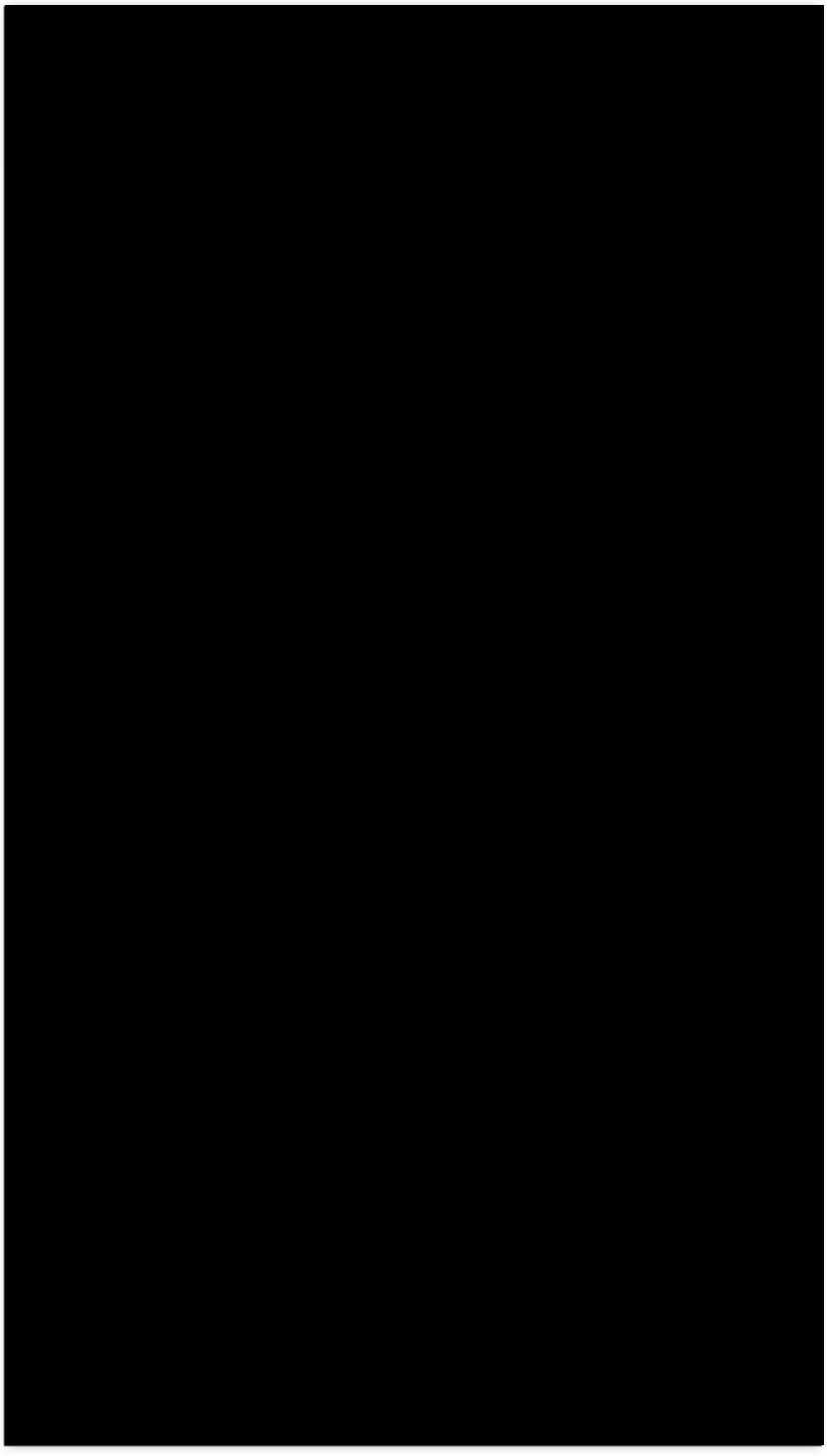

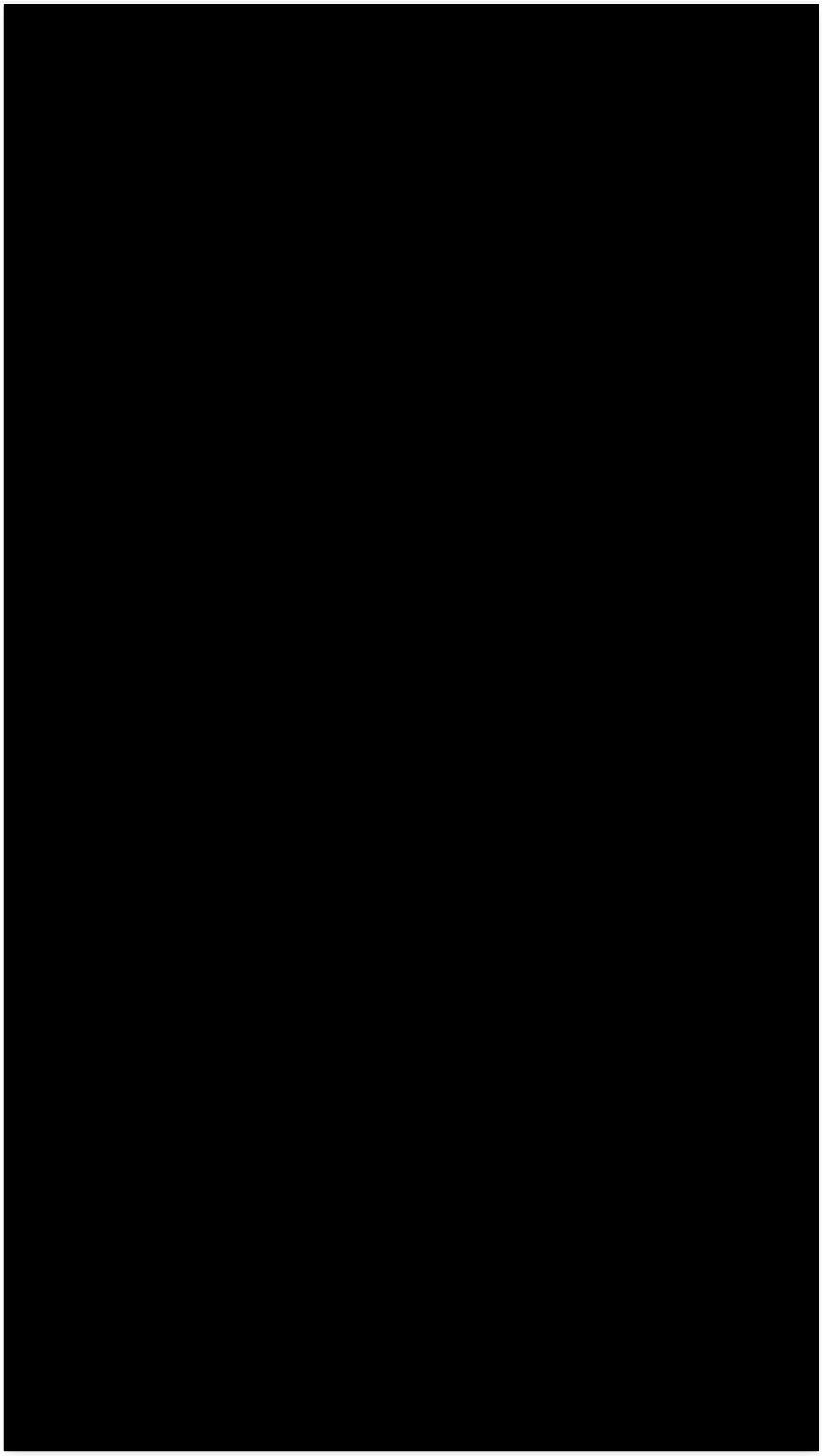

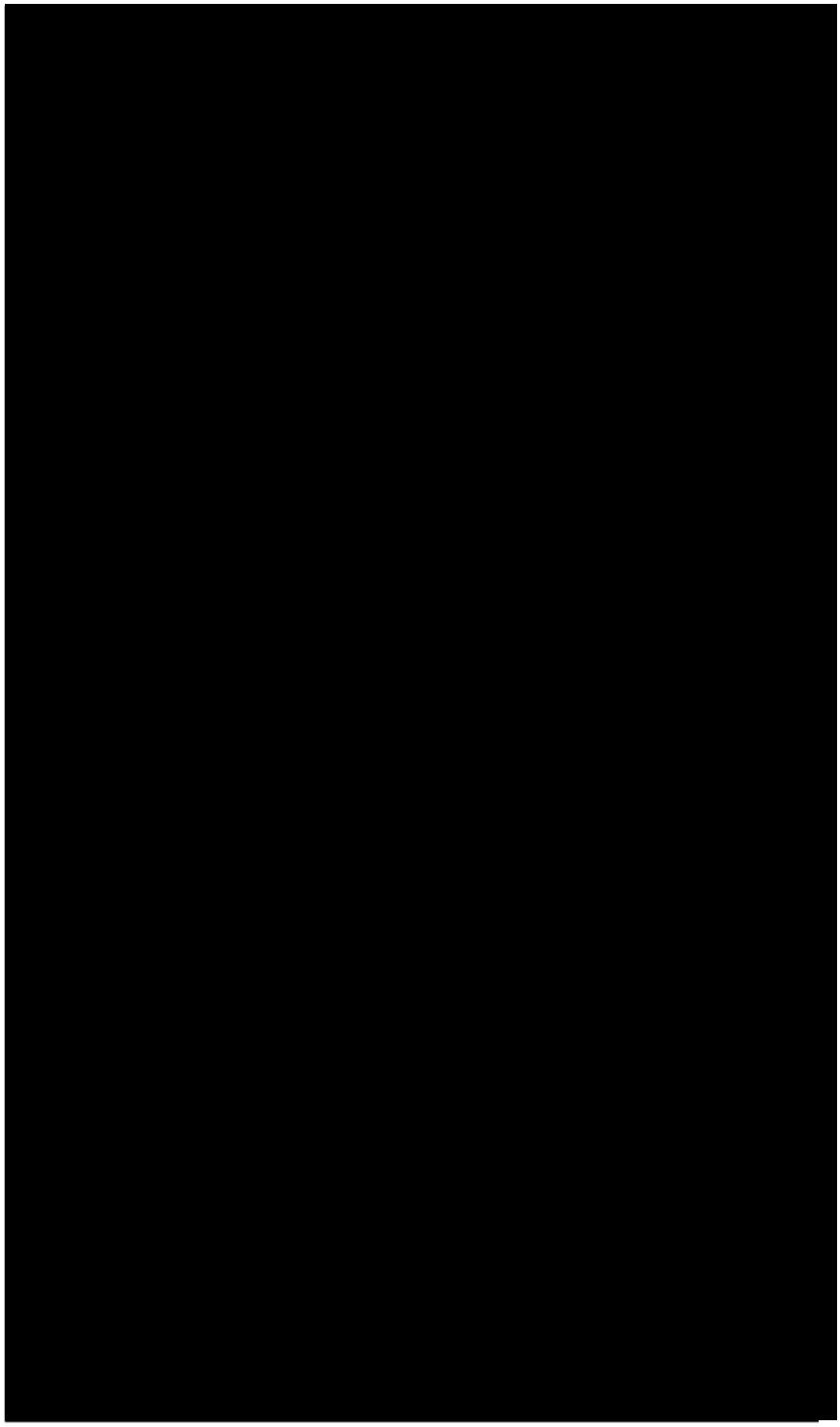

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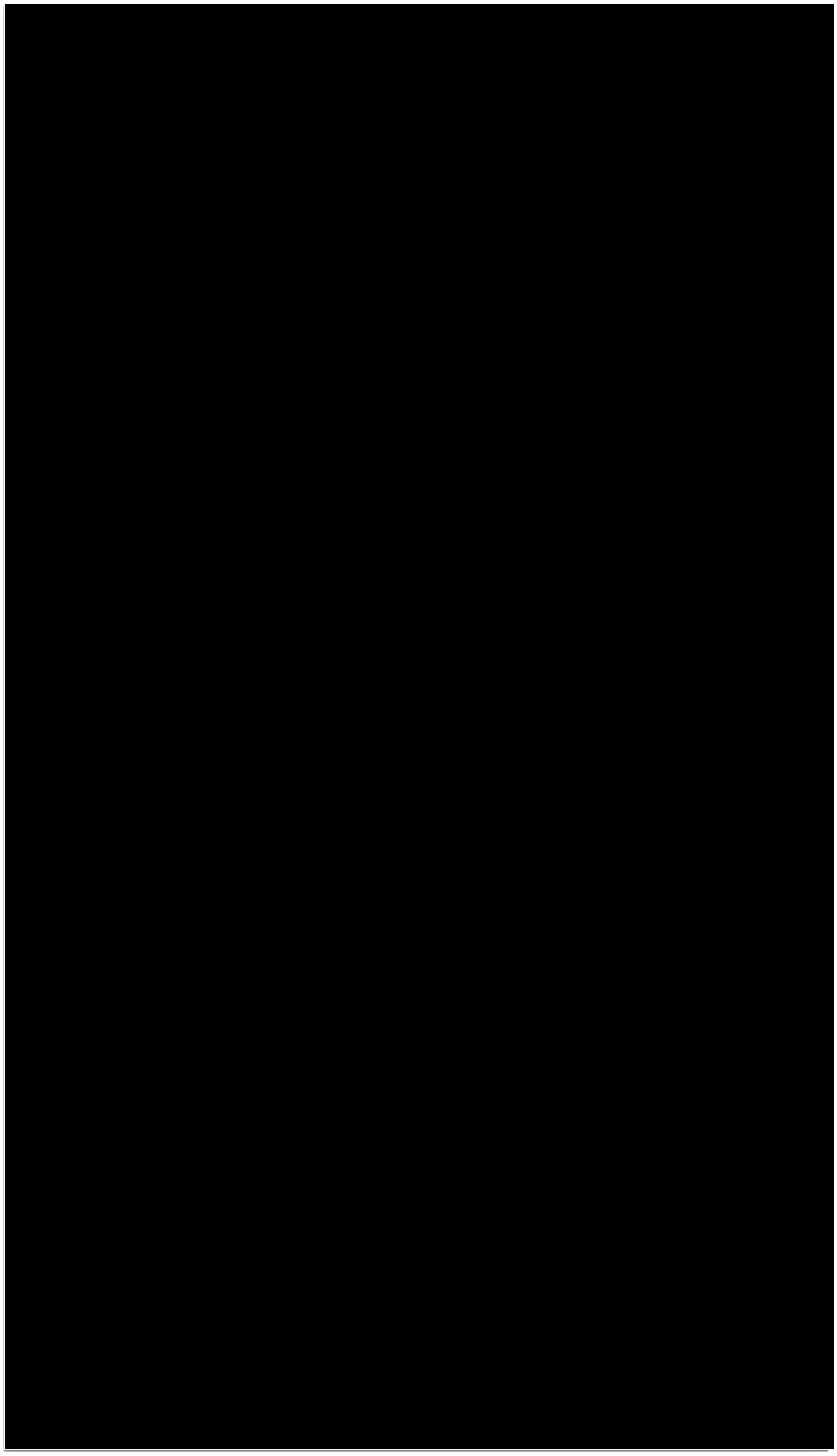

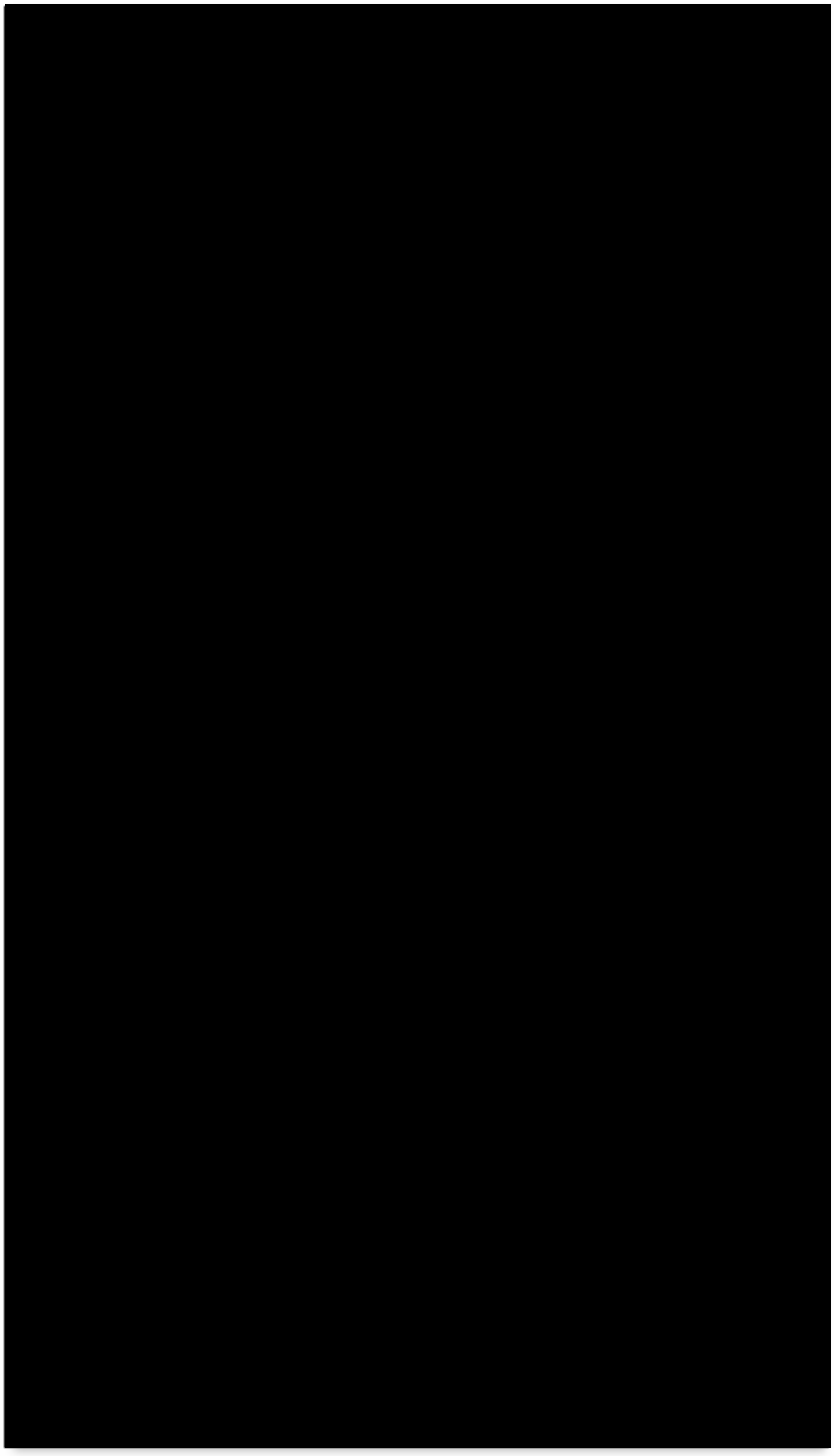

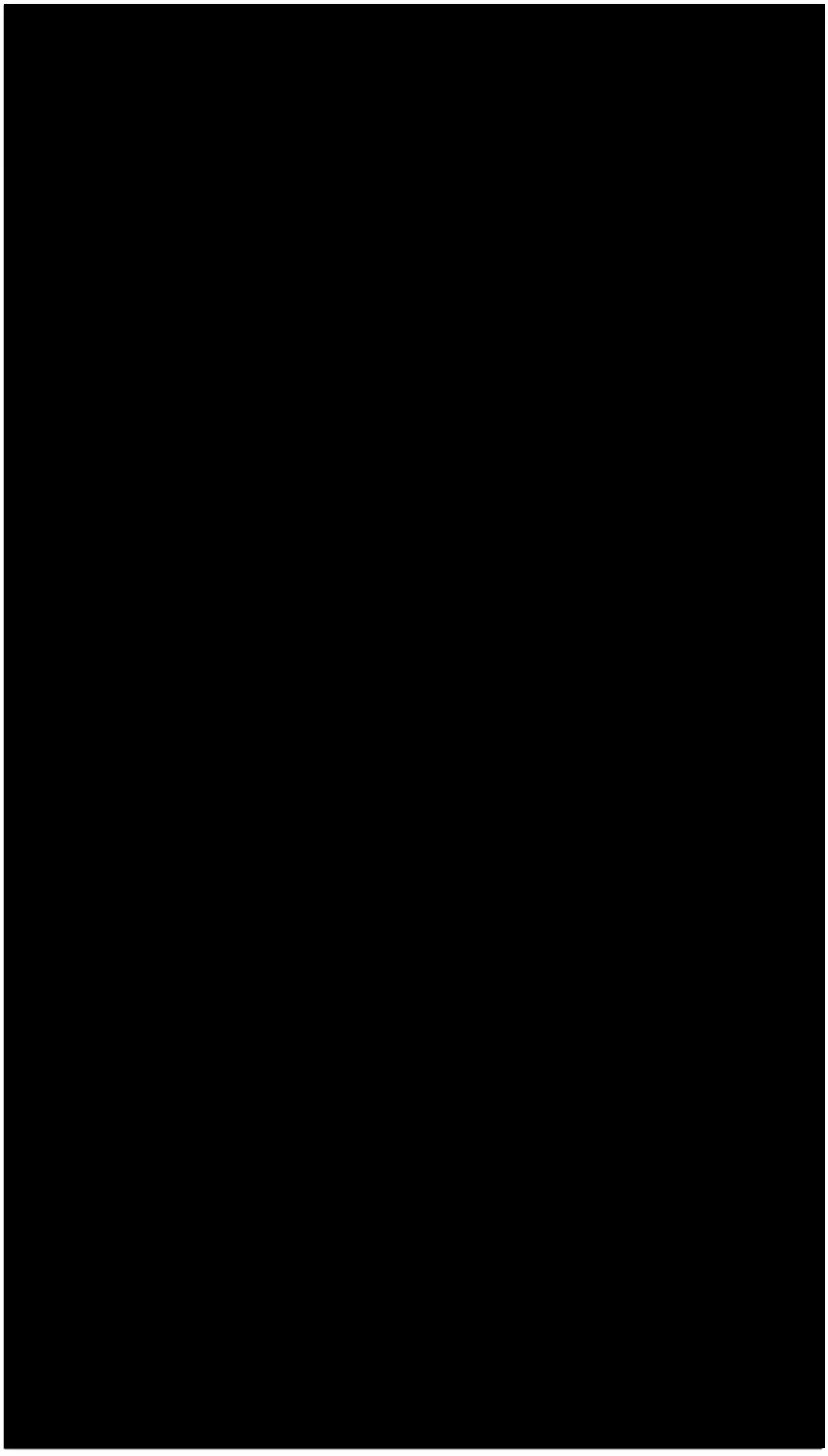

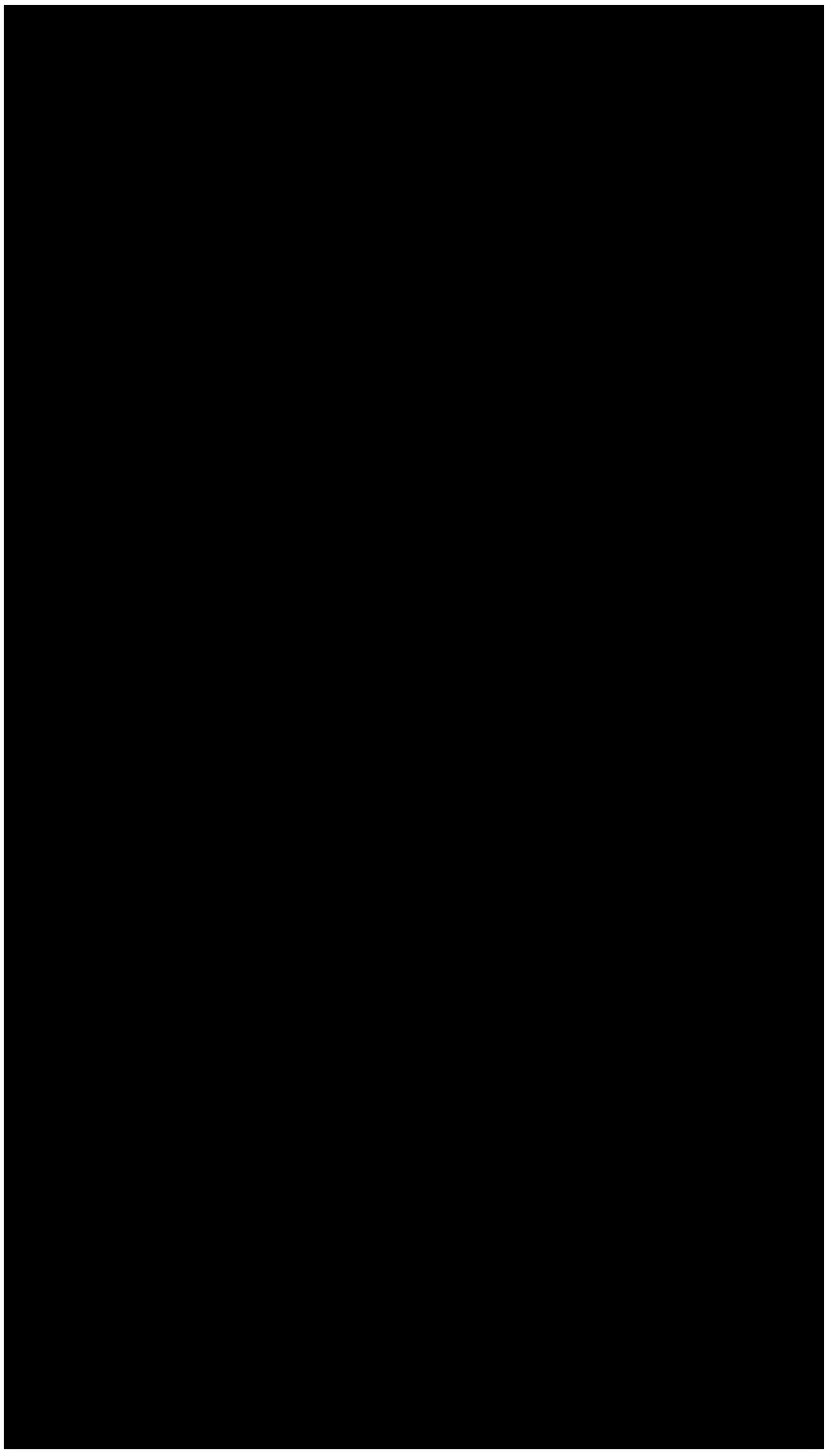

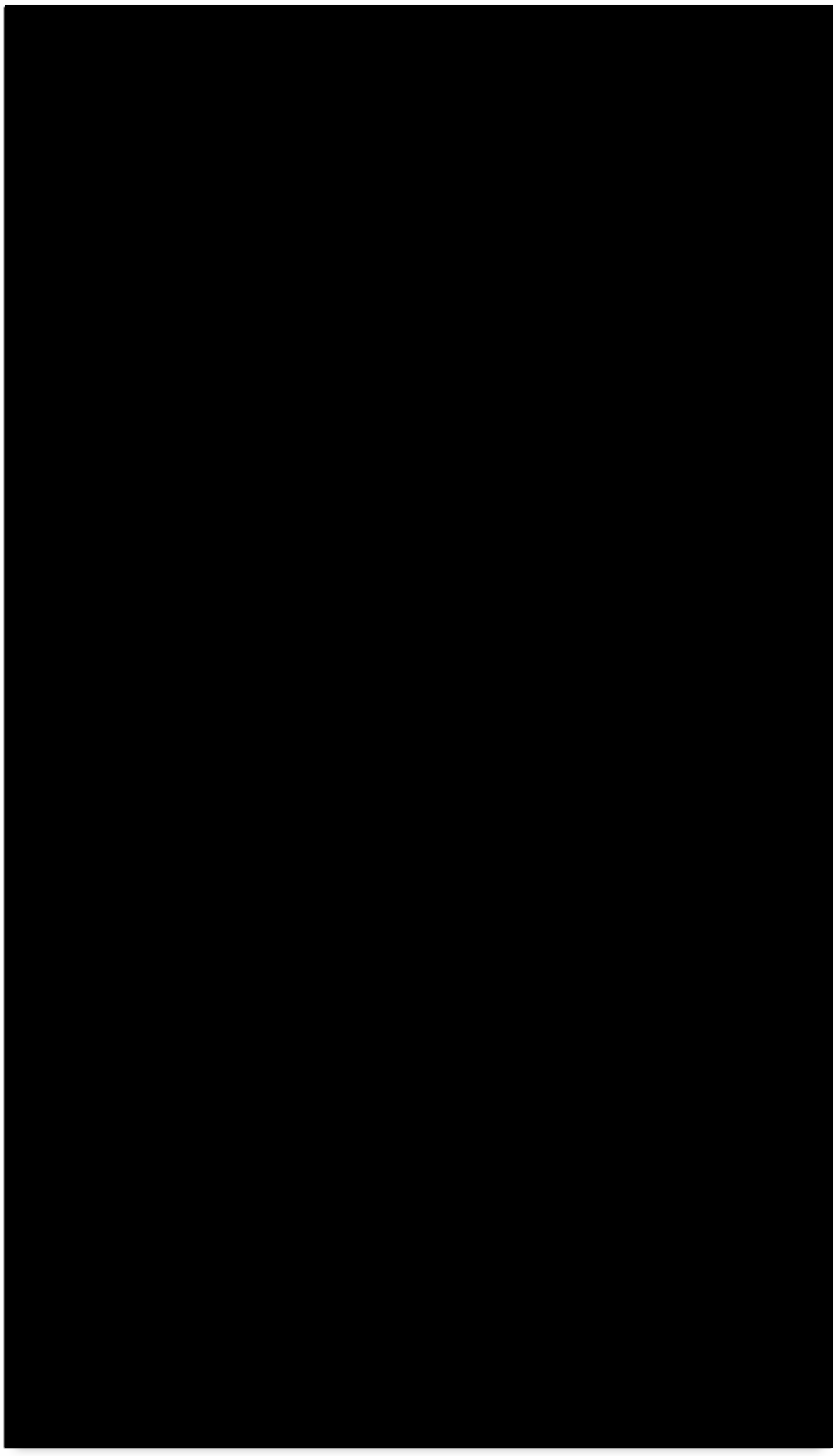

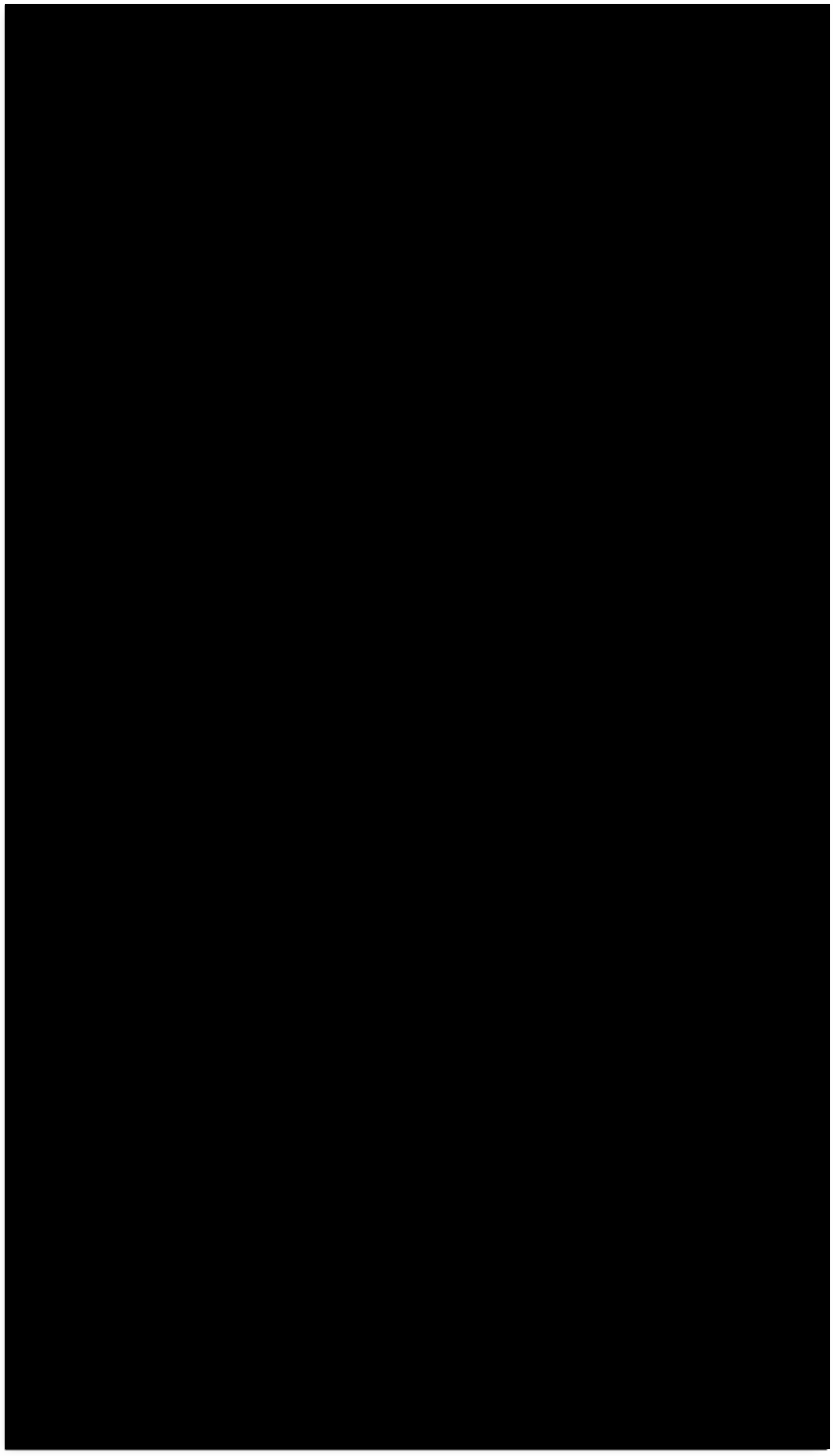

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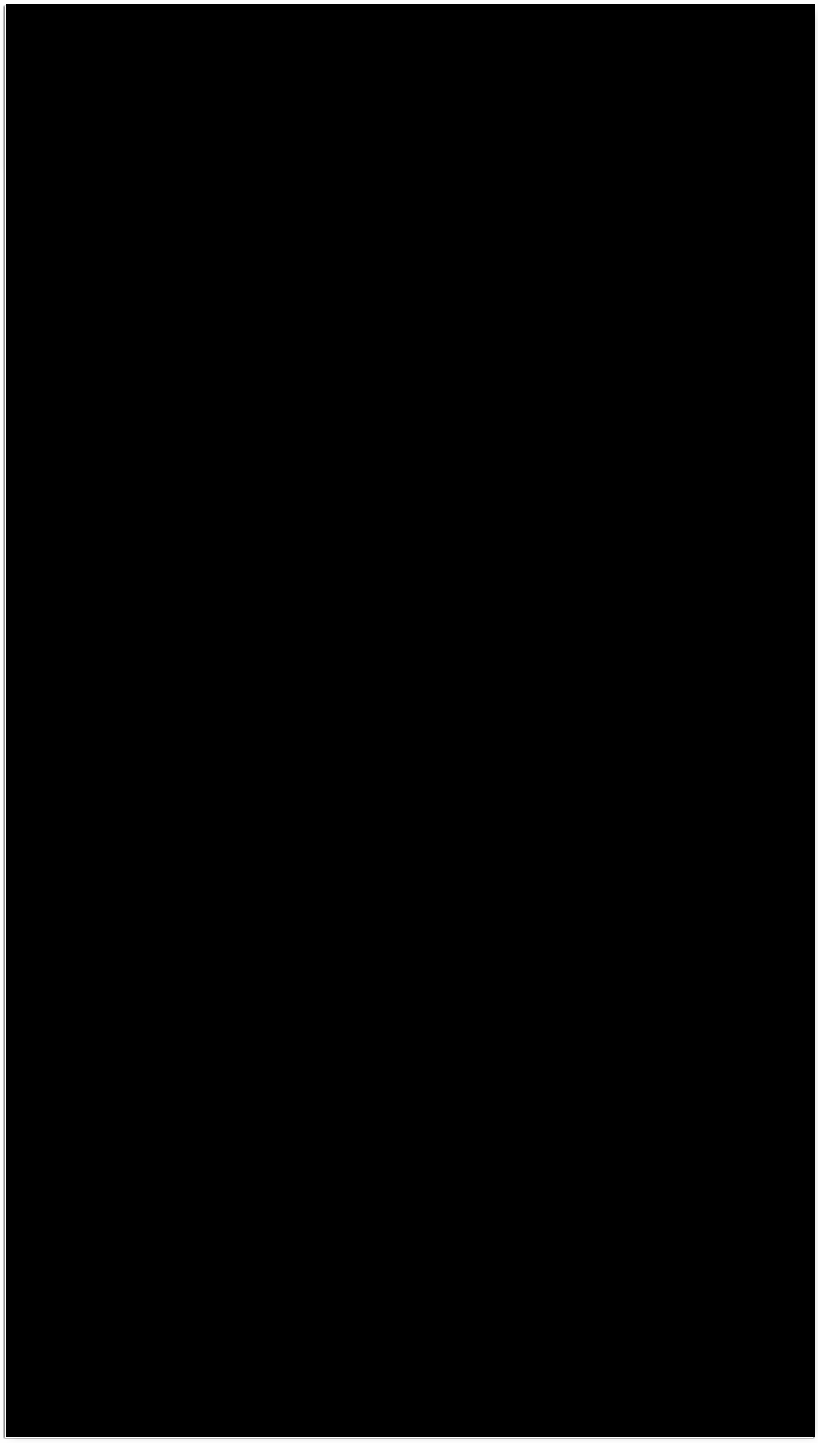

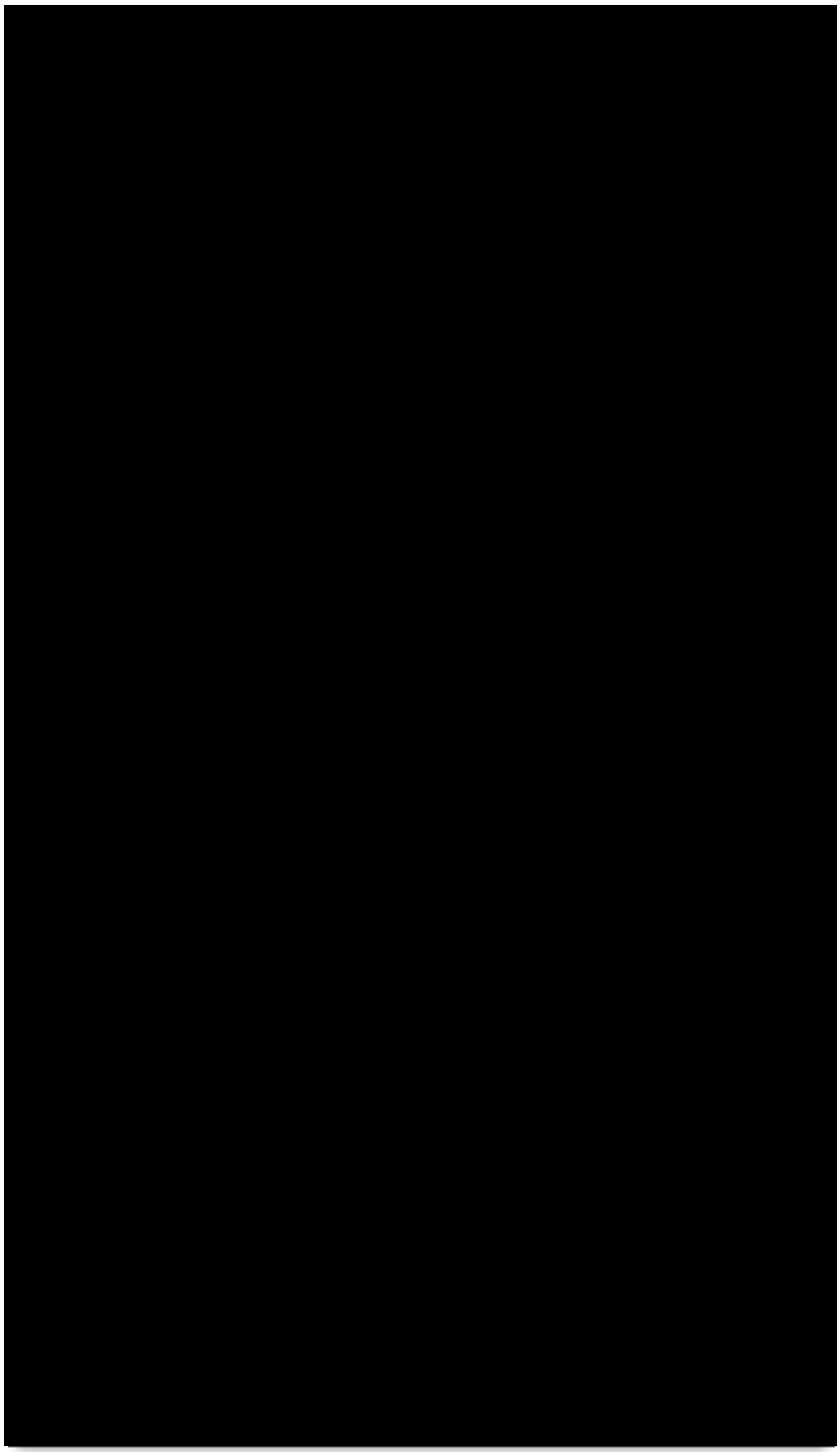

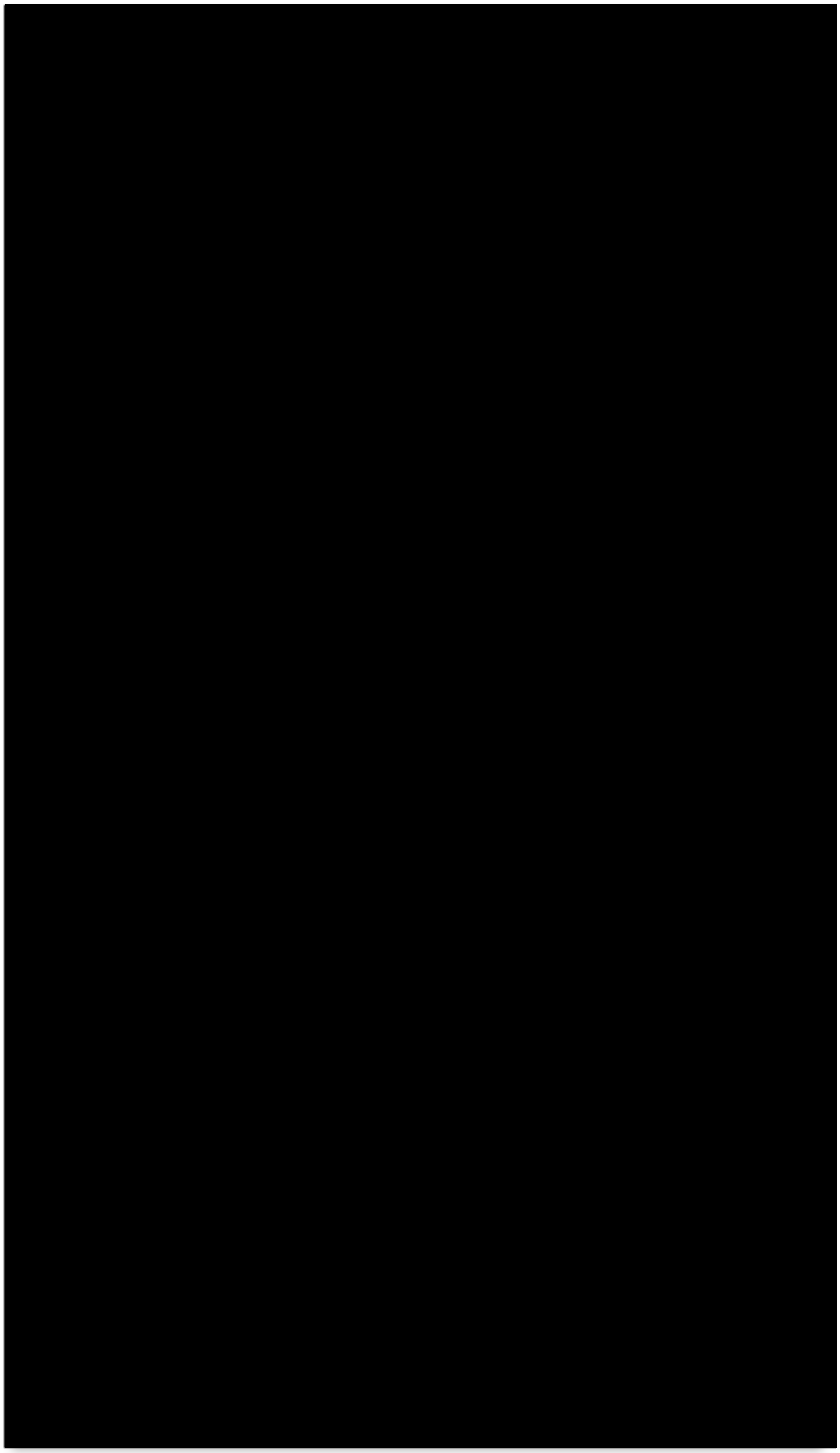

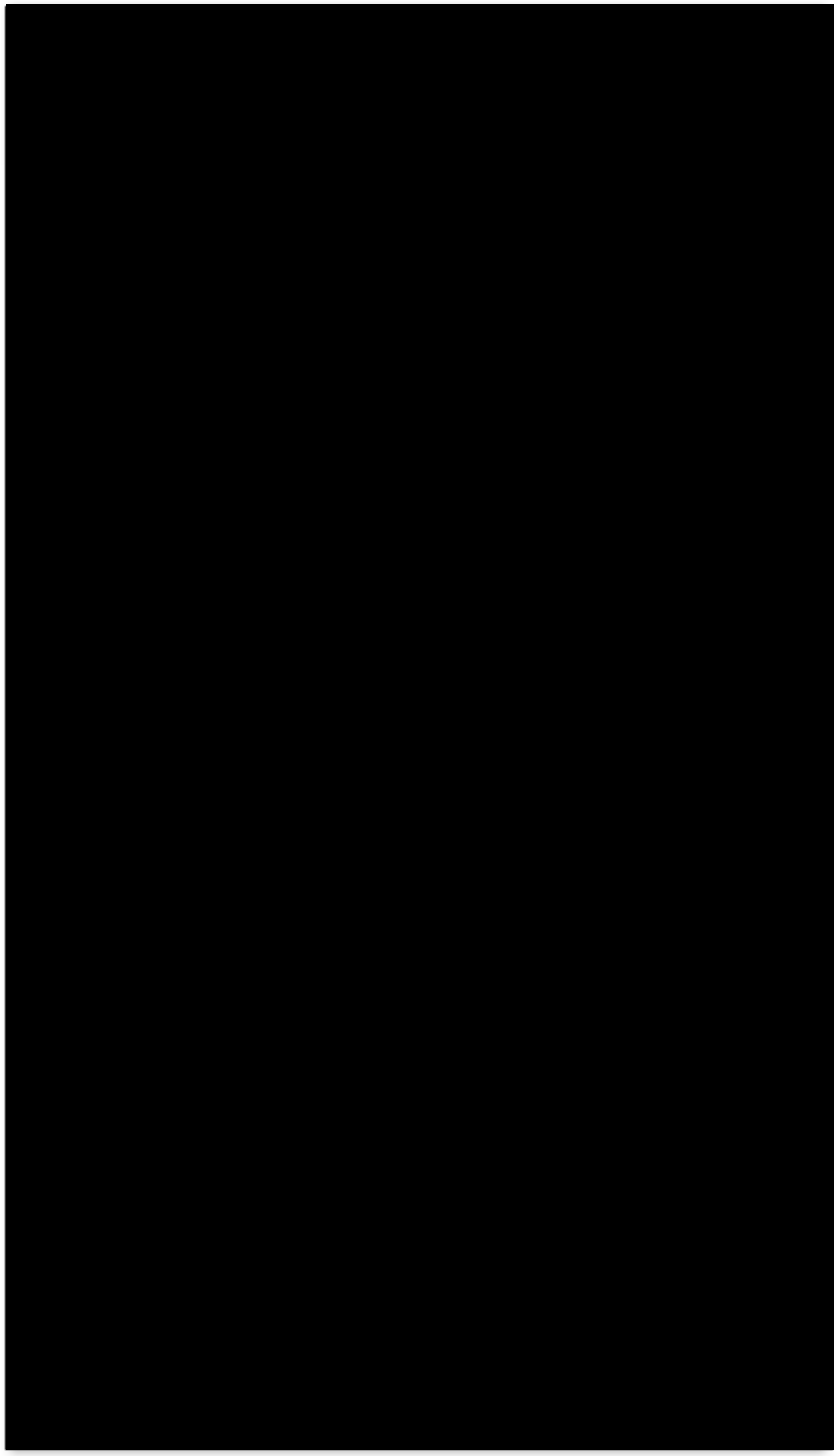

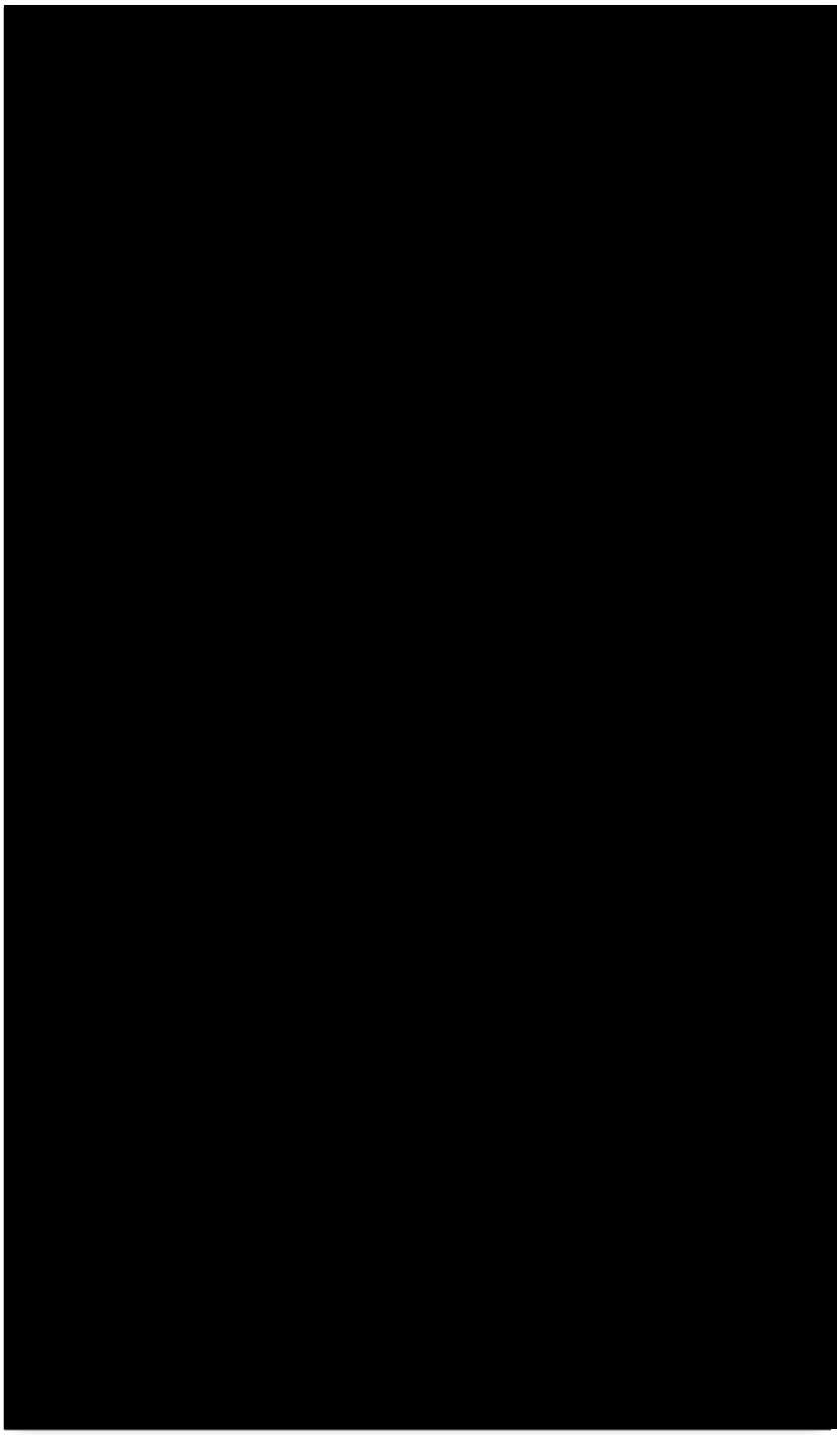

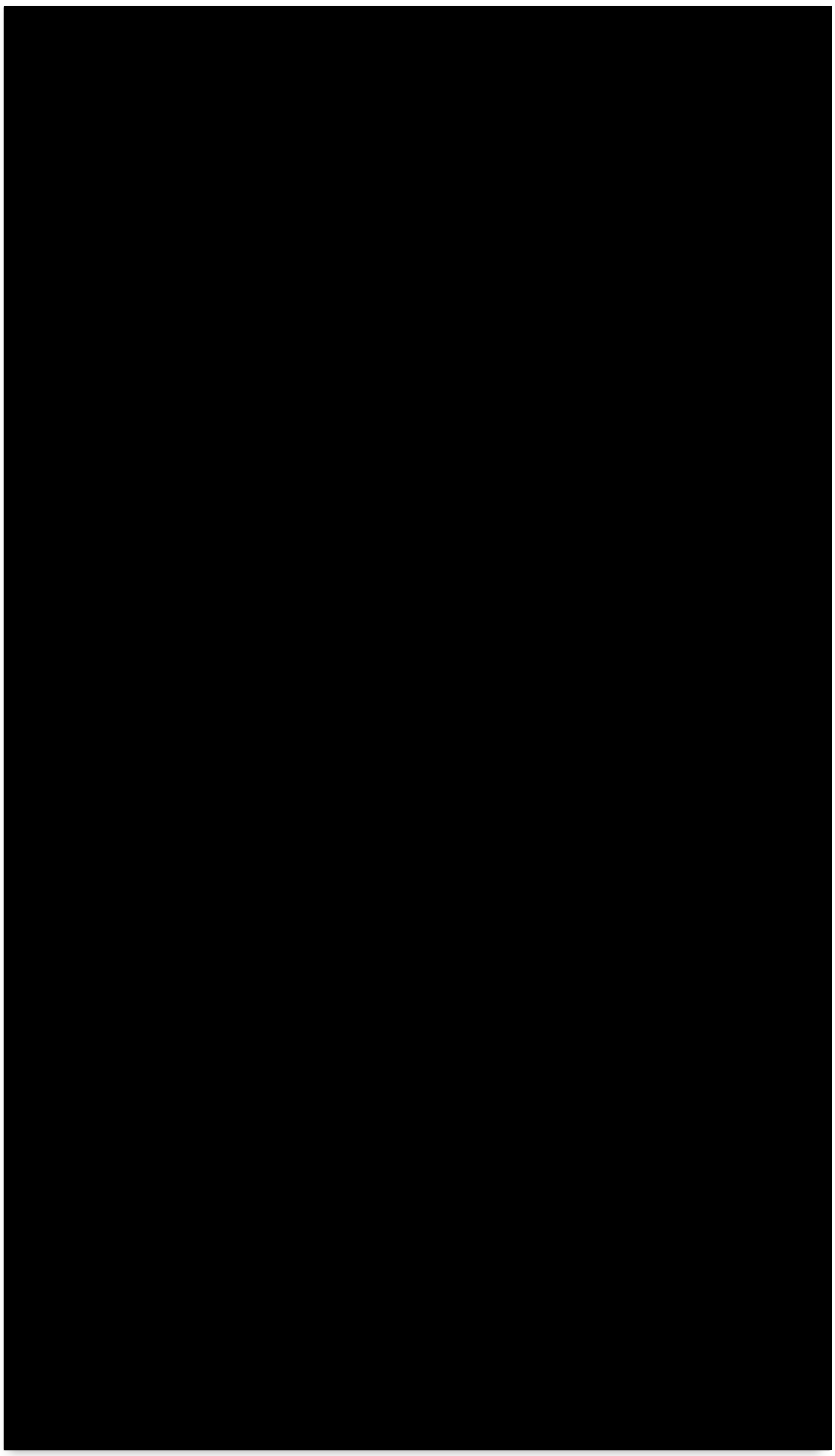

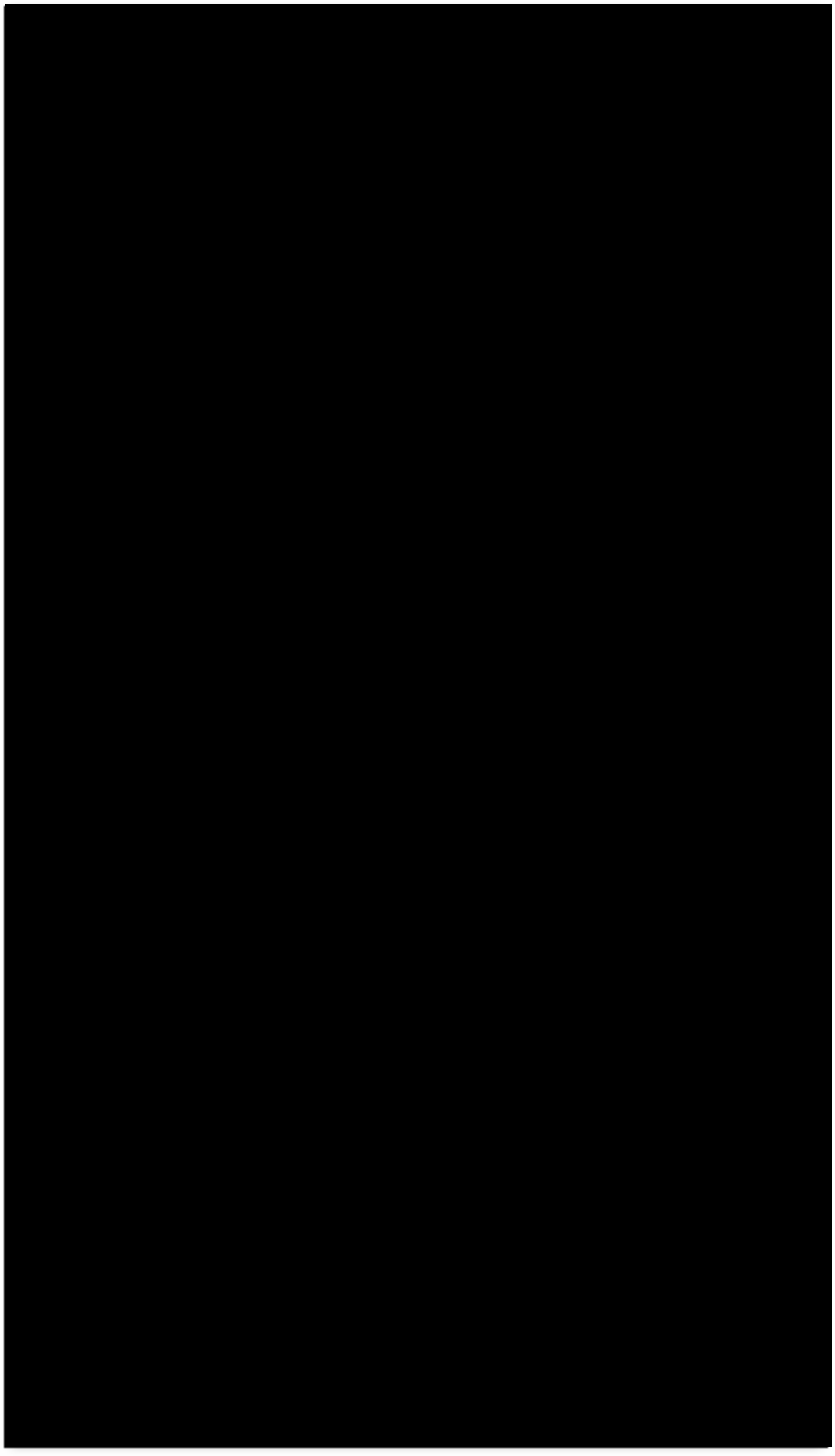

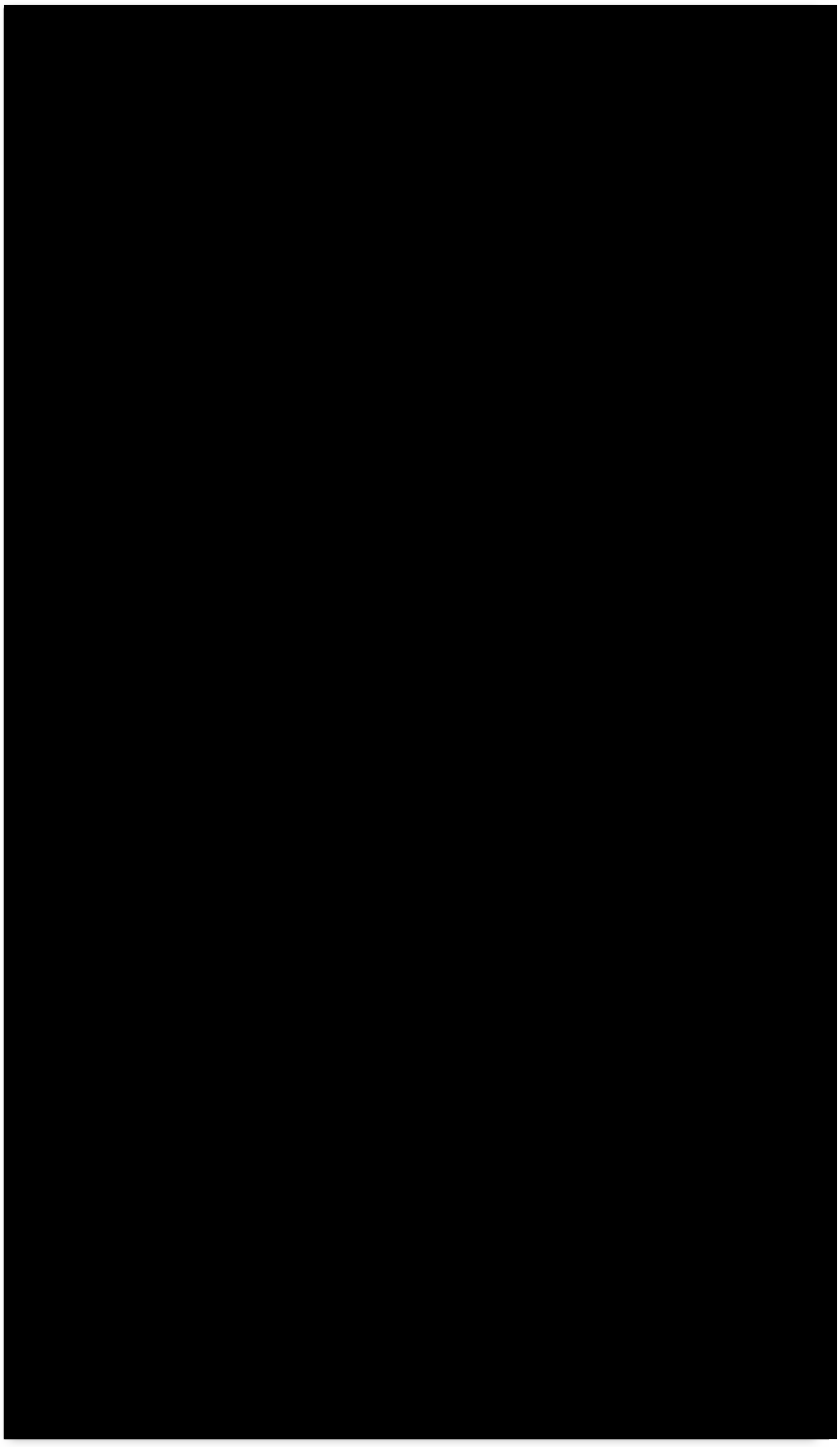

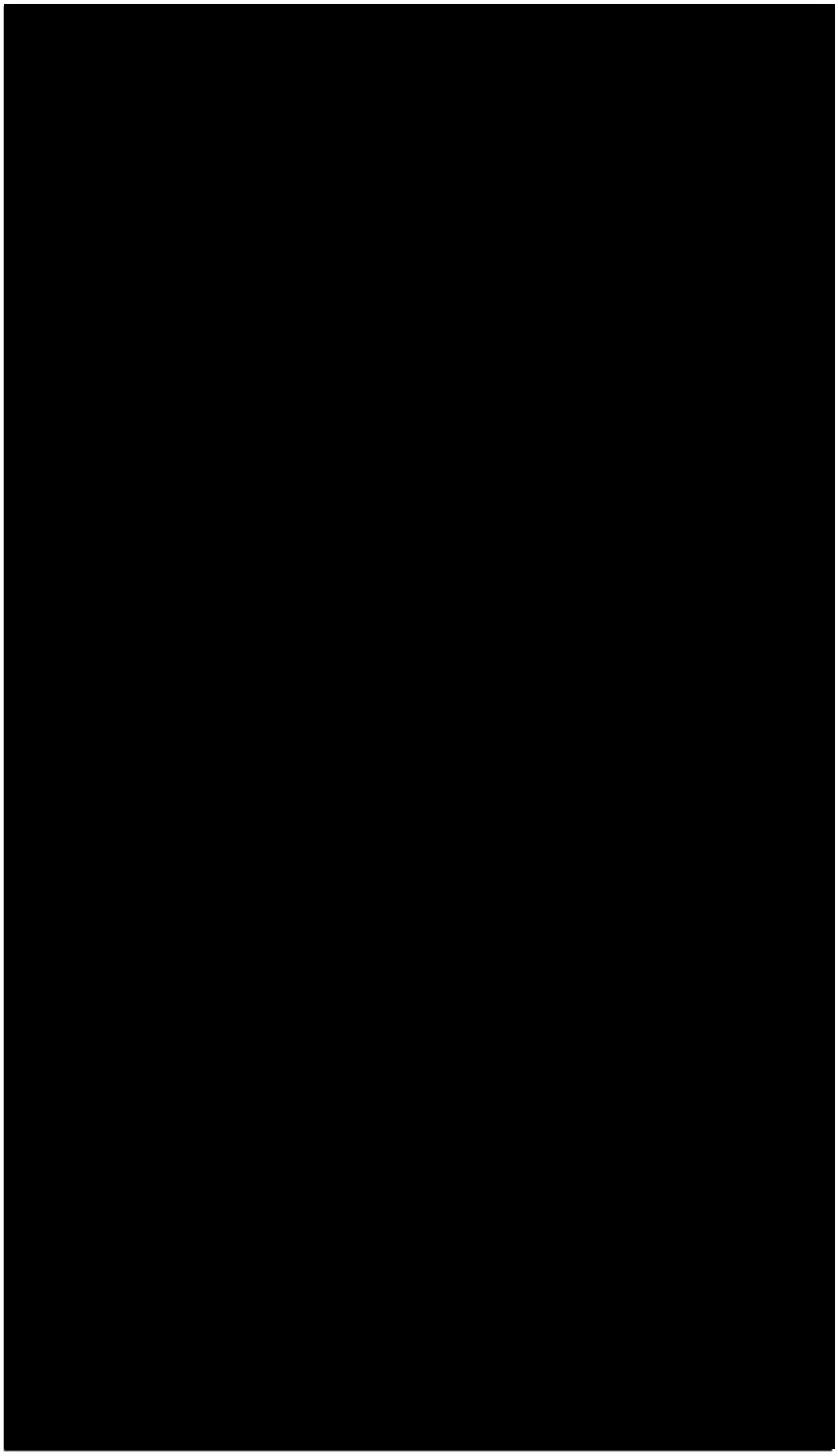

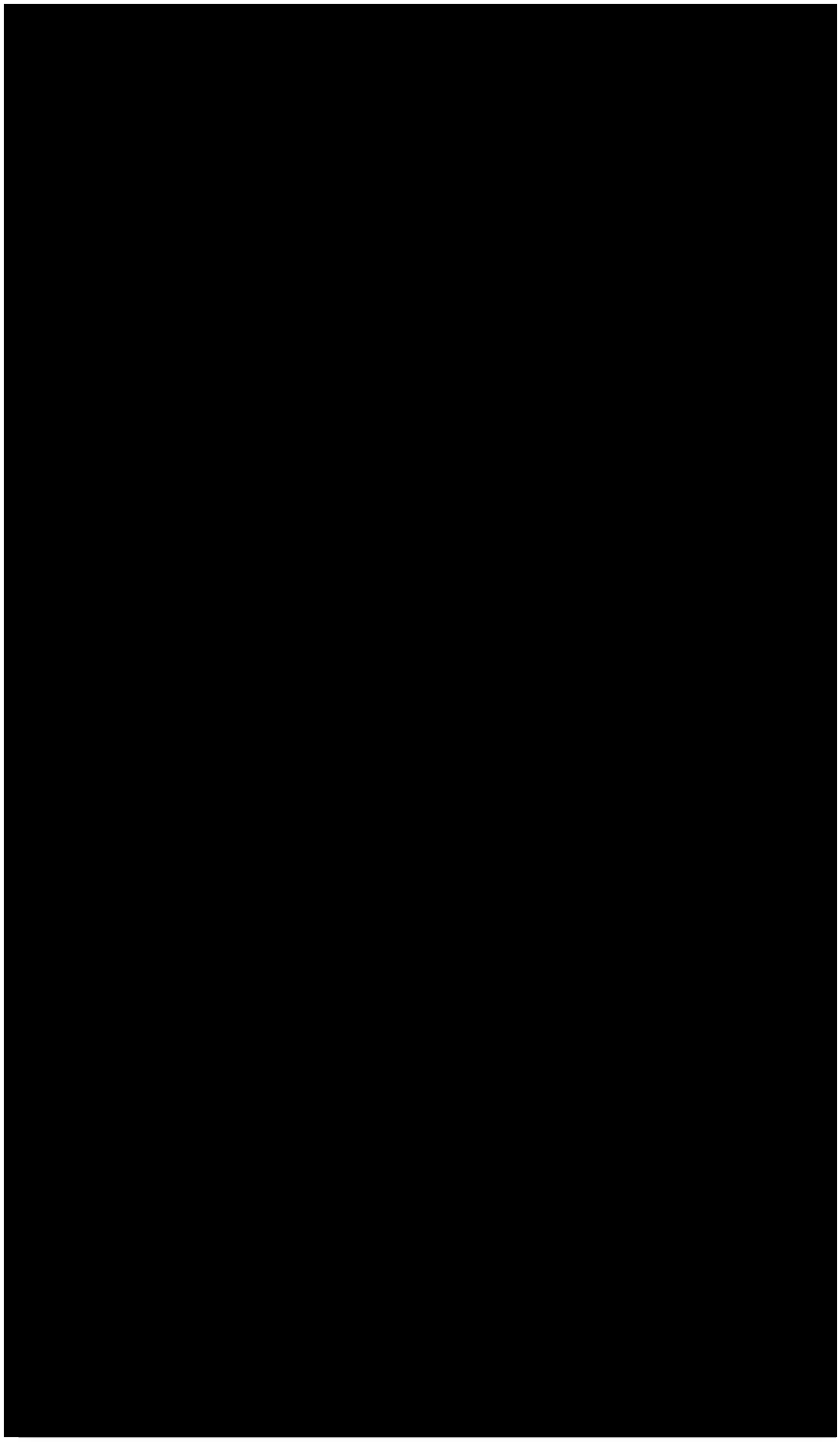

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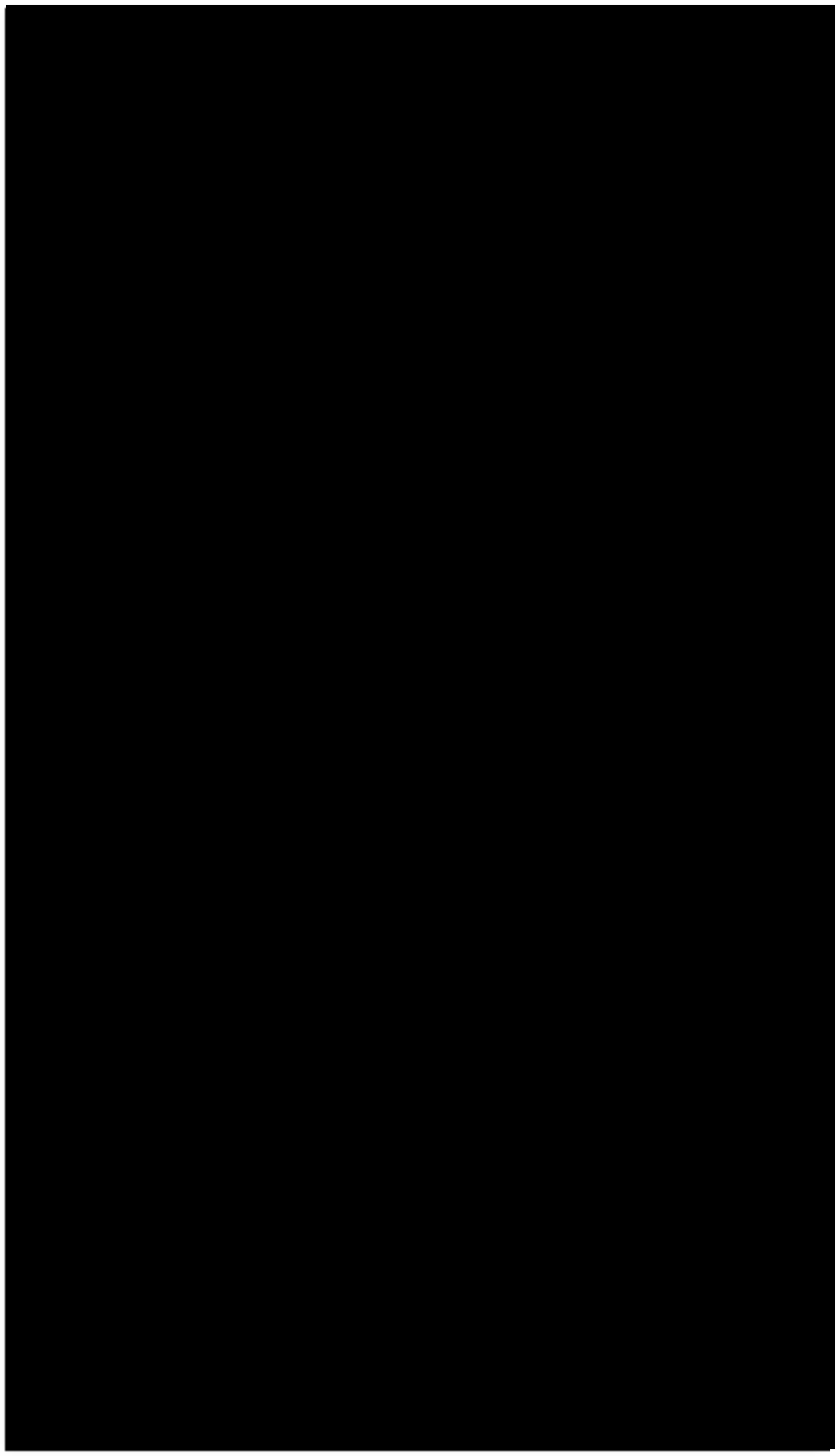

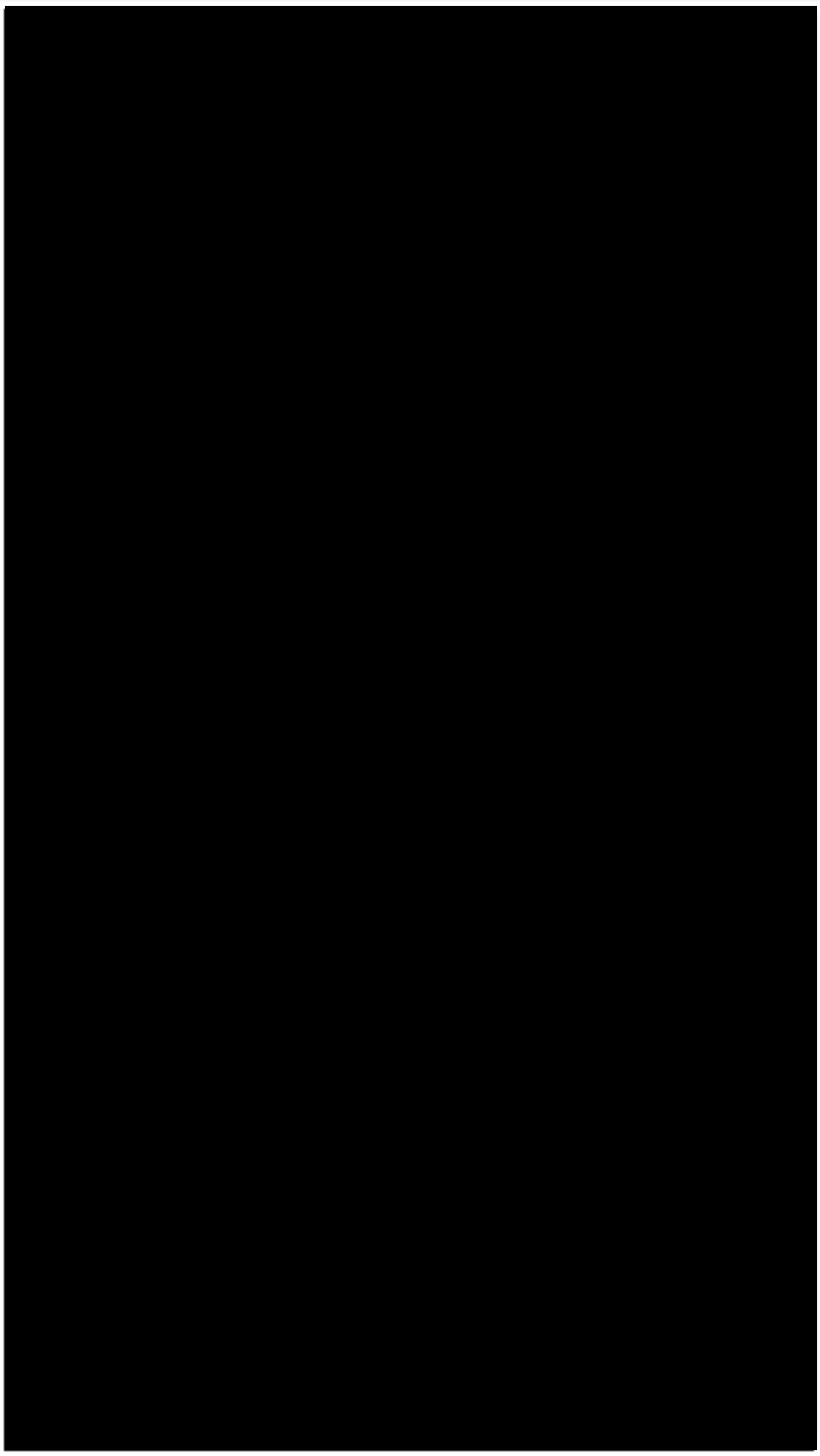

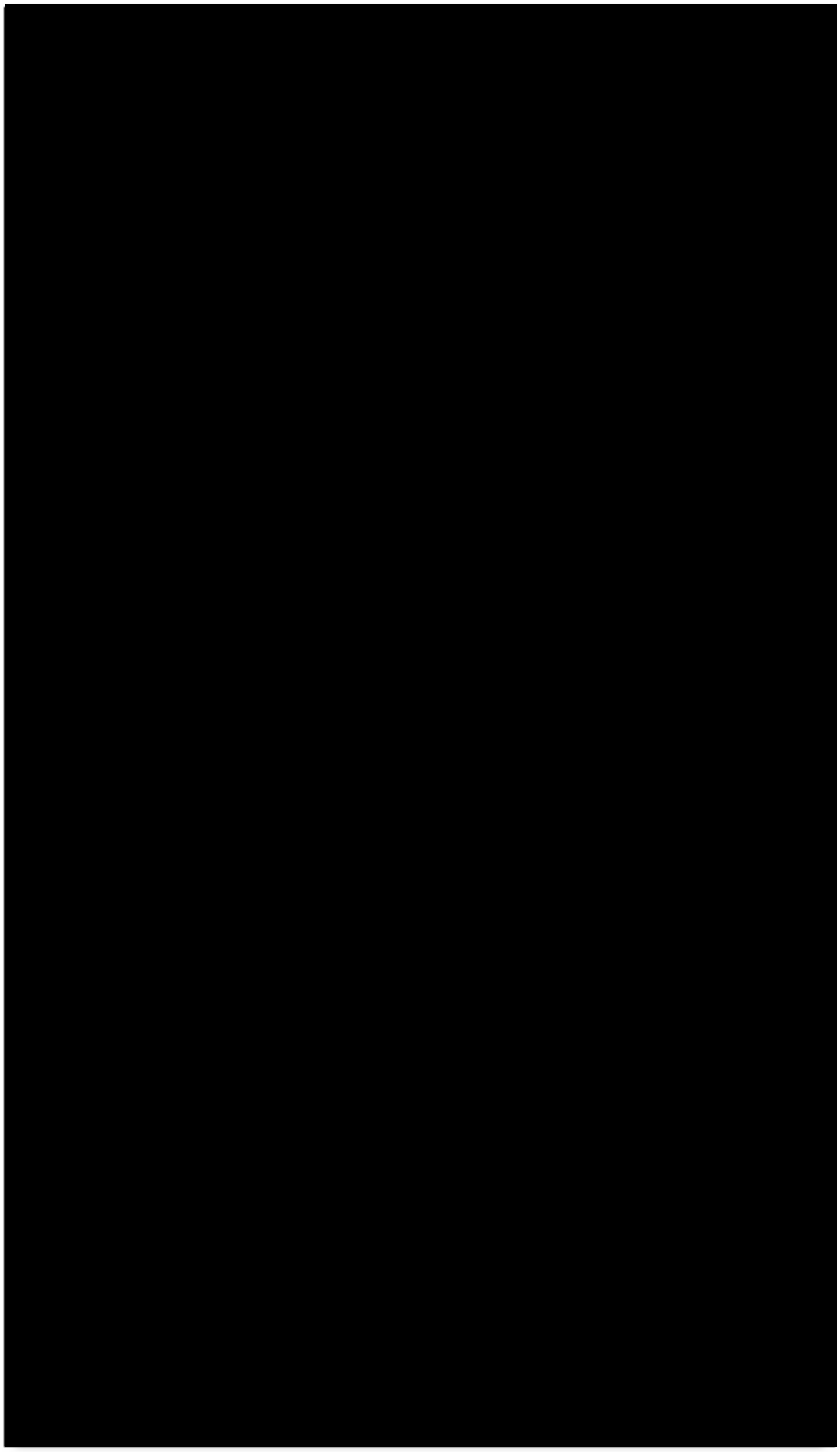

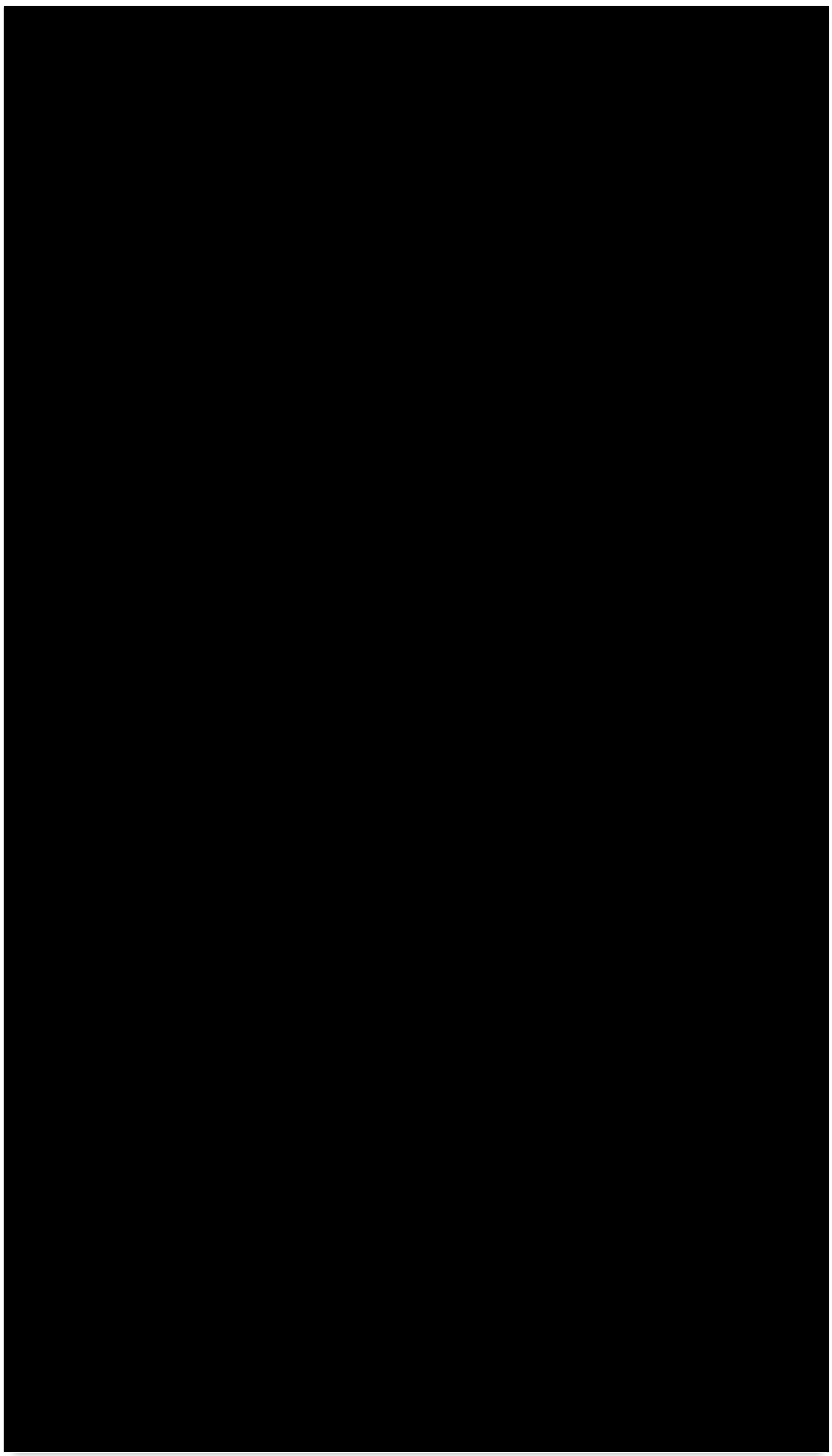

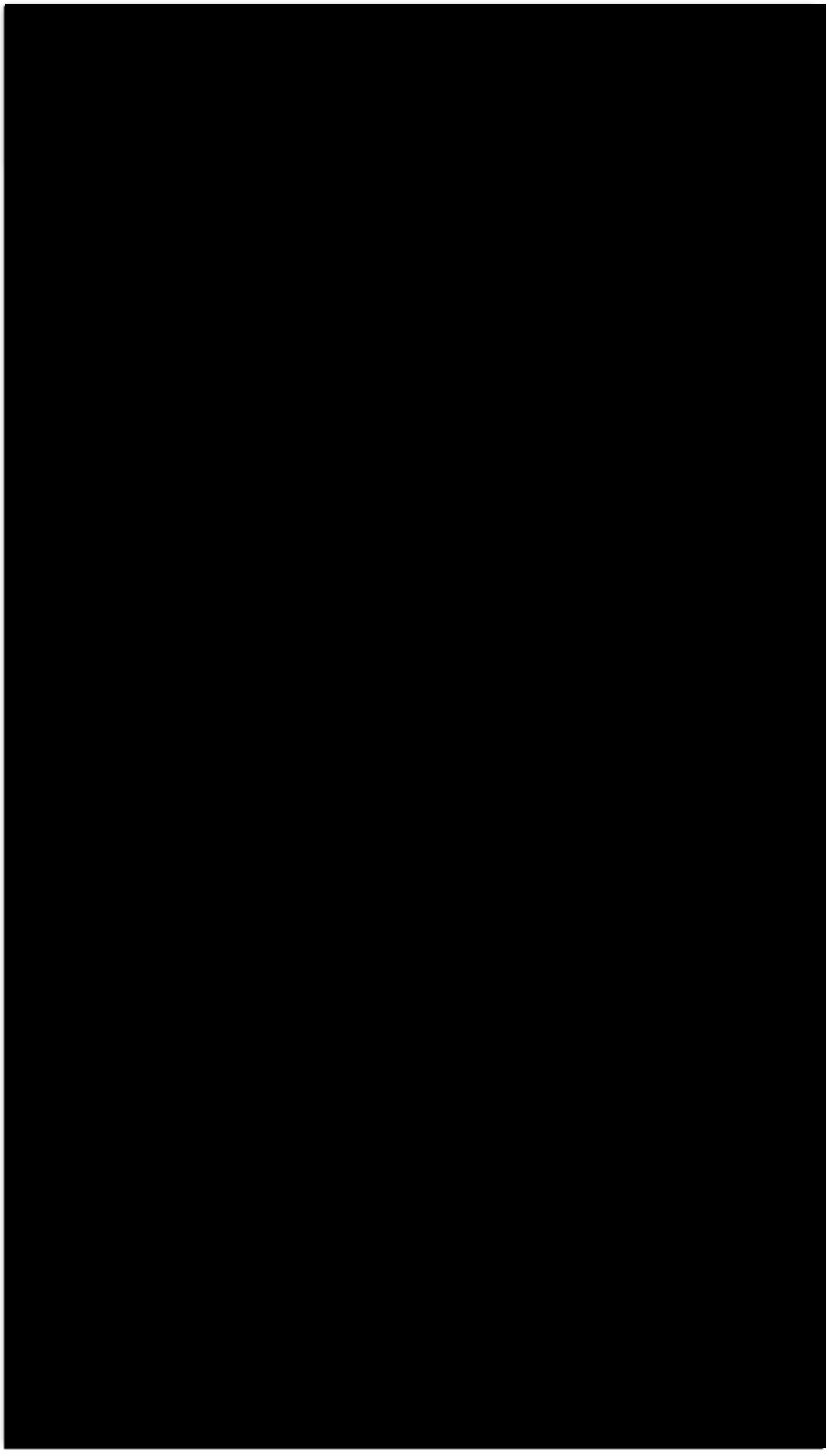

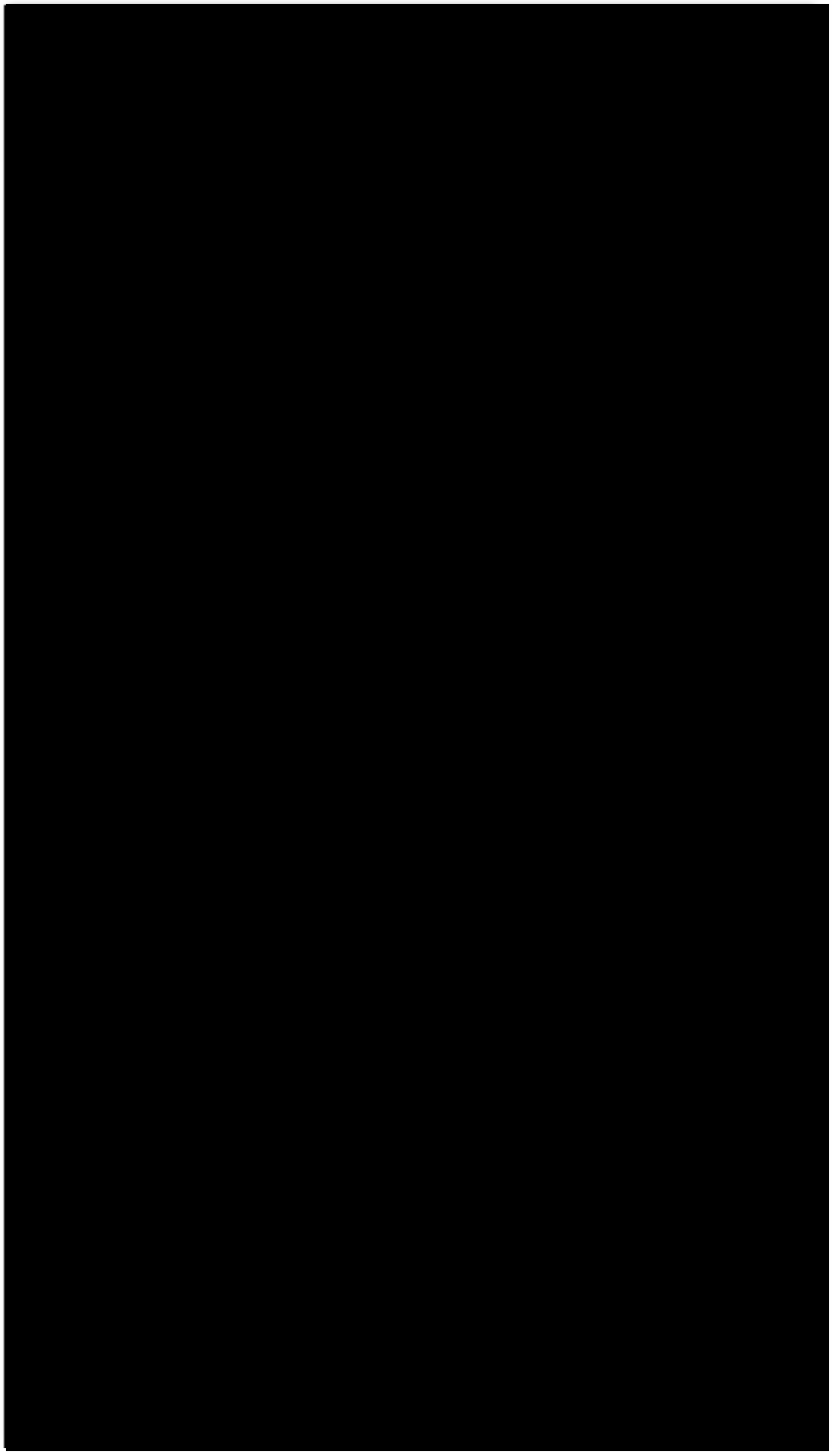

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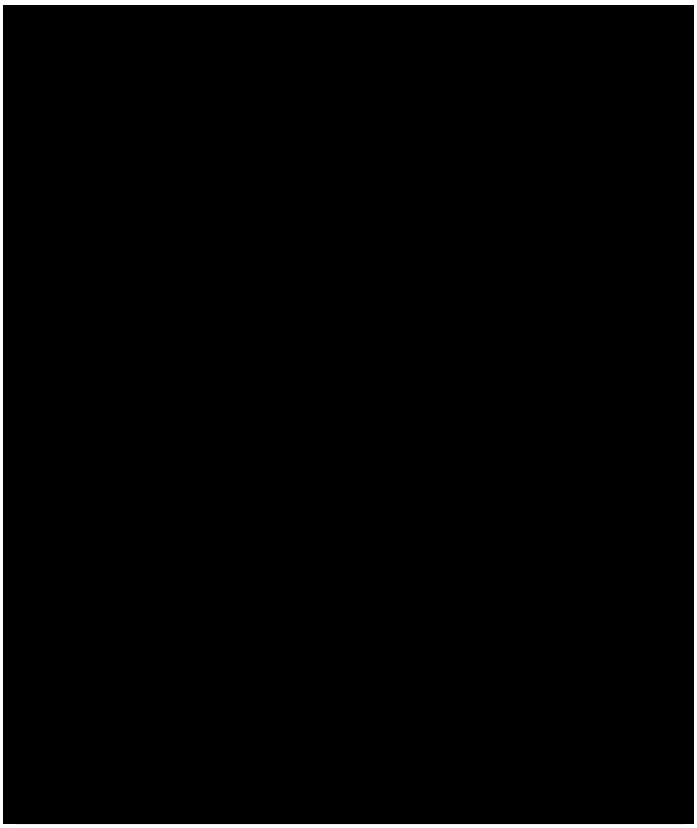

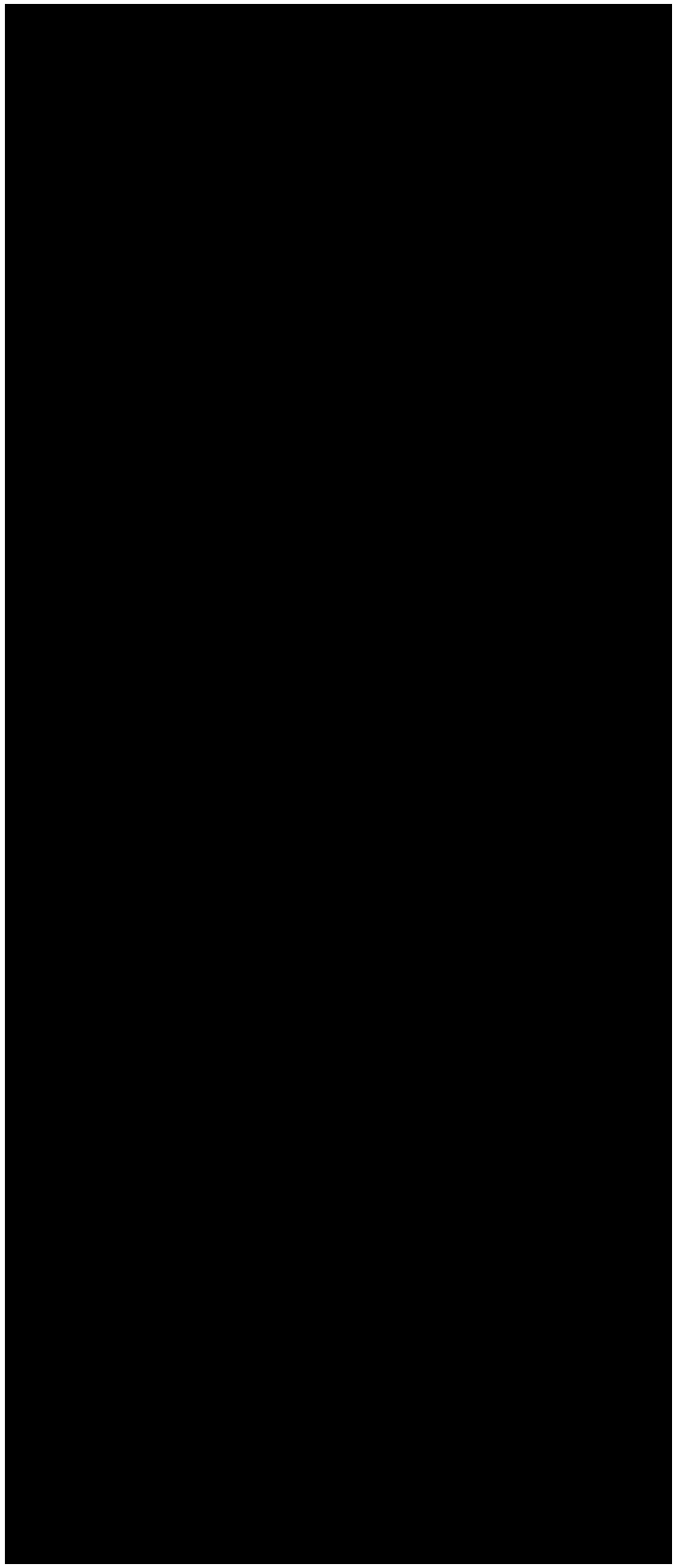

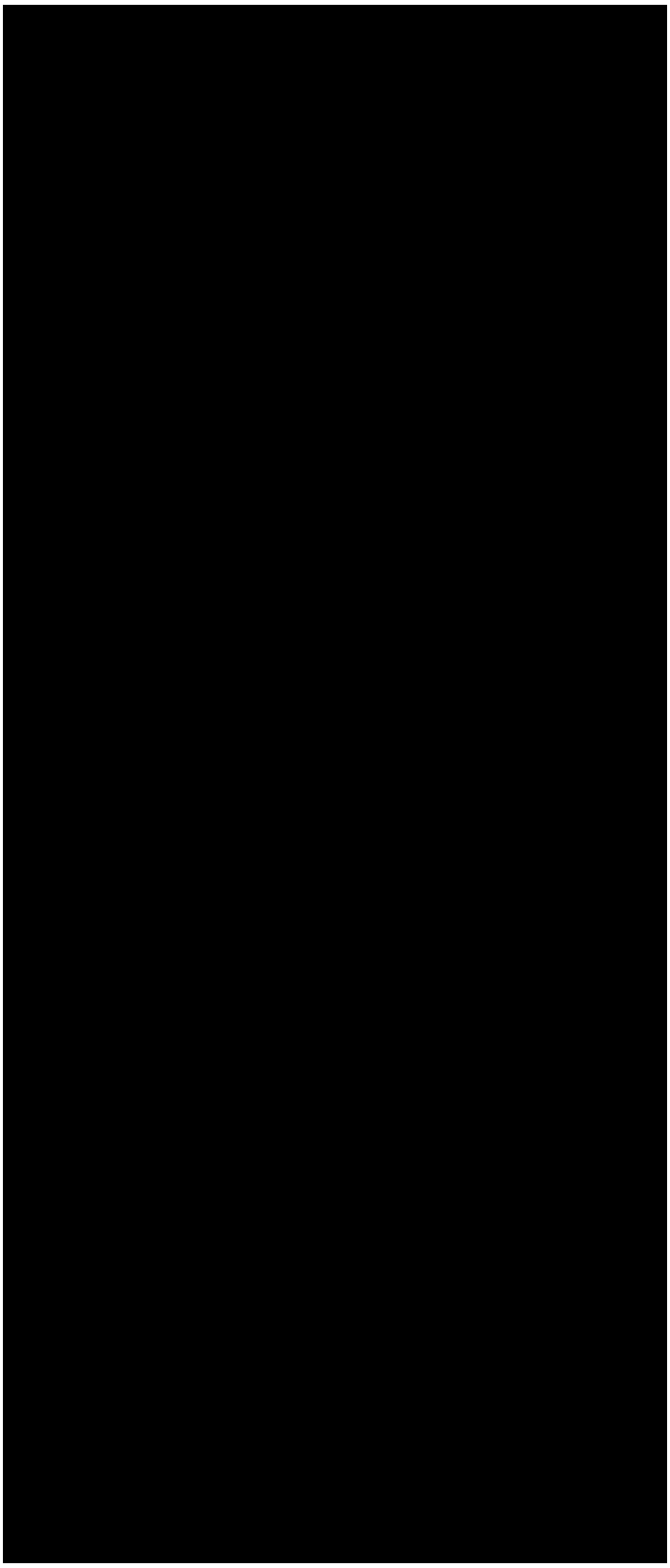

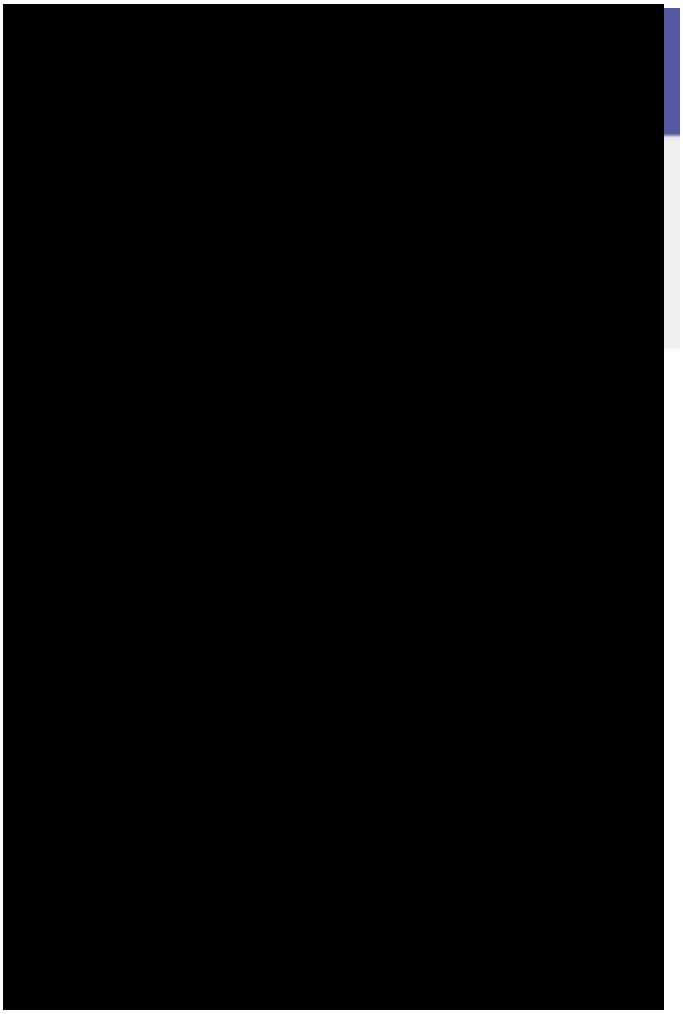

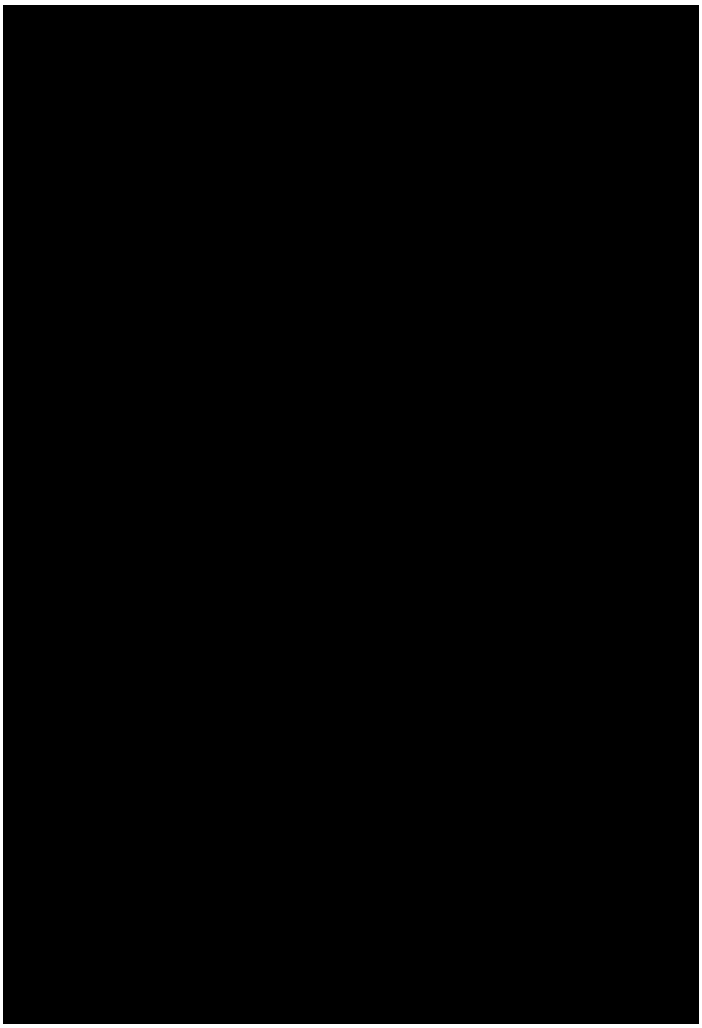

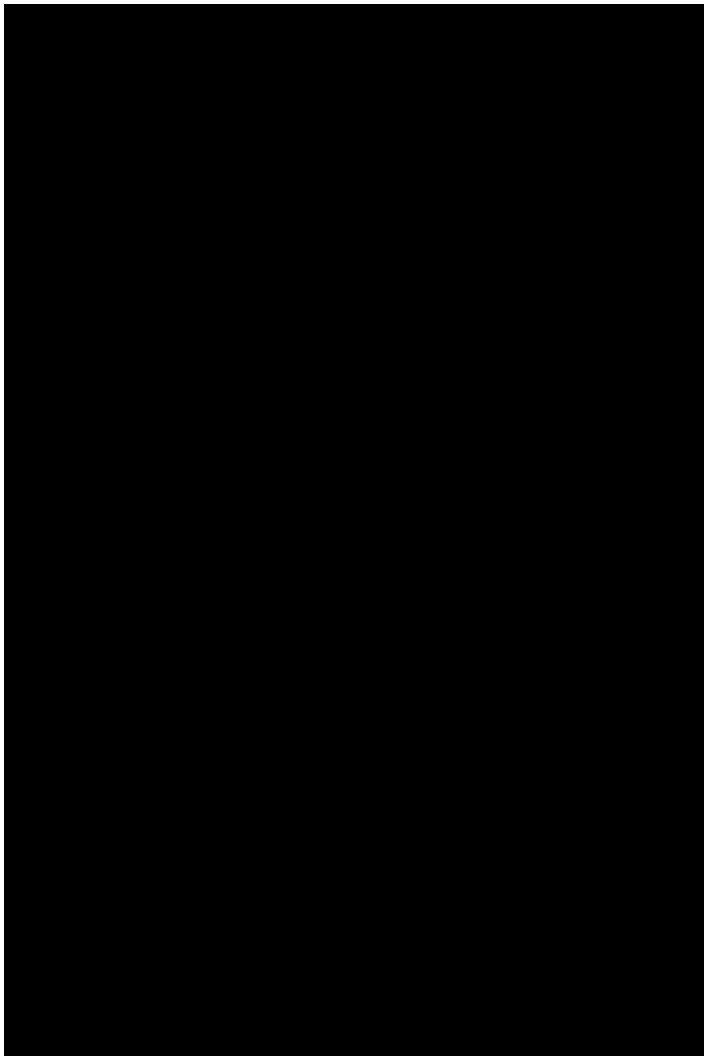

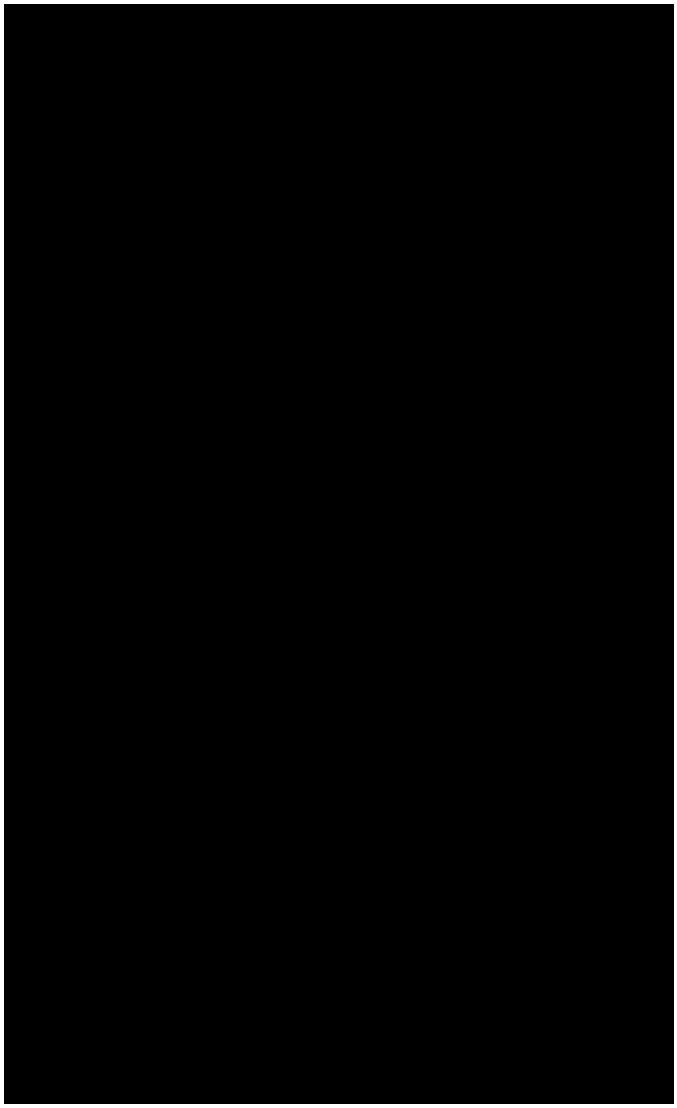

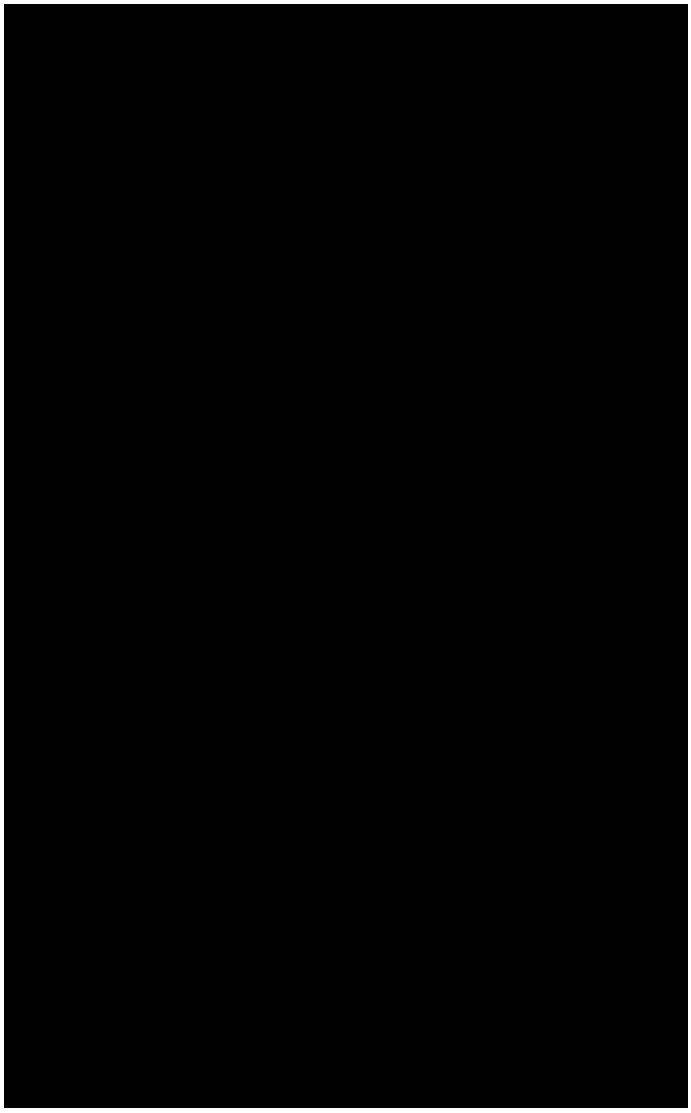

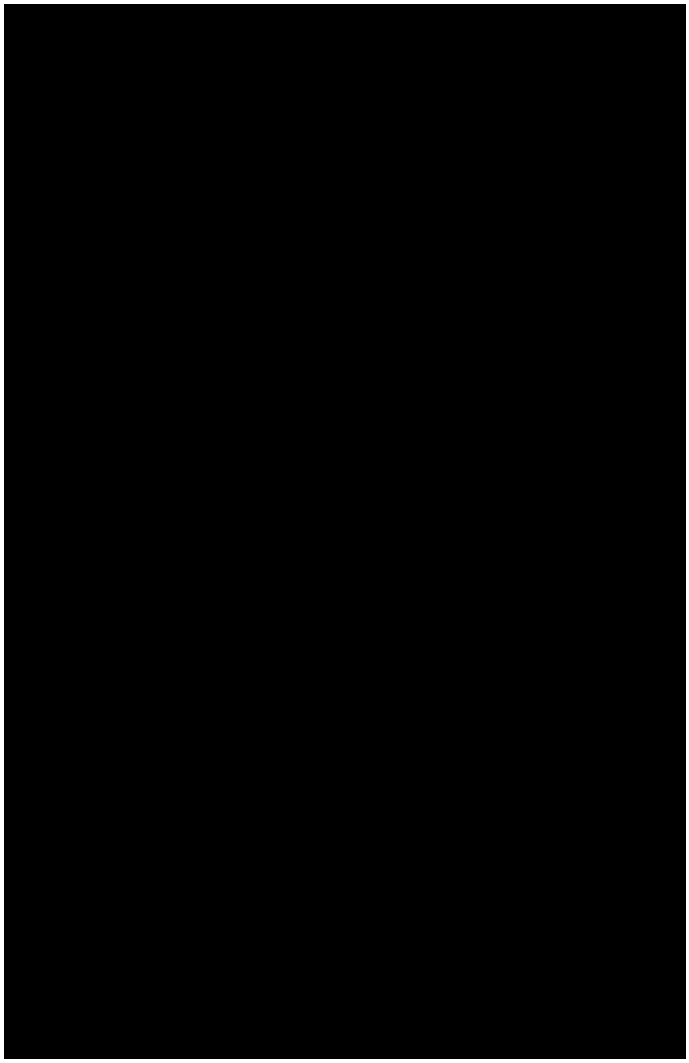

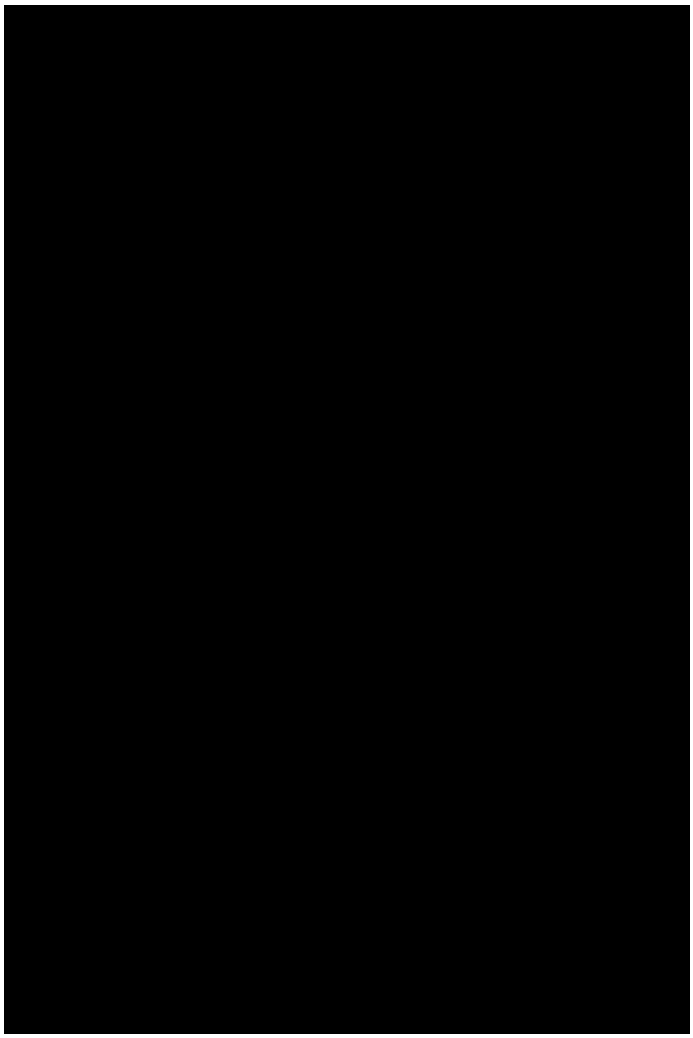

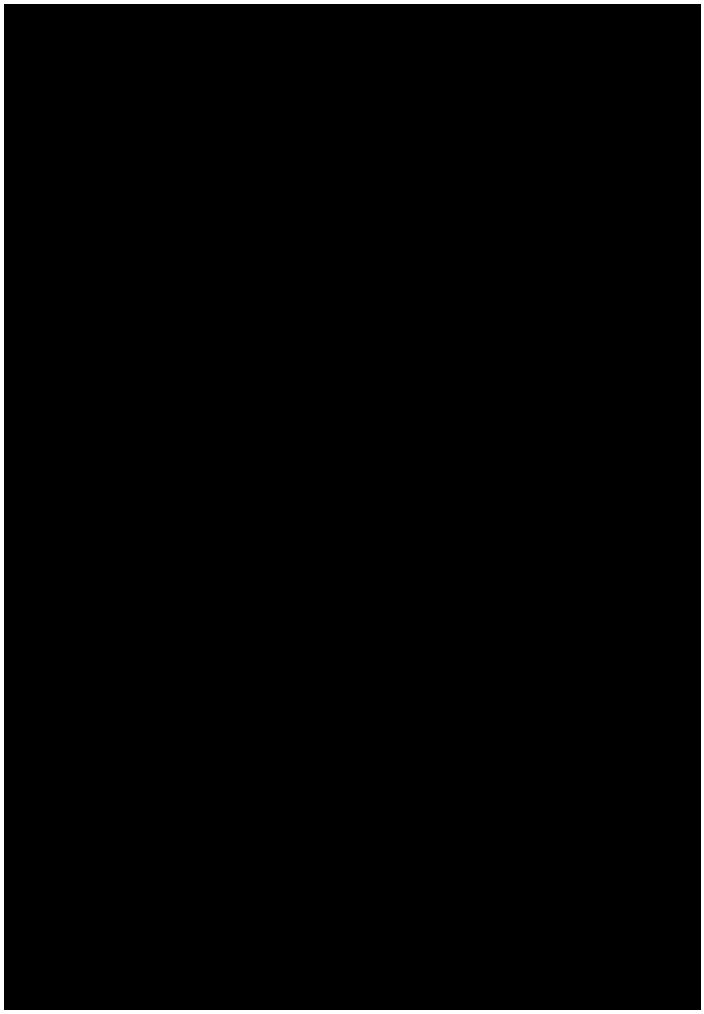

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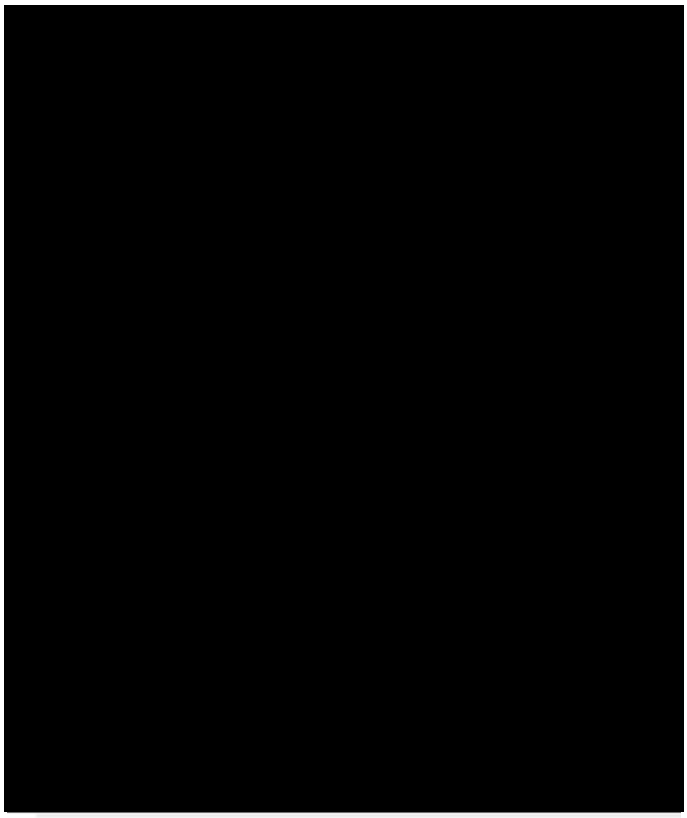

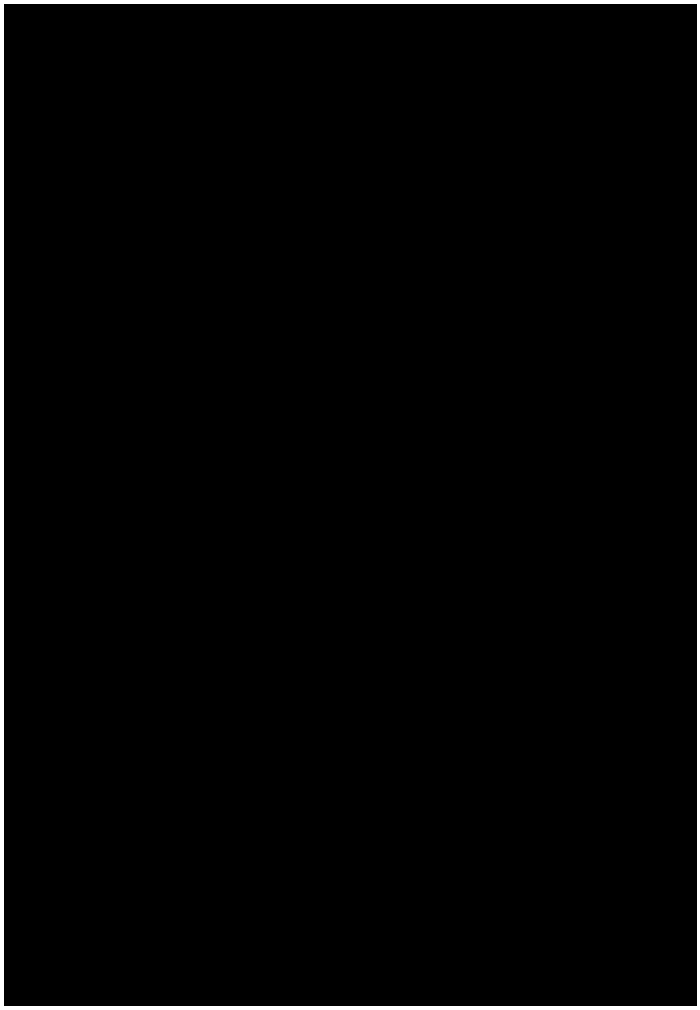

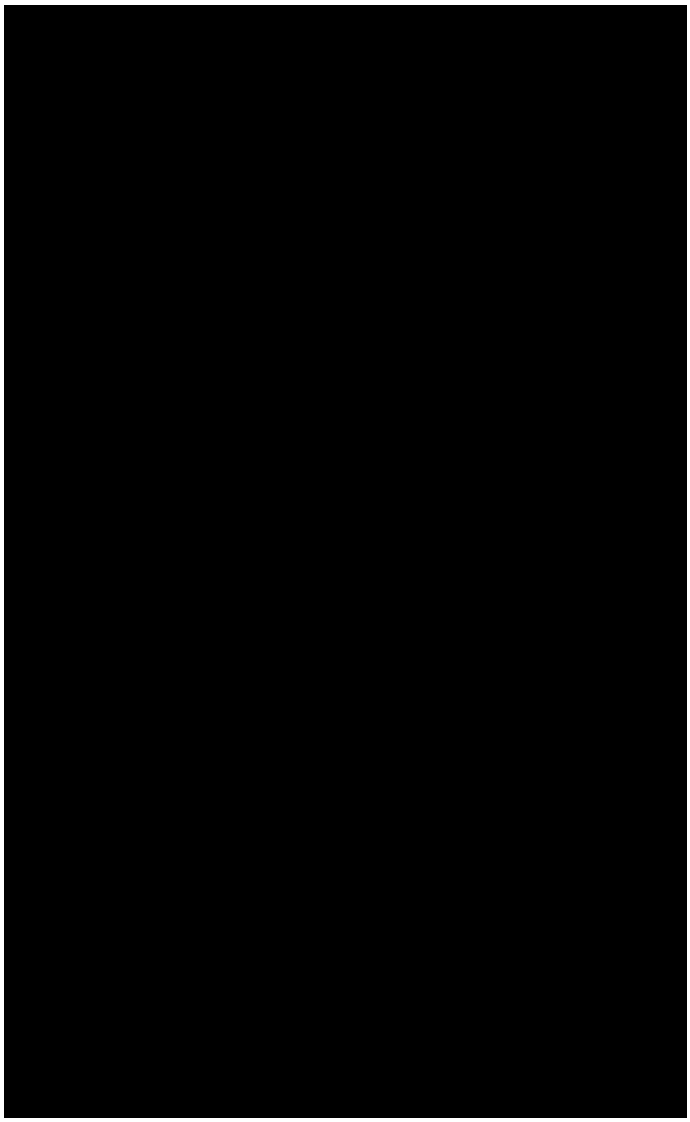

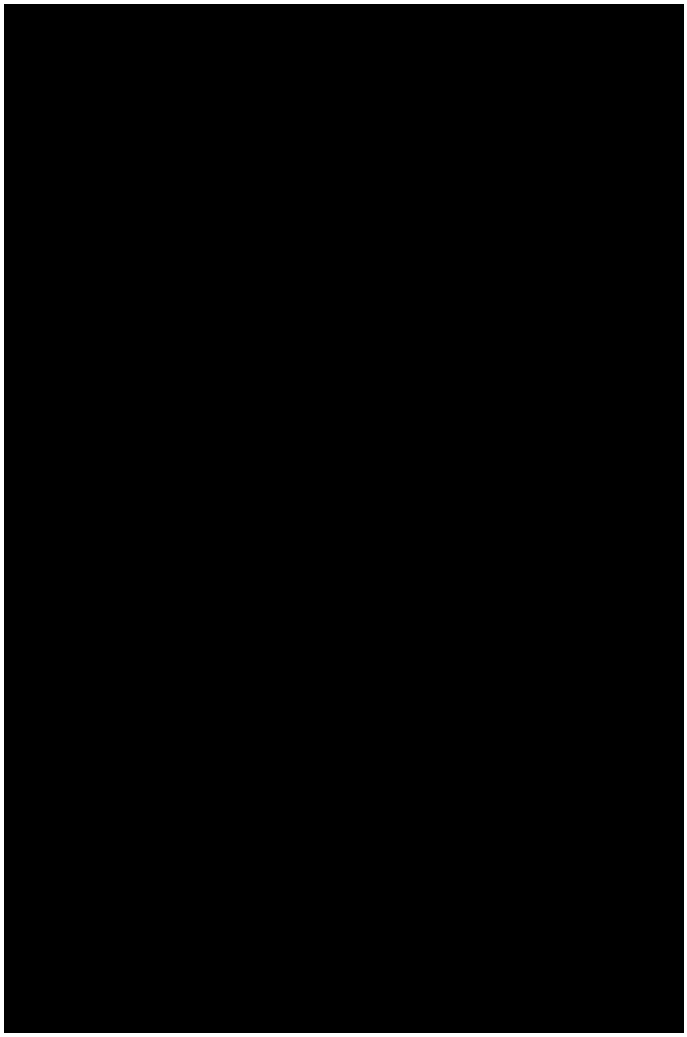

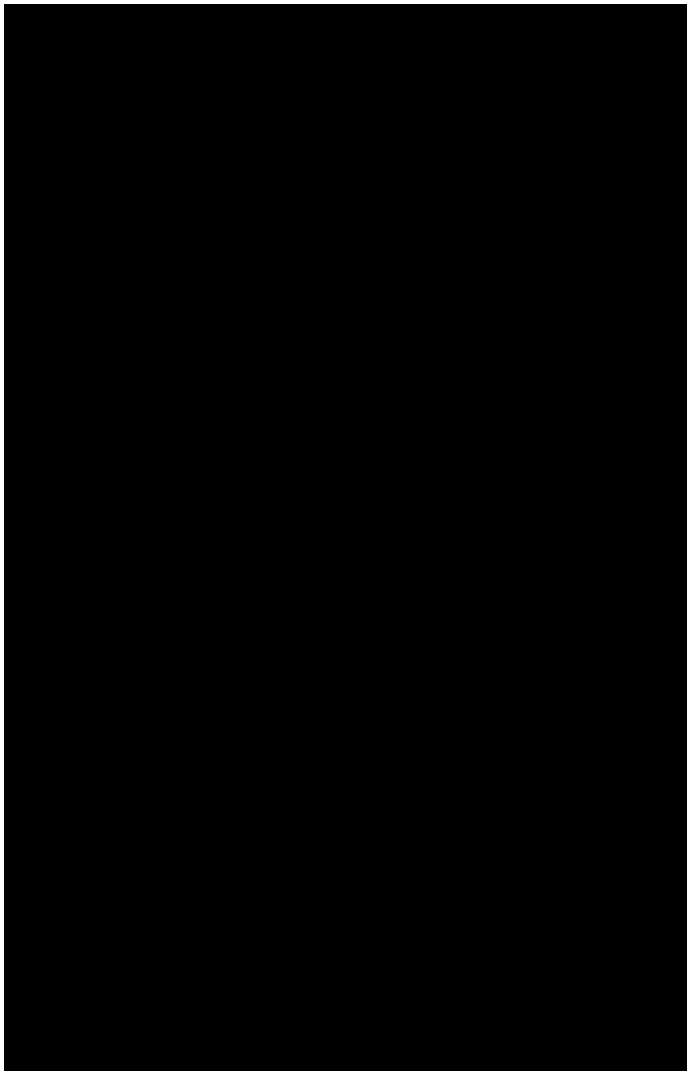

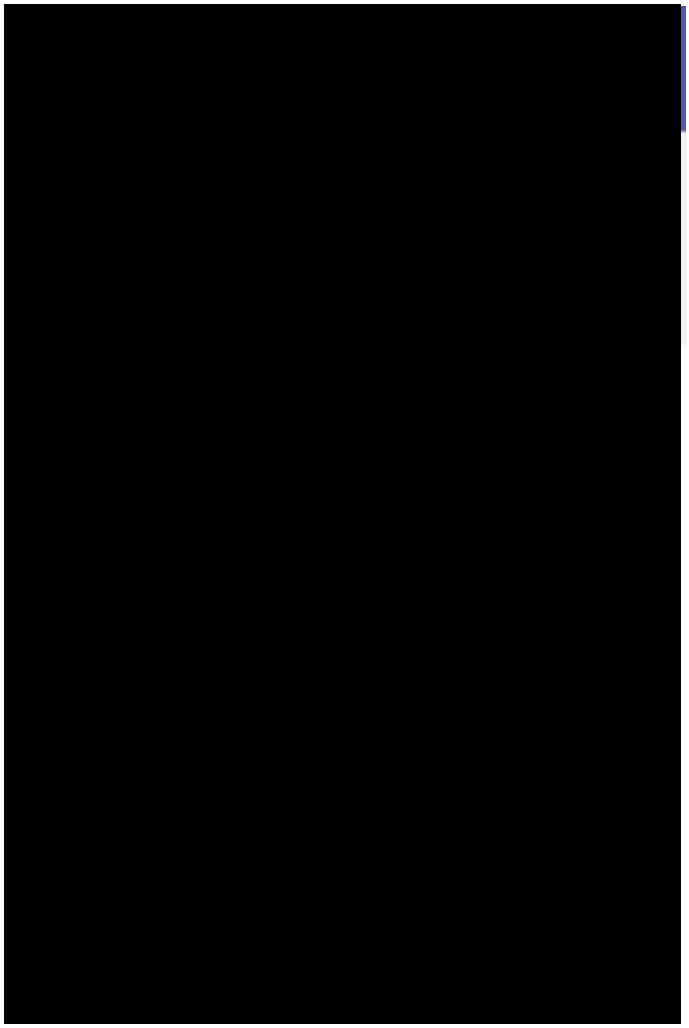

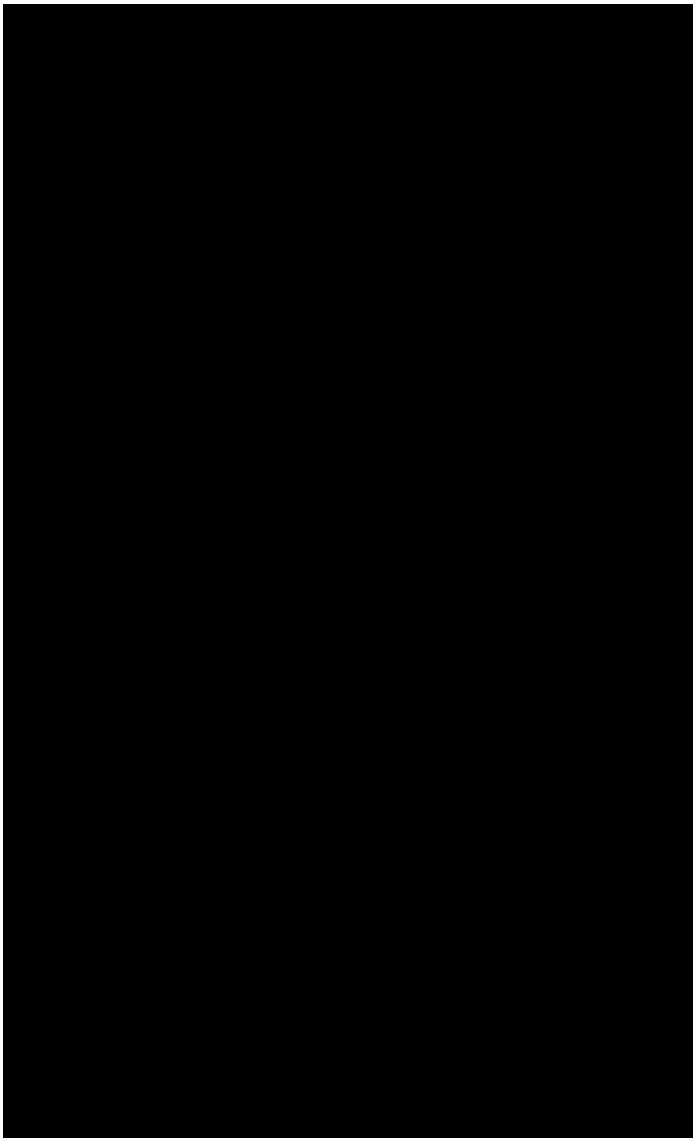

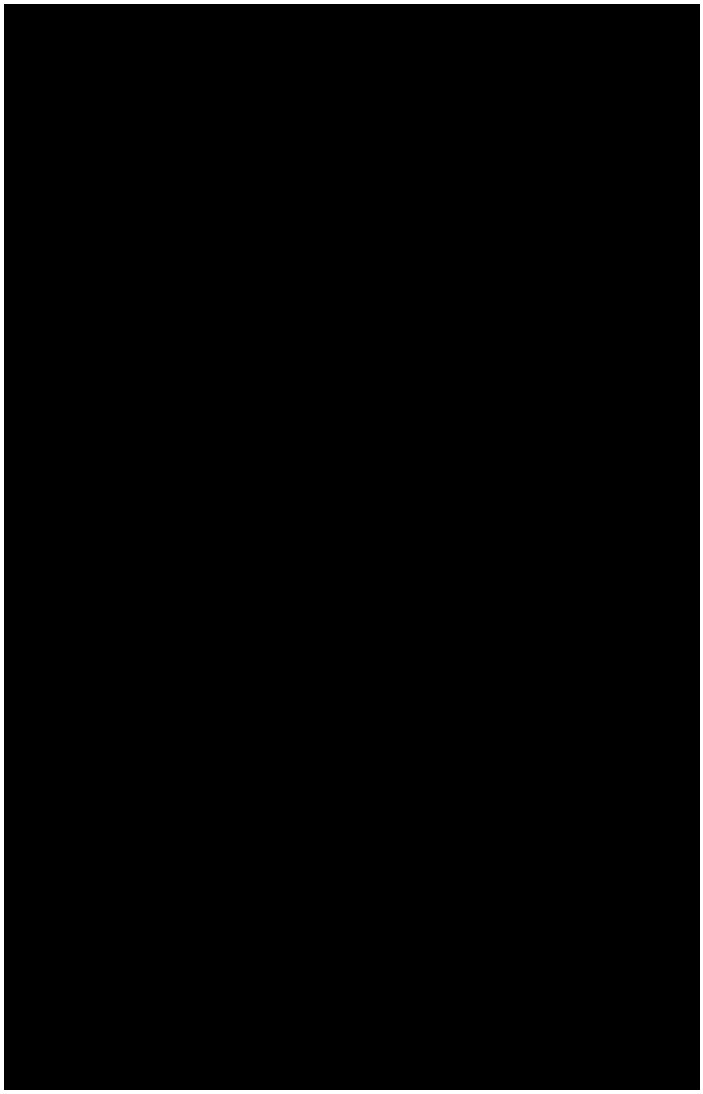

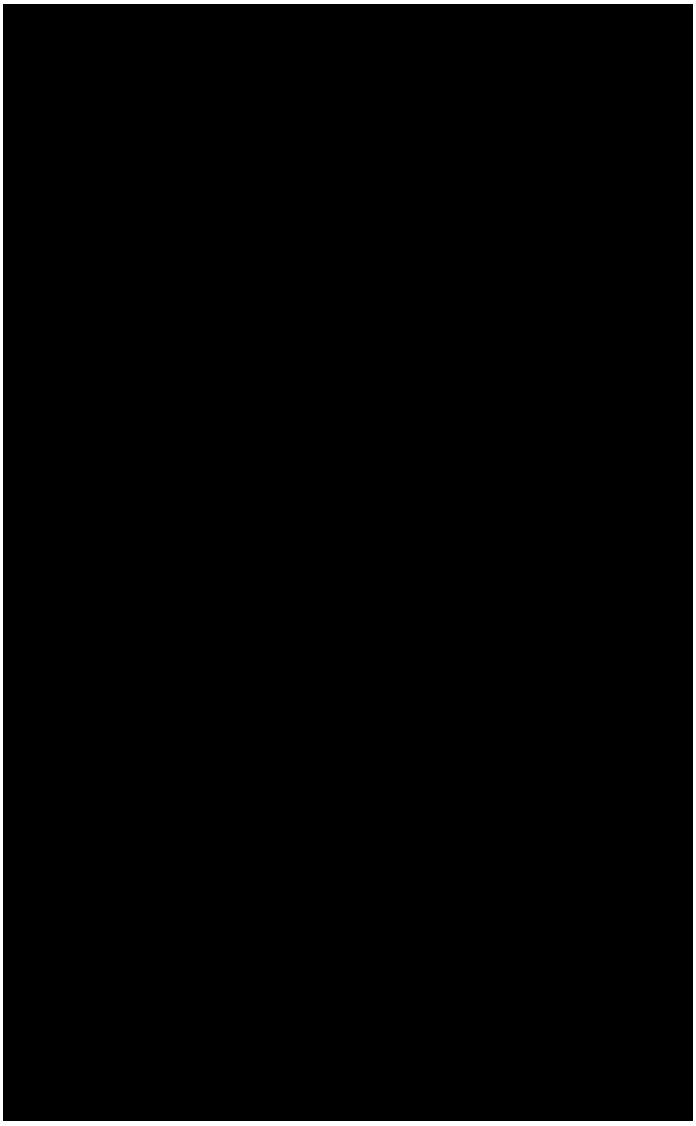

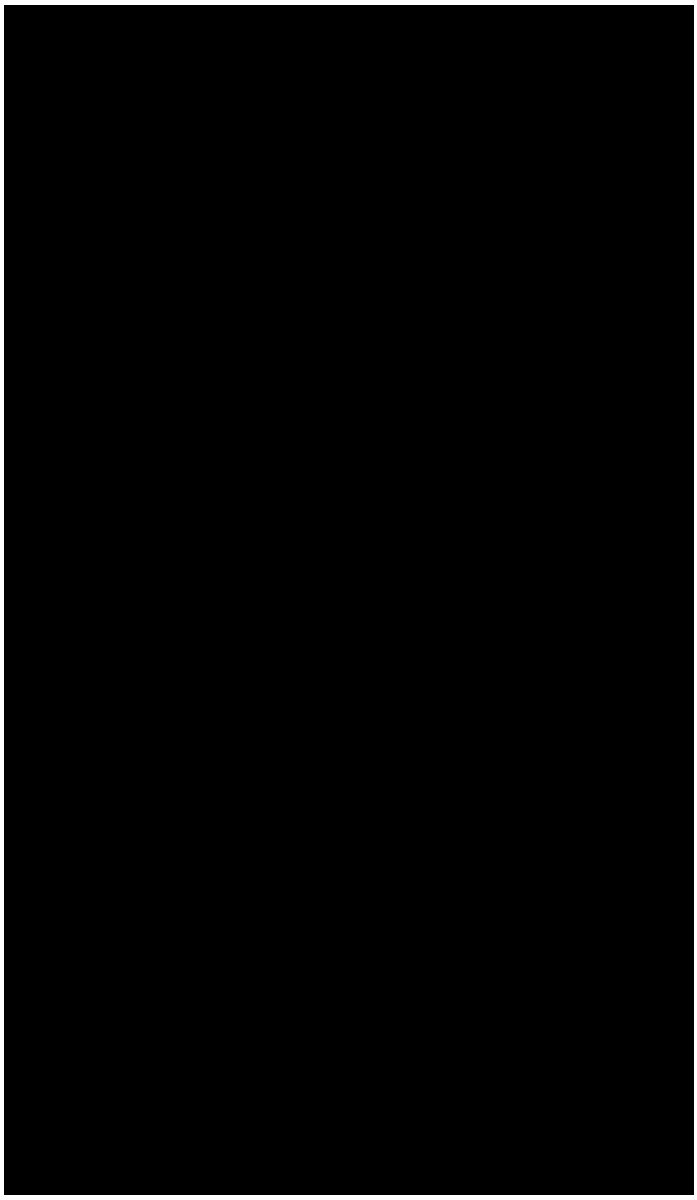

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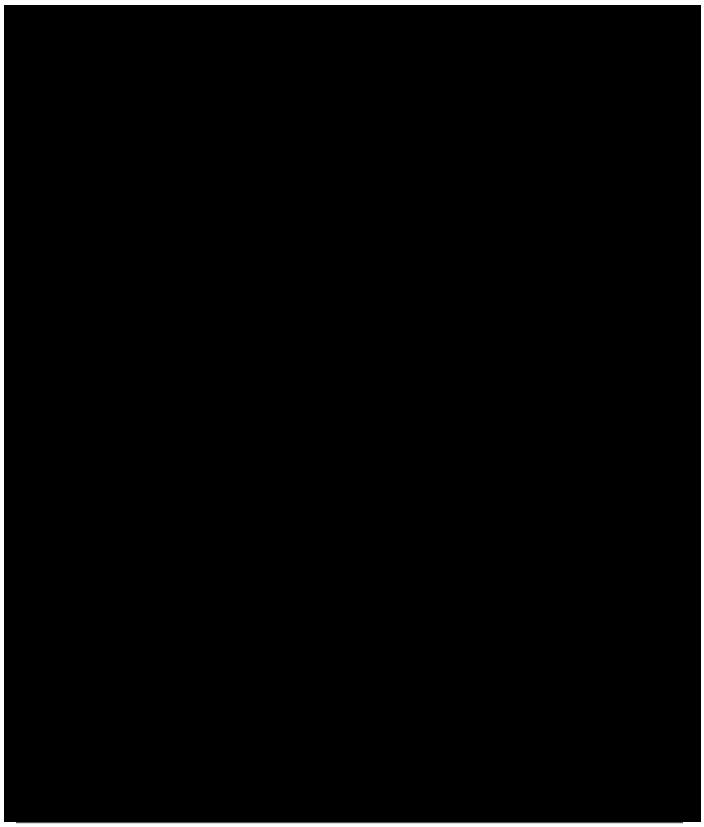

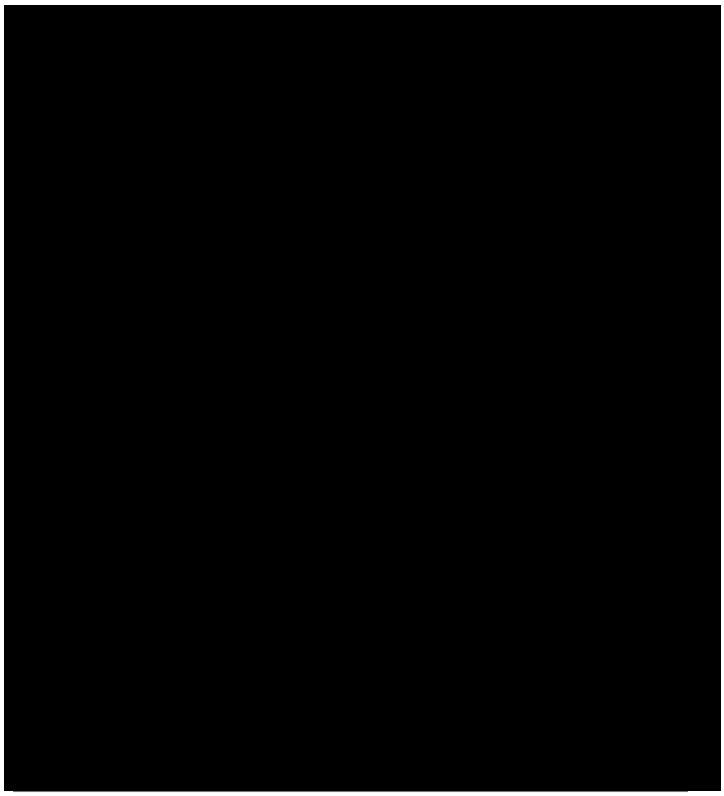

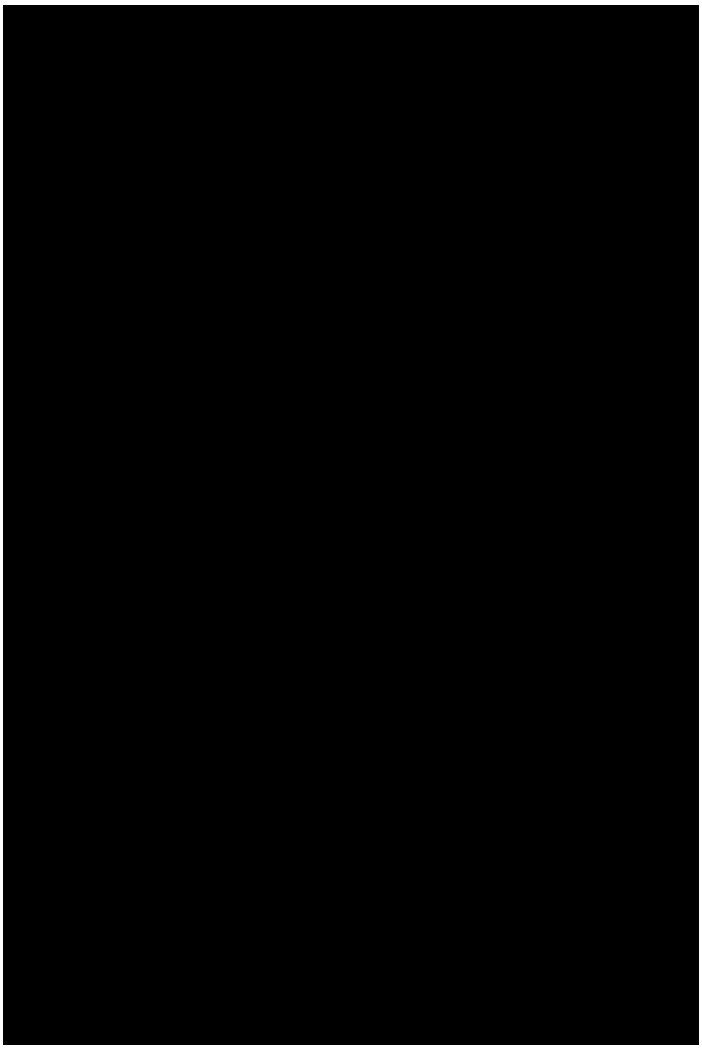

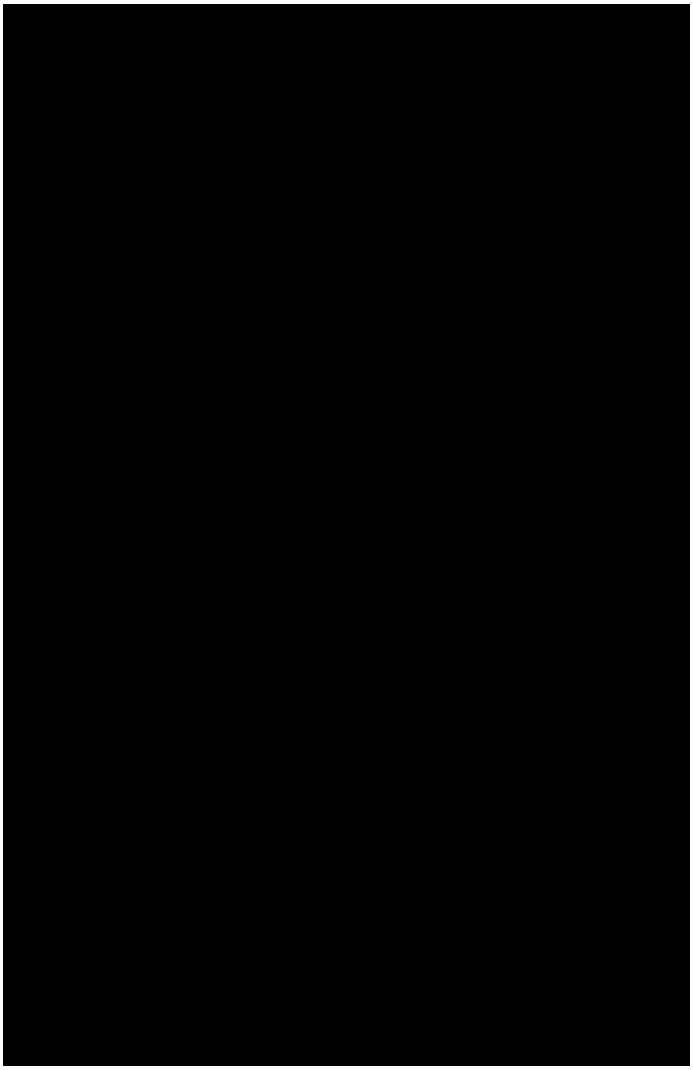

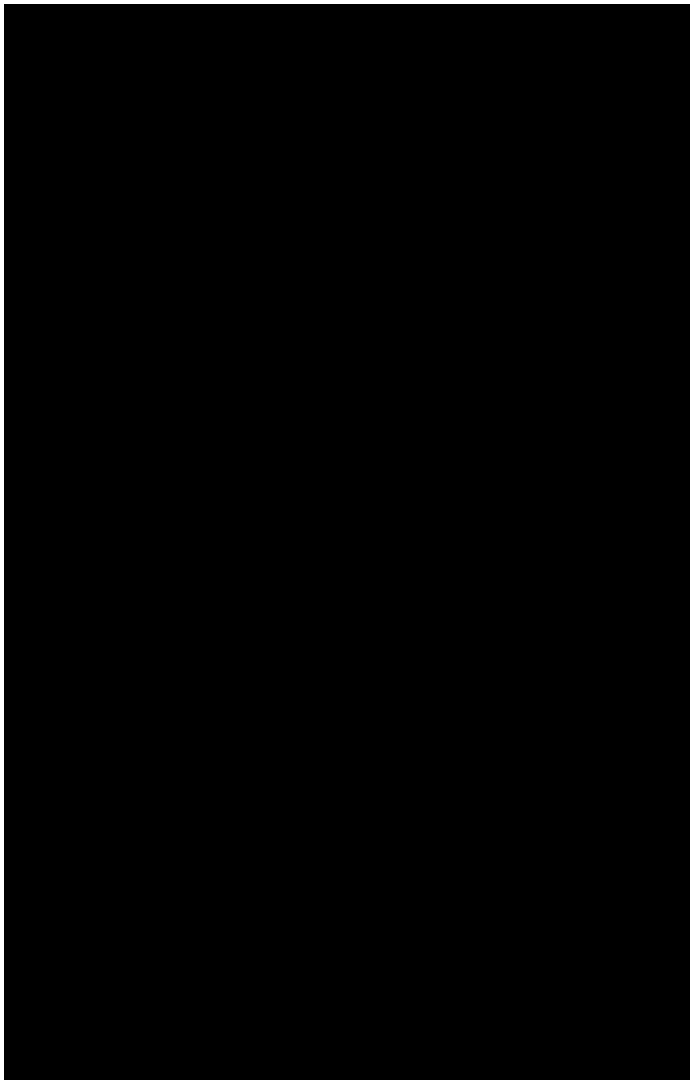

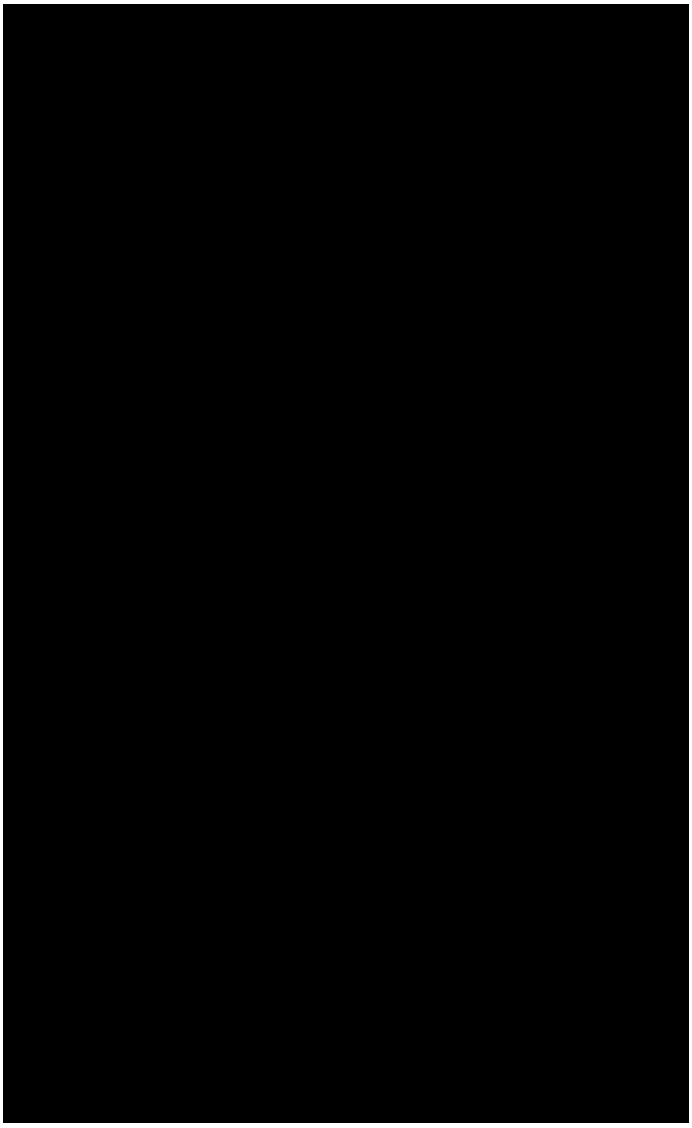

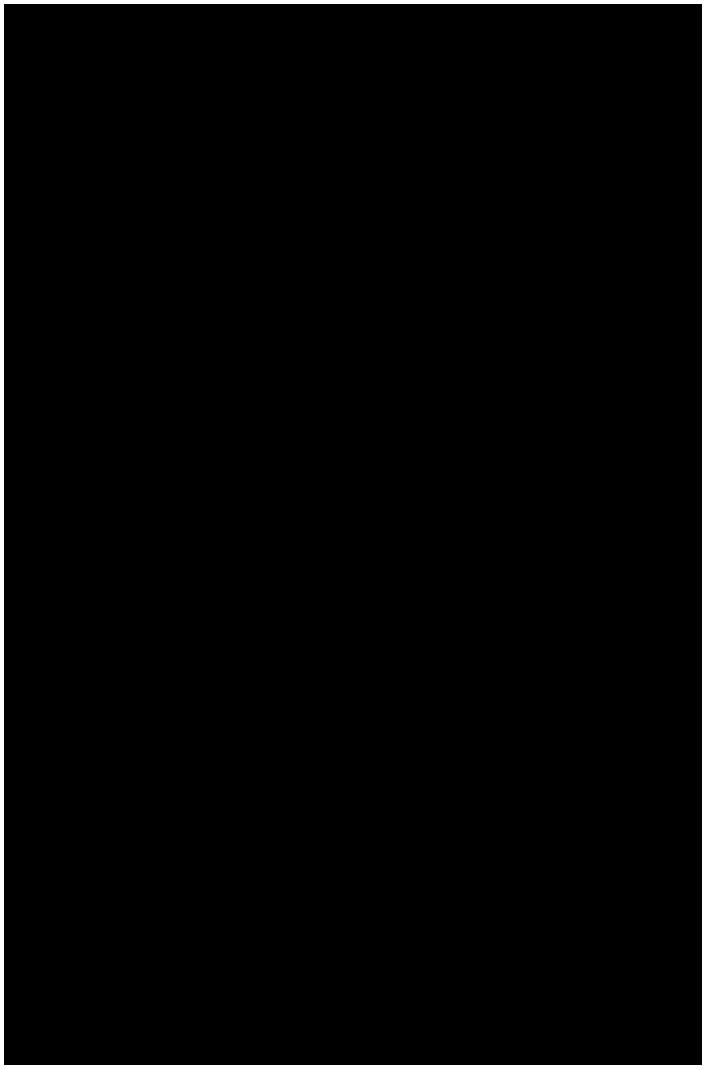

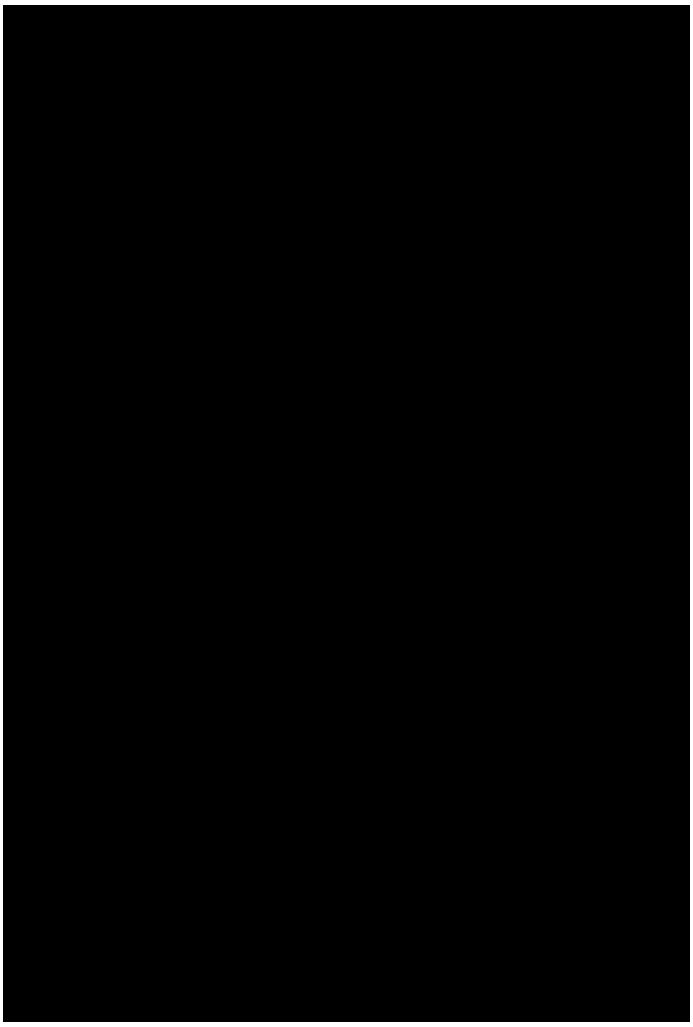

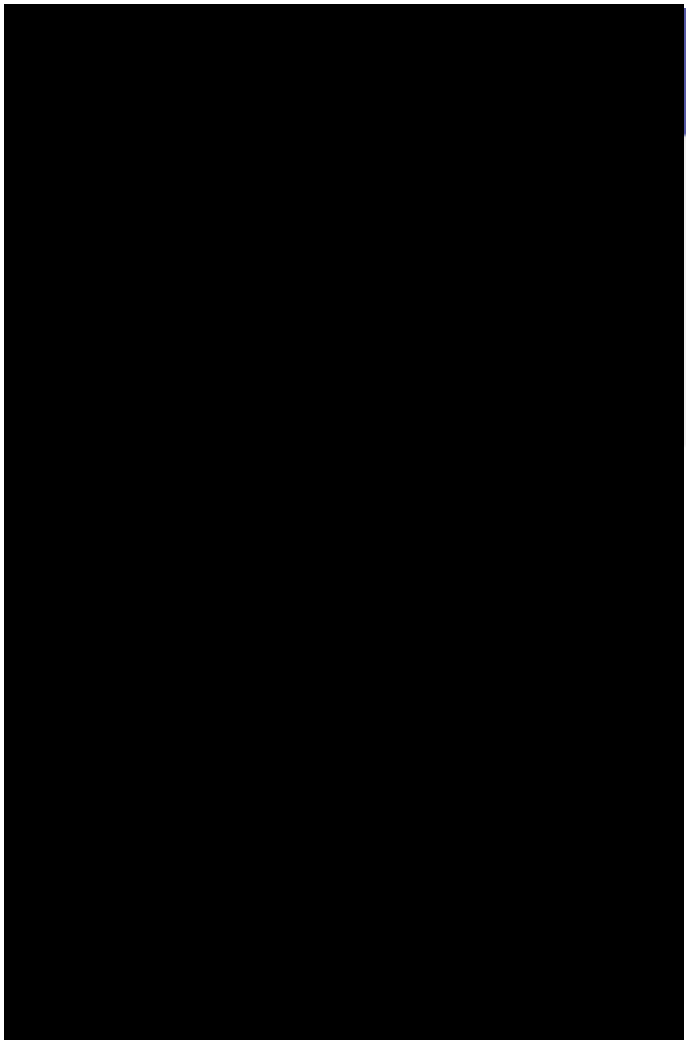

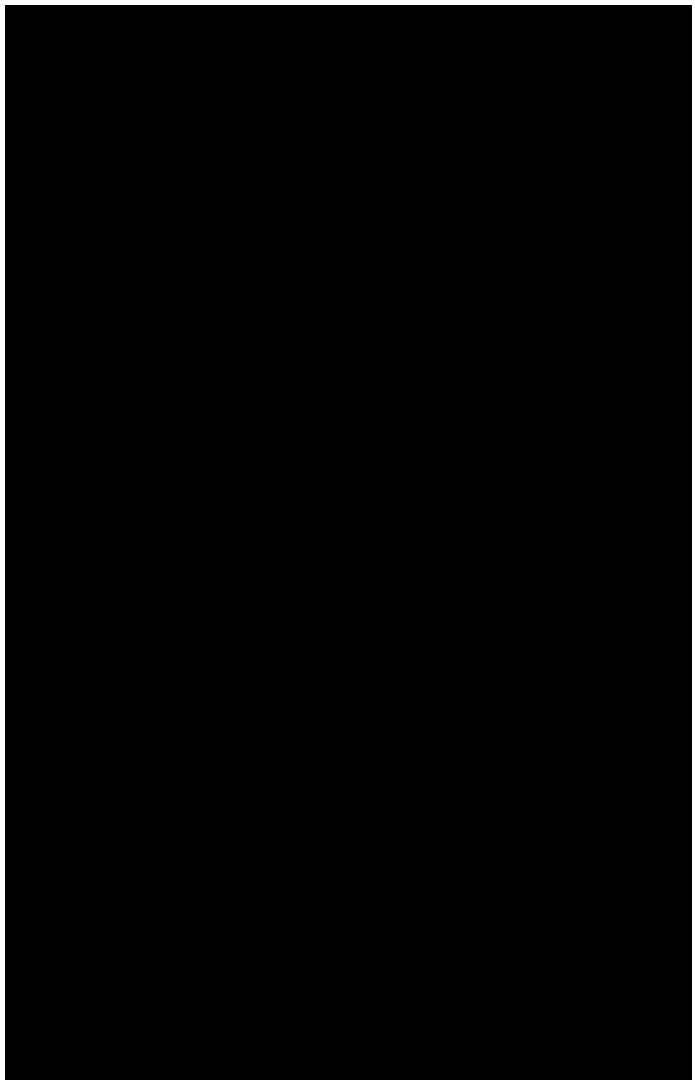

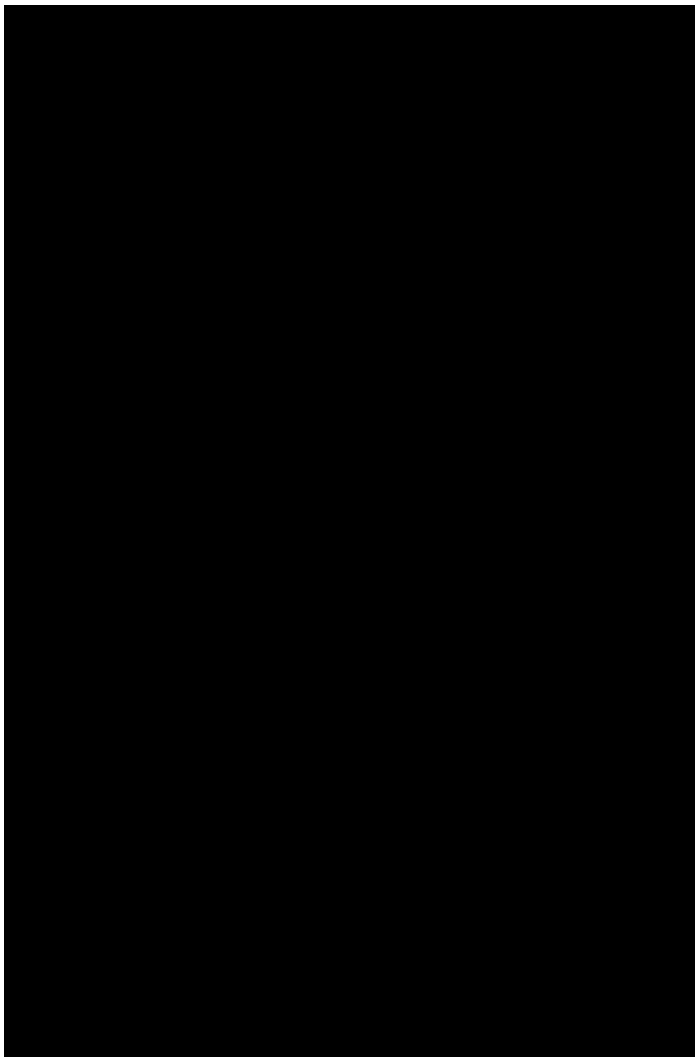

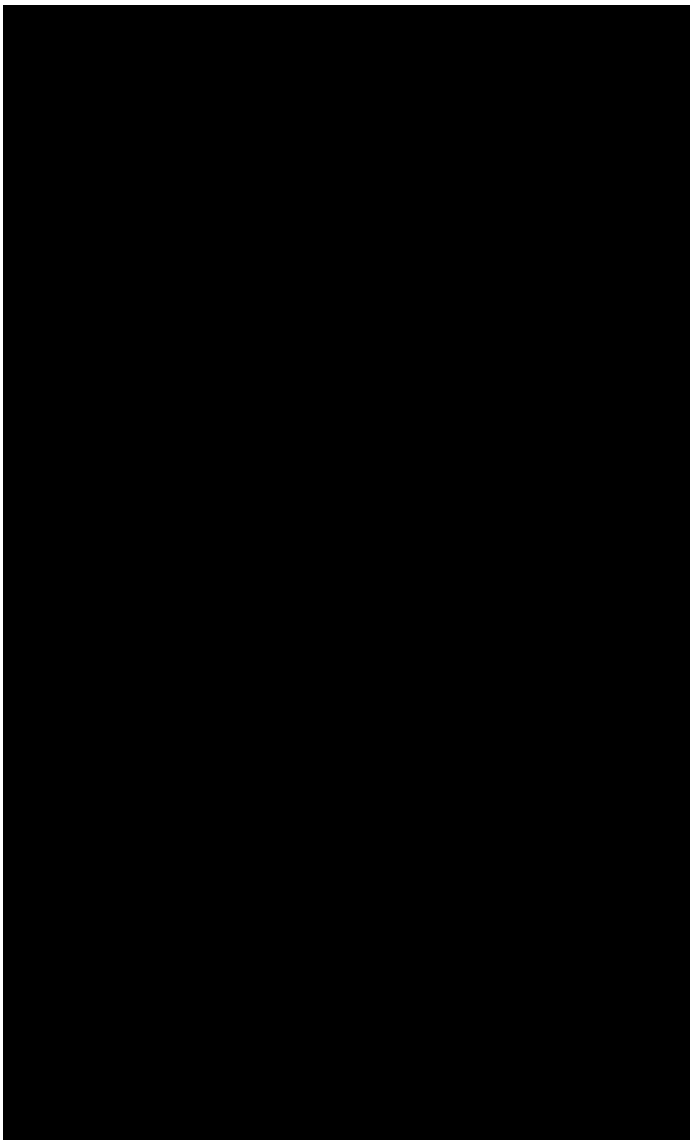

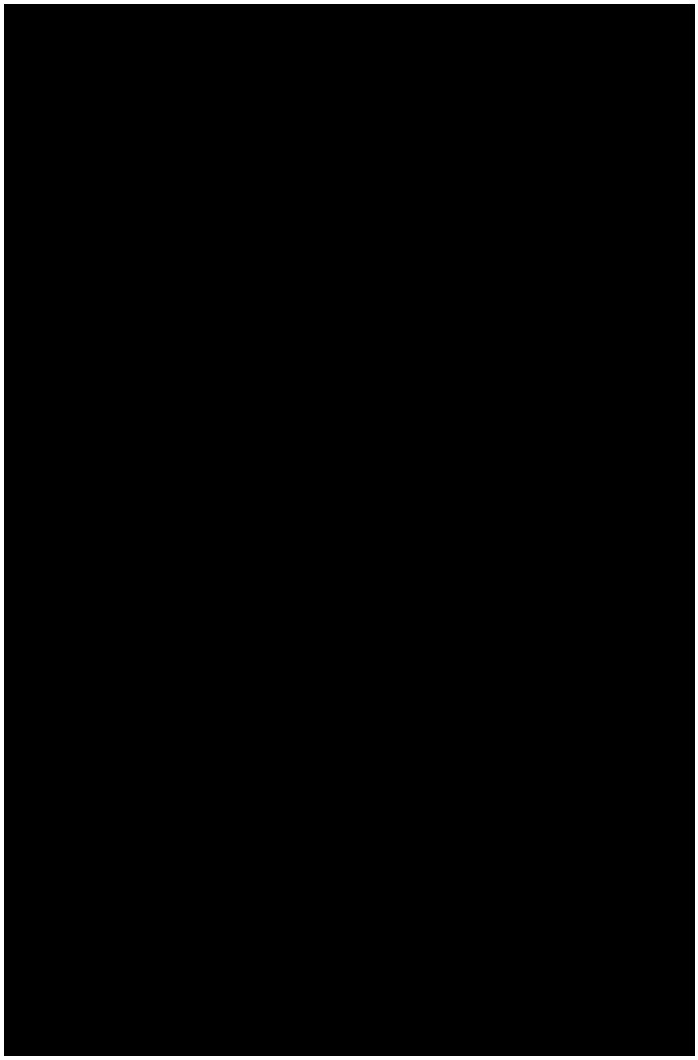

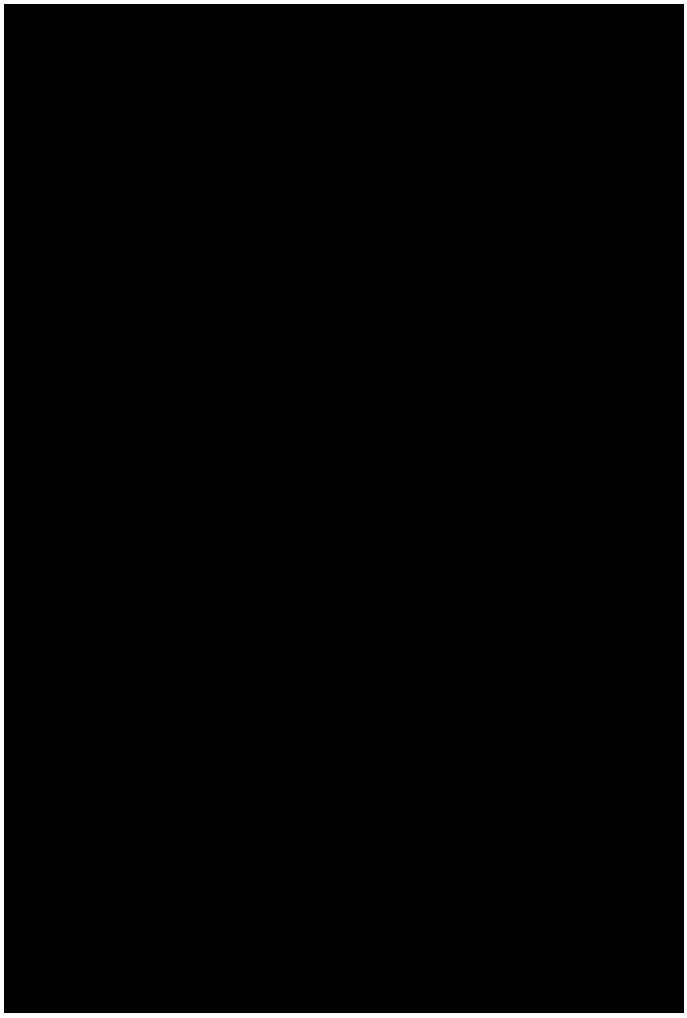

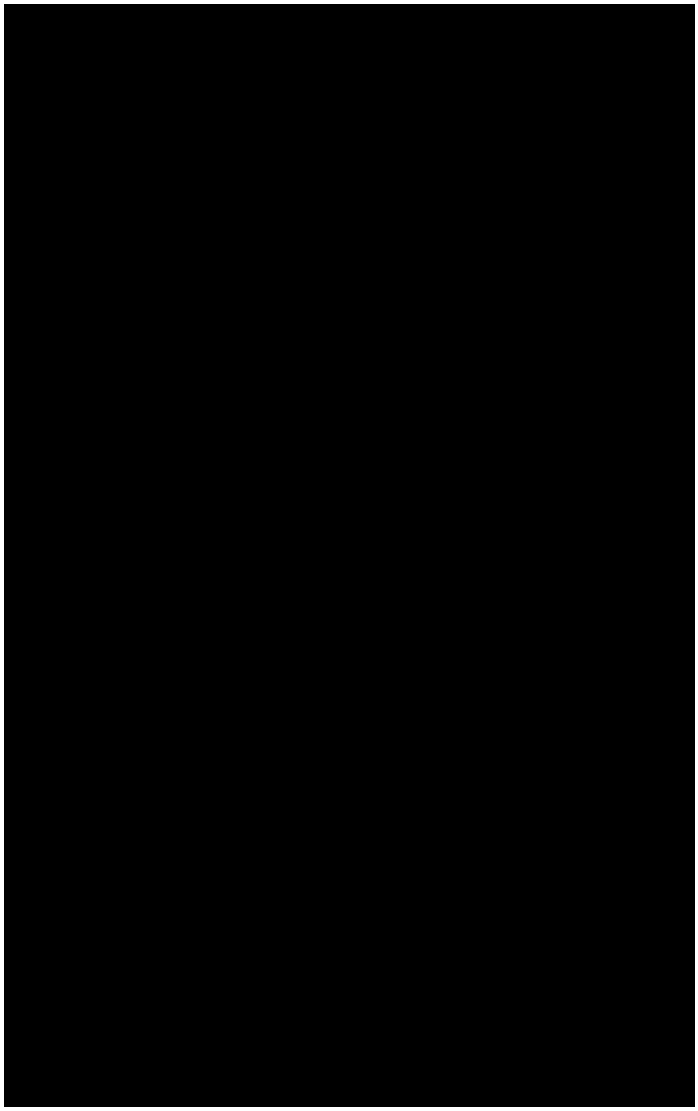

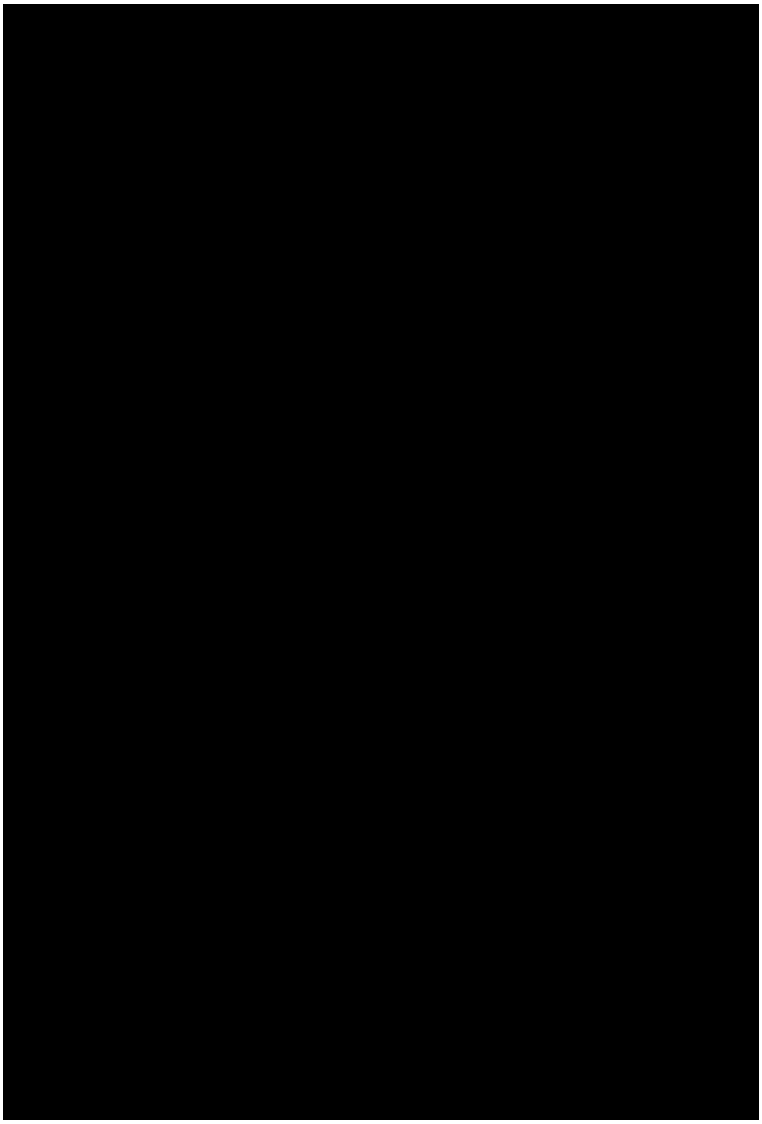

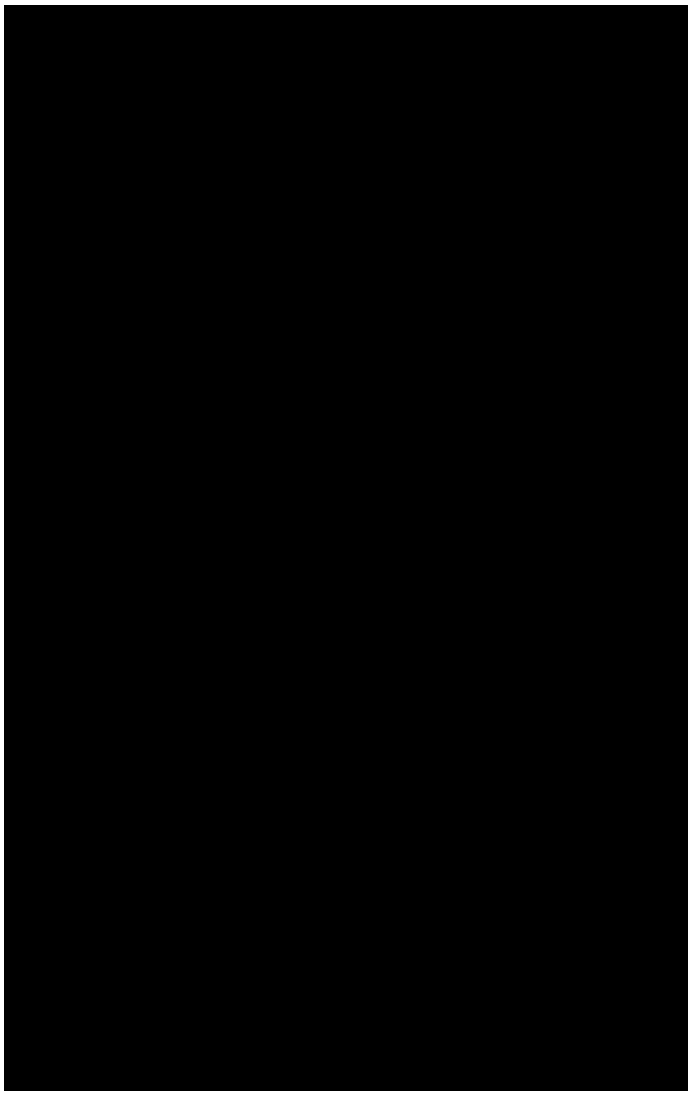

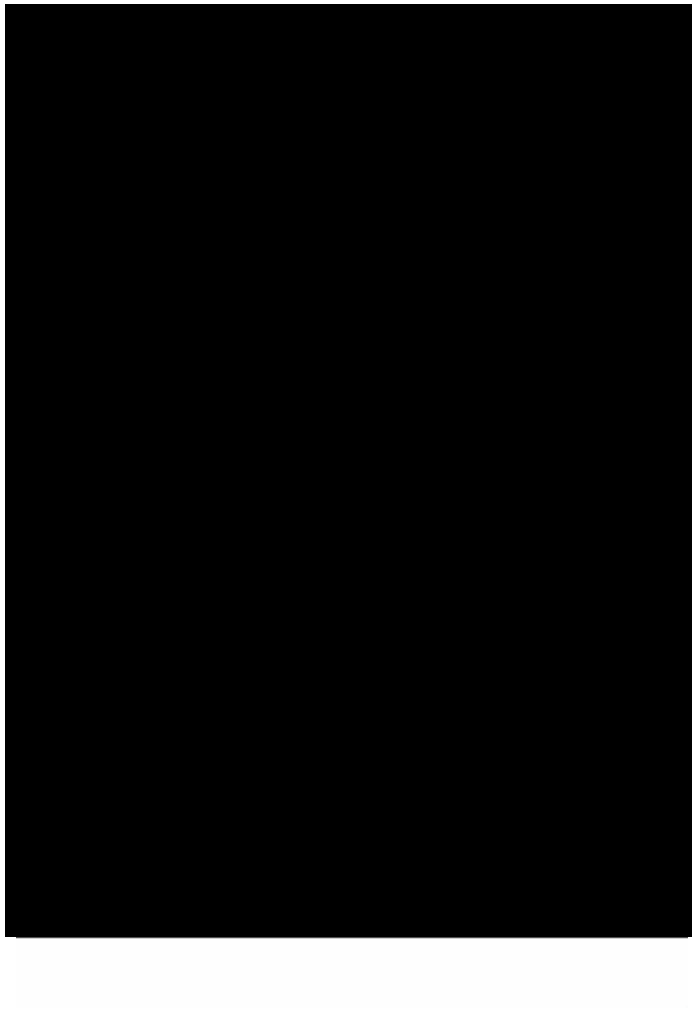

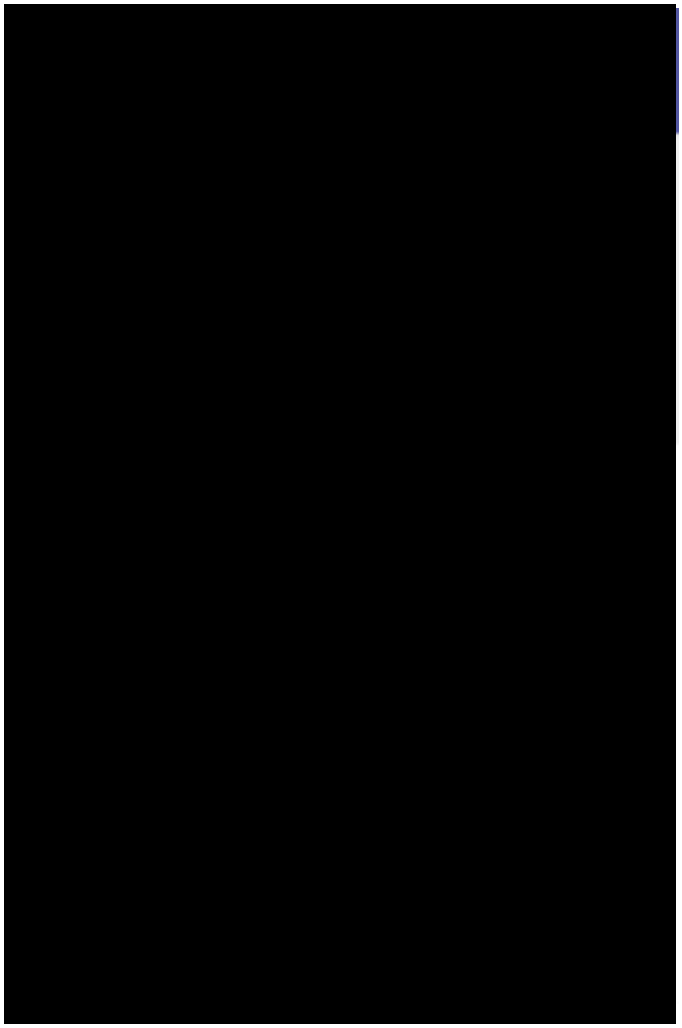

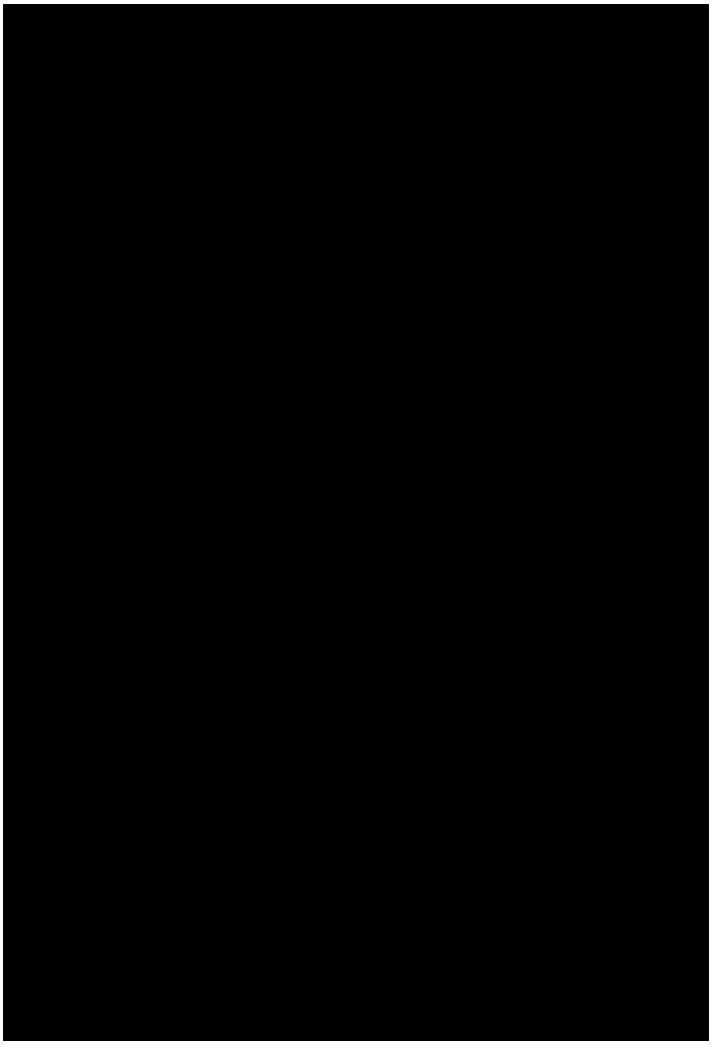

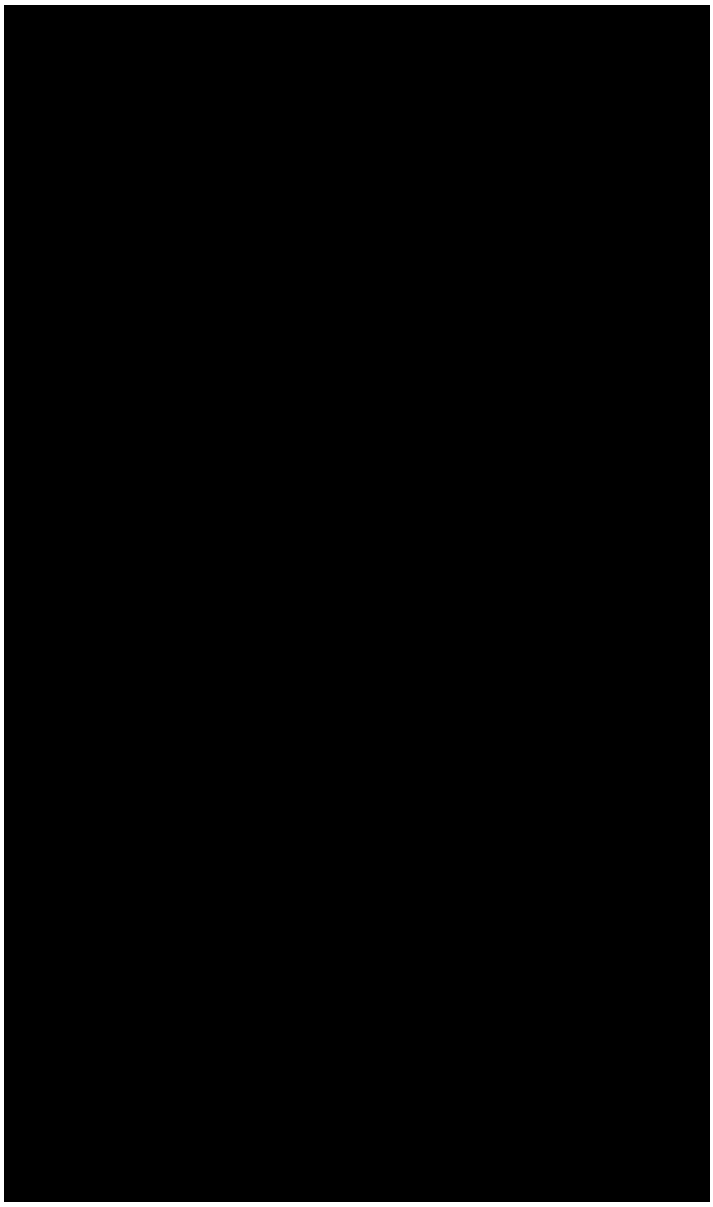

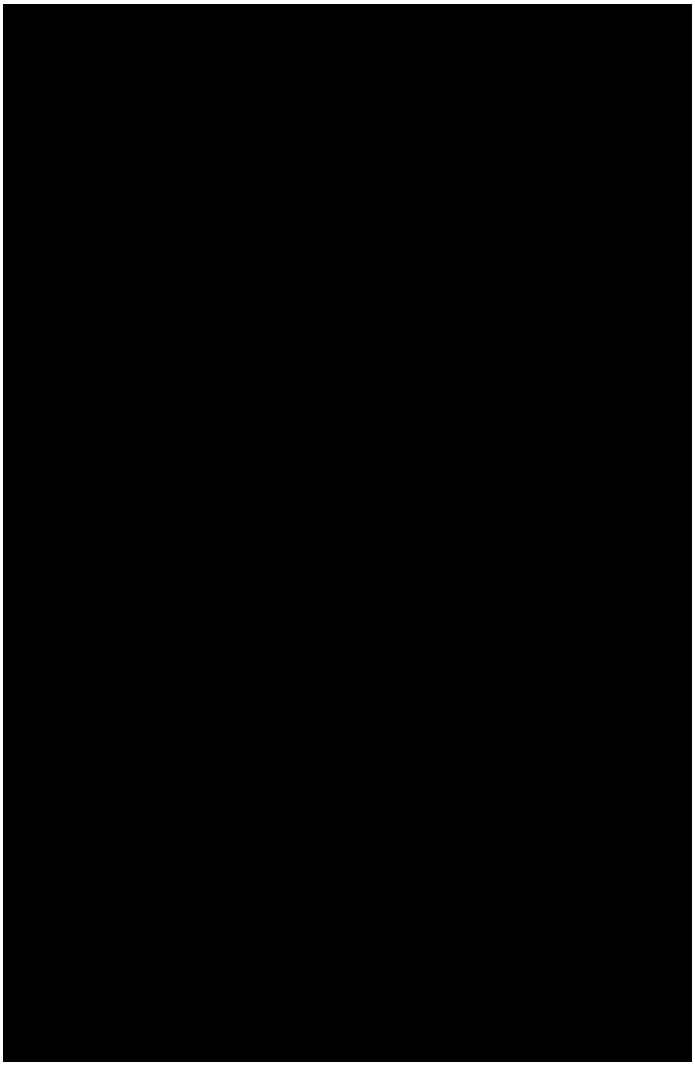

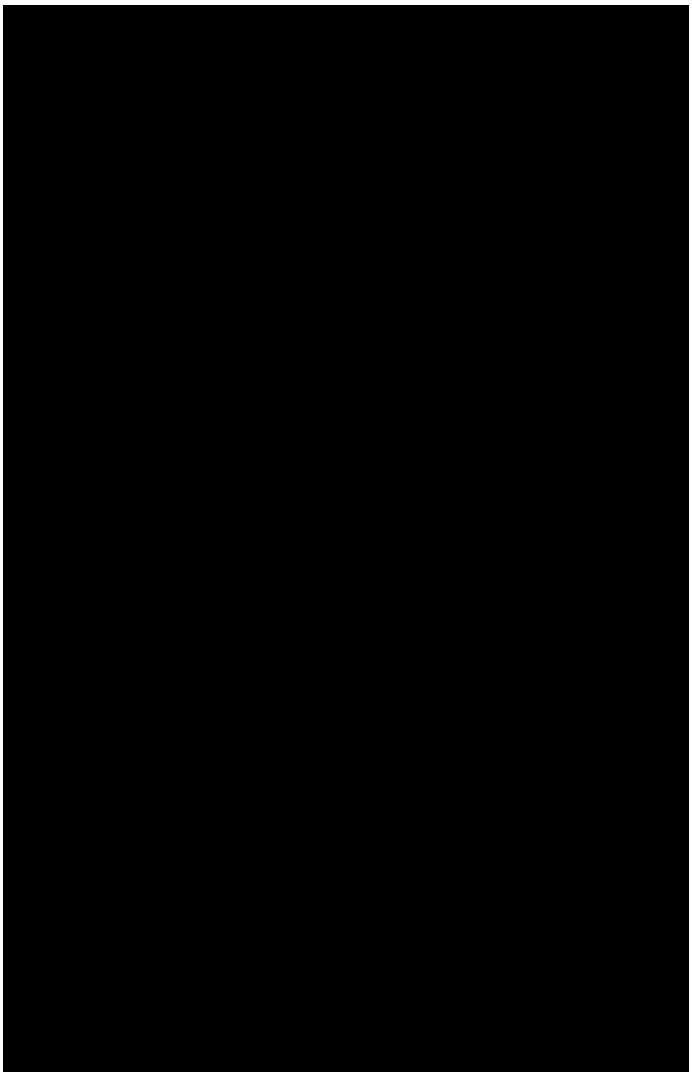

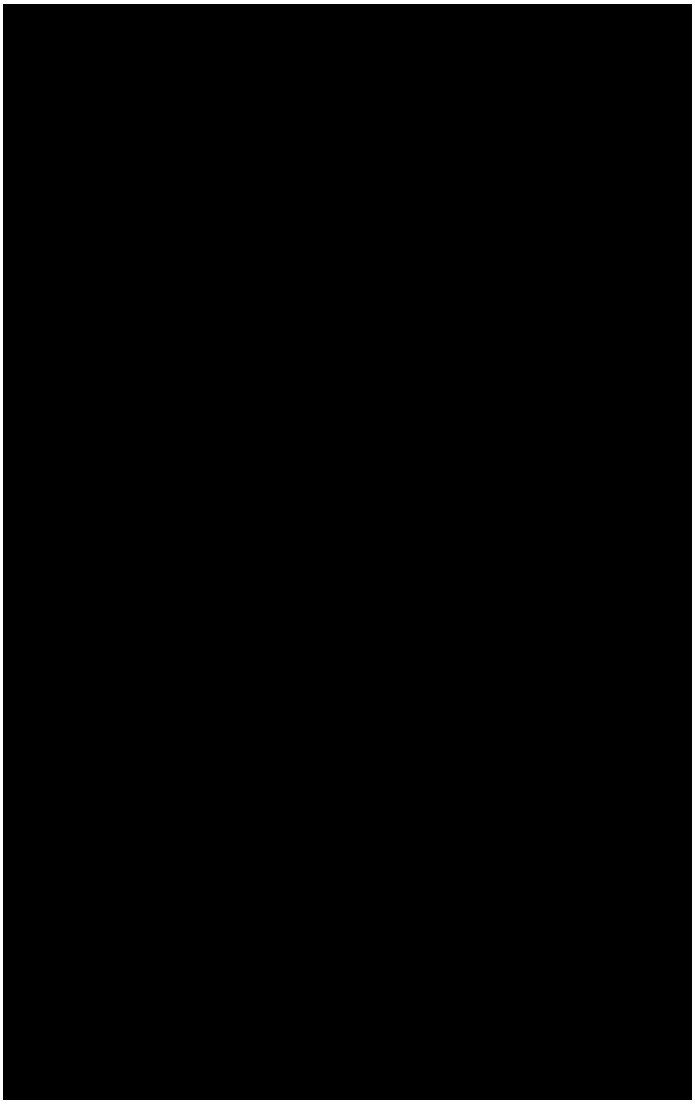

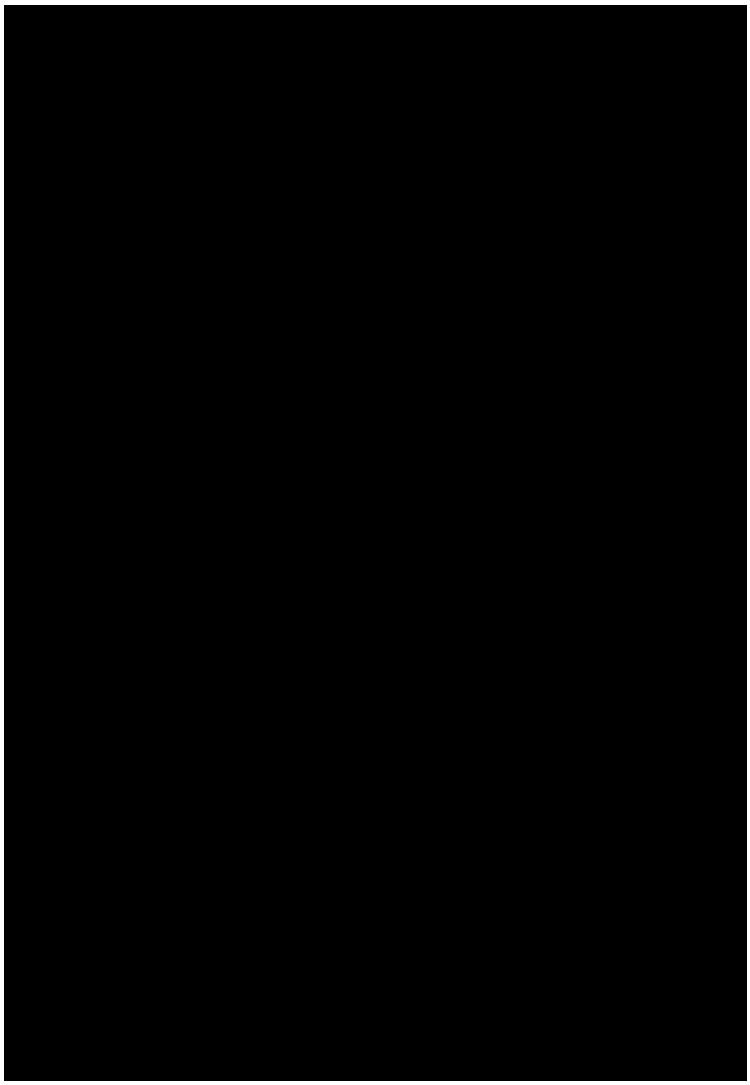

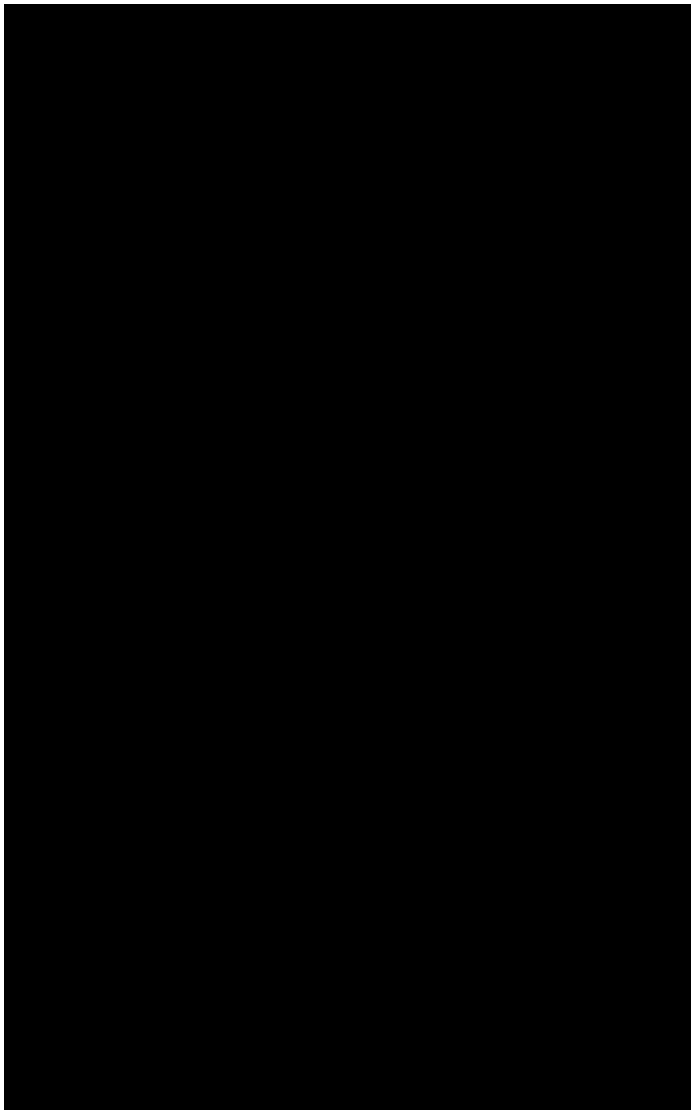

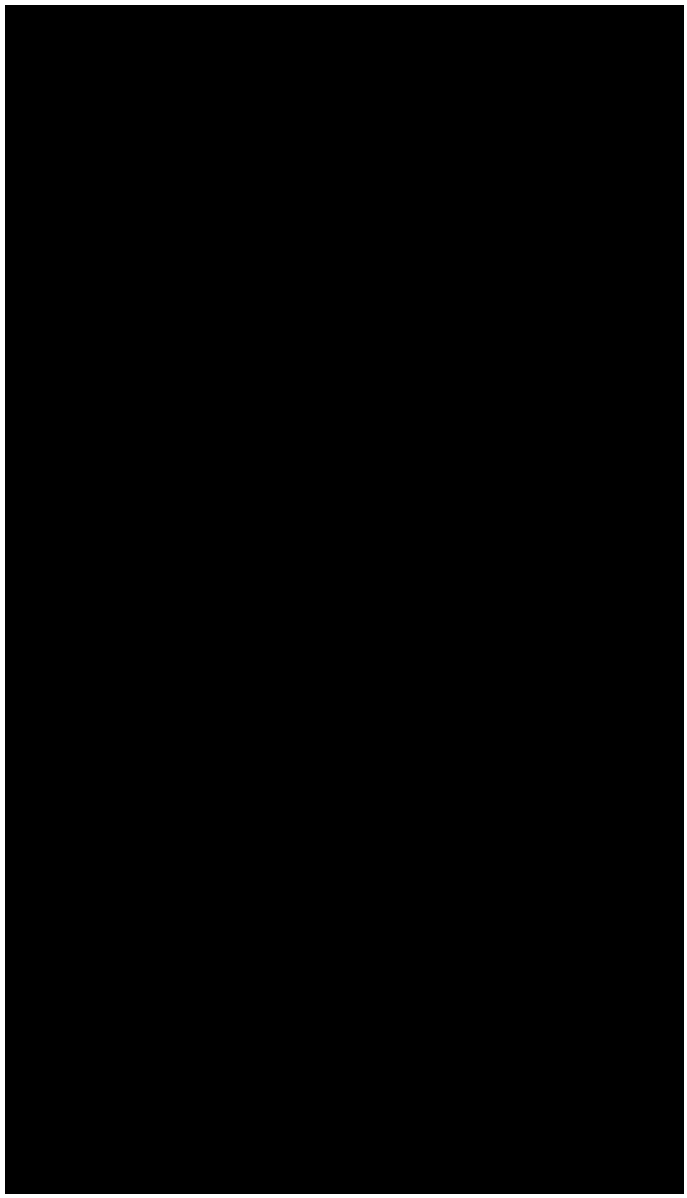

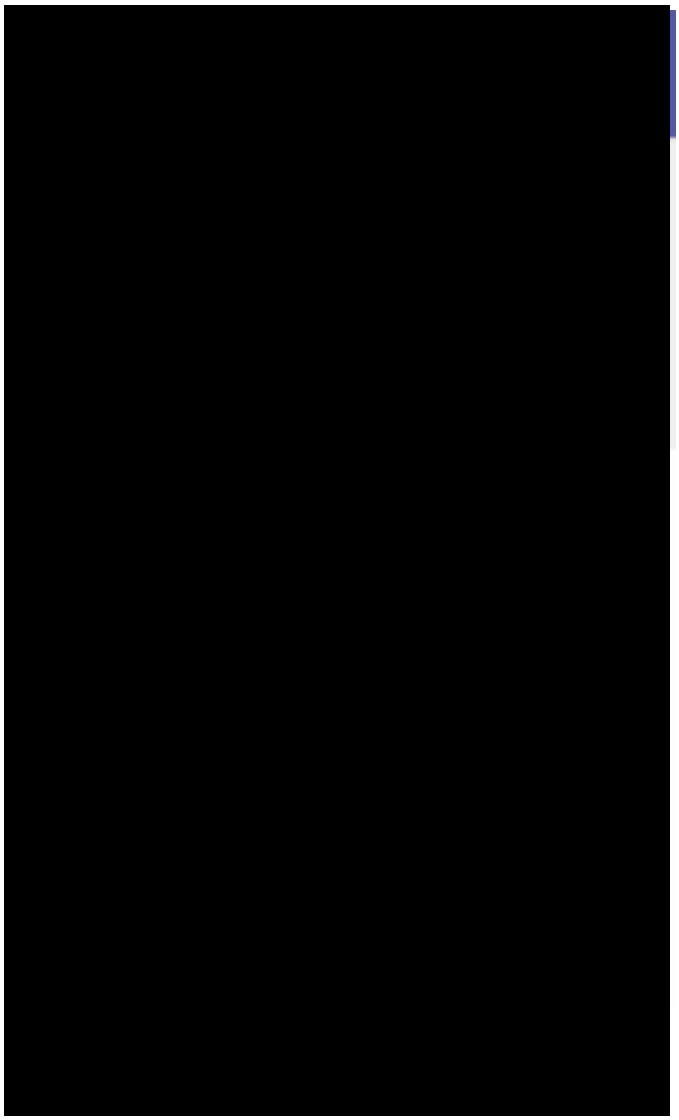

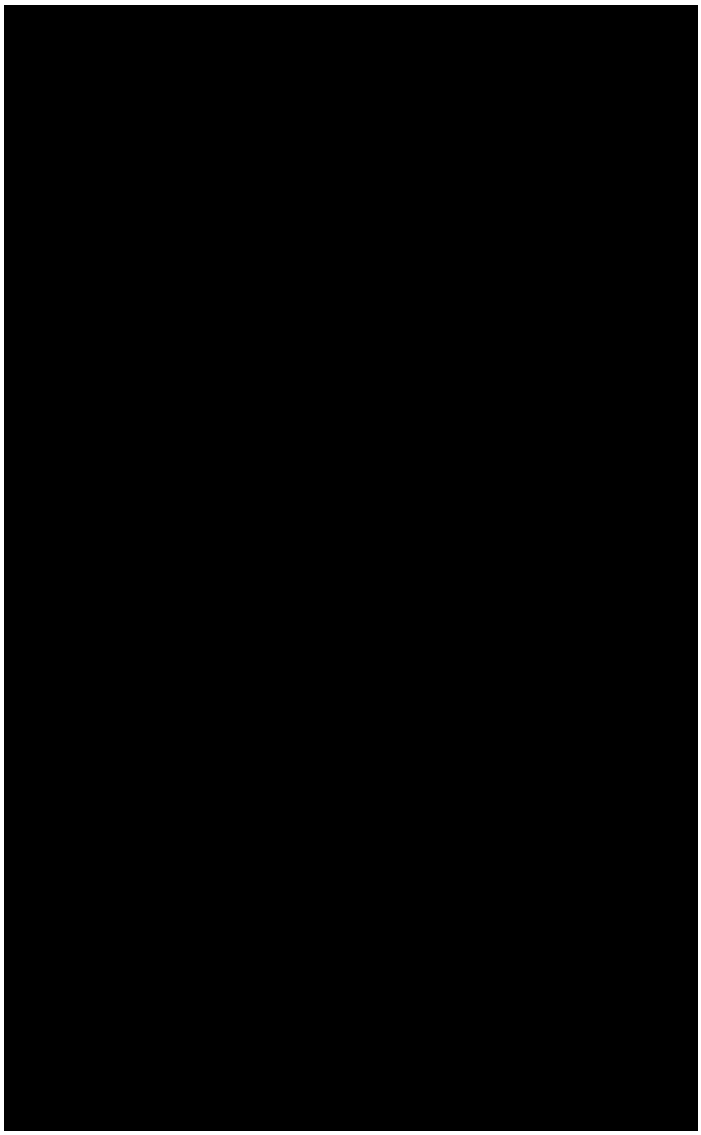

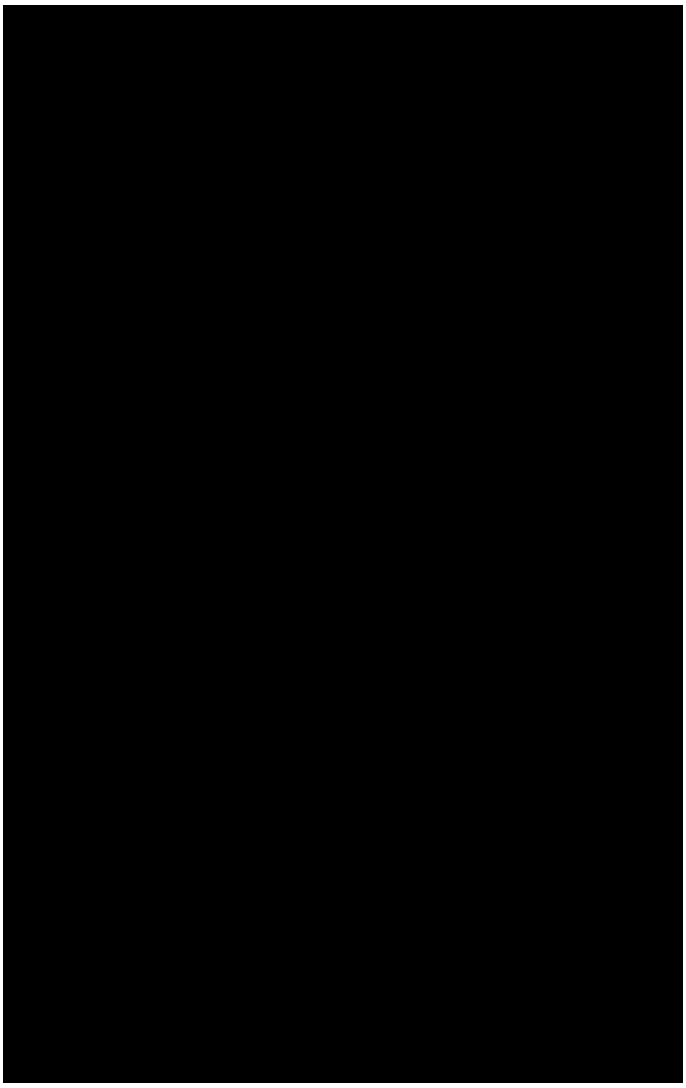

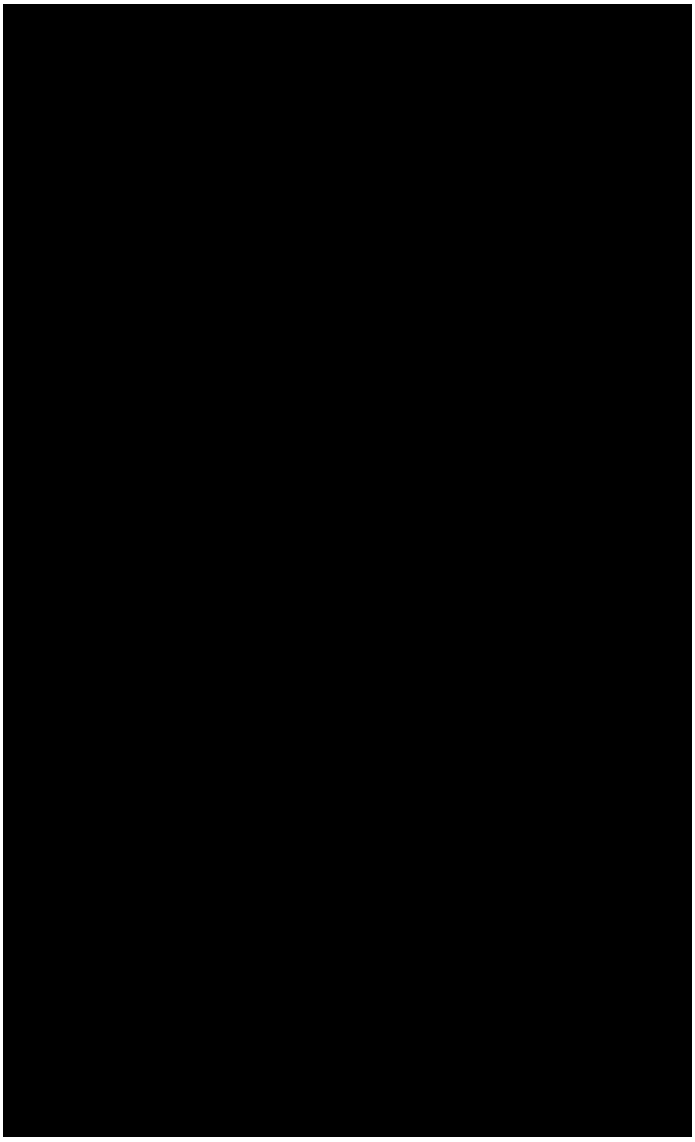

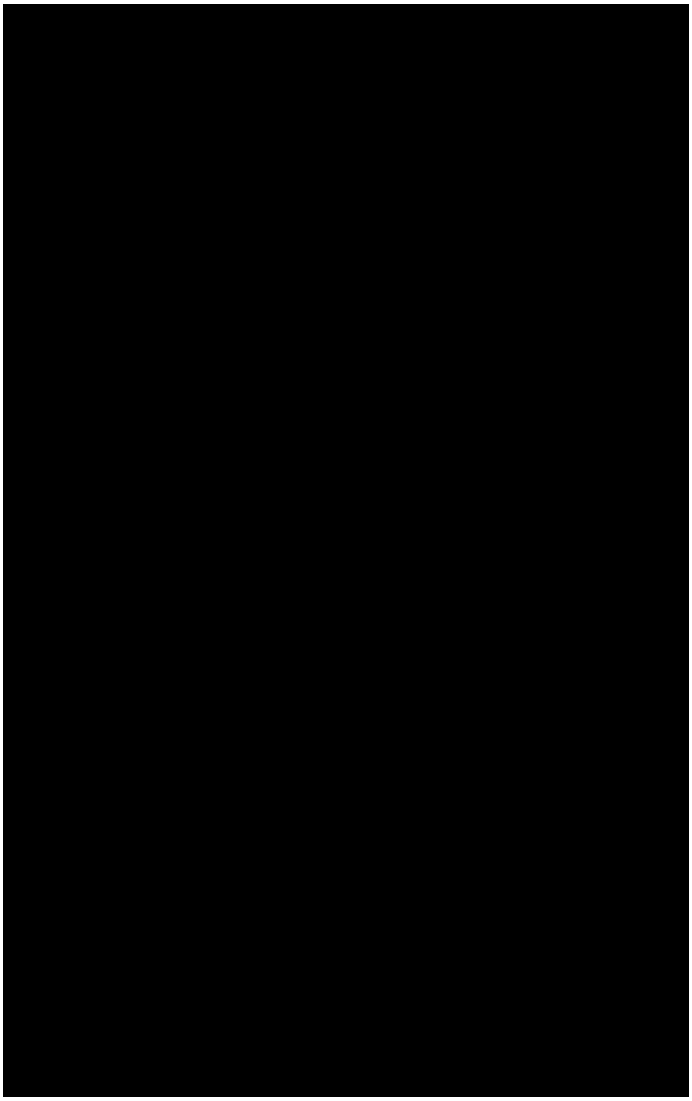

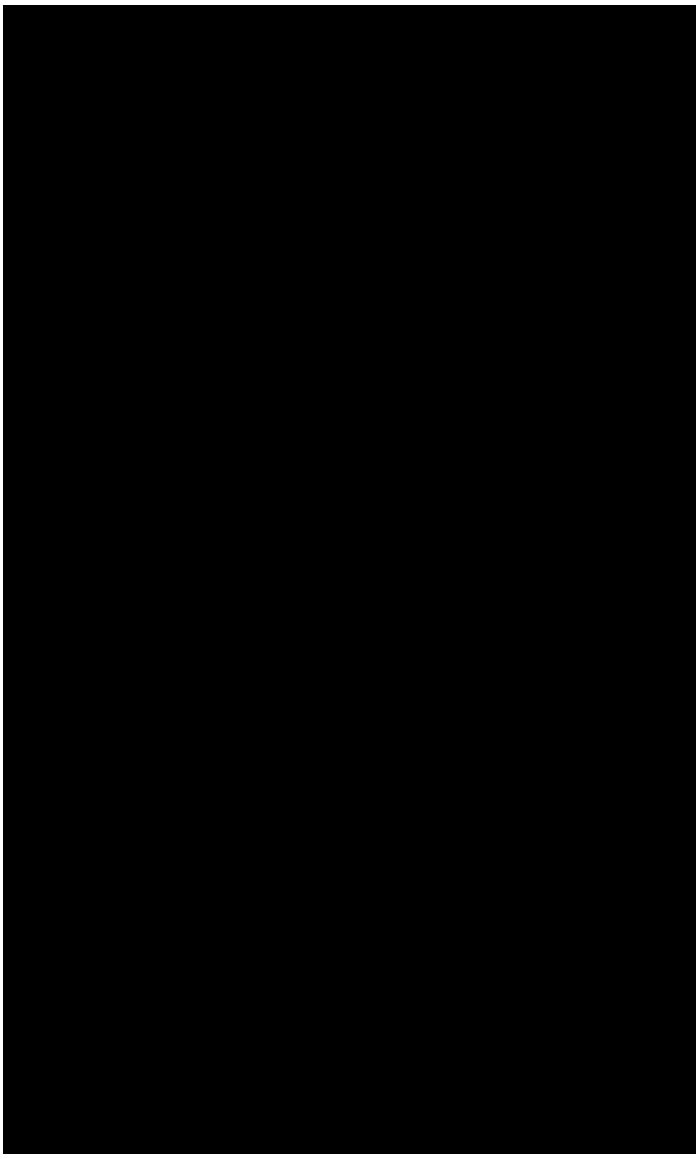

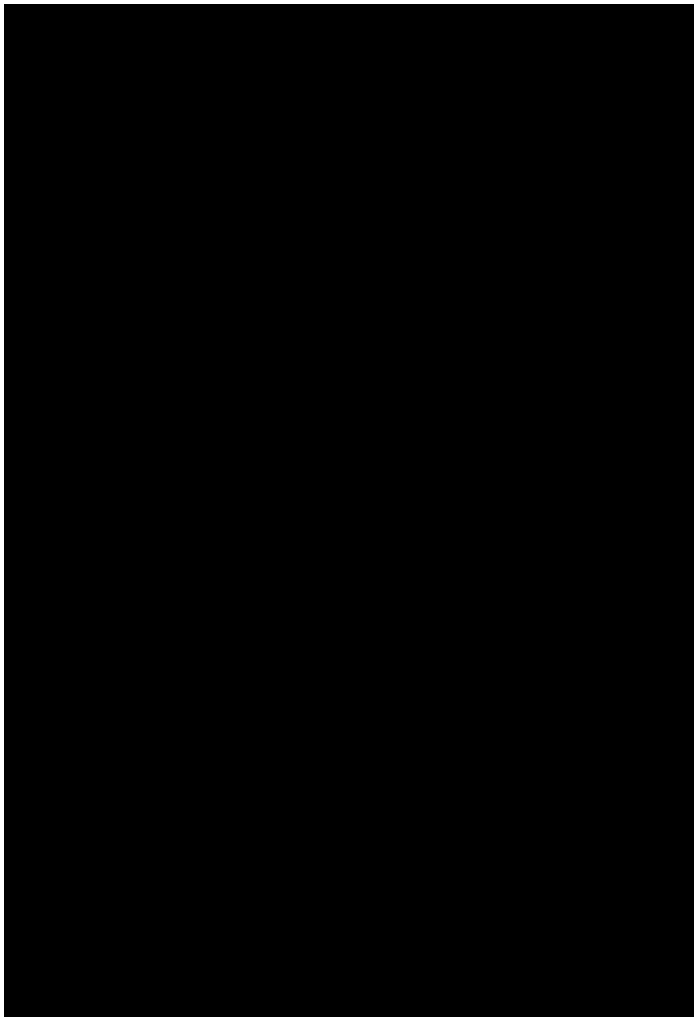

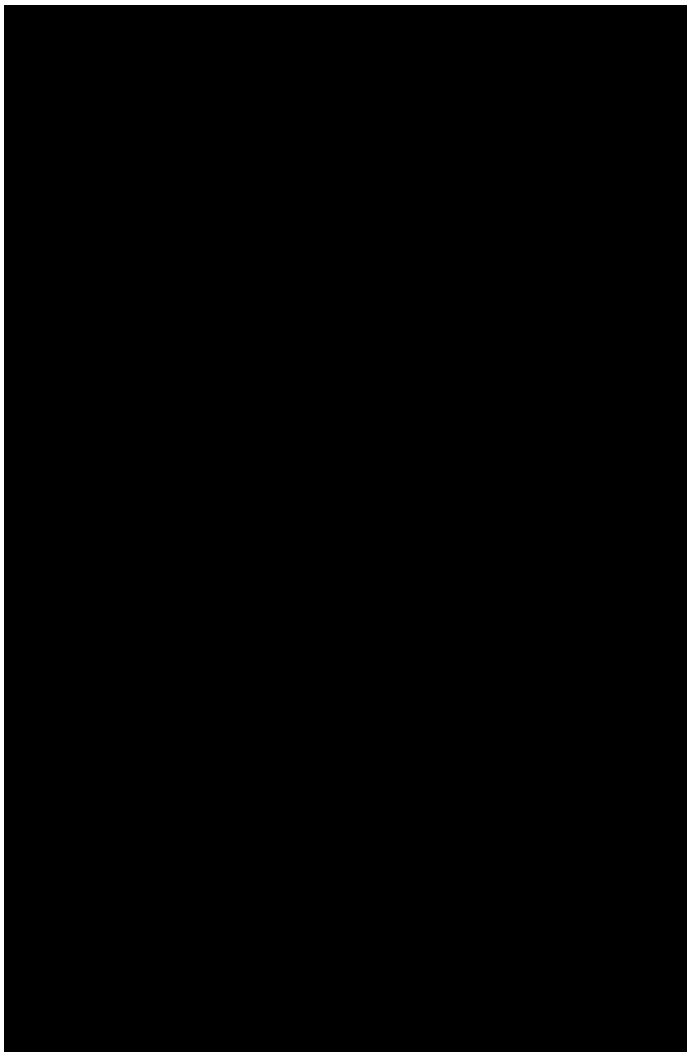

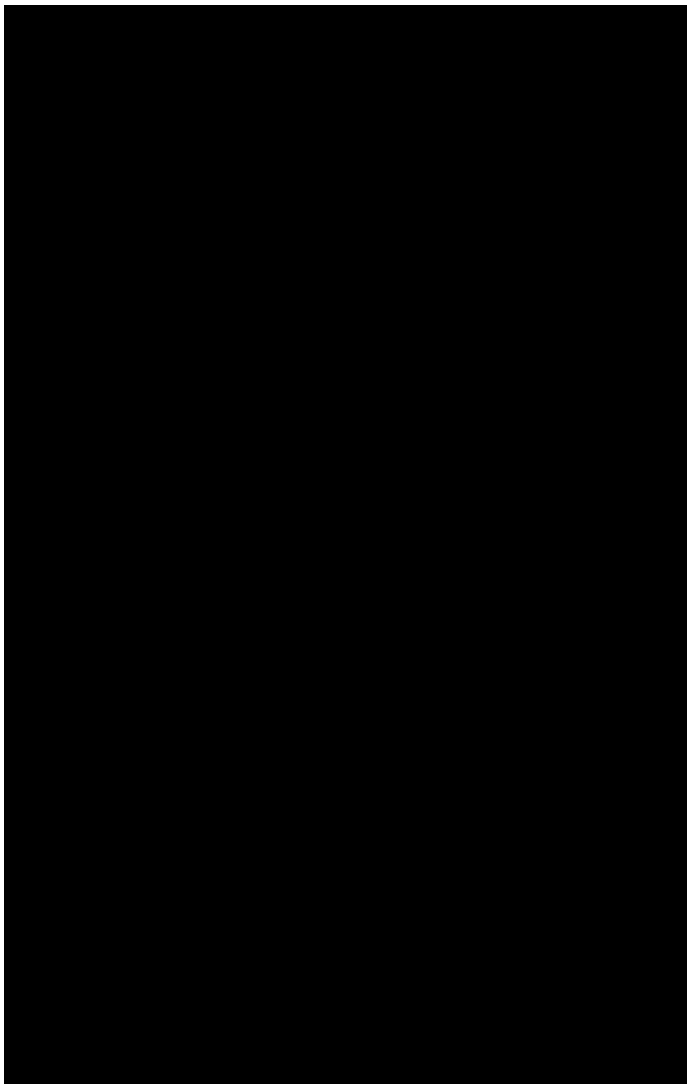

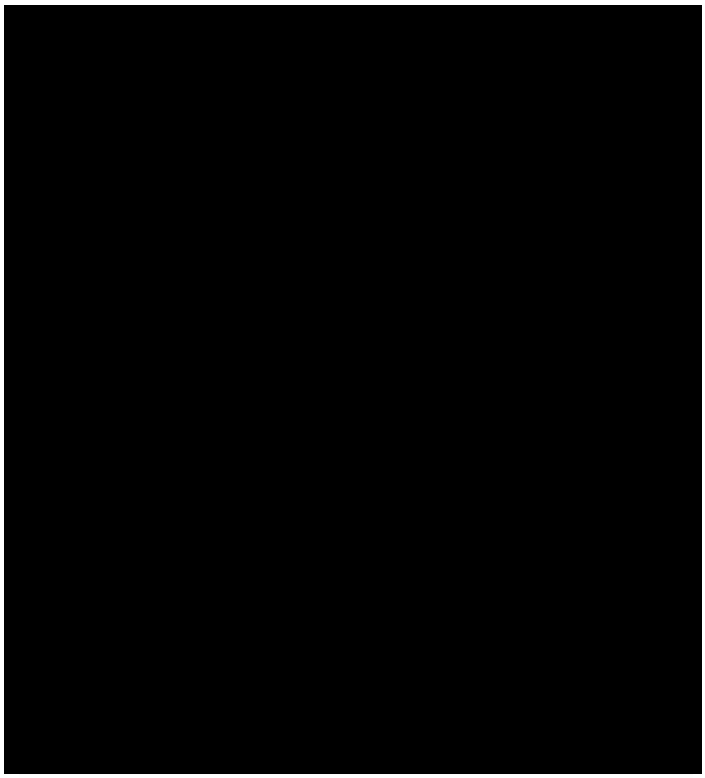

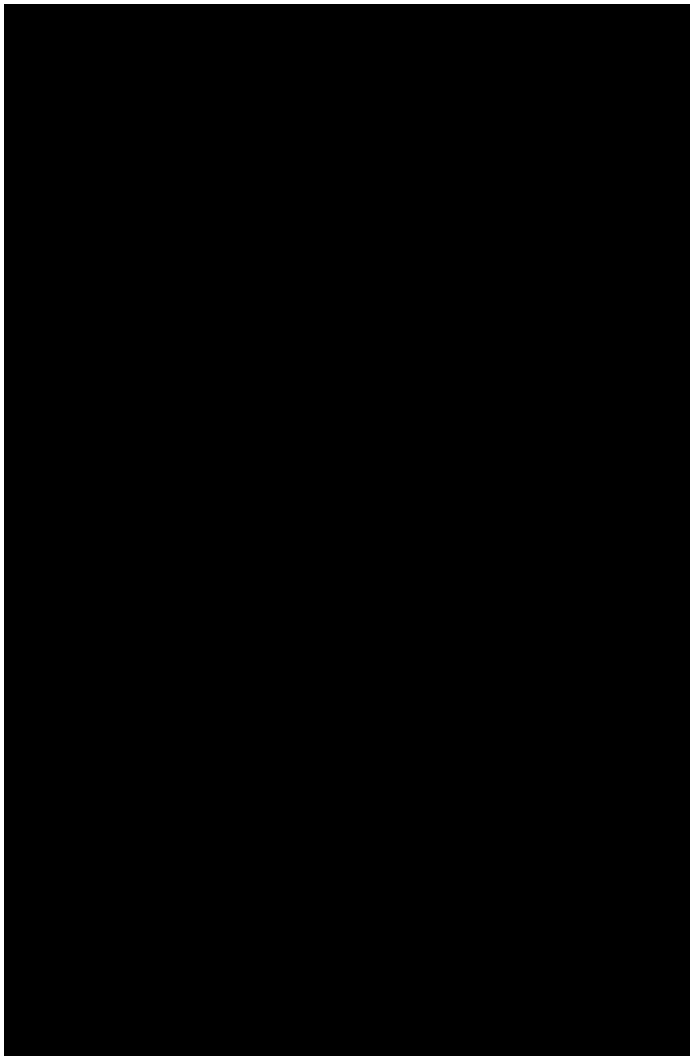

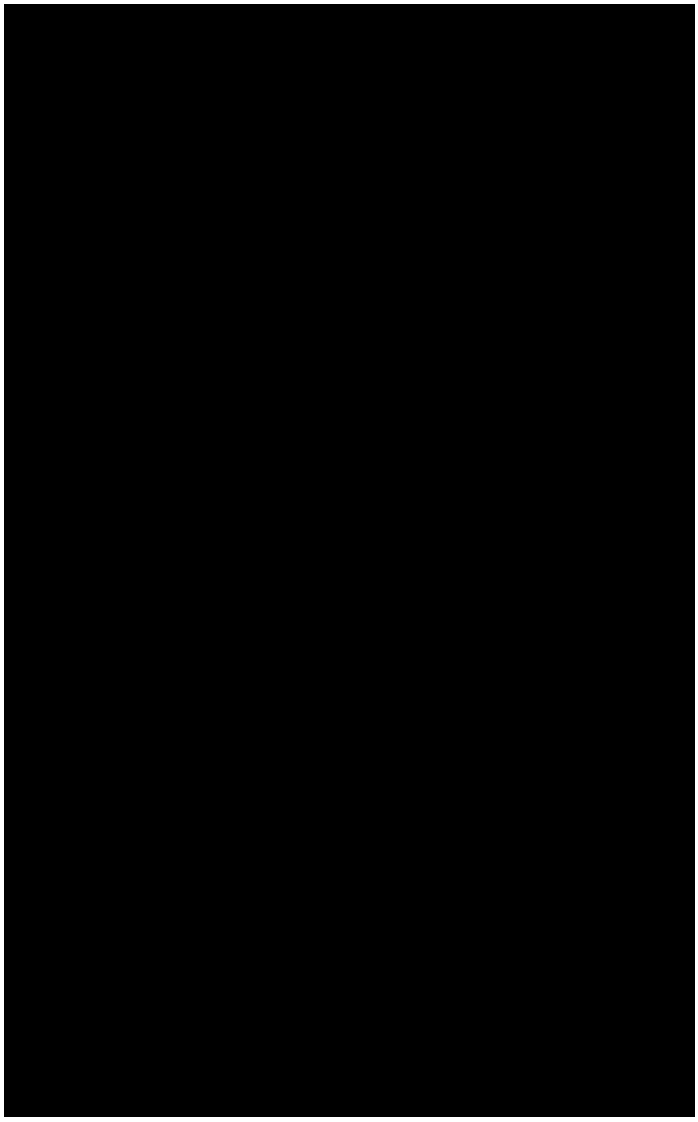

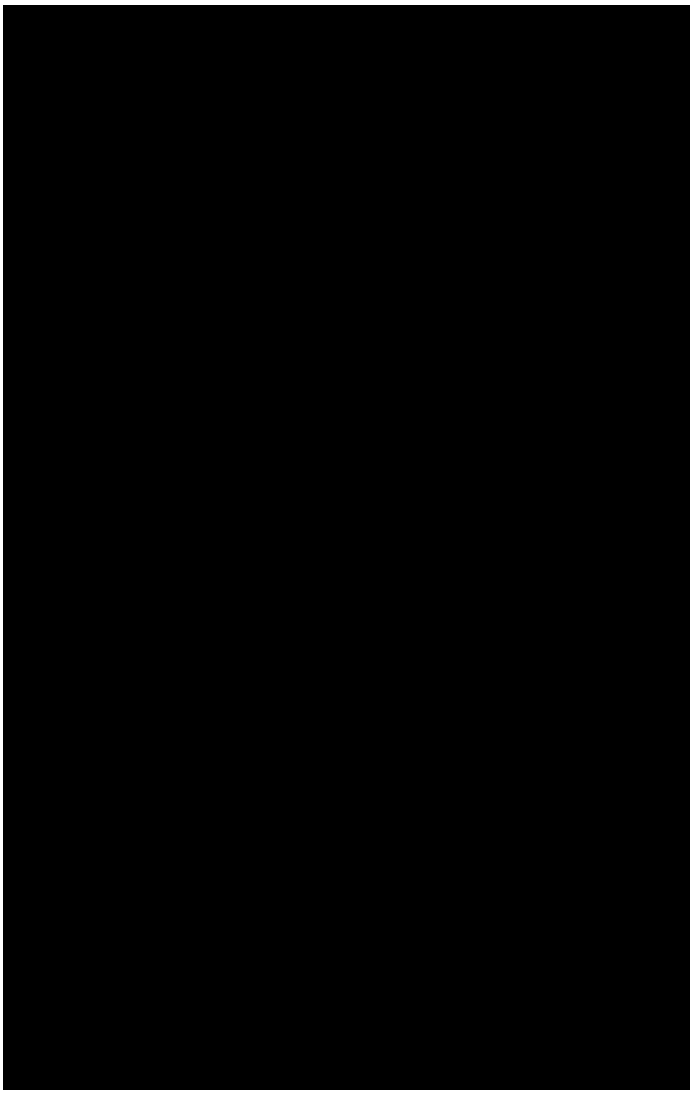

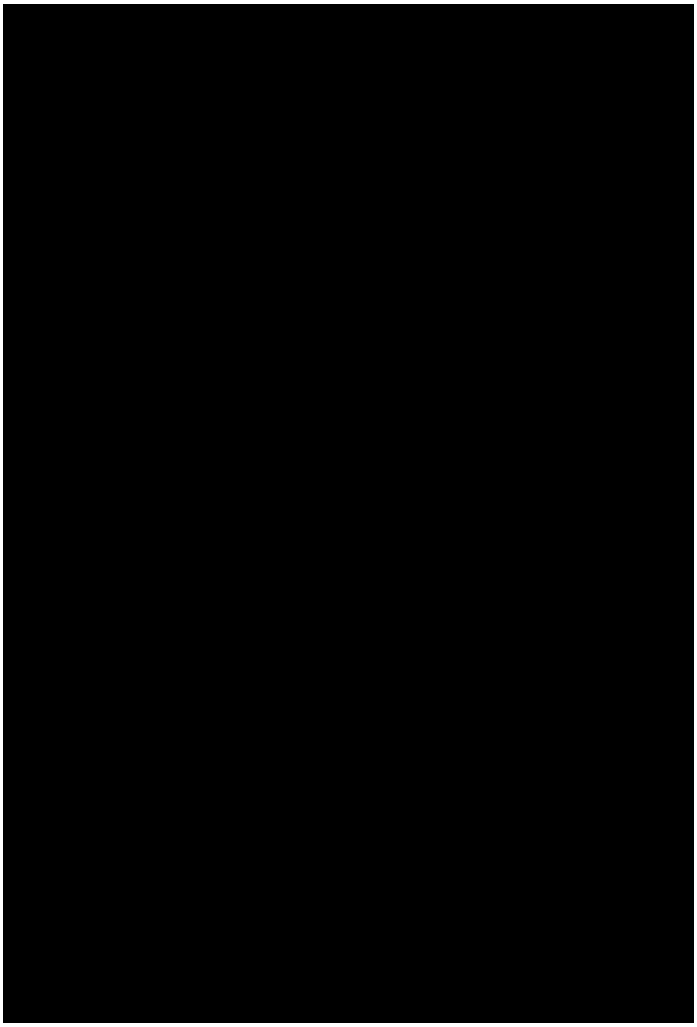

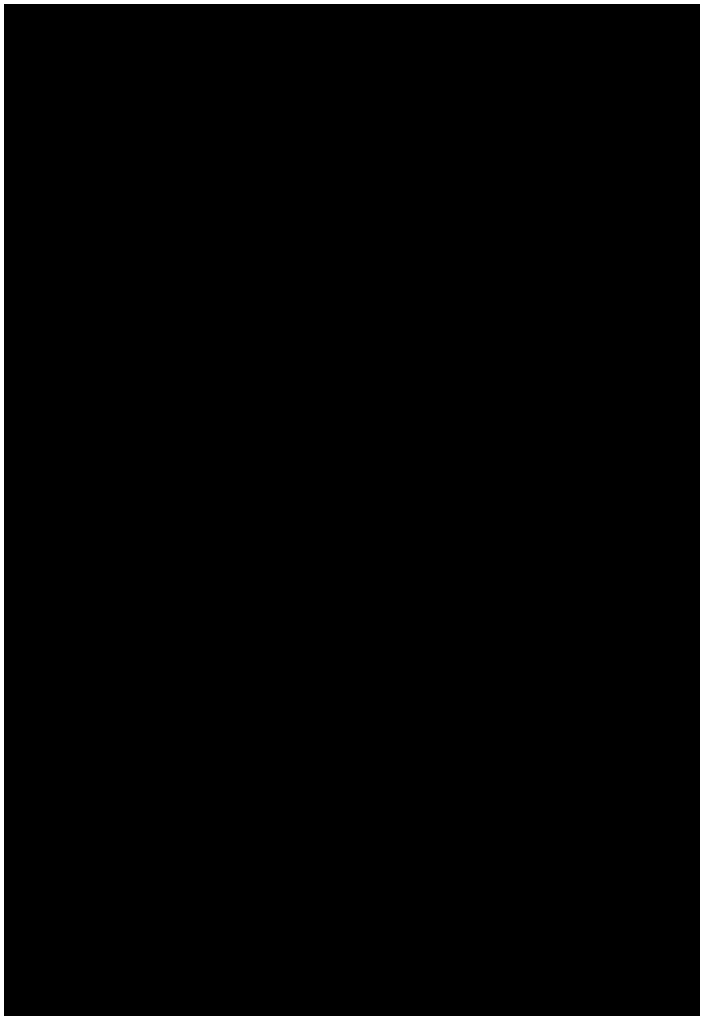

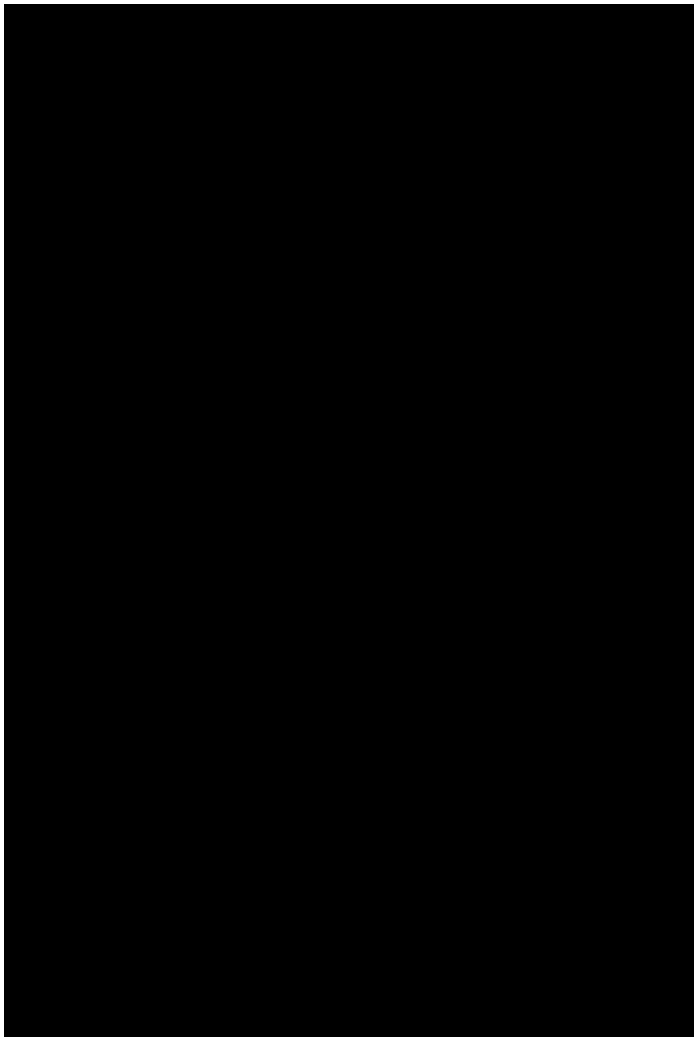

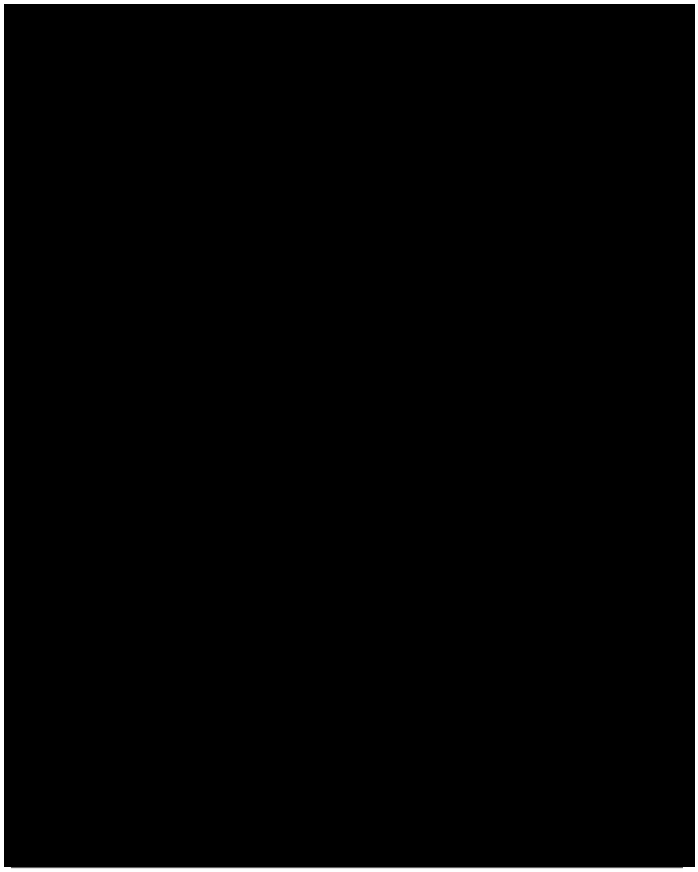

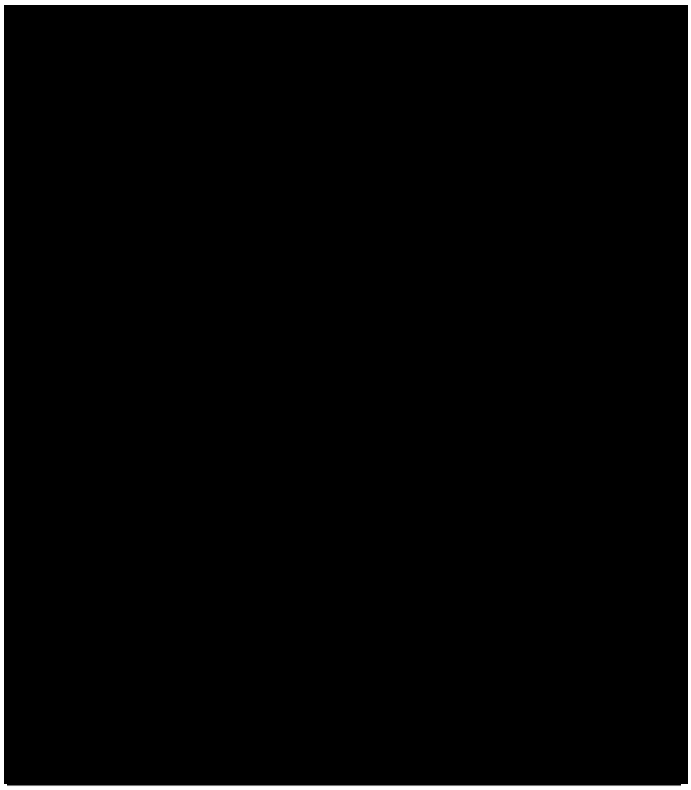

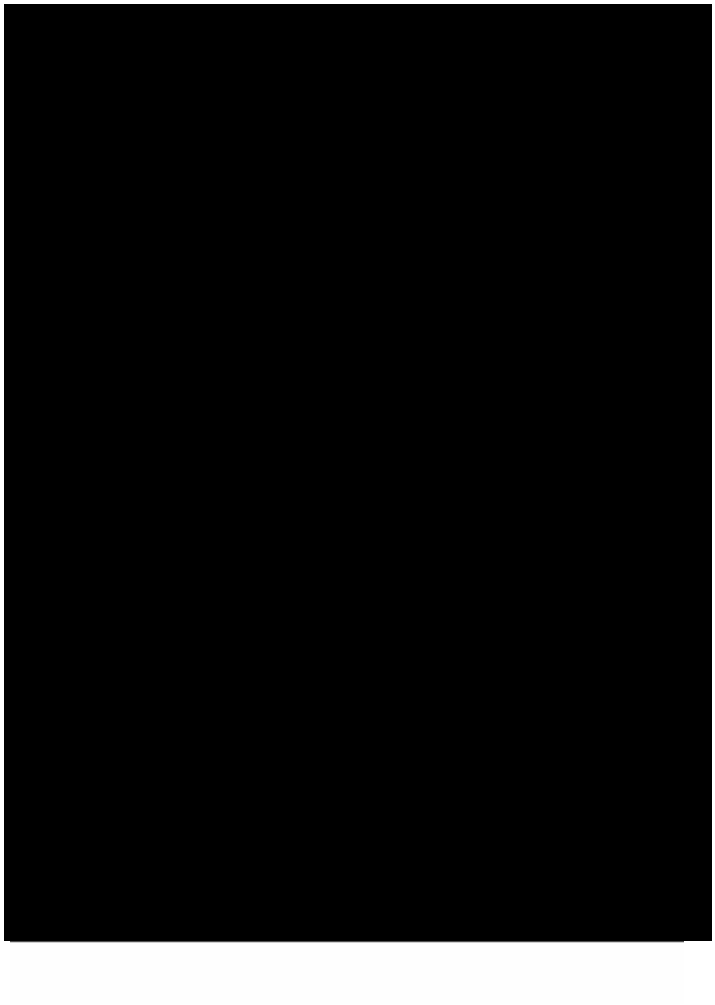

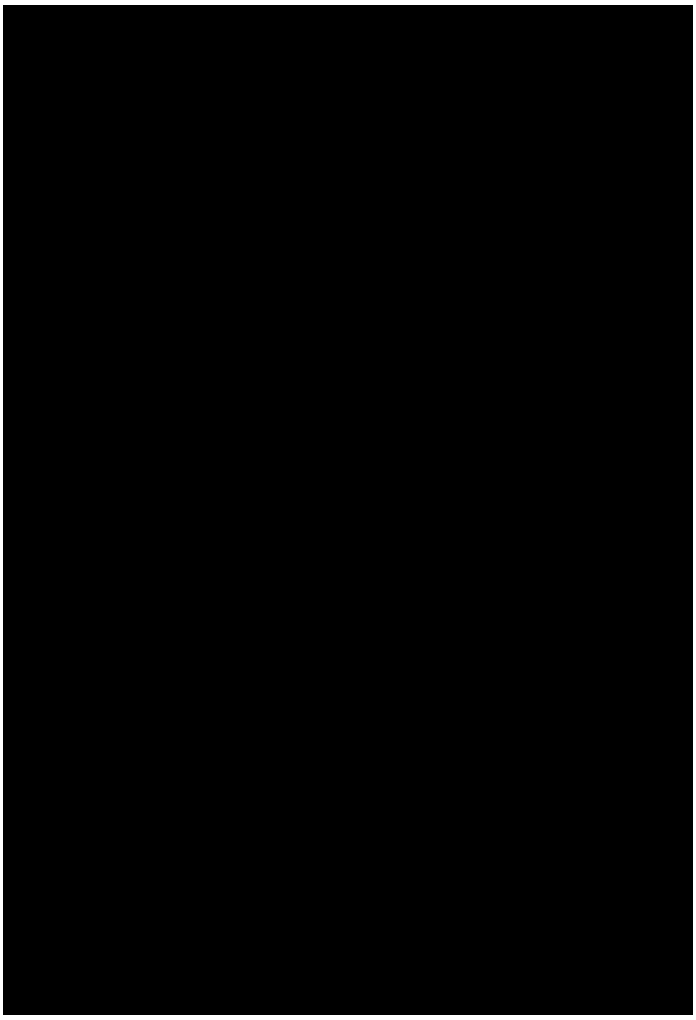

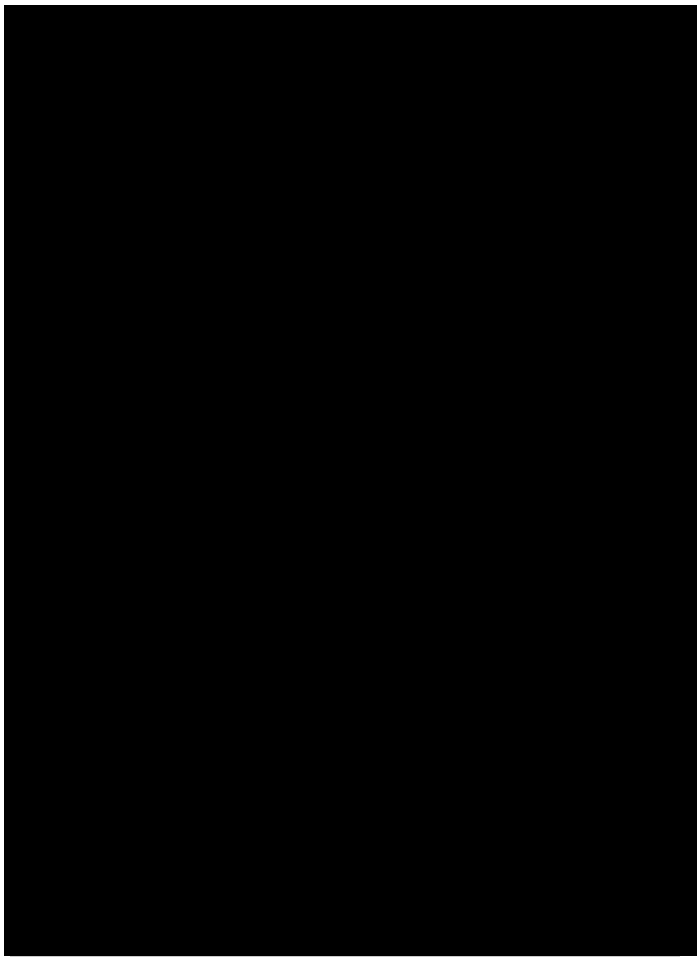

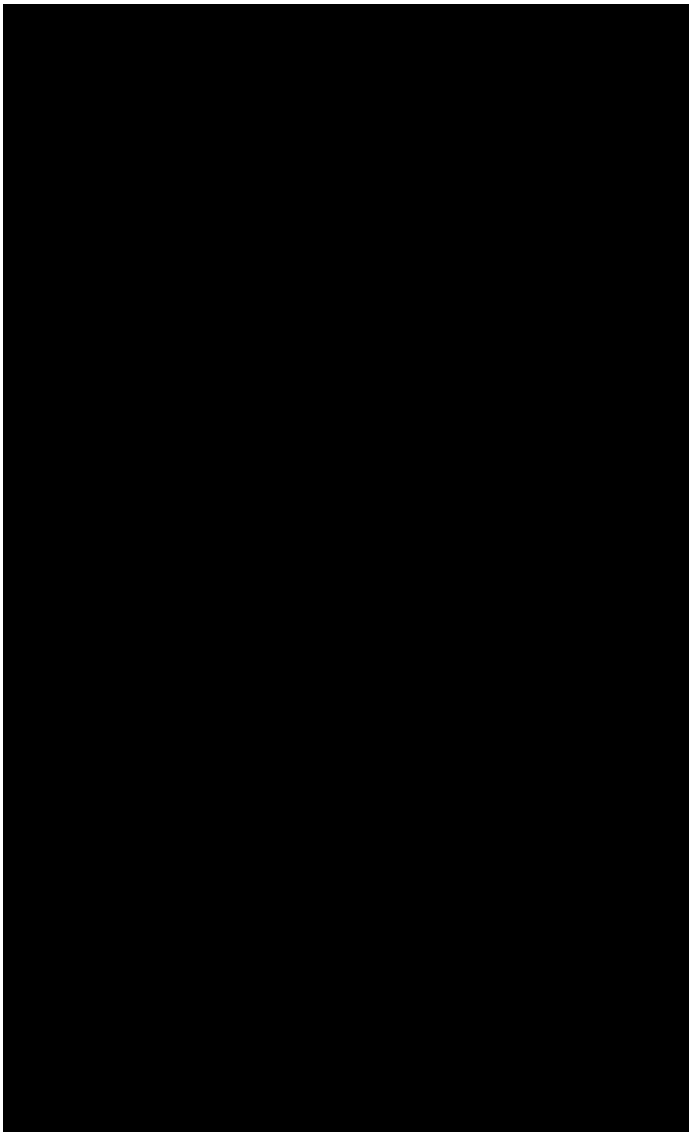

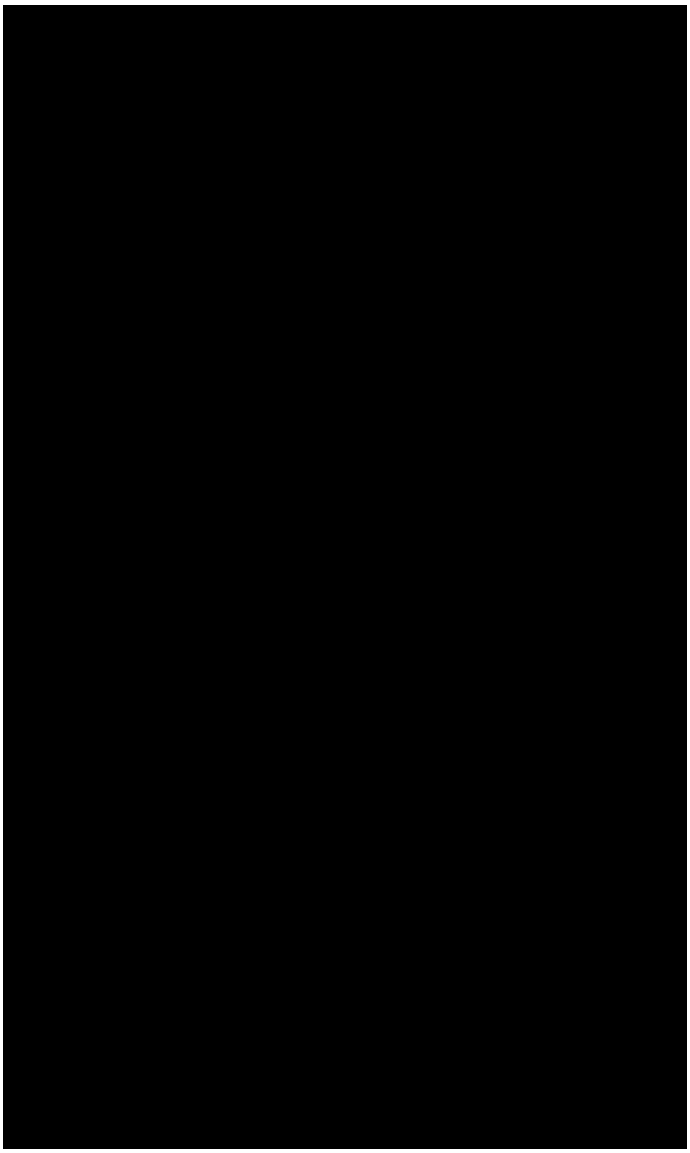

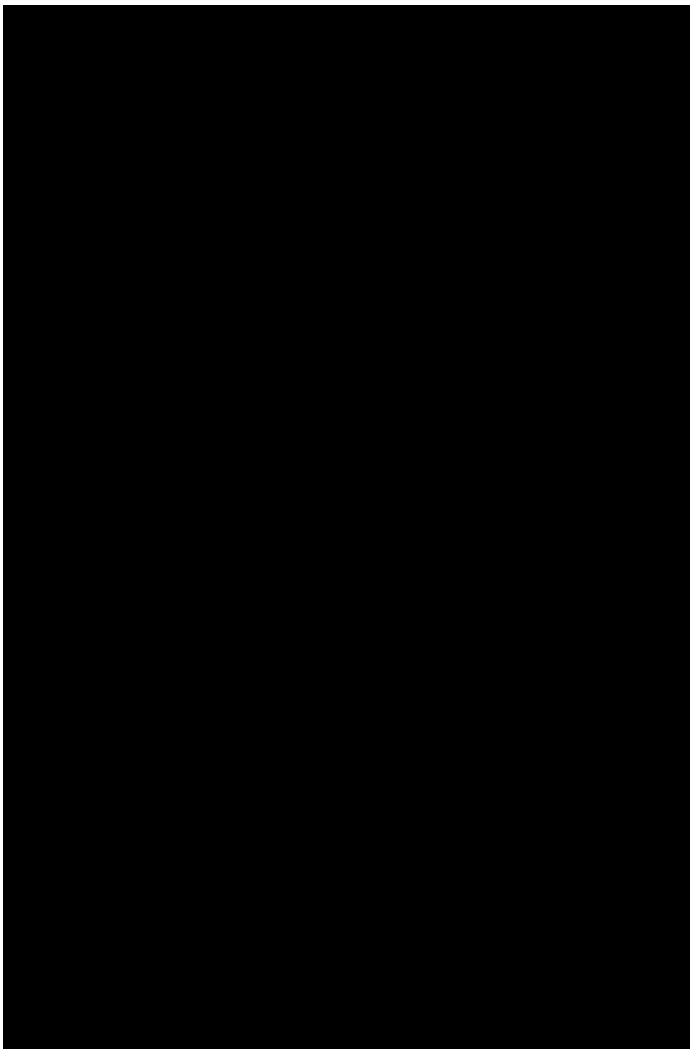

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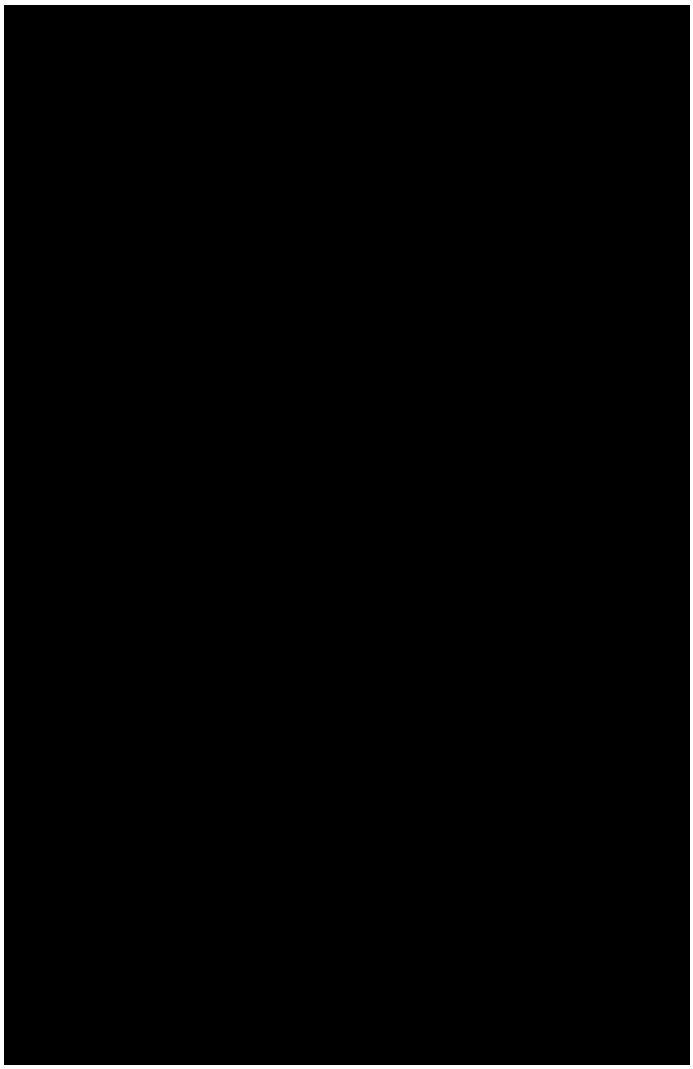

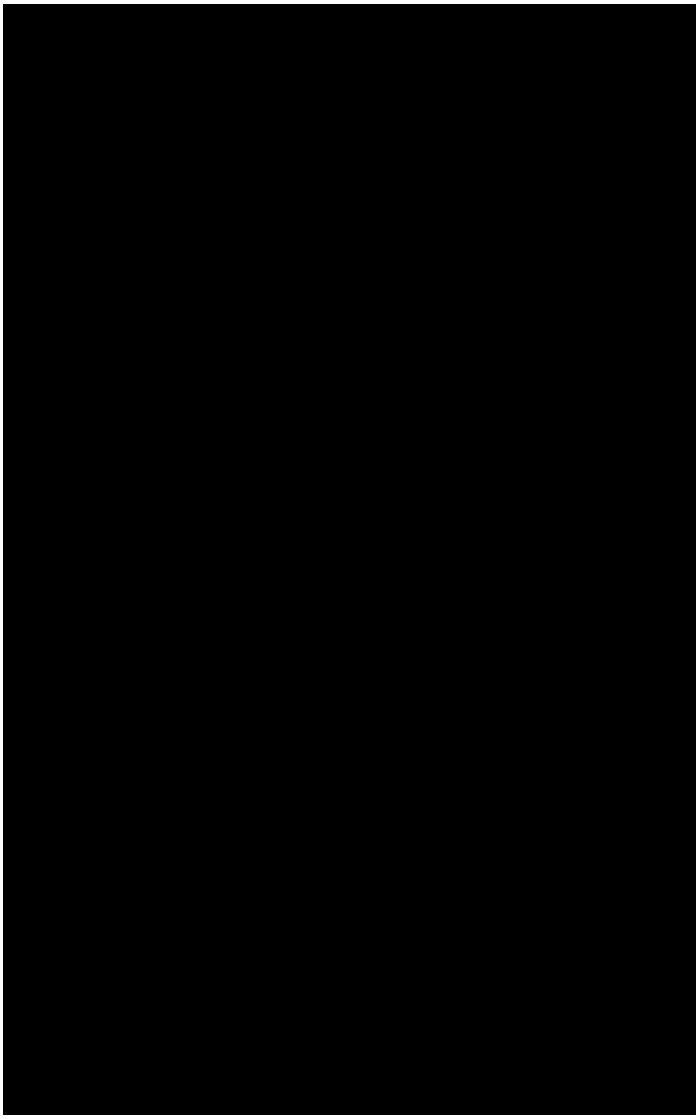

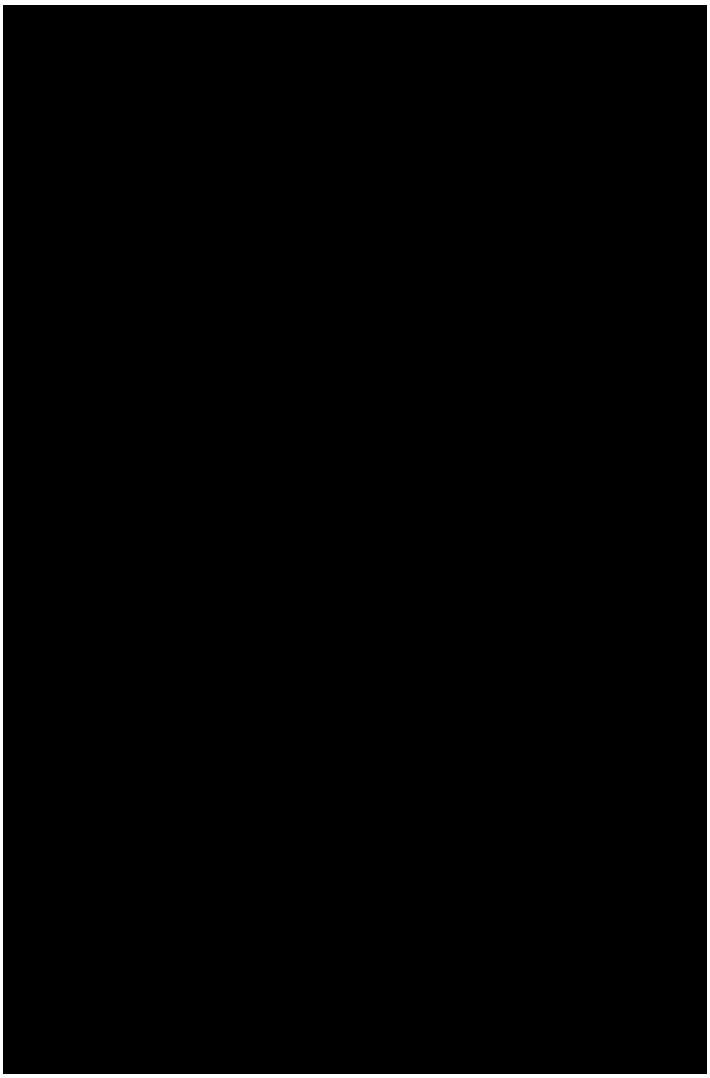

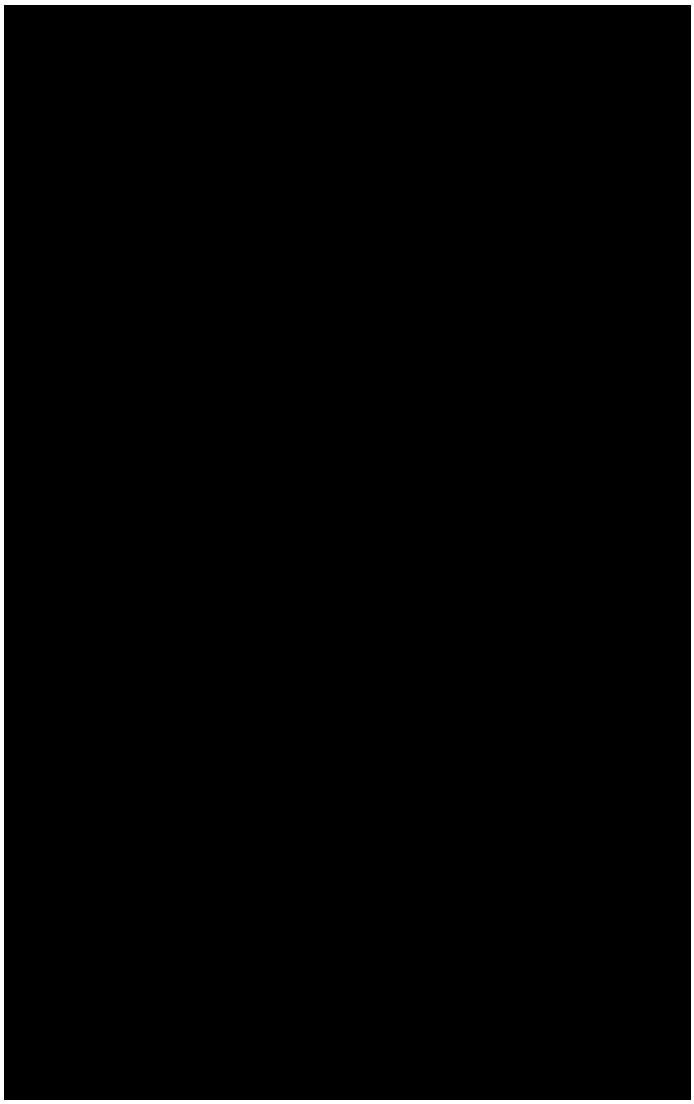

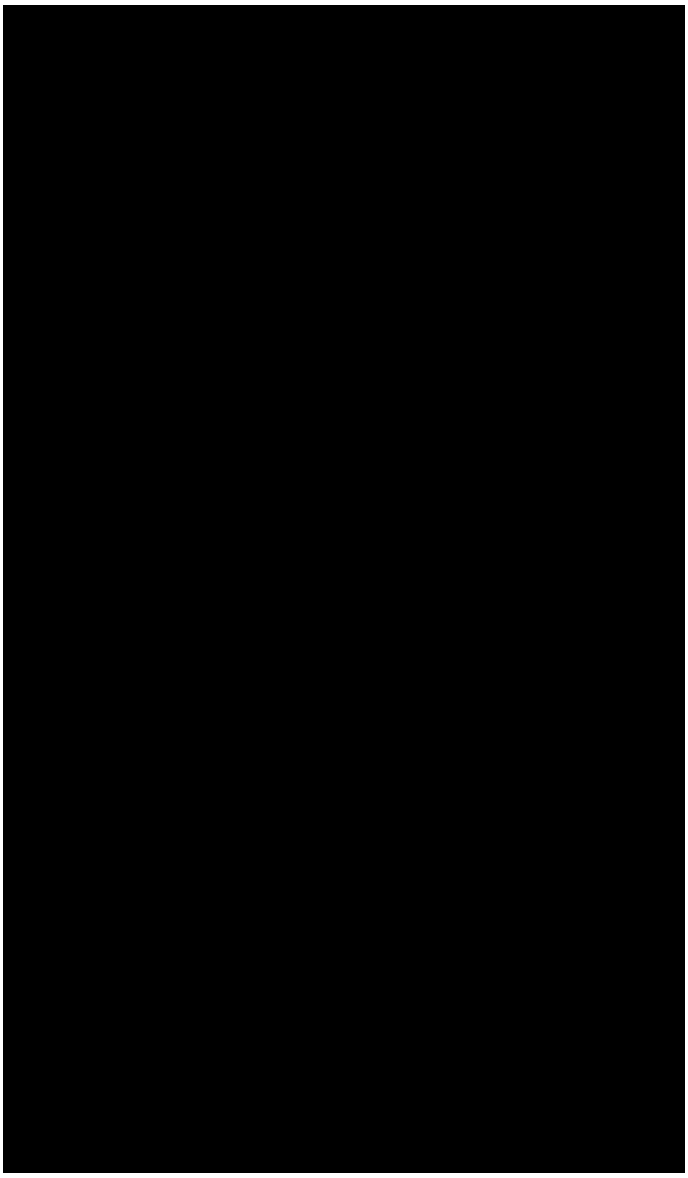

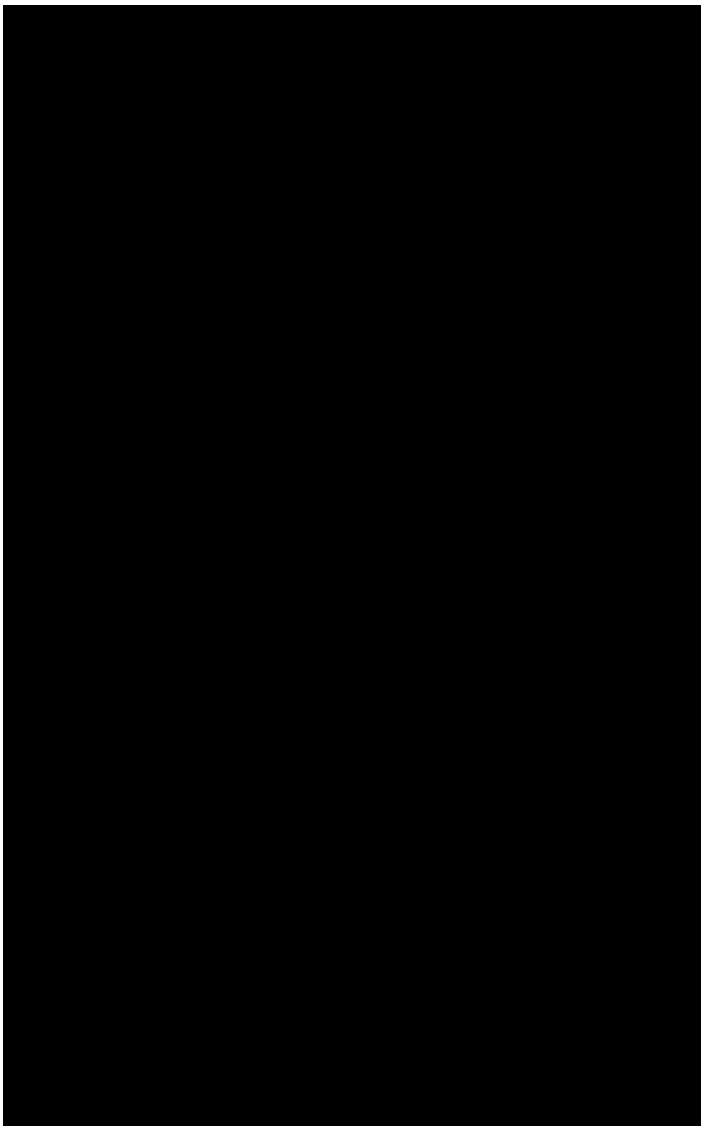

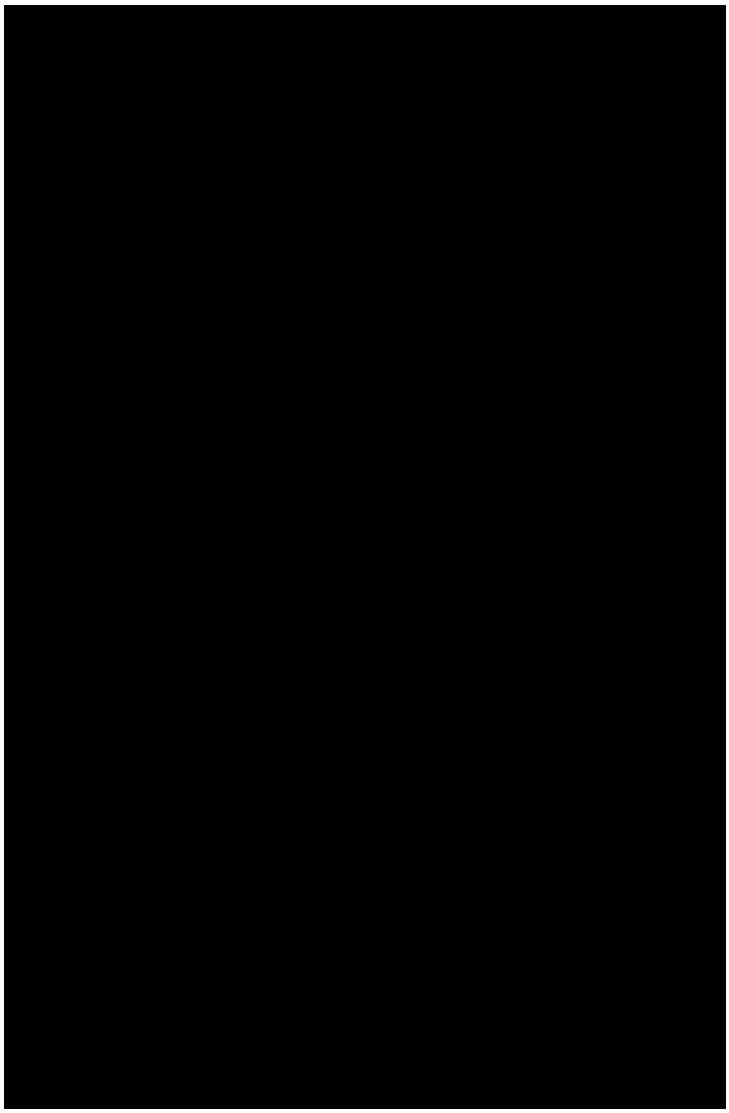

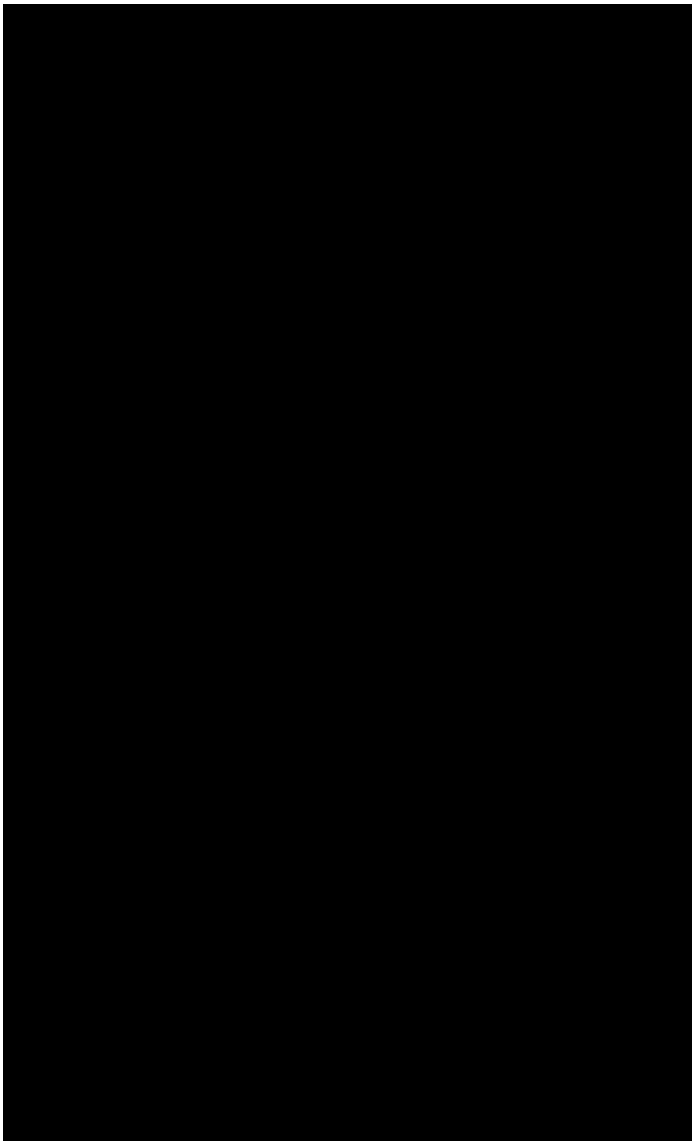

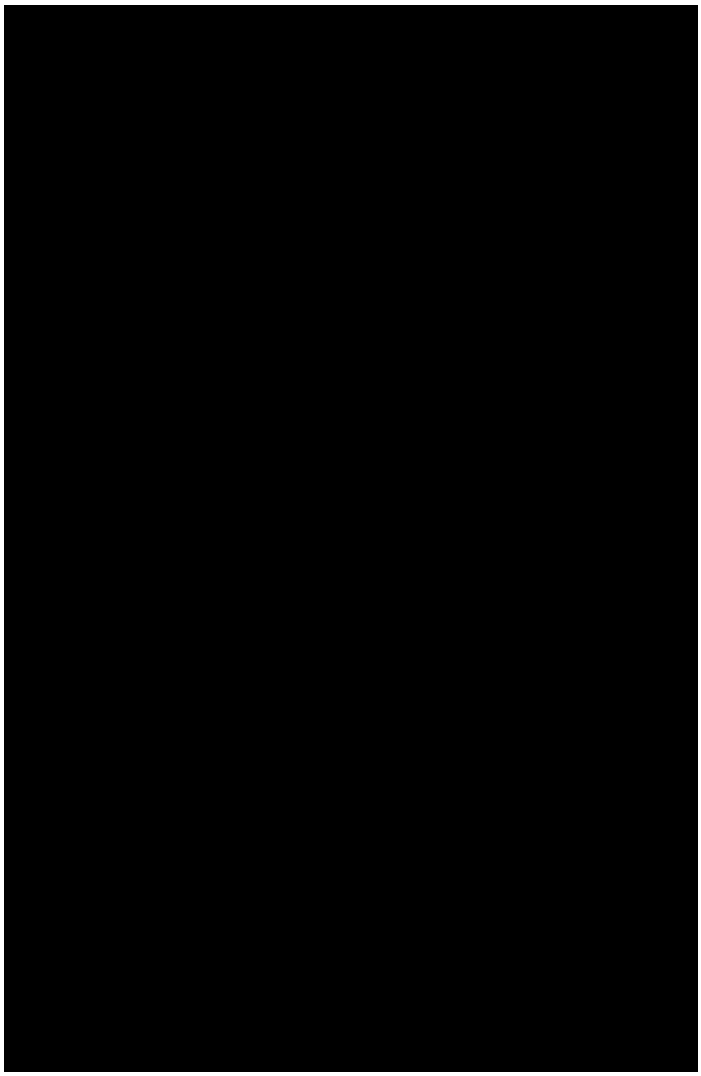

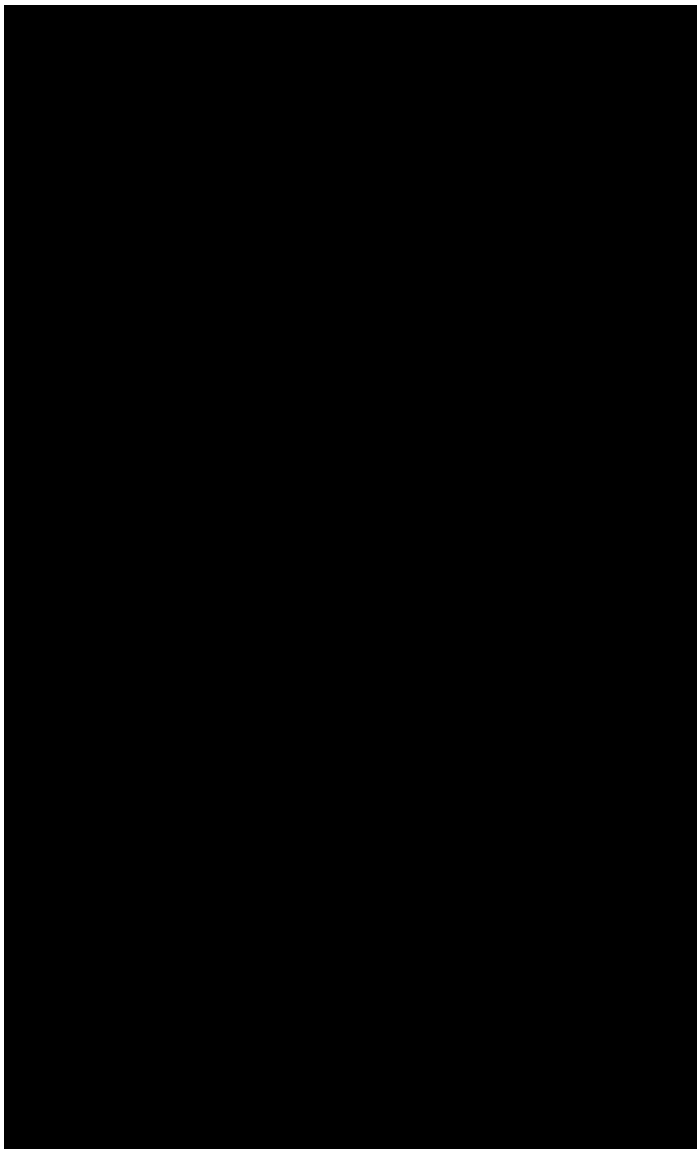

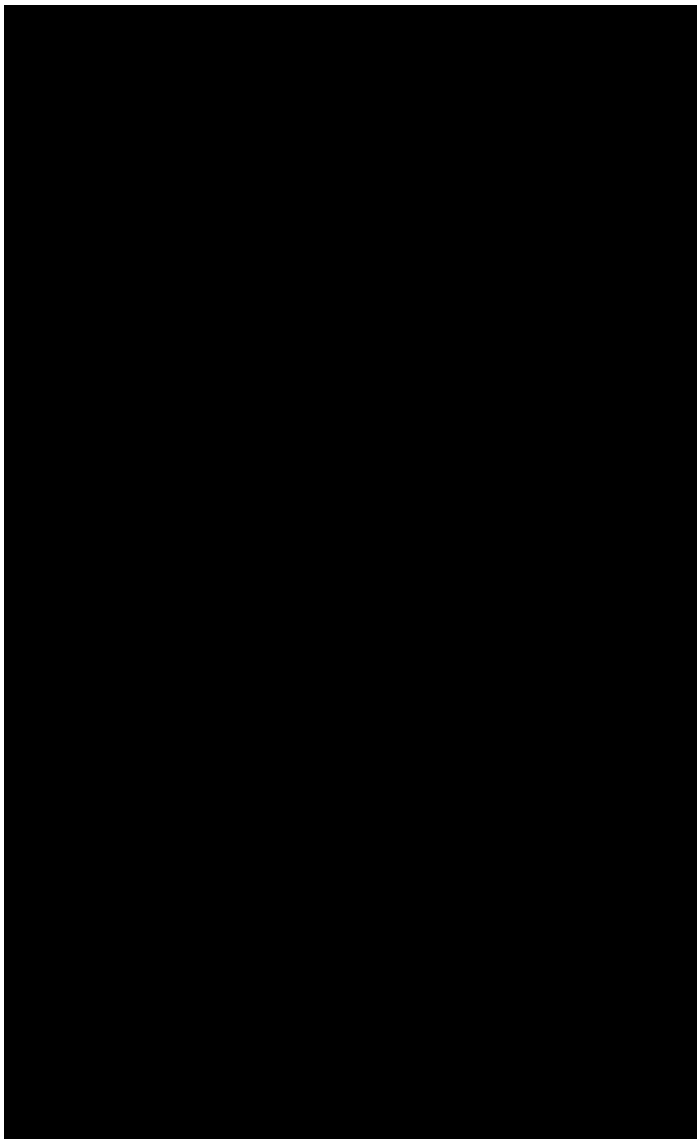

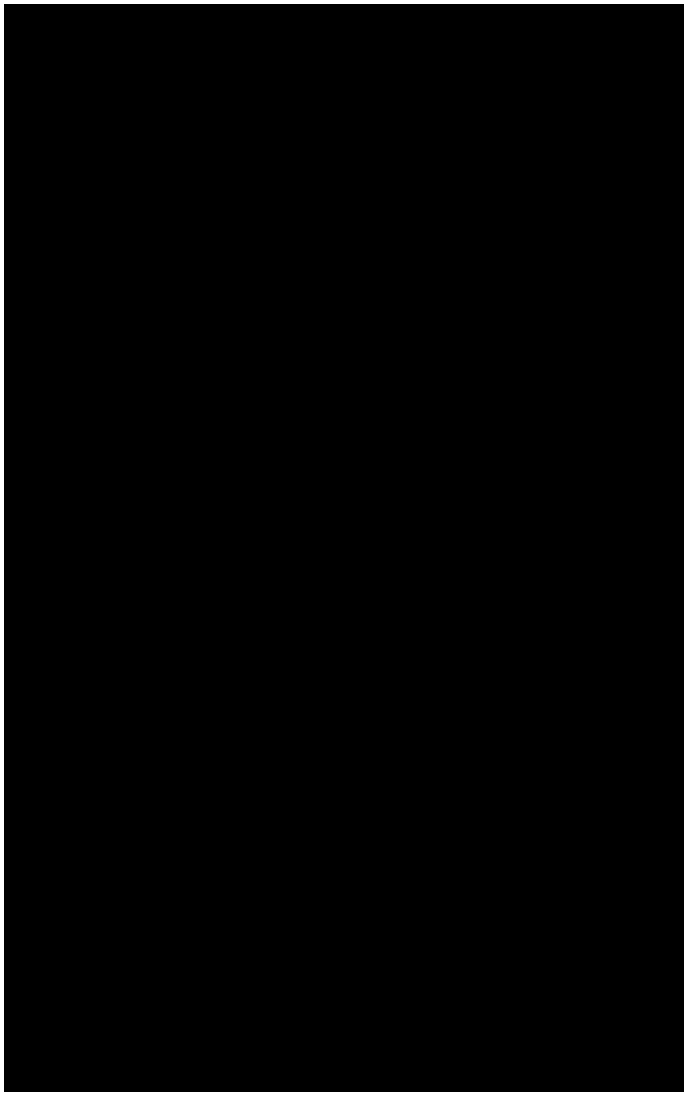

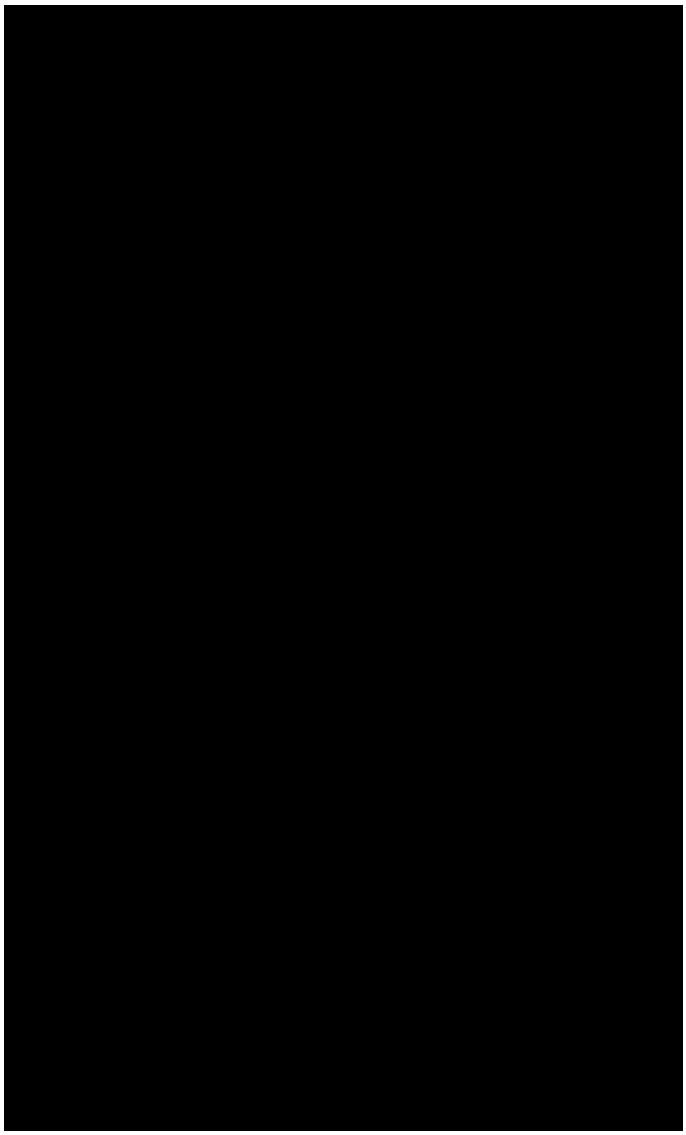

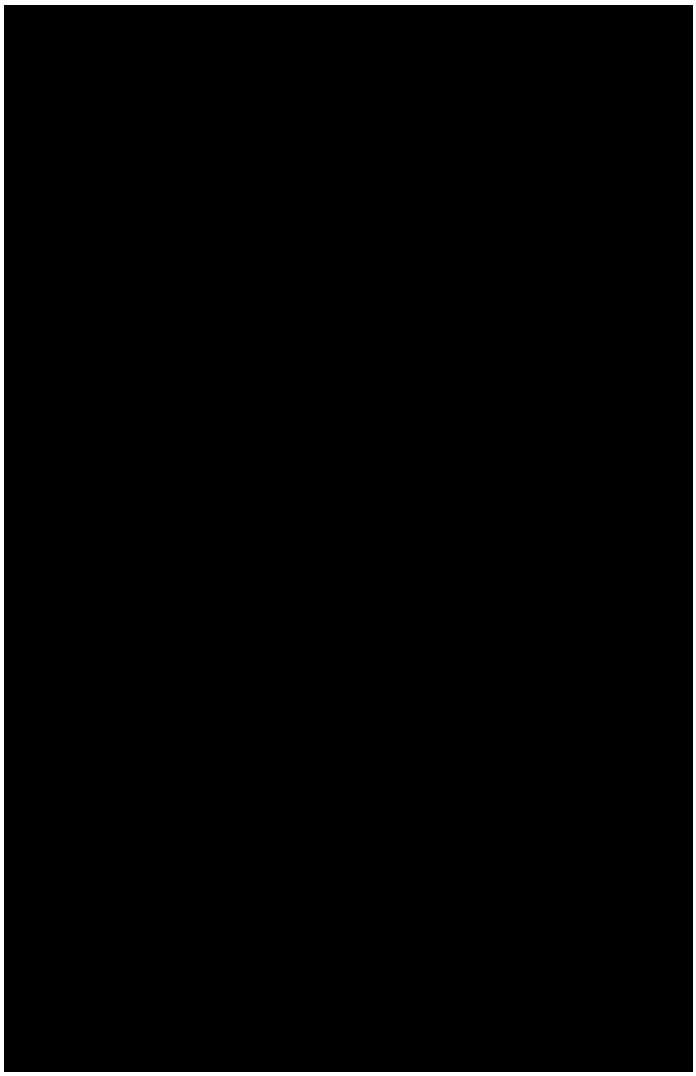

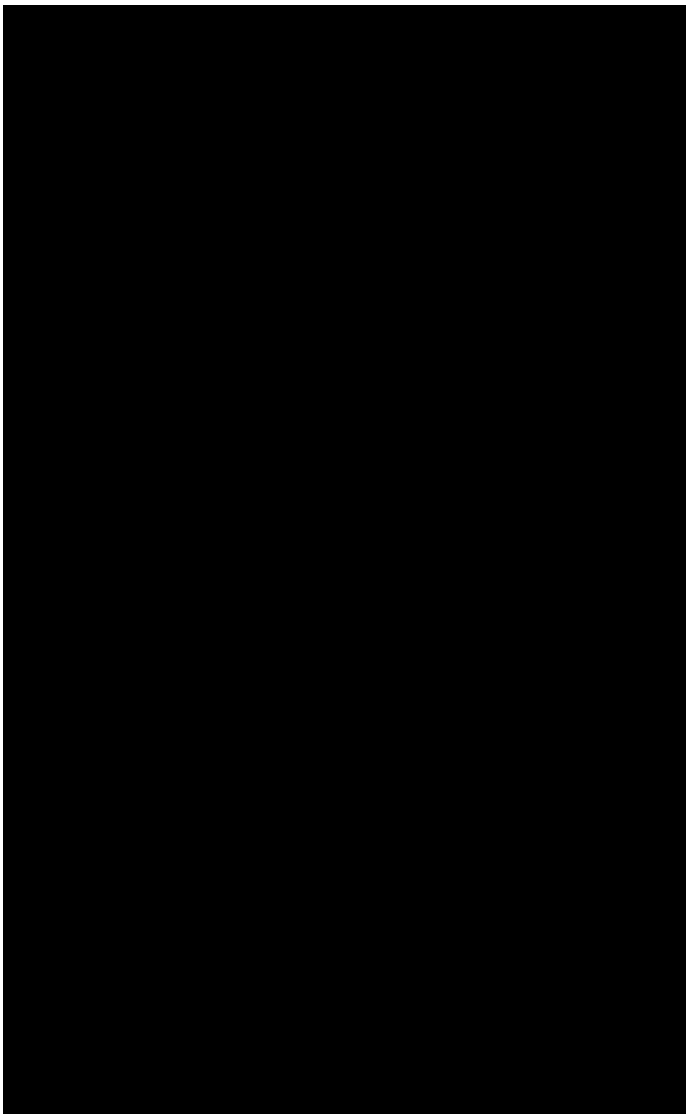

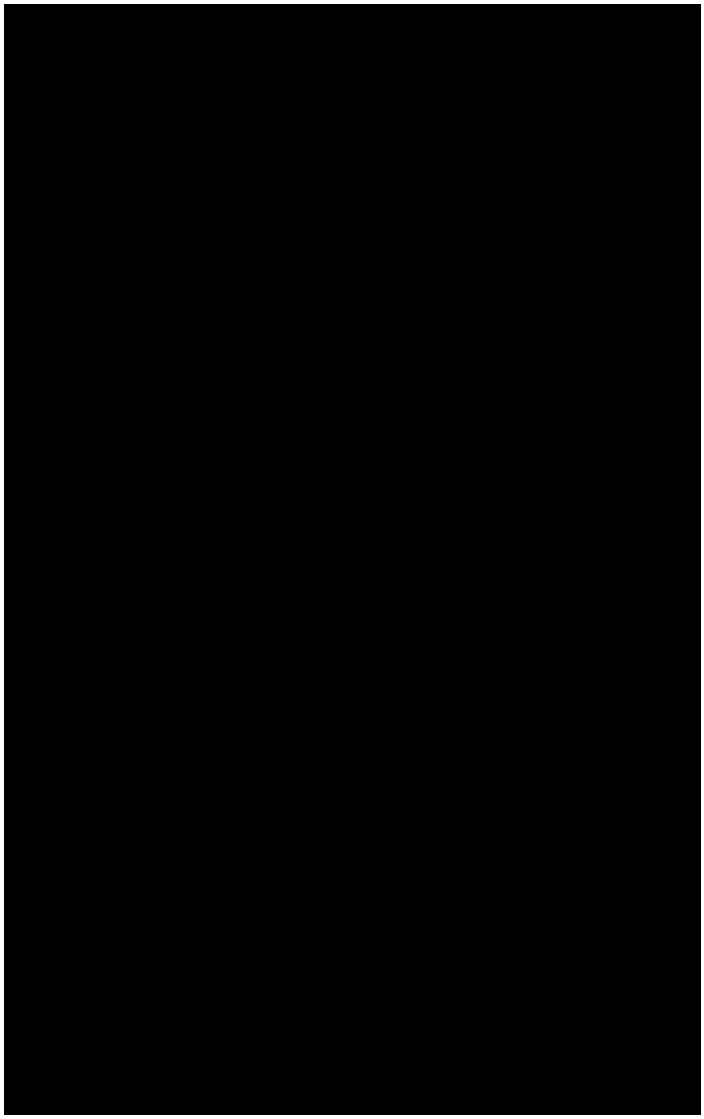

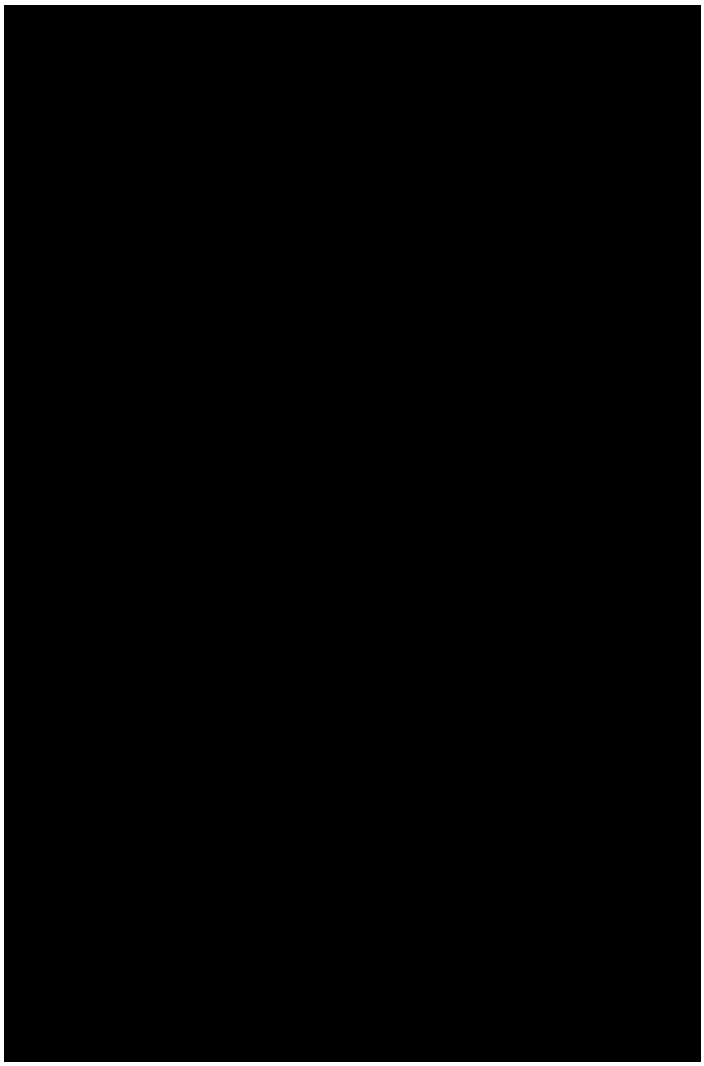

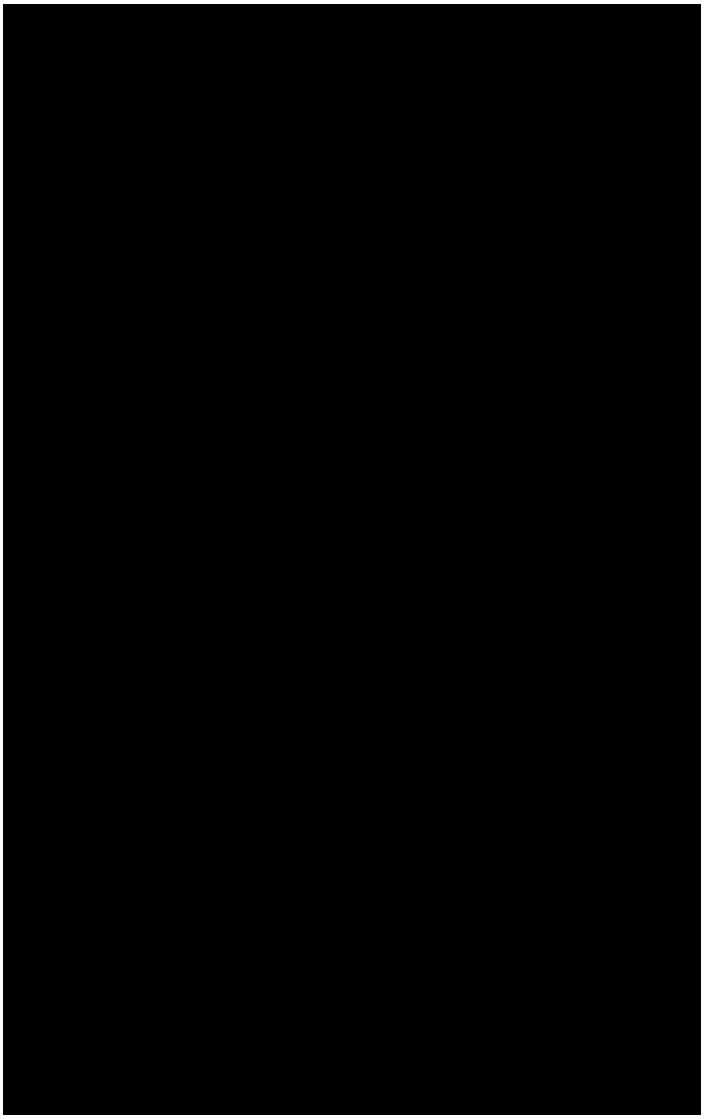

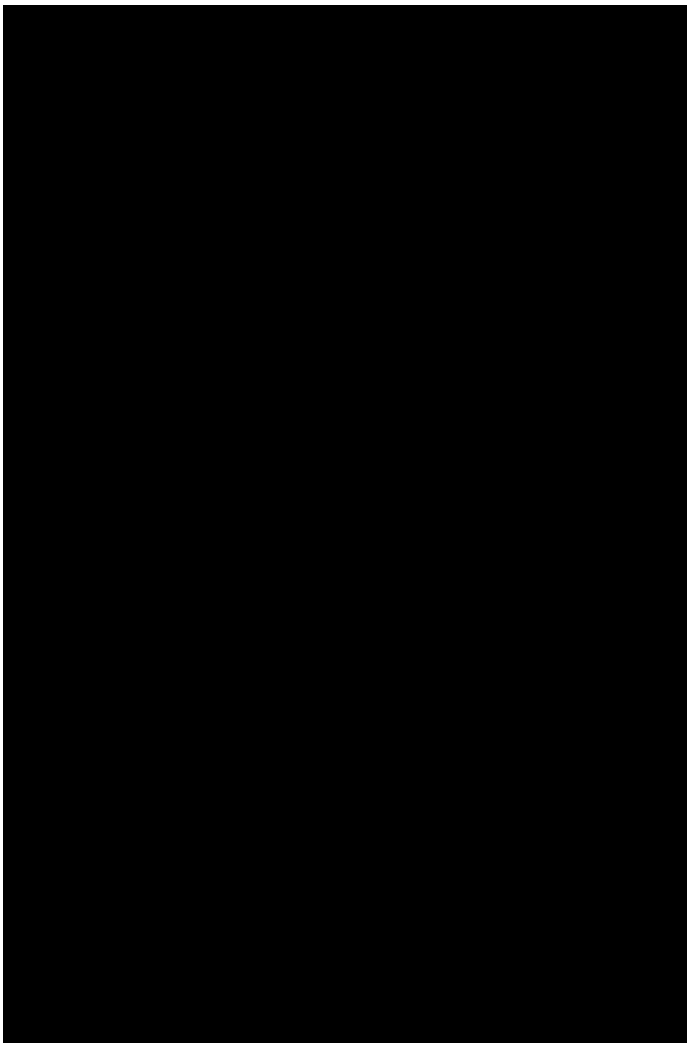

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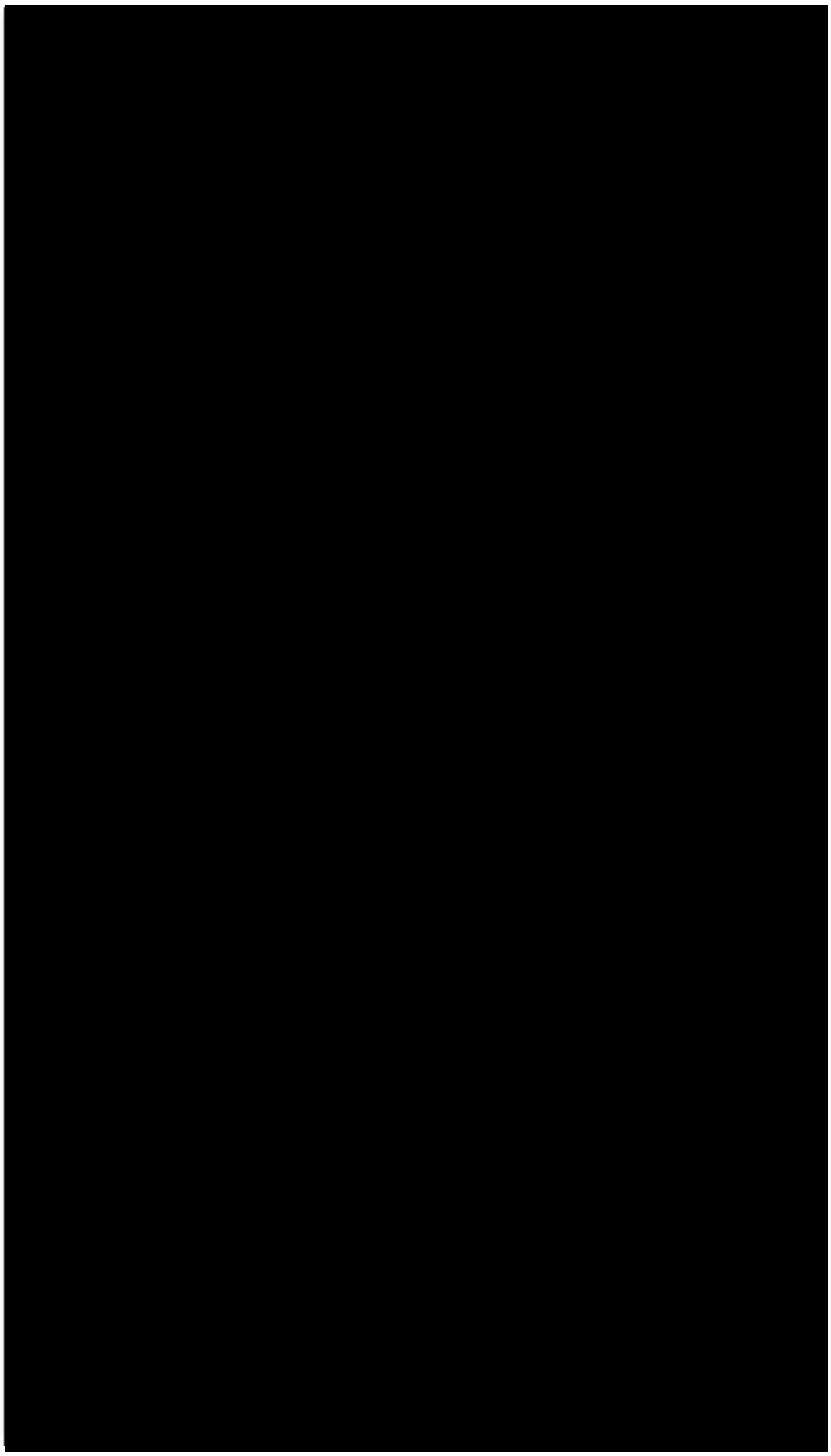

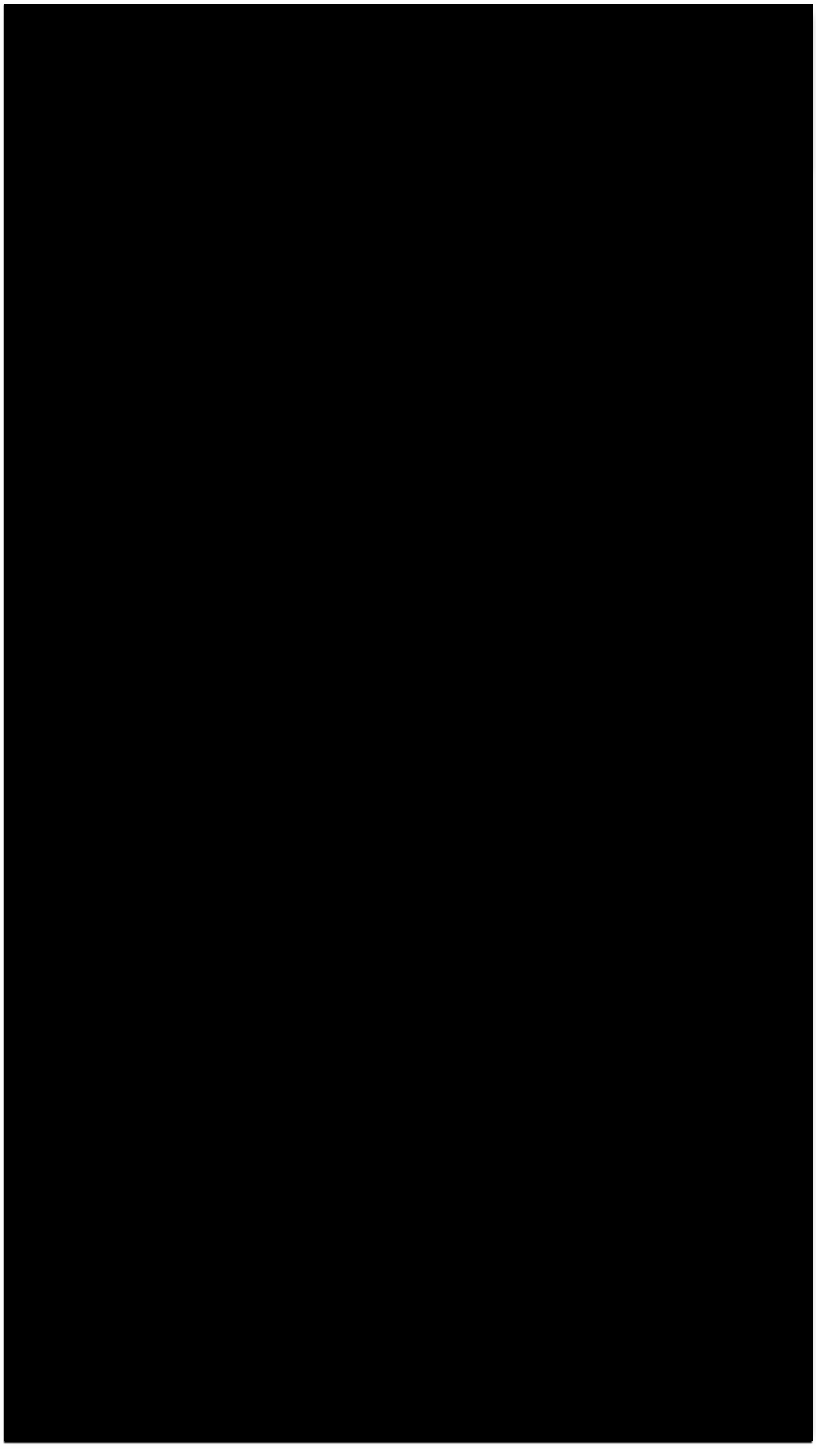

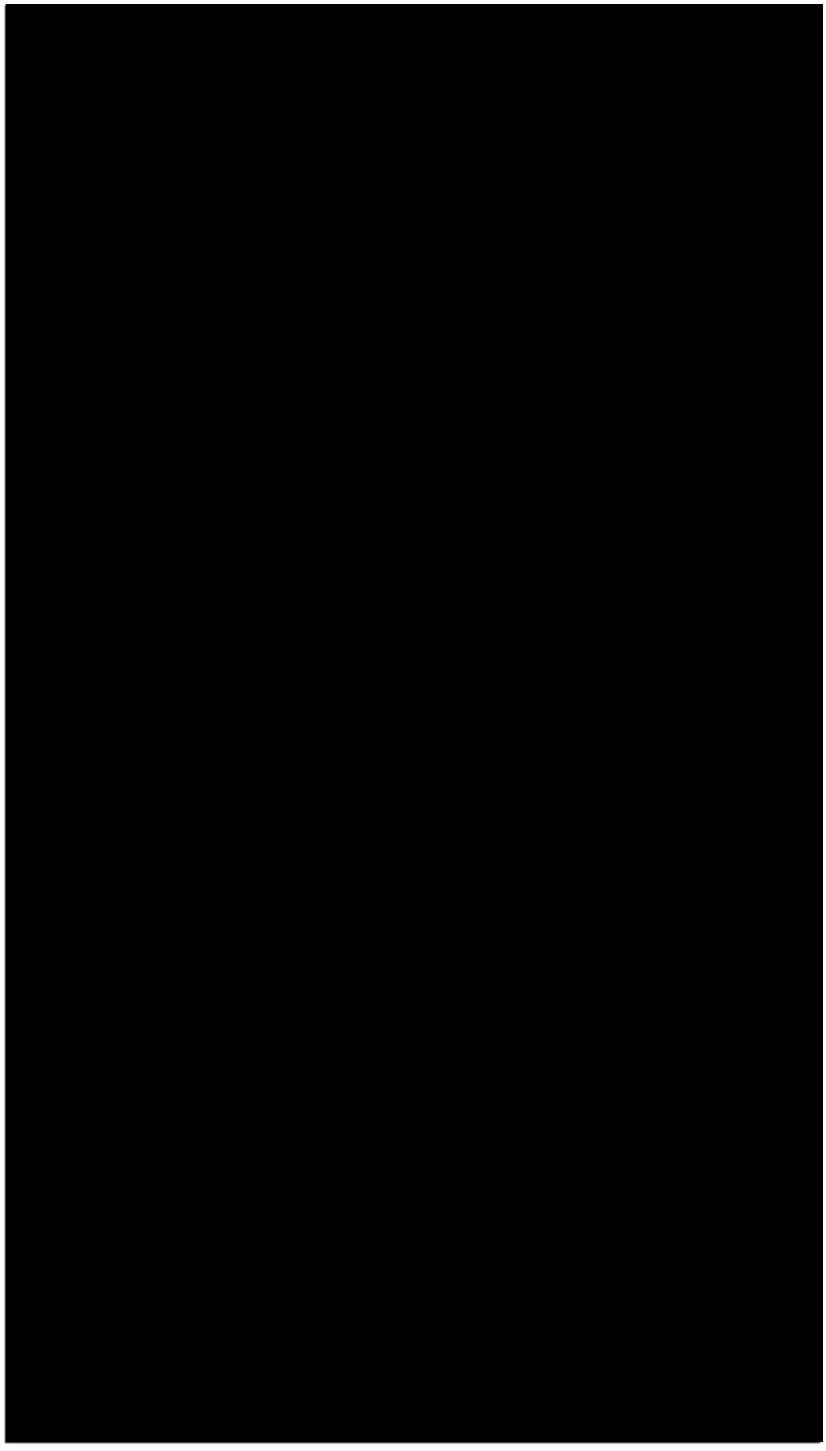

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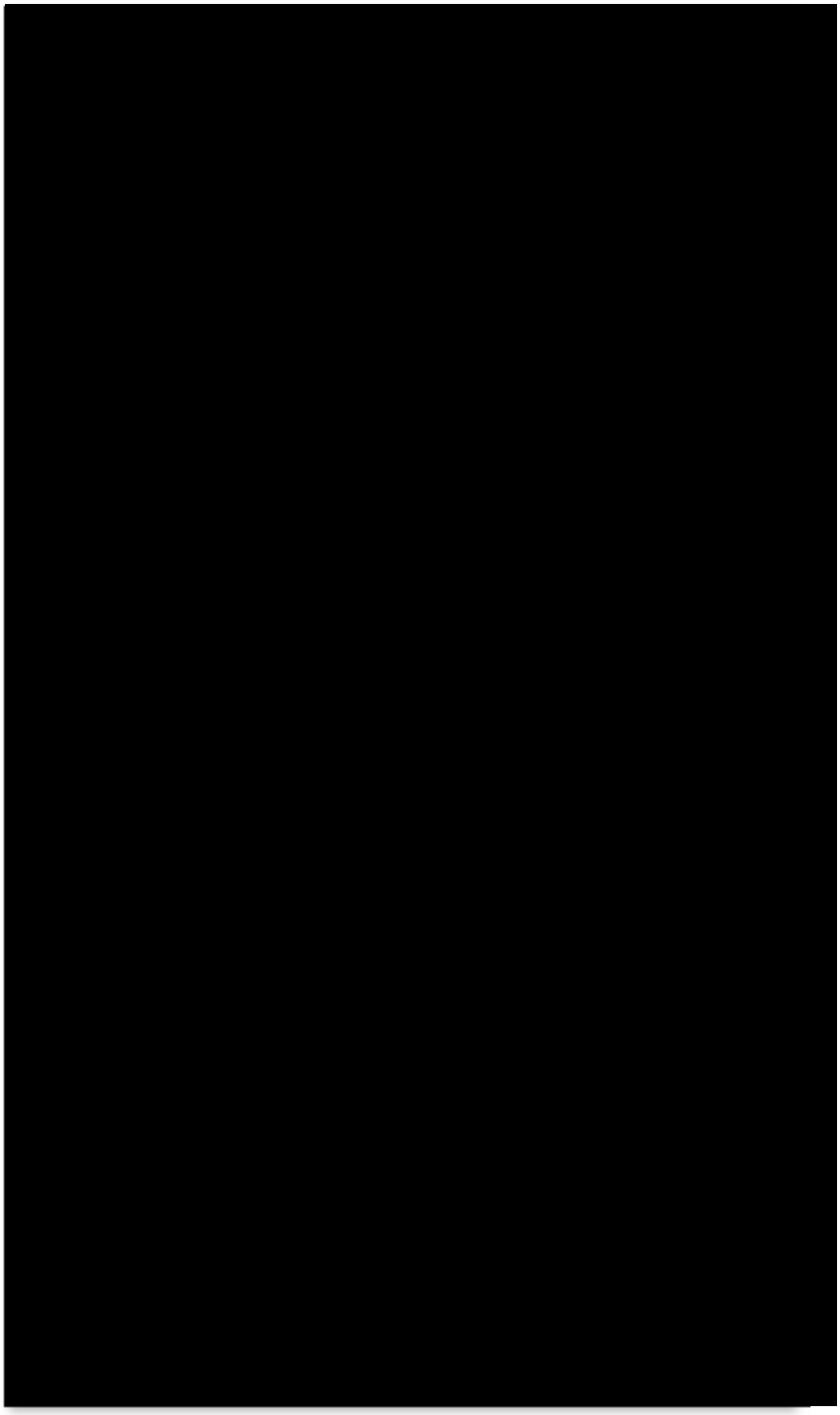

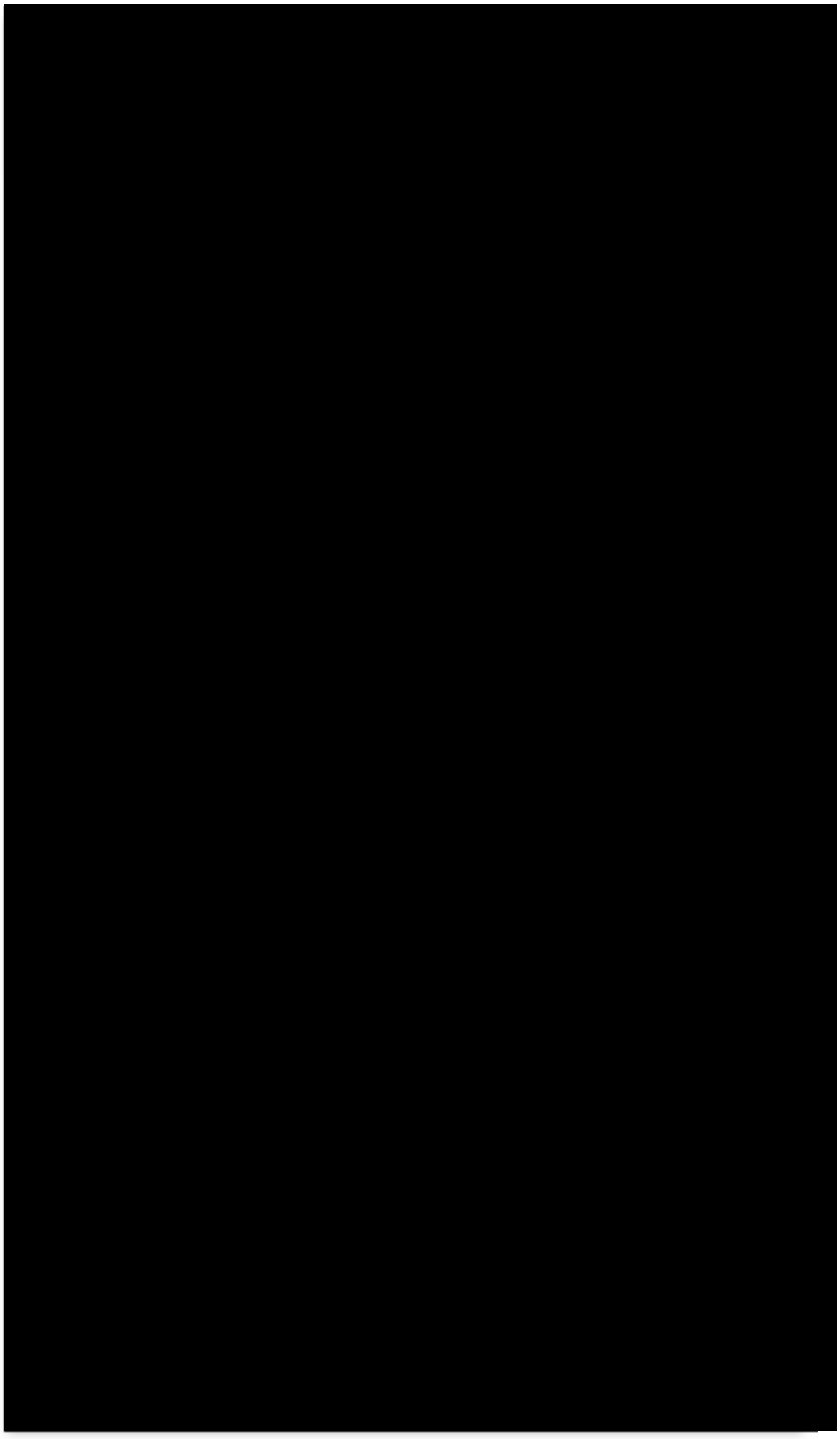

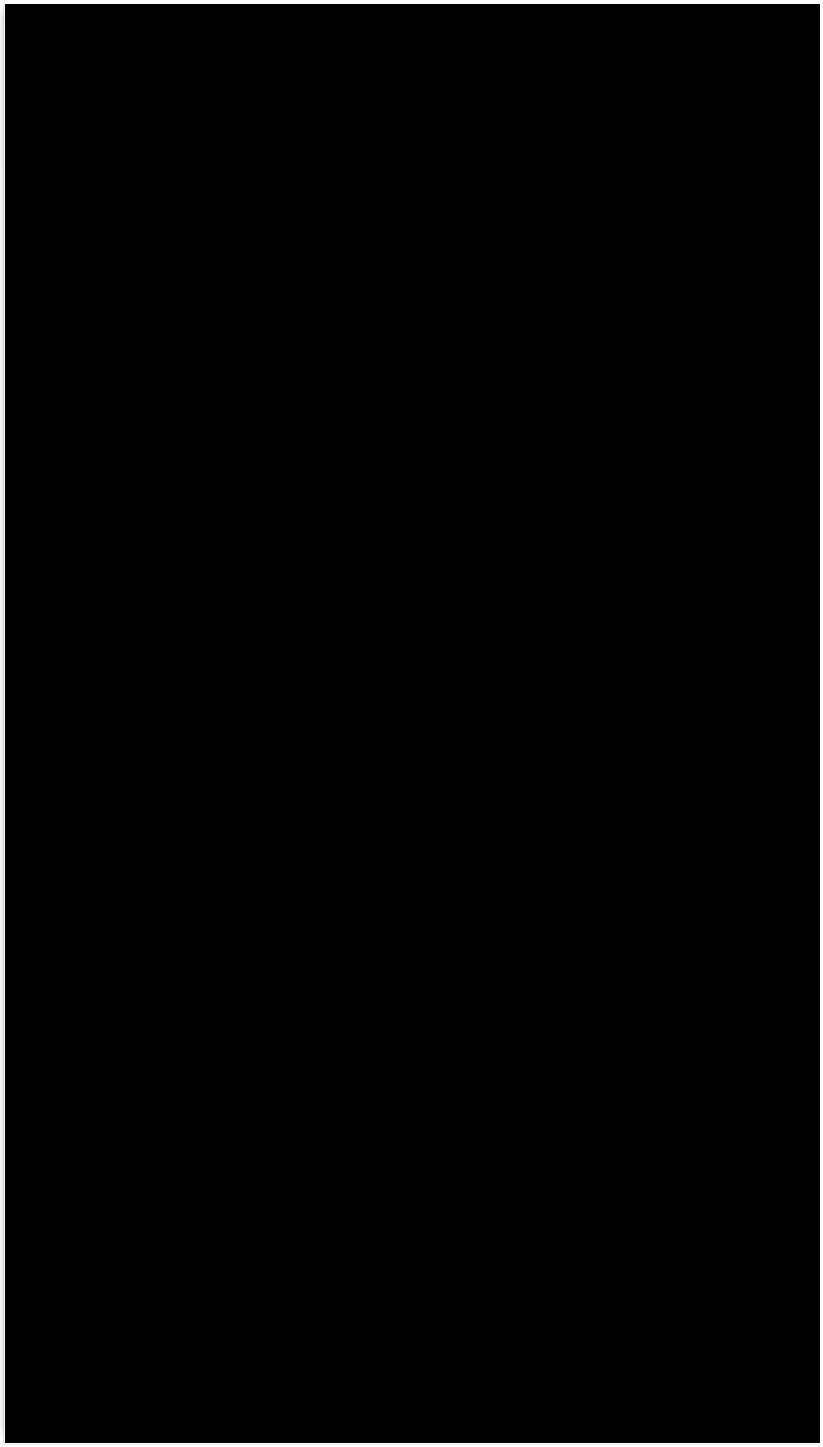

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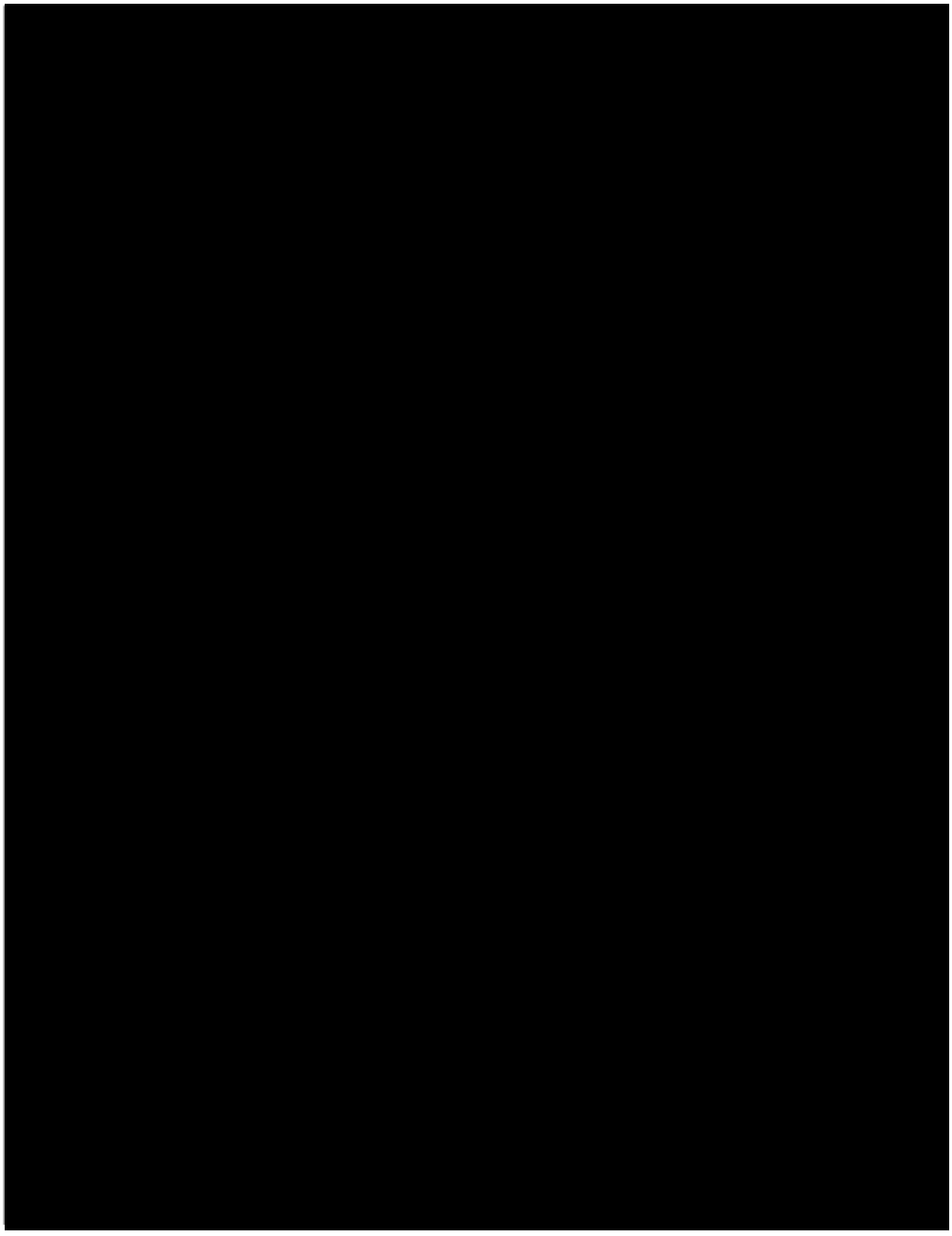

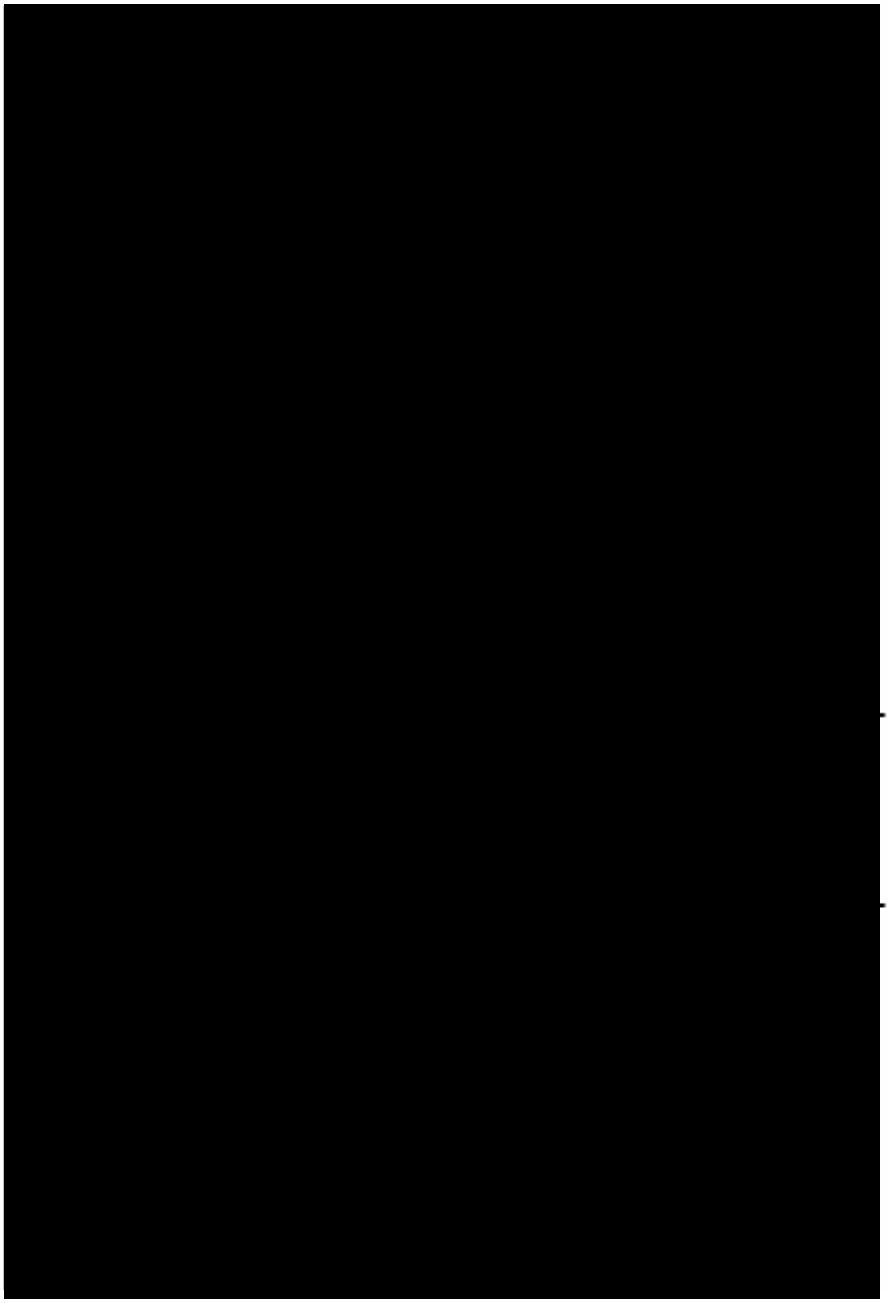

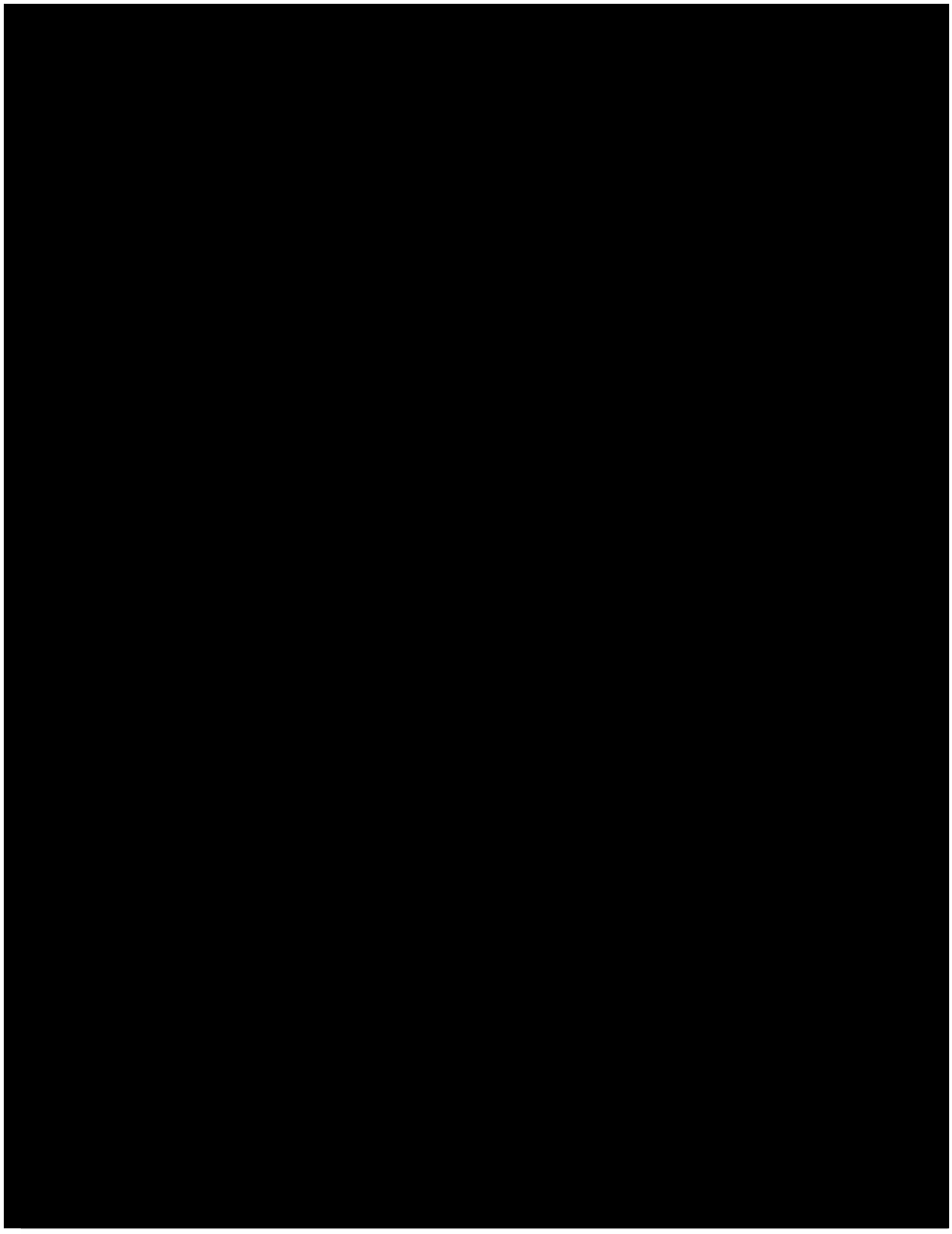

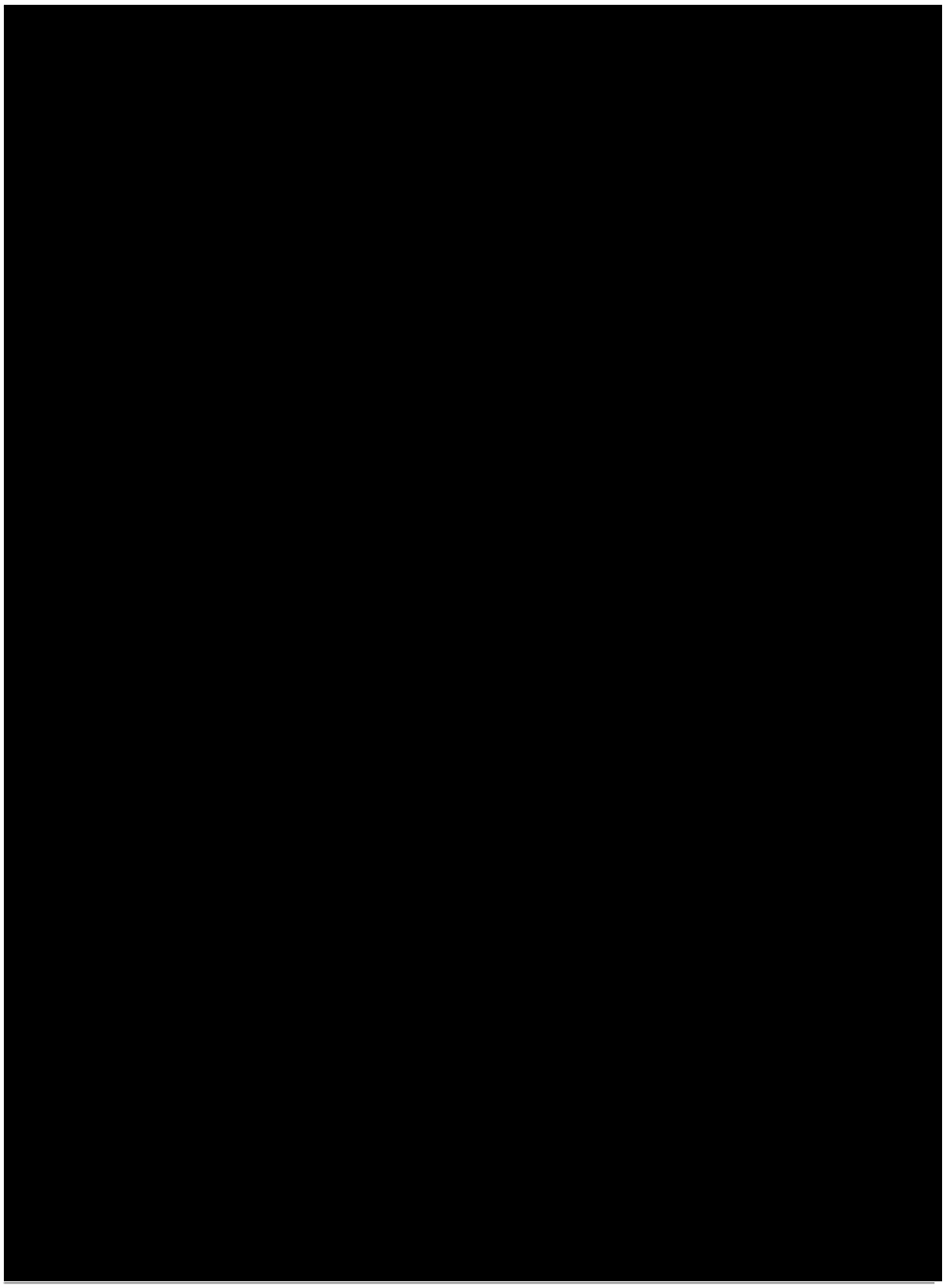

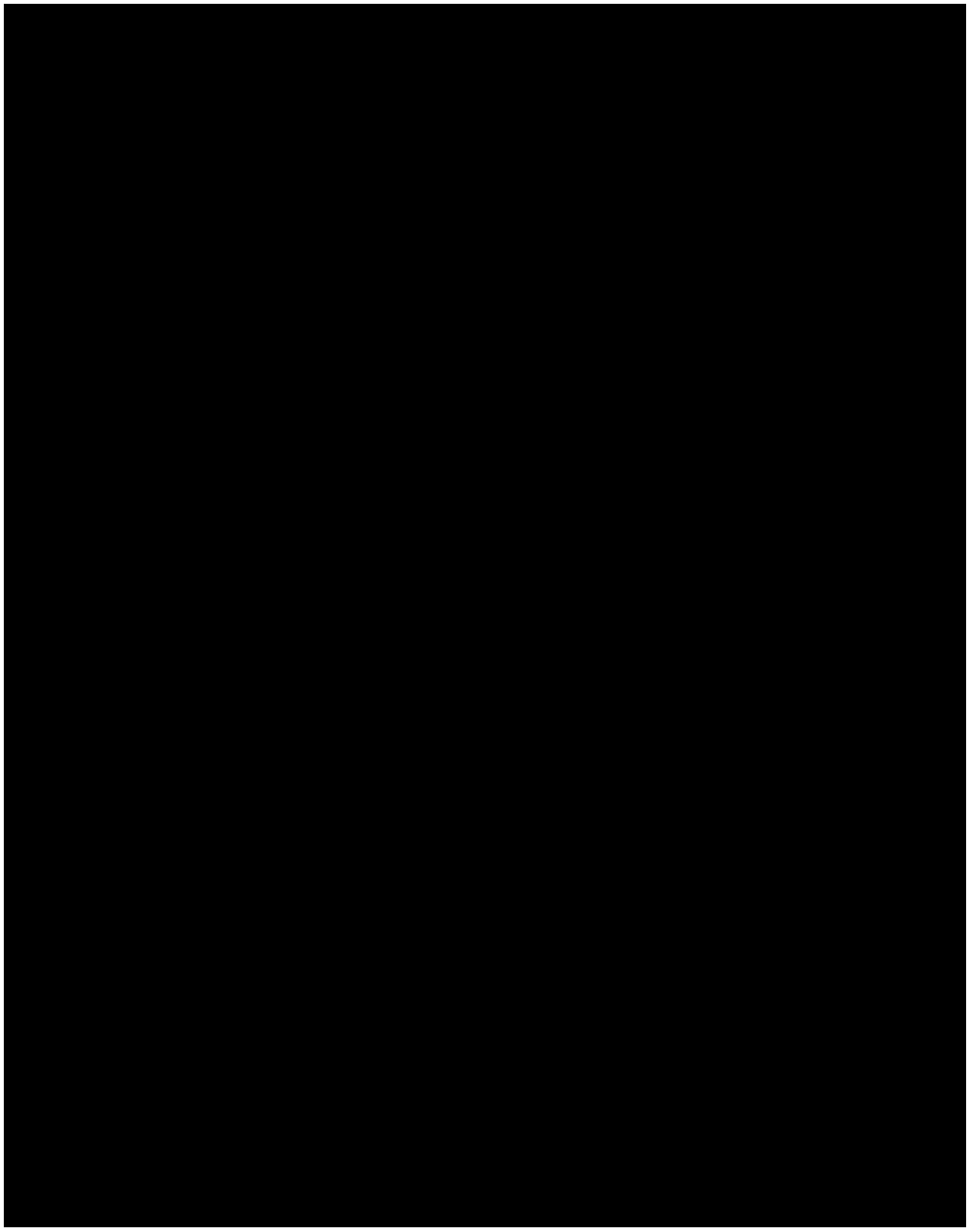

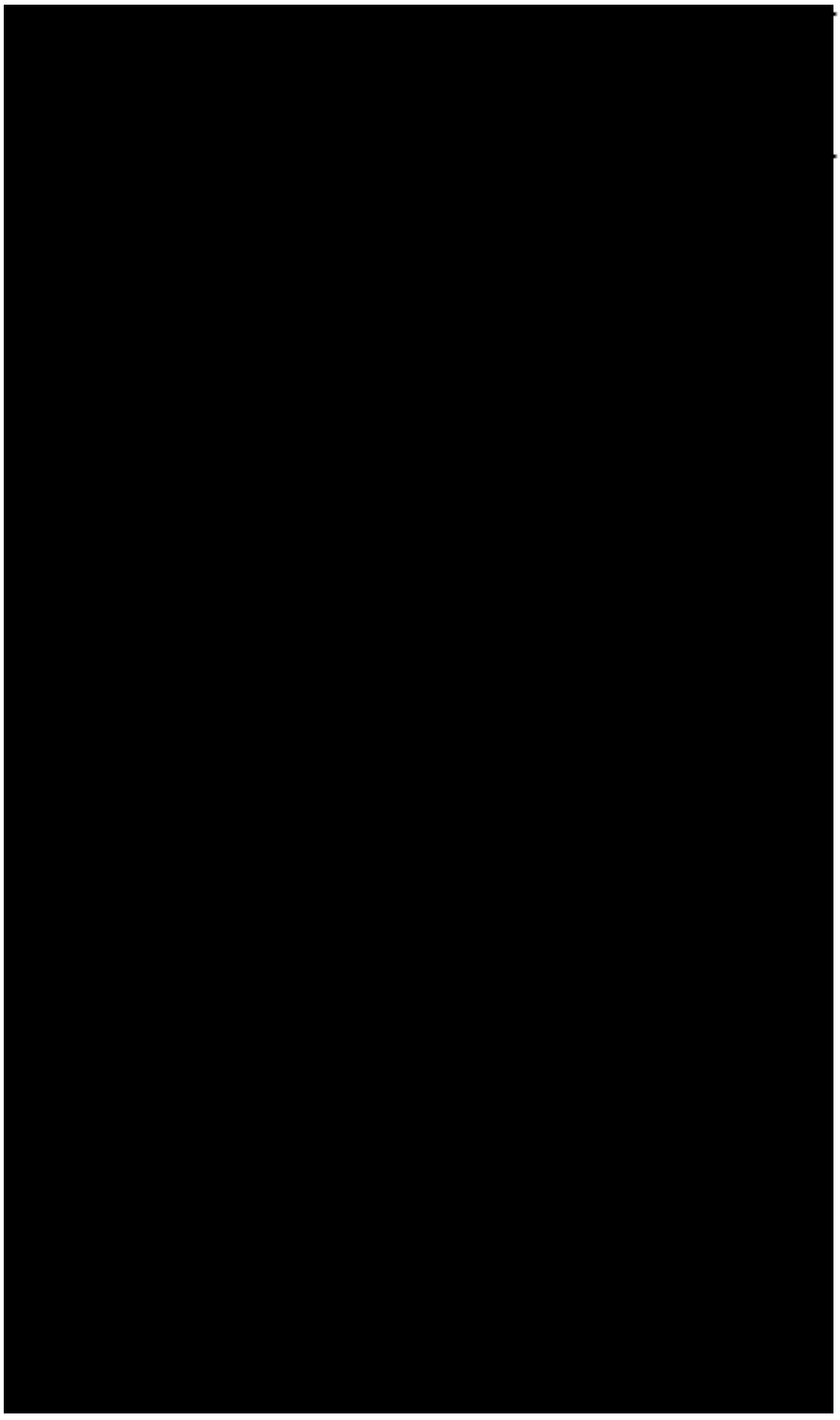

Appendix E Bluetooth devices and associated material

The following devices and associated material will be used during the study. Detailed instructions for use will be provided to the patients and included in the study operational manual.

GLUCOMETER AND ANCILLARY SUPPLIES

Class 3 Devices/Products

- MyGlucoHealth Wireless Blood Glucose Monitoring System model MGH-BT1 (manufacturer: Infopia)
- MyGlucoHealth test strips model MGH-TS50 (manufacturer: Infopia)
- MyGlucoHealth Control Solution model MGH-CS3 (manufacturer: Infopia)

Class 2 Device

- Lancets (manufacturer: Taidoc)

PULSE OXIMETER

- Finger pulse oximeter model 9560 ONYX II (manufacturer: Nonin)

BLOOD PRESSURE CUFF

- Blood pressure cuff model, HEM 9200T (manufacturer: OMRON)

WEIGHT SCALE

Per Entra “For the weight scale, there is no requirement for a license in Canada, unless the scale calculates BMI or Fat Analysis. The scale is branded with Entra Health’s name.

MSC15146 16.1.1 Protocol

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	13-Mar-2017 12:08 GMT+0100
[redacted]	Clinical Approval	15-Mar-2017 09:24 GMT+0100
[redacted]	Regulatory Approval	16-Mar-2017 22:02 GMT+0100