Medicinrådet

Bilag til Medicinrådets anbefaling vedr. ciltacabtagene autoleucel til behandling af patienter med knoglemarvs-kræft, som har fået mindst tre tidligere terapier

- herunder et immunmodulerende middel, en proteasomhæmmer og et anti-CD38-antistof, og som har udvist sygdomsprogression under den sidste terapi

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. ciltacabtagene autoleucel
2. Forhandlingsnotat fra Amgros vedr. ciltacabtagene autoleucel
3. Ansøgers endelige ansøgning vedr. ciltacabtagene autoleucel

Janssen-Cilag A/S

Bregnerødvej 133

DK-3460 Birkerød

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28. August 2023

Til Medicinrådet

Janssen-Cilags tilbagemelding på Medicinrådets udkast til anbefaling vedr. ciltacabtagene autoleucel til behandling af patienter med knoglemarvskræft, som har fået mindst tre tidligere terapier.

Validiteten af datagrundlaget

Medicinrådet beskriver at der er usikkerhed forbundet med den indirekte sammenligning. Vi er enige i at indirekte sammenligninger kan være usikre, men finder det vigtigt at påpege, at Janssen har taget mange forbehold for at minimere denne usikkerhed. Den eksterne kontrolarm der anvendes, er baseret på data fra LocoMMotion studiet, som er et prospektivt studie der undersøger effekten af standard of care (SOC) og har lignende inklusionskriterier som CARTITUDE-1. LocoMMotion inkluderer dermed relevante patienter, der får SOC i samme periode som CARTITUDE-1 patienterne behandles. Desuden er studiet initieret af Janssen, hvilket gør at vi har adgang til data på individniveau, og med disse data er det blandt andet muligt at matche data fra CARTITUDE-1 og LocoMMotion langt bedre end med andre metoder til indirekte sammenligning (herunder MAIC).

Sikkerhed

På side 46 konkluderer Medicinrådet, at der er flere og sværere bivirkninger forbundet med Carvykti end med SOC. Vi er uenig i den vurdering. Det er korrekt at bivirkningsprofilen til Carvykti er anderledes, men de specifikke bivirkninger til immunterapi (CRS og ICANS) er håndterbare og typisk forbigående. Internationalt er der udkommet forskellige retninglinjer der hjælper med at sikre dette[1,2]. Danske læger har allerede oparbejdet omfattende erfaring med behandling af CRS og ICANS via flere kliniske studier med CAR-T og bispecifikke antistoffer. Ved markedsføring af Carvykti vil Janssen samtidig lancere et "risk minimization program" der giver information om CRS og ICANS, og som del af dette program stille vejledninger til tidlig opsporing og håndtering til rådighed.

Ligeledes har Janssen ved analyse af CARTITUDE-1 data identificeret riskofaktorer for udvikling af ”Parkinsonisme” - høj tumorbyrde og protraheret CRS. En tilpasset profylaktisk handlingsplan med specifikke forholdsregler blev anvendt i CARTITUDE-4 studiet og reducerede hyppigheden af "Parkinsonismen" til under 1% (1 ud af 176 patienter (Grade 1)).

[1] Markouli, M.; Ullah, F.; Unlu, S.; Omar, N.; Lopetegui-Lia, N.; Duco, M.; Anwer, F.; Raza, S.; Dima, D. Toxicity Profile of Chimeric Antigen Receptor T-Cell and Bispecific Antibody Therapies in Multiple Myeloma: Pathogenesis, Prevention and Management. Curr. Oncol. 2023, 30, 6330–6352

[2] Ludwig H, Terpos E, van de Donk N, Mateos MV, Moreau P, Dimopoulos MA, Delforge M, Rodriguez-Otero P, San-Miguel J, Yong K, Gay F, Einsele H, Mina R, Caers J, Driessen C, Musto P, Zweegman S, Engelhardt M, Cook G, Weisel K, Broijl A, Beksac M, Bila J, Schjesvold F, Cavo M, Hajek R, Touzeau C, Boccadoro M, Sonneveld P. Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network. Lancet Oncol. 2023 Jun;24(6):e255-e269. doi: 10.1016/S1470-2045(23)00159-6. PMID: 37269857.

I kontrast dertil medfører SOC en akkumulering og intensivering af "konventionelle" bivirkninger som f. eks. knoglemarvspåvirkning (CTX, Pomalidomid), Diabetes Mellitus og psykisk påvirkning (glucocorticoider), thromboembolier (Pomalidomid), kardiotoxicitet (Carfilzomib).

Usikkerheden mht. potentielle langtidsbivirkninger kan ikke undgås ved implementering af en ny behandlingsmodalitet. Vi kan tilføje at Janssen derfor har iværksat et Post Authorization Safety Studie (PASS) for at sikre opfangelse af eventuelle langtidsbivirkninger.

CARTITUDE-4 data

Medicinrådets sekretariat nævner flere gange at der forventes resultater fra CARTITUDE-4, som er et randomiseret fase III studie i tidligere behandlingslinjer. De første af disse resultater er publiceret i NEJM i juni 2023 og Janssen har delt artiklen med Medicinrådets sekretariat[3]. Disse data bekræfter de gode resultater fra CARTITUDE-1, viser en væsentlig reduktion i "parkinsonisme" og styrker den samlede datapakke for Carvykti. Denne datapakker inkluderer også LEGEND-2 studiet som Medicinrådet ikke nævner vurderingen, men som nu har over 4 års follow-up og også bekræfter resultaterne for Carvykti[4].

Følsomhedsanalyser

Generelt resulterer følsomhedsanalyserne i meget ens inkrementelle QALY's, hvilket indikerer at usikkerheden er begrænset. Medicinrådets sekretariat vælger dog en meget ukritisk tilgang til håndtering af usikkerhed vedr. ekstrapolering af overlevelse. Kort sagt, så vælger man at lave sensitivitetsanalyser med alle ekstrapoleringer, uden nogen vurdering af hvorvidt disse er klinisk plausible. Det medfører blandt andet at den mest pessimistiske ekstrapolering inkluderes, på trods af den ikke er klinisk plausibel.

Som vi forstår rapporten, så anerkender sekretariatet, Janssen's valg af metodisk tilgang og argumentationen for den valgte ekstrapolering. En af de metodiske tilgange valgt af Janssen var at undersøge *smoothed hazards* fra studierne (CARTITUDE-1 og LocoMMotion). For CARTITUDE-1 viser *smoothed hazards* en faldende tendens over tid for både PFS og OS - hvilket virker klinisk plausibelt. Sekretariatet ændrer ikke på antagelserne vedr. ekstrapolation i deres base case, hvilket må betyde, at de finder Janssens valg af ekstrapolation klinisk plausibel.

Alle andre ekstrapolationer som Janssen har præsenteret (med undtagelse af den eksponentielle og gen. gamma fordelingerne) giver også faldende *hazards* over tid. Den eksponentielle fordeling har konstante *hazards* pr. definition og gen. gamma har stigende *hazards* over tid, hvilket er det modsatte af hvad *smoothed hazards* for CARTITUDE-1 indikerer, og dermed i modstrid med antagelsen om klinisk plausibilitet der ligger til grund for sekretariatets (og Janssen's) base case. Derudover, har gen. gammafordelingen utvetydigt det værste statistiske fit ifølge AIC- og BIC-score.

Kort sagt, så er gen. gammafordelingen den der statistisk set passer data dårligst, og den er ydermere ikke klinisk plausibel. Hvis sekretariatet finder antagelsen om faldende *hazards* plausibel, så bør sensitivitetsanalyserne begrænses til at inkludere de ekstrapolationer der opfylder dette kriterie.

På vegne af Janssen

Fredrik Gerstoft og Jeppe S. Christensen

[3] https://www.nejm.org/doi/full/10.1056/NEJMoa2303379

[4] Zhao, W.-H., et al., Four-year follow-up of LCAR-B38M in relapsed or refractory multiple myeloma: a phase 1, single-arm, open label, multicenter study in China (LEGEND-2).

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06.09.2023

DBS/MGK

Forhandlingsnotat

Dato for behandling i Medicinrådet	27.09.2023
Leverandør	Janssen-Cilag
Lægemiddel	Carvykti (ciltacabtagene autoleucel)
Ansøgt indikation	ciltacabtagene autoleucel til behandling af patienter med knoglemarvskræft, som har fået mindst tre tidligere terapier
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel (Advanced Therapy Medicinal Products (ATMP) – en CAR-T behandling) - engangsbehandling

Prisinformation

Amgros har forhandlet følgende priser på Carvykti (ciltacabtagene autoleucel). I forhandlingen har Amgros modtaget to pristilbud, som begge er betinget af en anbefaling:

Pristilbud 1: Flad rabat.

Tabel 1: Forhandlingsresultat Carvykti - Flad rabat

Lægemiddel	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Carvykti*	[redacted]	[redacted]	[redacted]

[redacted]

Pristilbud 2:

[redacted]

Tabel 2: Forhandlingsresultat Carvykti – initierende rabat + effektbaseret aftale baseret på PFS

Lægemiddel	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Carvykti betaling ved infusion til patienten*	[redacted]	[redacted]	[redacted]

[redacted]

Tabel 3: [redacted]

	Rabatprocent ift. startbetaling	Tilbagebetaling SAIP (DKK)	Samlet betaling per patient SAIP (DKK)	Forventet PFS Carvykti *
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Aftaleforhold

[redacted]

[redacted]

[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Cavykti er indiceret til behandling af voksne patienter med recidiverende og refraktær myelomatose, som har fået mindst tre tidligere terapier, herunder et immunmodulerende middel, en proteasomhæmmer og et antiCD38-antistof, og som har udvist sygdomsprogression under den sidste terapi. Der er på nuværende tidspunkt ikke godkendt andre specifikke behandlinger til 4. linje.

I de kommende to år er flere nye lægemidler på vej til behandling i 4. linje. Flere af lægemidler er på vej gennem EMA og få af dem har ansøgt Medicinrådet:
CAR-T behandling:

- Abecma, Idecabtagene vicleucel, BMS. Godkendt i EMA, BMS har ikke ansøgt i Medicinrådet.

Bi-specifikke antistoffer:

- Tecvayli (teclistamab), Janssen. Godkendt i EMA, Janssen har ansøgt Medicinrådet.
- Talvey (talquetamab), Janssen. Under vurdering i EMA. Janssen har anmodet om vurdering i Medicinrådet.
- Elranatamab, Pfizer. Under vurdering i EMA.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	[redacted]	Link til information
Sverige	Under vurdering	[redacted]	Link til information
England	Ansøgning er trukket tilbage fra Janssen	[redacted]	Link til information
Holland	Under vurdering	[redacted]	link til information

Konklusion

[redacted]

Bilag 1.

Aftalen på Carvykti:

Denne aftale på Carvykti er en væsentlig anderledes aftale end de sædvanlige aftaler Amgros indgår på nye lægemidler.

Kontrakten indeholder uddybende beskrivelse af logistik-flow, ordresystem og ordre flow, håndtering af patientdata og betalingspræmisser.

Udover disse parametre indeholder aftalen også en del ekstra appendiks. Disse appendikser involverer også andre interessenter, da ét appendiks f.eks. er den kvalitetsaftale, som der er behov for ved CAR-T, mellem blodbank og leverandør. Andre appendiks beskriver behov for træning og uddannelse af relevante personer.

Af direkte relevans for prisen på lægemidler er det specificeret, hvornår der betales for lægemidlet. I denne aftale falder betalingen, når patienten modtager det færdige lægemiddel. Indtil da er det leverandøren som tager risikoen; fra bestilling, til cellehøst og færdigproduktion af lægemidlet inkl. transport til hospitalet. Først når den aktuelle patient får infusionen af Carvykti – betales der for behandlingen.

De store linjer i aftalen er blevet beskrevet og besluttet. Der mangler dog få mindre detaljer i aftalen som vil blive håndteret hvis Medicinrådet anbefaler Carvykti til ibrugtagning. Derudover mangler udarbejdelse af det praktiske ifm. den effektbaseret aftale, hvilket også skal inkluderes i aftalen.

Bilag 2:

Effektbaseret aftale:

[redacted]

[redacted]

[redacted]

Monitorering af behandlingseffekten ved Myelomatose
Myelomatose skal monitoreres på forskellige parameter for at tage højde for patienternes individuelle sygdomskarakteristika.

Kriterier for progression af Myelomatose er iht IMWG således:

Stigning med >25% fra det laveste opnåede niveau ***i en af de følgende****:*

- *Serum M-komponent (mindst 5g/L) og/eller*
- *Urin M-komponent (mindst 200 mg/24 h) og/eller*
- *Kun i patienter der hverken har målbart serum eller urin M-komponent – Differencen mellem involveret og ikke-involveret letkæde. Den absolutte stigning skal være mindst 100 mg/L*
- *Knoglemarvs infiltration med plasmaceller; absolut procent infiltration skal være over 10%*
- *Definitiv udvikling af nye knoglelæsioner eller ekstrameddulære plasmacytomer eller definitiv øget størrelse af eksisterende knoglelæsioner eller ekstrameddulære plasmacytomer (En definitiv øget størrelse er vækst med 50% (minimum 1 cm) målt seriell ved summen af produktet for krydsdiametere af målbare læsioner)*
- *Udvikling af hypercalcæmi (korrigeret serum Ca 2,65 mmol/L) som udelukkende skyldes Myelomatose*

Alle relaps kriterier skal konfirmeres i ***to på hinanden følgende målinger*** *før sygdommen kan klassificeres som i progression og PFS ender.*

For yderligere detaljer henvises til Kumar et al 2016. *Kumar S et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016 Aug;17(8):e328-e346. doi: 10.1016/S1470-2045(16)30206-6. PMID: 27511158.*

Application for the assessment of Carvykti® (ciltacabtagene autoleucel) for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

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Information marked with yellow represents confidential information. This covers the chapter 8.2 and the Appendix G and J where the title is marked yellow but the full chapter and appendix is considered confidential.

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1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	Carvykti®
Generic name	Ciltacabtagene-autoleucel (cilta-cel)
Marketing authorization holder in Denmark	Janssen-Cilag A/S
ATC code	N/A
Pharmacotherapeutic group	-
Active substance(s)	Autologous human T cells genetically modified ex-vivo with a lentiviral vector encoding a chimeric antigen receptor for B-cell maturation antigen (also known as JNJ-68284528 or LCAR-B38M CAR-T cells).
Pharmaceutical form(s)	Single intravenous infusion. Each dose of Carvykti® is specifically tailored to, and manufactured for, an individual patient using the patient's own blood cells, representing a personalised approach to the manufacturing, logistics and administration of treatment.

Overview of the pharmaceutical	
Mechanism of action	Carvykti® is a genetically modified autologous CAR-T therapy that targets B-cell maturation antigen (BCMA), a molecule highly expressed on the surface of late-stage B cells, plasma cells and malignant B-lineage cells such as myeloma cells [1, 2]. Its mechanism of action is similar to that of cytotoxic T-cells, allowing it to kill malignant cells and thereafter, potentially maintain ongoing anti-tumour surveillance [3]. A patient's own T-cells are genetically engineered to express a CAR construct, which contains an external target-binding domain responsible for recognising BCMA-expressing myeloma cells, and an internal activating domain, which initiates T-cell activation, thereby inducing malignant cell death [4]. The extracellular binding domain of Carvykti® consists of two VHH domains, that are directed against two distinct BCMA epitopes [5, 6]. These domains enable high-avidity binding to BCMA and distinguish Carvykti® from other CAR-T cell therapies, which typically only have one BCMA binding domain.
Dosage regimen	Carvykti® is provided as a single dose for intravenous infusion. The dose is 0.5-1.0 x 10^6 CAR-positive viable T-cells per kg of body weight, with a maximum dose of 1 x 10^8 CAR-positive viable T-cells per single infusion [7].
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Carvykti® is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.
Other approved therapeutic indications	-
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	
Packaging – types, sizes/number of units, and concentrations	N/A
Orphan drug designation	Yes

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2. Abbreviations

AIC	Akaike information criterion
ASCT	Autologous stem cell transplantation
ASTCT	American Society for Transplantation and Cellular Therapy
ATC	Anatomical Therapeutic Chemical code
ATT	Average treatment effect on treated
BCMA	B-cell maturation antigen
BIC	Bayesian information criterion
CAR-T	Chimeric antigen receptor T cell
CBR	Clinical benefit rate
CEM	Cost-effectiveness model
Cilta-cel	Ciltacabtagene autoleucel (Carvykti®)
CNS	Central nervous system
CPI	Consumer price index
CR	Complete response
CRAB	Hypercalcaemia, renal impairment, anaemia, bone lesions
CRS	Cytokine release syndrome
CUA	Cost utility analysis
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DRG	Diagnosis related group
DSA	Deterministic sensitivity analysis
ECOG	Eastern Cooperative Oncology Group
EHA	European Hematology Association
EMA	European Medicines Agency

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EMD	extramedullary disease
EORTC	European Organization for Research and Treatment of Cancer
EPAR	European Public assessment report
EQ-5D	EuroQol 5-dimensions
EQ-5D-5L	EuroQol 5-dimension, 5 levels
ESMO	European Society for Medical Oncology
FLC	Free light chain
GHS	Global health score
GLOBOCAN	Global Cancer Incidence, Mortality, and Prevalence
HDAC	Histone deacetylase
HIV	Human immunodeficiency virus
HSUV	Health state utility value
HR	Hazard ratio
HRQoL	Health related quality of life
HTA	Health technology assessment
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICD-10	International Classification of Diseases, 10th revision
ICER	Incremental cost effectiveness ratio
ICF	Informed consent form
Ig	Immunoglobulin
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IPD	Individual participant data
IPW	Inverse probability weighting
IRC	Independent review committee
Isa	Isatuximab
ISS	International Staging System

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ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
Ixa	Ixazomib
KOL	Key opinion leader
K	Carfilzomib
KCd	Carfilzomib/cyclophosphamide/dexamethasone
KCTd	Carfilzomib/cyclophosphamide/thalidomide/dexamethasone
Kd	Carfilzomib-dexamethasone
KPI	Key performance indicator
KRd	Carfilzomib-lenalidomide-dexamethasone
KVd	Carfilzomib-bortezomib-dexamethasone
LDH	Lactate dehydrogenase
LOT	Lines of therapy
mAb	Monoclonal antibody
MAIC	Matching-adjusted indirect treatment comparison
MGUS	Monoclonal gammopathy of undetermined significance
mITT	Modified intention to treat
MM	Multiple myeloma
MMRF	Multiple Myeloma Research Foundation
MoA	Mechanism of action
MP	Melphalan, prednisone
MPT	Melphalan, prednisone, thalidomide
MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network

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NCI	National Cancer Institute
NDMM	Newly diagnosed multiple myeloma
NICE	National Institute for Health and Care
NR	Not reported
OOS	Out of specification
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
P	Pomalidomide
PAD	Bortezomib/dexamethasone/doxorubicin
PCR	Polymerase chain reaction;
Pd	Pomalidomide/dexamethasone
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	Proteasome inhibitor
PICO	Patient Intervention Comparator Outcomes
PK	Pharmacokinetics
PO	Oral intervention
PPP	Pharmacy purchasing price
PPS	Pharmacy selling price
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSP	Pharmacy selling price

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PVd	Pomalidomide-bortezomib-dexamethasone
QALY	Quality adjusted life years
Rd	Lenalidomide/dexamethasone
RCT	Randomized controlled trial
RRMM	Relapsed or refractory multiple myeloma
RVd	Lenalidomide/bortezomib/dexamethasone
RWCP	Real world clinical practice
RWE	Real world evidence
sCR	Stringent complete response
S-d	Selinexor plus dexamethasone
SLR	Systematic literature review
SMD	Standardized mean difference
SMM	Smoldering multiple myeloma
SOC	Standard of care
SmPC	Summary of product characteristics
SQ	Subcutaneous
TTD	Time to disease
TTNT	Time to next treatment
TTR	Time to response
USA	Unites States of America
V	Bortezomib
VAT	Value added tax
VCd	Bortezomib/cyclophosphamide/dexamethasone
Vd	Bortezomib-dexamethasone
VGPR	Very good partial response
VRd	Bortezomib-lenalidomide-dexamethasone
VTD	Bortezomib/thalidomide/dexamethasone

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3. Tables and Figures

3.1 List of Tables

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3.2 List of Figures

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4. Summary

4.1 Population

The target patient population for this assessment consist of adult Danish patients with relapsed and refractory multiple myeloma (RRMM), who have received at least three prior therapies, including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI) and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy and is in line with the expected indication of Carvykti® (ciltacabtagene autoleucel; cilta-cel). Key patient characteristics

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and efficacy was based on CARTITUDE-1, the pivotal clinical trial for Carvykti®, which correspond well to Danish patients with triple class exposed RRMM eligible for CAR-T therapy.

RRMM is defined as a disease which becomes non-responsive or progressive on therapy or within 60 days of the last treatment in patients who had achieved a minimal response (MR) or better on prior therapy. To estimate the number of patients who would be eligible for the treatment with Carvykti® in Denmark, reported incidence and prevalence for multiple myeloma was used and an assumption that approximately 70 patients would be triple-class exposed, matching the patients in CARTITUDE-1 and be fit enough for Carvykti®. Based on input from a clinical expert in Denmark, approximately 20 patients are expected to be eligible for treatment with Carvykti® and apheresed.

4.2 Intervention: Carvykti®

Carvykti®, is an advanced chimeric antigen receptor T-cell (CAR-T) therapy. A gene therapy medicinal product containing autologous T cells (i.e., a patient's own T-cells) genetically engineered to target B-Cell Maturation Antigen (BCMA), a molecule expressed on the surface of mature B lymphocytes and malignant plasma cells. Carvykti® is infused at a target dose of $0{\cdot}75 \times 10^6$ CAR-positive viable T cells per kg. A conditioning regimen (also called lymphodepleting regimen) of cyclophosphamide 300 mg/m2 intravenous and fludarabine 30 mg/m2 intravenous should be administered daily for 3 days. Carvykti® infusion should be administered 5 to 7 days after the start of the conditioning regimen.

4.3 Comparator: Physician's choice

Although the increasing number of therapeutic options for RRMM has led to improved outcomes, patients typically receive a multitude of different drug types within numerous treatment regimens over the course of their disease. Whilst some patients may be retreated with the same therapies, other patients can try different types of PIs or IMID, where possible, with or without the addition of chemotherapy. The available Danish treatment guidelines do not include any specific treatment in the triple class exposed RRMM population and treatment consists of a mix of available SoC treatments. The most relevant comparator to Carvykti® is a mix of currently available SoC regimens, hereafter called physician's choice. The assumed composition of approved, or otherwise recommended combination therapies of physician's choice relevant for Denmark is:

- Pomalidomide-cyclophosphamide-dexamethasone (PCd)
- Pomalidomide-dexamethasone (Pd)
- Bortezomib-dexamethasone (Vd)
- Carfilzomib-lenalidomide-dexamethasone (KRd)
- Carfilzomib-dexamethasone (Kd)
- Ixazomib-lenalidomide-dexamethasone (IRd)
- Elotuzumab-lenalidomide-dexamethasone (ERd)
- Daratumab-bortezomib-dexamethasone (DVd)
- Daratumumab monotherapy (D)
- Bortezomib-cyclophosphamide-dexamethasone (VCd)
- Venetoclax monotherapy

4.4 Comparative analysis

The CARTITUDE-1 study represents a key source for the efficacy of Carvykti®. In the Phase 1b portion, the primary endpoint was safety as characterized by the number of participants with AEs and their severity. In the Phase 2 portion, the primary endpoint was evaluation of the overall response rate (ORR). Other outcomes included progression-free survival (PFS), overall survival (OS), response rates (for example, complete response), time to next treatment (TTNT), adverse events (AEs) of treatment and health-related quality of life (HRQoL).

The efficacy data for the comparator were based on the LocoMMotion trial, an external control arm for CARTITUDE-1, with inclusion and exclusion criteria matching CARTITUDE-1. In LocoMMotion, 248 patients were enrolled matching the 113 all enrolled patients in CARTITUDE-1 which is the relevant population for this assessment.

Adjusted comparisons were performed to balance patients in terms of prognostic factors. Comparative effectiveness was assessed for OS, PFS assessed by a review committee, TTNT and evaluated measures of treatment response (ORR; VGPR; ≥CR) in both all the all enrolled (ITT) population and all treated population (mITT). This assessment will focus on the ITT (all enrolled patients) comparison.

4.5 Safety

Safety was included as both a primary and secondary endpoint in CARTITUDE-1. It was characterised by the number of participants with adverse events (AEs) and their severity. Safety outcomes were consistent with those expected for CAR-T therapy in MM and effectively managed with available treatments [8]. Carvykti® is an innovative, safe and efficacious new CAR-T therapy. As shown in CARTITUDE-1 trial. The treatment provides unprecedented benefits to triple-class exposed RRMM patients, including deep, durable responses and the potential for prolonged long-term survival [8, 9].

4.6 Health economic analysis

A cost-effectiveness analysis with a partitioned survival model (PSM) structure was used to assess the economic value of Carvykti® in Denmark, compared to physician's choice over a lifetime perspective. The outcomes from the analysis include total costs as well as treatment benefits measure by life years (LY)s and quality adjusted life years (QALYs) gained from a Danish limited societal payer perspective. Furthermore, incremental differences were reported and summarised as incremental cost effectiveness ratios (ICERs).

The base case results showed that Carvykti® was associated with 5.28 additional LY and 4.20 additional QALYs compared to physician's choice. Treatment with Carvykti® led to incremental cost of DKK 2,345,652 DKK and was resulting in an ICER of DKK 558,527 per QALY gained over a lifetime Danish limited societal perspective.

Table 1. Base case result (discounted)

	Increment
Total life years (LYs)	5.28
Total quality adjusted life years (QALYs)	4.20
Total cost	2,345,652
ICER	**558,527**

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 Multiple Myeloma

Multiple myeloma (MM) is a rare and genetically complex haematological cancer [10]. The disease initiates in plasma cells, a type of white blood cell that is responsible for the production of antibodies (immunoglobulins [Ig]) (Figure 1).

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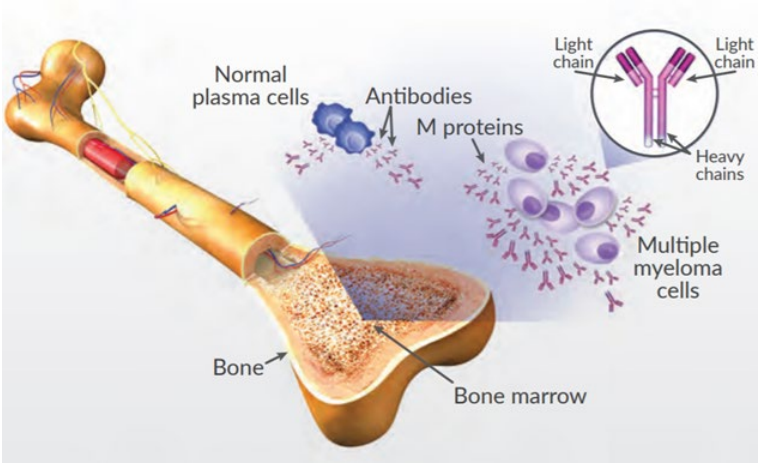
MM arises when a single plasma cell undergoes an oncogenic event that leads to its over-proliferation and/or decreased apoptosis. This results in an abnormally high number of plasma cell clones being situated in the bone marrow, leaving less space for healthy cells and interfering with the production of other blood cells such as red blood cells and platelets [10].

In MM, plasma cell clones are often characterised by the overproduction of an abnormal immunoglobulin known as M protein [10]. This protein can accumulate in the kidneys or blood and may lead to renal failure or blood hyperviscosity, respectively. Additionally, plasma cell clones frequently migrate to adjacent bones, where their invasion and subsequent over-proliferation can destroy skeletal structures, causing bone pain and fractures. Malignant cells may also circulate in the blood (plasma cell leukemia) and populate multiple organs throughout the body (extramedulary disease) [10].

Figure 1. Production of abnormal plasma cells and antibodies in MM



Abbreviations: MM = multiple myeloma.
Source: MMRF, 2017 [11]

MM develops from the continued accumulation of genetic abnormalities over time. This results in subclones of plasma cells with considerable genetic heterogeneity that contributes to the progression of MM and the development of drug resistance [12, 13].

As a result of this heterogeneity, MM can take a different clinical course [14, 15]. Although the disease is typically characterised by multiple relapses, with patients becoming refractory to treatment over time, with marked reduction in prognosis (Figure 2). The vast majority of patients eventually experience resistant disease and have a high clinical, quality of life, and economic burden [16, 17].

Figure 2. Trajectory of MM and RRMM – cycles of response, remission and relapse in the presence of treatment and clonal evolution

[redacted]

Development is preceded by a pre-malignant, asymptomatic state that has two clinically relevant stages: monoclonal gammopathy of undetermined significance (MGUS), the earliest recognisable stage of the disease, and smouldering multiple myeloma (SMM), an intermediate stage between MGUS and MM that has a higher disease burden than MGUS [19, 20]. Consensus diagnostic criteria for MM, RRMM, and their asymptomatic precursors are available from the International Myeloma Working Group (IMWG) and form the basis of the diagnostic criteria in the European Hematology Association (EHA)/European Society of Medical Oncology (ESMO) clinical practice guidelines [21-23]. In brief, diagnoses of MGUS and SMM require the absence of CRAB complications i.e. the most typical clinical manifestations of MM, being hypercalcemia, renal failure, anaemia, and bone disease [21, 22].

A description of these complications and their estimated prevalence in MM is presented in Table 2. SLiM represents an update to to the diagnostic criteria for MM, made by IMWG in 2014. The update includes the addition of three specific biomarkers that can be used to diagnose the disease in patients who did not have CRAB features [24]. Other less frequent complications of MM include hyperviscosity syndrome, peripheral neuropathy, recurrent infections, weight loss, venous thrombosis and extramedullary disease (EMD) [25-34].

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Table 2. SLiM CRAB criteria

Complication	Description & Presentation
S: Clonal cells	≥ 60% more clonal bone marrow plasma cells-[24]
Li: Light chains	Serum free light chain (FLC) ratio ≥ 100 provided involved FLC level is 100mg/L or higher [24]
M: MRI	More than one focal lesion on MRI [24]
C: Hypercalcaemia	Elevated blood calcium often prominent late in the course of MM [26] Primarily a consequence of tumour-induced bone disease—widespread destruction of bone tissue and bone resorption leading to calcium efflux [35, 36] Patients may exhibit confusion, obtundation, muscle weakness, polyuria, cardio arrhythmia [26] Prevalence hypercalcaemia: up to 30% [26, 37, 38]
R: Renal impairment	Common and potentially serious complication of MM resulting from the accumulation of excess M protein in the renal tubules [39] Prevalence renal impairment: 21 % at MM presentation [40]; up to 55% during course of the disease [41-44]
A: Anaemia	Low red blood cell count resulting from disruption of red blood cell production [45] Caused by overproliferation of plasma cell clones in the bone marrow [42] Prevalence anaemia: ~62%-73% at MM diagnosis [29, 45]
B: Bone disease	Most common complication of MM [26, 42] Invasion and expansion of plasma cell clones from the bone marrow weakens and damages the bone [46] Results in formation of osteolytic bone lesions and development of bone fractures, spinal cord compression, hypercalcemia, and osteoporosis [46] Prevalence bone disease: 80%-90% [26]

The terms 'relapsed' and 'refractory' are used to define MM patient populations in relation to the sensitivity of their disease to previous treatment:

- Relapsed MM is defined as previously treated MM that progresses and requires initiation of salvage therapy but does not meet criteria for refractory MM.
- Refractory MM is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease (PD) while on therapy [47].

5.1.2 Epidemiology

MM is a rare condition and is designated as a rare disease in the European Union (EU) [48] . In the EU, rare disease is defined as a condition that affects fewer than five in 10,000 individuals. Globally, MM is estimated to account for approximately 1% of all cancers [49].

In Denmark the incidence of MM have increased over time. In 2019 there was 609 patients diagnosed with MM of which approximately 60% were males. Also the total prevalence of MM has increased over the last 30 years which may be explained by the extended disease survival (new therapies joined the market) and the ageing of the Danish population. In 2018 there were 1,020 males and 811 women living with the disease in Denmark [50].

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Figure 3. Incidence MM in Denmark by gender

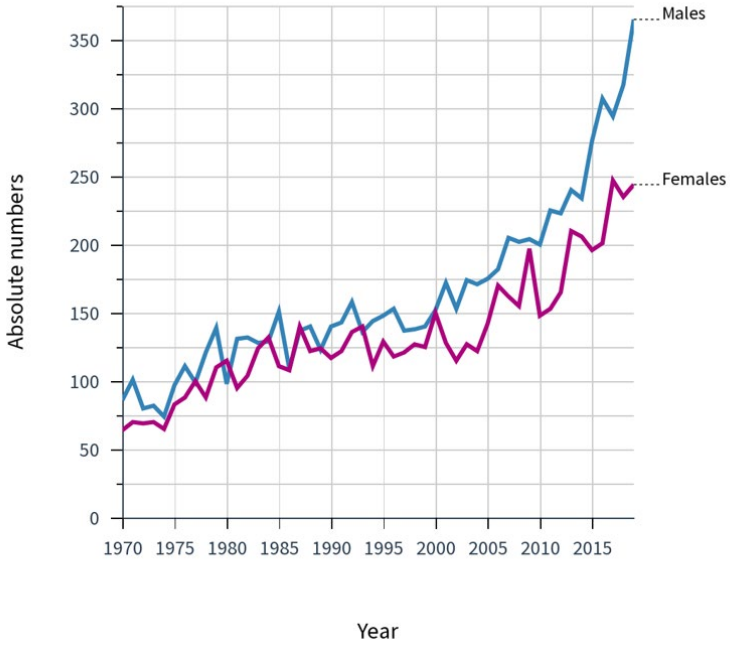
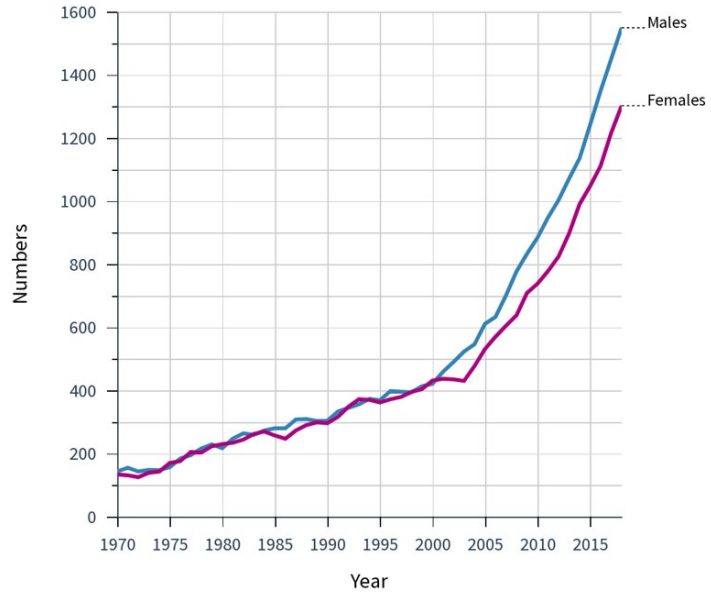


Figure 4. Prevalence MM in Denmark by gender



Based on these data it is not possible to derive incidence at each relapse in RRMM, however, it is known that the majority of patients with MM eventually experience disease relapse [22], and approximately 20% of patients die between each subsequent line of therapy [12, 13, 49, 51-53].

The number of patients with prior exposure to a PI, an IMiD and an anti-CD38 mAB (i.e., triple-class exposed) is expected to be small. Additional data from a German real-world evidence (RWE) study found 411 patients to be triple-class

exposed, out of a total 3,384 RRMM patients (i.e. ca 12%). Furthermore, that only 134 patients, out of the 411, had an ECOG score 0-1, in-line with the inclusion criteria in the pivotal clinical trial for Carvykti®, CARTITUDE-1 [54].

The incidence and prevalence for MM is presented Table 3 below and the eligible patients with triple-class exposed RRMM and the expected number of patients to be treated with Carvykti® is presented in Table 4 [50]. To estimate the number of patients who would be eligible for the treatment with Carvykti®, reported incidence and prevalence was used. The assumption is that about 12%, approximately 70 patients, have had three prior lines of therapy and are assumed to have received a PI, IMiD and anti-CD38 mAb. Not all the eligible patients are expected to receive treatment with Carvykti®, due to various reasons, including but not limited to the complexity of the treatment and expected learning curve amongst the treating community.

Based on input from a Danish clinical expert, 20 patients are expected to be apheresed in 2023, followed by 22 patients in the following years. As incidence seem to be constant over time, we assumed that around 70 patients are eligible per year, over the projected five years. Based on the CARTITUDE-1 trial, not all apheresed patient get infusion with Carvykti®. In CARTITUDE-1, 86% of the apheresed patients received an infusion with Carvykti®. Additionally, 4.1% of the CAR-T product are assumed to be out of specification (OOS) (Table 4).

Table 3. Incidence and prevalence in the past 5 years

Year	2015	2016	2017	2018	2019
Incidence in Denmark (MM)	472	508	541	552	609
Prevalence in Denmark (MM)	1,514	1,612	1,736	1,832	1,967

Sources: [50]

Table 4. Estimated number of patients eligible for treatment

Year	2023	2024	2025	2026	2027
Number of patients in Denmark who are expected to use the pharmaceutical(apheresed)	20	22	22	22	22
Number of patients in Denmark who are eligible to use the pharmaceutical	70	70	70	70	70

5.1.3 Patient populations relevant for this application

The target population in this assessment consists of adult Danish patients with RRMM, who have received at least three prior therapies, including an IMiD, a PI and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy and is in line with the approved indication for Carvykti®. This will position Carvykti® as a fourth- or subsequent-line treatment.

Subgroup analyses within this application and the economic evaluation were not included because the target population expected to be treated in clinical practice is considered as the one described above. In addition, given the relatively small sample sizes, subgroup analyses of cost-effectiveness by number of lines of previous therapy or other variables were not feasible.

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The baseline characteristics for the overall eligible population used in the cost effectiveness analysis was based on the CARTITUDE-1 all enrolled (ITT) population presented in Table 5. The mean age of 61 at treatment initiation was assumed to be representative for the Danish patient population relevant for CAR-T and the median age in CARTITUDE-1 is considered representative for the patients that will be treated with Carvykti®, since they are expected to be slightly younger than the overall median age for MM in Denmark, which is tested in a scenario analysis.

Table 5. Baseline characteristics: CARTITUDE-1

Characteristic	Value
Age, mean (SD)	61.7 (9.1)
Proportion female	42.5%
Body weight, mean (SD)	80.7 (17.1)
Body surface area, mean (SD)	1.91 (0.22)

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

In Denmark evidence-based treatment guidelines for MM are provided by The Danish Medicines Council (DMC) and The Danish Myeloma Study Group (DMSG) [55, 56]. The most recently published treatment guidelines (at the time of this assessment) were available in April 2022 and November 2019 from DMC and the DMSG respectively. The guidelines prepared by the DMC provide treatment recommendations for the first three lines of therapy (primary treatment, first relapse and second relapse), as well as fourth line and subsequent lines.

The DMC treatment guidelines for fourth and subsequent treatment lines recommend the same treatment offer as patients with disease progression during or after third line therapy. This treatment line includes two patient subgroups: those who are refractory to carfilzomib and those who are refractory to pomalidomide. Additionally, these guidelines recommend that participation in clinical trials (protocol treatments) may be considered [57].

The DMSG provides treatment guidelines specifically for relapsed disease. Treatments at first and second relapse could include different combination regimens of drugs from the following classes: IMiDs, PIs, mAbs and chemotherapy agents. The choice of treatment is dependent on what treatment was previously administered, the patient's refractory status to these treatments and toxicities experienced. The strongest recommendation for MM patients with subsequent relapse/progression is to follow a pomalidomide containing regimen i.e., pomalidomide plus dexamethasone, pomalidomide plus cyclophosphamide and dexamethasone or pomalidomide plus bortezomib and dexamethasone (

Figure 5). Additionally, the choice of treatment should be discussed with the patient, with consideration to comorbidities and complications related to previous treatments. At the third and subsequent relapse, no specific recommendation exists. Treatment choice at this stage is based on the discretion of the physician and generally includes a mix of available standard of care (SoC) regimens.

The lack of definitive treatment choices at this line or therapy and reliance on the discretion of the physician, explains why the physician's choice treatment basket is so heterogenous. There are several treatment combinations, owing to the fact that at this line of therapy, patients would have most likely received treatment with many of the recommended drugs, and thus require a tailored treatment regimen.

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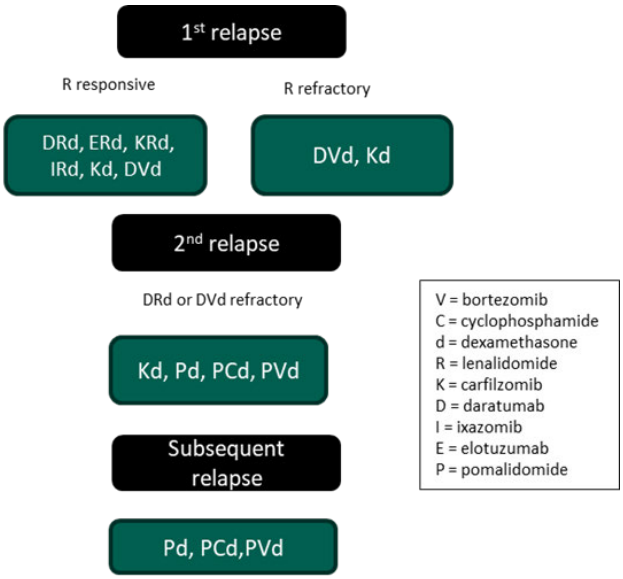
Figure 5. Danish Myeloma Study Group Treatment guidelines for Relapsed Multiple Myeloma



Source: [55]

5.2.2 Choice of comparator(s)

A new heavily pre-treated RRMM patient subset has emerged in recent years that has been exposed to all three SoC drug classes: PIs, IMiDs, and anti-CD38 mAbs and therapy. Whilst some patients may be retreated with the same therapies, other patients can try different types of PIs or IMID, where possible, with or without the addition of chemotherapy, clinical trial participation, or in some cases, only palliative care. The available treatment guidelines do not include any specific treatment in the triple class exposed RRMM population and treatment consists of a mix of available SoC treatments of physician's choice.

The relevant comparator to Carvykti® is a mix of currently available SoC regimens (physician's choice). The assumed composition of approved, or otherwise recommended combination therapies relevant is:

- Pomalidomide-cyclophosphamide-dexamethasone (PCd)
- Pomalidomide-dexamethasone (Pd)
- Bortezomib-dexamethasone (Vd)
- Carfilzomib-lenalidomide-dexamethasone (KRd)
- Carfilzomib-dexamethasone (Kd)
- Ixazomib-lenalidomide-dexamethasone (IRd)
- Elotuzumab-lenalidomide-dexamethasone (ERd)
- Daratumumab-Bortezomib-dexamethasone (DRd)
- Dartumumab monotherapy (D)
- Bortezomib-cyclophosphamide-dexamethasone (VCd)
- Venetoclax monotherapy

CARTITUDE-1 is a single-arm study with no active control arm. An external control arm for CARTITUDE-1 was constituted from the LocoMMotion study (NCT04035226), a prospective efficacy and safety study of real-life SoC in triple-class exposed patients with RRMM with, to a large degree, the same inclusion and exclusion criteria as CARTITUDE-1 [44]. Other sources for the efficacy of physician's choice have been identified, however all of them have a retrospective study

design and the prospective design of LocoMMotion were deemed preferable. Thus, LocoMMotion considered the most relevant data source for the comparative evidence to CARVYKTI® serves as a synthetic external control arm for CARTITUDE-1.

Eligible patients were enrolled between August 2019 and October 2020 from 75 sites across nine European countries (n=225) and the USA (n=23) [76]. In LocoMMotion, 248 patients were enrolled matching the 113 enrolled patients in CARTITUDE-1 (ITT). 170 patients were alive and progression free after 52 days (mITT) in LocoMMotion matching the 97 patients that were infused with Carvykti® all treated population (mITT) in CARTITUDE-1. The 52 days represent the time from apheresis to infusion in CARTITUDE-1 trial [77]. The effectiveness outcomes in this assessment are based on the LocoMMotion all enrolled population from an adjusted treatment comparison (presented in section 7).

An alternative to LocoMMotion is MAMMOTH, a retrospective, patient level, pooled analysis of outcomes of patients with multiple myeloma refractory to anti-CD-38 mAbs. The MAMMOTH study was conducted to provide context for interpretation of efficacy results in CARTITUDE-1. MAMMOTH identified a patient population (n=190), corresponding to the CARTITUDE-1 all-apheresed population, and one (n=122) corresponding to the study all-treated population.

The adjusted comparative analysis for Carvykti® compared to physician's choice is presented in section 4.3.

The approximate proportion of patients on each regimen from LocoMMotion representative for Denmark used for costing in the health economic analysis was informed by a market dynamics survey that collated input from 12 haematologists in Denmark [58]. These proportions were further validated by a Danish MM clinical expert, with additional input received [59] (see further 8.4.3 on costing)

5.2.3 Description of the comparator(s)

Since the comparator is a mix of different treatment regimens, the pharmaceutical form, posology and method of administration were based on the respective product summary of product characteristics (SmPCs) and treatment guidelines, and was validated the Danish clinical expert [7, 59].

- Generic name(s) (ATC-code) N/A
- Mode of action N/A
- Pharmaceutical form N/A
- Posology N/A
- Method of administration N/A
- Dosing N/A
- Should the pharmaceutical be administered with other medicines? N/A
- Treatment duration/criteria for end of treatment N/A
- Necessary monitoring, both during administration and during the treatment period N/A
- Need for diagnostics or other tests (i.e., companion diagnostics) N/A
- Packaging N/A

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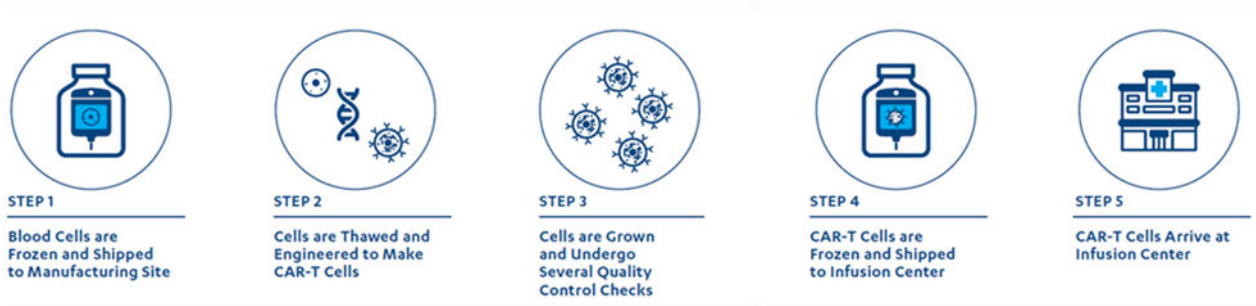
5.3 The intervention

In contrast to conventional drug therapy, each dose of Carvykti® is specifically tailored to, and manufactured for, an individual patient using the patient's own blood cells, representing a personalized approach to the manufacturing, logistics and administration of treatment. The multistep supply chain is summarized below and in Figure 6[60].

- Step 1: The patient is admitted to hospital, and their mononuclear cells are collected by the site clinical staff via a process known as leukapheresis. The patient's cells are then transferred to the site's cell-processing lab for sampling, cryopreservation, and subsequent shipment to the manufacturing facility.
- Step 2: At the manufacturing facility, the T-cells are genetically modified into CAR T-cells by introducing CAR transgenic DNA material into the T-cells. This new DNA programs the T-cells to become CAR T-cells.
- Step 3: The CAR T-cells then undergo ex vivo expansion on antibody-coated beads, and multiple quality controls analyses.
- Step 4: CAR T-cells are frozen in liquid nitrogen and shipped to the infusion centre.
- Step 5: The CAR T-cells arrive at the infusion centre, in anticipation of being re-infused into the patient.

Figure 6. Carvykti® supply chain



Manufacturing of Carvykti® will occur at the Janssen Raritan site in New Jersey and is anticipated to take approximately four weeks after receipt of the patient's cells by the site until delivery of the engineered cells to the infusion center ("receipt to release" [R2R]). Once the infusion center is notified by Janssen in writing after manufacturing and quality testing of Carvykti®, patients are eligible to receive their pre-infusion conditioning regimen.

The patient treatment pathway includes five steps (excluding the manufacturing process (explained above): cell collection via apheresis, bridging therapy, conditioning therapy, CAR-T cell infusion, and monitoring (Figure 7). During apheresis, blood is withdrawn from the patient's body and the blood is separated using a centrifuge. Peripheral blood mononuclear cells are collected, which include T-cells, and then the remaining blood is returned to the body. The T-cells are then frozen and sent to a manufacturing facility to be transduced with the CAR-T lentiviral vector and expanded before being returned to the hospital where the patients are treated. Prior to infusion, a patient receives lymphodepleting chemotherapy therapy to enhance treatment efficacy by eliminating regulatory T-cells and competing elements of the immune system [60]. During the time from apheresis to CAR-T infusion, some patients may receive a bridging therapy to stabilize disease, as per CARTITUDE-1 trial, until CAR-T cells are ready for infusion (Figure 7).

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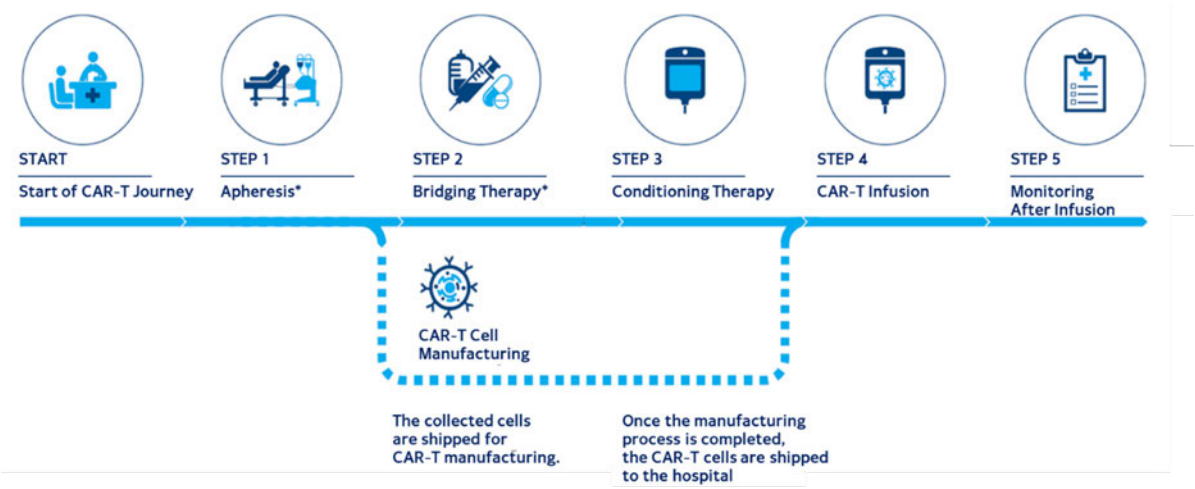

5.3.1 Dosing

Carvykti® is provided as a single dose for intravenous infusion. The dose is 0.5-1.0 × 10^6 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1 × 10^8 CAR-positive viable T cells per single infusion [60].

A conditioning regimen (also called lymphodepleting regimen) of cyclophosphamide 300 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous should be administered daily for 3 days. Carvykti® infusion should be administered 5 to 7 days after the start of the conditioning regimen infusion [60]. If resolution of toxicities due to the lymphodepleting regimen to Grade 1 or lower takes more than 14 days, thereby resulting in delays to Carvykti® dosing, the lymphodepleting regimen should be re-administered after a minimum of 21 days following the first dose of the first conditioning regimen.

Conditioning regimen must be delayed if a patient has serious adverse reactions from preceding bridging chemotherapies (including active infection, cardiac toxicity, and pulmonary toxicity) infusion [60].

Carvykti® infusion should be delayed if a patient has any of the following conditions [60]:

- Clinically significant active infection.
- Grade ≥ 3 non-haematologic toxicities of cyclophosphamide and fludarabine conditioning, except for Grade 3 nausea, vomiting, diarrhoea, or constipation.
- Carvykti® infusion should be delayed until resolution of these events to Grade ≤ 1.

5.3.2 Method of administration

The following pre-infusion medications should be administered to all patients 30 to 60 minutes prior to Carvykti® infusion [60]:

- Antipyretics (oral or intravenous paracetamol 650 to 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).
  The use of prophylactic systemic corticosteroids should be avoided as it may interfere with the activity of Carvykti® infusion [60].

Carvykti® is provided as a single dose for intravenous infusion. The dose is 0.5-1.0 × 10^6 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1 × 10^8 CAR-positive viable T cells per single infusion [60].

Carvykti® must be administered in a qualified treatment centre. Therapy should be initiated under the direction and supervision of a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with Carvykti®. Precautions is to be taken before handling or administering the medicinal product.

This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Carvykti® should take appropriate precautions to avoid potential transmission of infectious diseases in line with local guidelines on handling of human blood (cells) infusion [60].

Prior to infusion, the qualified treatment center must have at least 1 dose of tocilizumab available for use in the event of cytokine release syndrome (CRS), with access to an additional dose within 8 hours of each previous dose. Emergency equipment must be available prior to infusion and during the recovery period. Patients are expected to enrol and be followed in a registry in order to better understand the long-term safety and efficacy of Carvykti® infusion [60].

The product must not be thawed until it is ready to be used. The timing of Carvykti® thaw and infusion should be coordinated; the infusion time should be confirmed in advance, and the start time for thaw must be adjusted so that Carvykti® is available for infusion when the patient is ready. The product should be administered immediately after thawing and the infusion should be completed within 2.5 hours of thawing infusion [60].

5.3.3 Treatment duration/criteria for treatment discontinuation:

Carvykti® is provided as a single dose

5.3.4 Should the pharmaceutical be administered with other medicines?

See above

5.3.5 Necessary monitoring, during administration, during the treatment period, and after the end of treatment

Patients should be monitored daily for 14 days after the Carvykti® infusion at a qualified clinical facility, and then periodically for an additional 2 weeks after Carvykti® infusion, for signs and symptoms of CRS, neurologic events and other toxicities. Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion [60].

5.3.6 Need for diagnostics or other tests (i.e., companion diagnostics)

No

5.3.7 Summary

Carvykti® is an innovative, efficacious, and well-supported new CAR-T therapy. As shown in CARTITUDE-1 trial, Carvykti® provides unprecedented benefits to triple-class exposed patients, including deep, durable responses and the potential for prolonged long-term survival [9, 61]. Carvykti® is also associated with substantial improvements in patient HRQoL compared with baseline[61-63]. Safety outcomes are consistent with those expected for CAR-T therapy in MM and effectively managed with available treatments [61]. The results from an adjusted comparison (further described in section 7.1.8 suggest that Carvykti® is associated with significantly improved ORR, PFS, and OS results compared real world SoC therapy of physician's choice, from the LocoMMotion study.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

The two key clinical studies investigating Carvykti® (NCT03548207) are the CARTITUDE-1 study and the LEGEND-2 study (NCT03090659). Carvykti® (then referred to as 'LCAR-B38M CAR-T cells') was first investigated in humans in the LEGEND-2 study. Subsequently, the CARTITUDE-1 study was conducted.

CARTITUDE-1 provides the basis for the efficacy and safety evidence in this assessment as it is the pivotal clinical trial for Carvykti® and most recently conducted. The clinical development program for Carvykti® in RRMM includes two additional ongoing clinical trials: CARTITUDE-2 (Phase 2), and CARTITUDE-4 (Phase 3).

The study LocoMMotion (MMY4001) provides the basis for the efficacy and safety evidence for physician's choice (comparator) in this assessment. This study was considered the most relevant data source for the comparative evidence for Carvykti® due to it serving as a synthetic control arm for CARTITUDE-1, similar inclusion criteria to CARTITUDE-1 and prospective trial design. In addition, the efficacy of Carvykti® has been compared with SoC therapy in different indirect treatment comparisons (ITCs) described further in section 7.1.2.

A systematic literature review (SLR) was not the basis for choice of comparative effectiveness, as the most relevant documentation for efficacy and safety (intervention and comparator) were determined to be the above mentioned studies. However, Janssen has carried out an SLR and more information relating to that is found in Appendix A (including the full SLR).

6.2 List of relevant studies

Table 6 below gives an overview of the studies included in this assessment. In addition,

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Table 7 includes an overview of ongoing trials for Carvykti®. Detailed information about included studies, is included in this assessment is given in Appendix B Main characteristics of included studies.

Table 6. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Berdeja et al The Lancet, 398(10297), 314-324. (2021) Ciltacabtagene autoleucel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy, in relapsed/refractory multiple myeloma (R/R MM): Updated results from CARTITUDE-1. Usmani et al In: Wolters Kluwer Health. (2021). Updated Results from CARTITUDE-1: Phase 1b/2Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen-Directed Chimeric Antigen Receptor T Cell Therapy, in Patients With Relapsed/Refractory Multiple Myeloma. Martin et al. Blood, 138, 549. (2021).	CARTITUDE-1	NCT03548207	Ongoing The initial data cut-off date, 1 September 2020, corresponded to a time point at six months after the last subject received his or her initial dose of Carvykti®. The median duration of follow-up for all subjects was 12.42 months. The data cut-off update, 11 February 2021, included updated efficacy data at 12 months after the last subject received his or her initial dose of Carvykti®. The median duration of follow-up for all treated subjects was 18 months. The data cut-off update, 21 July 2021, included updated efficacy data with median duration of follow up of 22 months. The data cut-off update, 11 January 2022, included updated efficacy data with median duration of follow up of 27.7 months.
LocoMMotion: A prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed/refractory multiple myeloma (RRMM) receiving≥ 3 prior lines of therapy. Mateos et al. Wolters Kluwer Health (2021) LocoMMotion: A Prospective, Non-Interventional, Multinational Study of Real-Life Current Standards of Care in Patients With Relapsed/Refractory Multiple Myeloma Who Received≥ 3 Prior Lines of Therapy. Moreau, P et al. Blood, 138: p. 3057. (2021)	LocoMMotion	NCT04035226	Ongoing Eligible patients were enrolled between August 2019 and October 2020 Median follow-up 11.01 month at data cut 21 May 2021
A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell	LEGEND-2	NCT03090659	Active, not recruiting

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
maturation antigen, in patients with relapsed or refractory multiple myeloma. Zhao Q et al, J Hematol Oncol. (2018)			

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Table 7. Ongoing trials for Carvykti®

Study and RCT	Objective of the study (patient pop., etc.)	Intervention	Comparator	Outcome	**Starting date**
CARTITUDE-2 **Open-label Phase 2** **NCT04133636**	Cohort A: patients who had PD after 1 to 3 MM regimens, including a PI and IMiD individually or in combination and who are refractory to lenalidomide Cohort B: patients who had one line of previous therapy containing a PI and an IMiD and experienced disease relapse <12 months after front-line therapy or <12 months after ASCT Cohort C: patients who were previously treated with a PI, an IMiD, an anti-CD38 mAb, and BCMA-directed treatment Cohort D: NDMM patients with a history of 4 to 8 cycles of initial therapy Cohort E: NDMM patients classified as high risk per the ISS stage III criteria[b] who did not receive any prior therapy	Cohorts may receive R, D, V, or d in addition to Carvykti® Each cohort: n = 20	N/A	Primary: MRD negative rate Secondary: Response rates, TTR, DoR, duration and time to MRD negativity, BCMA levels, T-cell expansion/ persistence, AEs	Recruiting
CARTITUDE-4 **Open-label Phase 3** **NCT04181827**	RRMM patients who have received 1 to 3 prior lines of therapy and are refractory to lenalidomide	Arm A: Patients receive PVd or DPd Arm B: Carvykti® n = 400		Primary: PFS Secondary: ORR, CR, MRD, PFS, OS, time to worsening of symptoms, PFS2, AEs, HRQoL, systemic cytokine and CAR-T cell markers/antibodies	Recruiting

[a] As of February 15th, 2022, based on search results from Clinicaltrials.gov; [b] High risk per ISS stage III criteria is defined as beta 2 microglobulin >5.5 mg/L.
Abbreviations: AEs = adverse events; ASCT = autologous stem cell therapy; BCMA = B-cell maturation antigen; CAR-T = chimeric antigen receptor T-cell; CBR = clinical benefit rate; CZ = Changzheng; DPd = daratumumab, pomalidomide, dexamethasone; DoR = duration of response; FLC = free-light chain; HRQoL = health-related quality of life; IMiD = immunomodulatory drug; IMWG = International Myeloma Working Group; ISS = International staging system; JS = Jiansing; mAb = monoclonal antibody; MM = multiple myeloma; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PFS2 = progression-free survival on next-line therapy; PI = proteasome inhibitor; PVd = pomalidomide, bortezomib, dexamethasone;; RRMM = relapsed/refractory multiple myeloma; TTR = time to response
Source: clinicaltrials.gov

7. Efficacy and safety

7.1 Efficacy and safety of Carvykti® compared to physician's choice for triple exposed, RRMM patients

7.1.1 CARTITUDE-1

7.1.1.1 Study design

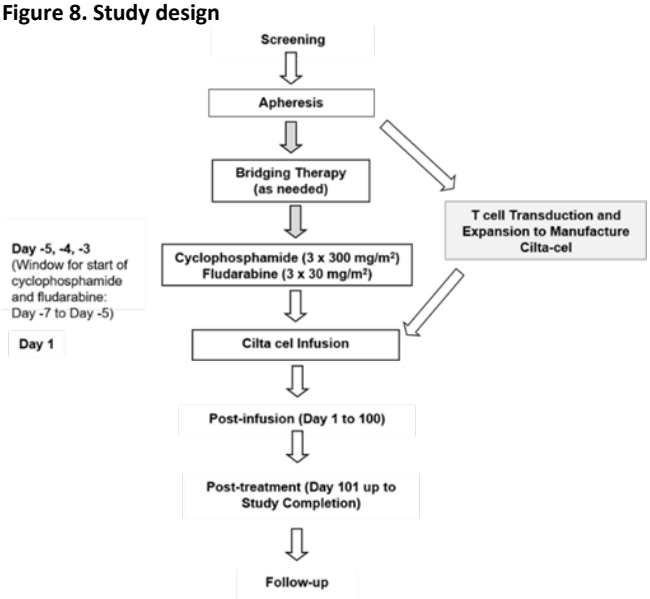
CARTITUDE-1 (NCT03548207) is an ongoing, Phase 1b+2, open-label, multicentre clinical trial being conducted in the US that is investigating Carvykti® in the treatment of triple-class exposed patients with RRMM [61]. The primary objective of the Phase 1b portion of the trial was to characterize the safety of Carvykti® and establish the appropriate dose for the Phase 2 portion. The objective of the Phase 2 portion was to use the recommended dose level from the Phase 1b portion to evaluate the efficacy and further characterize the safety of Carvykti® in the target patient population [61].

During the screening phase, patients were screened for study eligibility within 28 days prior to apheresis (

Figure 8) [61]. The study enrolment date was defined as the day of apheresis. All eligible patients who met the criteria for apheresis underwent apheresis for collection of peripheral blood mononuclear cells (PBMCs), and Carvykti® was generated from the collected T cells. Bridging therapy was allowed if clinically required (e.g., to stabilize disease).

After meeting the requirements for conditioning, a regimen of intravenous (IV) cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 was administered daily for three days to all eligible patients [61]. This conditioning regimen was used for lymphodepletion and to help promote CAR-T cell expansion in the patient after infusion. At five to seven days after the start of the conditioning regimen, Carvykti® was administered at a total targeted dose of 0.75 x 10^6 CAR positive viable T cells/kg. Day 1 of treatment was considered to be the day that Carvykti® was infused into the patient. Dose de-escalation or escalation could occur early in the Phase 1b portion of the trial depending on whether patients experienced an event of excess toxicity (i.e., >1 of the first 6 subjects met dose limiting toxicity [DLT] criteria) or met safety criteria (i.e., <20% of patients met DLT criteria), respectively [61].

Figure 8. Study design



Source: [61]

Safety evaluations were collected at four different time points from Day 1 to Day 100 post-infusion, and included assessment of AEs, laboratory test results, vital sign measurements, physical examination findings, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status grade [64]. In addition to safety data, pharmacokinetics and pharmacodynamics data were also collected. Disease progression and survival analyses are ongoing up until study completion. For the efficacy analyses, an Independent Review Committee (IRC) evaluated the disease status of each patient according to clinical judgement guided by the International Myeloma Working Group (IMWG) consensus recommendations for MM treatment response criteria [65].

The initial data cut-off date, 1 September 2020, corresponded to a time point at six months after the last subject received his or her initial dose of Carvykti®. The median duration of follow-up for all subjects was 12.42 months [61].

The latest updated data cut-off at time for this submission, 11th January 2022, included updated efficacy data for the all-treated population (mITT) and for the all-enrolled population (ITT) with a median duration of follow up of 27.7 months [66].

A total of 113 subjects, were enrolled and underwent apheresis. Among the 113 subjects enrolled, 101 (89.4%) received the conditioning regimen and 97 subjects (85.8%) went on to receive Carvykti®. At the time of 11 January 2022 clinical cutoffcut-off, three subjects (2.7%) received retreatment with Carvykti® infusion. As of the 11 January 2022 data cutoffcut-off, 30 subjects who received Carvykti® had died and the median duration of follow-up for the 97 subjects who received Carvykti® infusion was 27.7 months (range 1.5 months [subject died] to 40.38 months) [9, 67]. In this dossier, data from the latest availble data cut-off are presented with both the all-enrolled and all-treated analysis sets [63].

7.1.1.2 Inclusion and exclusion criteria

Patients were considered for participation in the CARTITUDE-1 trial if they met the following criteria [61, 64]:

- Age ≥18 years with documented MM according to IMWG criteria and an ECOG Performance Status grade of 0 or 1.
- Measurable disease based on either monoclonal paraprotein or serum Ig free light chain levels.
- Had received at least three prior treatment regimens including a PI, an IMiD, and an anti-CD38 mAb or were double refractory to an IMiD and a PI.
- Had documented disease progression during, or within 12 months, of their most recent anti-myeloma therapy.

Patients who received any prior CAR-T or BCMA-directed therapies were excluded. Patients who were diagnosed or treated for any invasive malignancy or received certain anti-tumour therapy within 7 to 21 days prior to apheresis were also excluded. Other comorbidities and conditions that resulted in study exclusion included select cardiac conditions, central nervous system involvement, certain infections, and blood disorders. A summary of the study's key inclusion and exclusion criteria is presented in Table 8.

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Table 8. Key inclusion and exclusion criteria in CARTITUDE-1

Inclusion Criteria	Exclusion Criteria
• Age ≥18 years with documented MM according to IMWG criteria • Measurable disease at screening as defined by any of the following: • Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or • Light chain MM without measurable M-protein in the serum or the urine: serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio • Received at least 3 prior lines or double refractory to an IMiD and PI • Prior therapy with a PI, and IMiD, and an anti-CD38 antibody • Undergone at least 1 complete cycle of treatment for each regimen, unless PD was the best response to the regimen • ECOG performance status grade of 0 or 1 • Pre-treatment clinical lab values meeting minimal thresholds defined by protocol	• Received prior CAR-T therapy • Received any therapy targeted to BCMA • Diagnosed with or treated for invasive malignancy other than MM, except: • Malignancy treated with curative intent and with no known active disease present for ≥2 years before enrolment; or • Adequately treated non-melanoma skin cancer without evidence of disease • Prior allogeneic stem cell transplant ≤6 months before apheresis • Prior autologous stem cell transplant ≤12 weeks before apheresis • Known active or prior history of CNS involvement or exhibits signs of meningeal involvement of MM • Stroke or seizure within 6 months of signing ICF • Certain medical conditions • Severe cardiac, oxygen supplementation, HIV, hepatitis, etc.

Abbreviations: BCMA= B-Cell Maturation Antigen; IMWG= International Myeloma Working Group; MM=Multiple Myeloma; PI= Proteosome inhibitor; IMiD= immunomodulatory agent, ECOG= Eastern Cooperative Oncology Group; CNS=central nervous system

Source: [64].

7.1.1.3 Study endpoints

As highlighted above, the CARTITUDE-1 trial is split into two parts, Phase 1b and Phase 2. In the Phase 1b portion, the primary endpoint was safety as characterized by the number of participants with AEs and their severity. In the Phase 2 portion, the primary endpoint was evaluation of the overall response rate (ORR) [64]. Secondary outcomes included progression free survival (PFS), overall survival (OS), mininal residual disease (MRD)-negative rates, duration of response (DoR), time to repsone (TTR), evaluation of health realted quality of life (HRQoL), BCMA expression levels, CAR-T cell expansion and proliferation levels, and systemic cytokine concentrations. Table 9 outlines the primary and secondary endpoints included in CARTITUDE-1 with their descriptions and methods of measurement.

Table 9. Study endpoints in CARTITUDE-1

Endpoint	Description
Primary Endpoints	
Number of participants with AEs (Phase 1b only)	An AE is any untoward medical event that occurs in a participant administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product
Number of participants with AEs by severity (Phase 1b only)	An assessment of severity grade will be made according to the NCI CTCAE, with the exception of CRS, and ICANS. CRS and ICANS should be evaluated according to the ASTCT consensus grading
ORR (Phase 2 only)	Defined as the proportion of participants who achieve PR or better according to IMWG criteria as assessed by the Independent Review Committee
Secondary Endpoints	
Number of participants with AEs (Phase 2 only)	An AE is any untoward medical event that occurs in a participant administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product
PFS	Defined as time from date of initial infusion of Carvykti® to date of first documented disease progression or death due to any cause, whichever occurs first. IMWG criteria for PD: Increase of 25% from lowest response value in any one of following: serum M-component (absolute increase must be ≥0.5 g/dL, urine M-component (absolute increase must be ≥200 mg/24 hours), Participants without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) Participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC % (absolute percentage must be ≥10%), definite development of new bone lesions or soft tissue plasmacytomas, or increase in size of bone lesions or tissue plasmacytomas
OS	Measured from the date of the initial infusion of Carvykti® to the date of the participant's death
Percentage of participants with negative MRD	Defined as the proportion of participants who achieve MRD negative status by the respective time point. MRD negativity will be evaluated as a potential surrogate for PFS and OS in MM treatment
Levels of BCMA expressing cells and soluble BCMA	Levels of expression of BCMA-expressing plasma cells in the bone marrow as well as the level of soluble BCMA in blood will be reported
Systemic cytokine concentrations	Serum cytokine concentrations (IL-6, IL-15, IL-10, and interferon [IFN-g]) will be measured for biomarker assessment
Level of CAR-T cells	CAR-T cell markers including, but not limited to, CD4+, CD8+, CD25+, and central memory, effector memory cells will be reported. An evaluation of cell populations may be performed by flow cytometry or cytometry by time of flight or both and correlated with response
Level of Carvykti® T-cell expansion (proliferation) and persistence	Levels of Carvykti® T-cell expansion (proliferation) and persistence via monitoring CAR-T positive cell counts and CAR transgene level will be reported
Number of participants with anti-Carvykti® antibodies	Number of participants exhibiting anti-drug antibodies for Carvykti® will be reported
VGPR or better rate	The VGPR or better rate (sCR + CR + VGPR), defined as the percentage of participants achieving VGPR or better response according to IMWG criteria during or after the study treatment. IMWG criteria for:

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	VGPR: serum and urine M-component detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours, CR: negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas, and <5% PC in bone marrow. sCR: CR plus normal FLC ratio and absence of clonal PCs by immunohistochemistry, immunofluorescence, or 2- to 4-colour flow cytometry.
Percentage of participants who achieve CBR	Clinical benefit rate is CR + VGPR + PR + MR based on IMWG defined response criteria
DoR	Calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of PD, as defined in the IMWG criteria.
TTR	Defined as the time between date of the initial infusion of Carvykti® and the first efficacy evaluation that the participant has met all criteria for PR or better
Change from baseline in HRQoL as measured by EORTC QLQ-C30 (Phase 2 only)	Subscale and single item scores are reported on a 0-100 scale, with higher scores representing better global health status, better functioning, and worse symptoms.
Change from baseline in HRQoL as measured by EORTC QLQ-MY20 (Phase 2 only)	Subscale and single item scores are reported on a 0-100 scale, with higher scores representing better global health status, better functioning, and worse symptoms.
Change from Baseline in Participant-reported Health Status Measured by EQ-5D-5L (Phase 2 only)	A total utility score is reported based on the health status, ranging from 0 to 1, where higher values indicate better health utility. The visual analogue scale ranges from 0 to 100, where higher values indicate better overall health status.
Change from Baseline in GHS Using PGIC Scale (Phase 2 only)	A single verbal rating scale ranges from 1 (a lot better now) to 7 (a lot worse now)
Change from Baseline in Pain Measured by PGIS Scale (Phase 2 only)	A single item to assess pain severity. The 5-point verbal rating scale ranges from 1 (none) to 5 (very severe).

Abbreviations: AE = adverse event; ASTCT = American Society for Transplantation and Cellular Therapy (ASTCT); BCMA = B-cell maturation antigen; CBR = clinical benefit rate; CR = complete response; CRS = cytokine release syndrome; DoR = duration of response; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-5L = EuroQol Group 5-dimension, 5 level; FLC = free light chain; GHS = global health status; ICANS = immune effector cell-associated neurotoxicity syndrome; IMWG = International Myeloma Working Group; MM = multiple myeloma; MR = minimal response; MRD = minimal residual disease; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OS = overall survival; PC = plasma cell; PD = progressive disease; PFS = progression-free survival; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PR = partial response; QLQ-C30 = Quality of Life Questionnaire Core-30; QLQ-MY20 = Quality of Life Questionnaire – Multiple Myeloma; TTR = time to response; VGPR = very good partial response.

Source: [64].

7.1.1.4 Baseline characteristics

The patient- and disease characteristics at baseline in CARTITUDE-1 for the 97 all treated (infused with Carvykti®) patients are presented in Table 10. The baseline characteristics for the ITT population were assessed around the time of apheresis, while the corresponding assessment for mITT population were carried out close to infusion.

Table 10. Baseline characteristics in CARTITUDE-1

Baseline Characteristic	Phase 1b + 2 All-treated (N = 97)	Phase 1b+2 All-enrolled (N=113)
Age, years		
Mean (SD)	62 (8.38)	61.7 (9.11)
Median (range)	61 (43-78)	62 (29-79)
Age category (%)		
<65 years	63.9	61.9
65 – 75 years	27.8	30.1
> 75 years	8.2	8.0
Male, n (%)	58.8%	57.5%
Weight, kg		
Mean (SD)	79.2 (16.69)	80.7 (17.06)
Median (range)	78.3 (39-126)	78.9 (43-132)
Height, cm		
Mean (SD)	169.7 (9.2)	169.7 (9.84)
Median (range)	170.2 (150-188)	170.2 (150-196)
Body surface area, m2		
Mean (SD)	1.92 (0.231)	1.94 (0.24)
Median (range)	1.94 (1.3-2.5)	1.95 (1.3-2.5)
ECOG score prior to infusion/apheresis, n (%)[a]		
0	40.2	47.8
1	55.7	52.2
2	4.1	0.0
ISS disease stage (%)[c]		
I	62.9	55.2
II	2.7	36.2
III	14.4	8.6
Cytogenetic profile*, n/N (%)		
Standard risk	70.1	61.9
High risk*	23.7	24.8
Unknown	6.2	13.3
Tumour BCMA expression (%),		
mean	76.3	76.3
≥50%	91.9	91.9
Median time since initial diagnosis (range), years	5.94 (1.6 – 18.2)	5.73 (1.0 – 18.2)
Refractory to last line of therapy, n (%)	96 (99.0%)	
Refractory status, n (%)		
PI + IMiD + anti-CD38 antibody	85 (87.6%)	100 (88.5%)
Any PI	87 (89.7%)	103 (91.2%)
Any IMiD	95 (97.9%)	111 (98.2%)
Any anti-CD38 antibody	96 (99.0%)	111 (98.2%)

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≥2 PIs + ≥2 IMiDs + anti-CD38 antibody	41 (42.3%)	52 (46.0%)
Refractory to, n (%)		
Bortezomib	66 (68.0%)	77 (68.1%)
Carfilzomib	63 (64.9%)	79 (69.9%)
Ixazomib	27 (27.8%)	29 (25.7%)
Lenalidomide	79 (81.4%)	95 (84.1%)
Pomalidomide	81 (83.5%)	96 (85.0%)
Thalidomide	8 (8.2%)	9 /8.0%)
Daratumumab	94 (96.9%)[b]	109 (96.5%)
Isatuximab	7 (7.2%)	7 (6.2%)
TAK-079[c]	1 (1.0%)	1 (0.9%)
Elotuzumab	19 (19.6%)	25 (22.1%)
Panobinostat	8 (8.2%)	9 (8.0%)

a) The last non-missing ECOG score on or prior to date of Carvykti® infusion is used. All patients met the inclusion criteria of ECOG score of 0 or 1 during screening; b) ISS were only available for 58 patients at the time of apheresis; c) TAK-079 is an investigational anti-CD38 antibody; d) Two additional subjects were refractory to other anti-CD38 antibodies.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory drug; mAb = monoclonal antibody; PI = proteasome inhibitor.

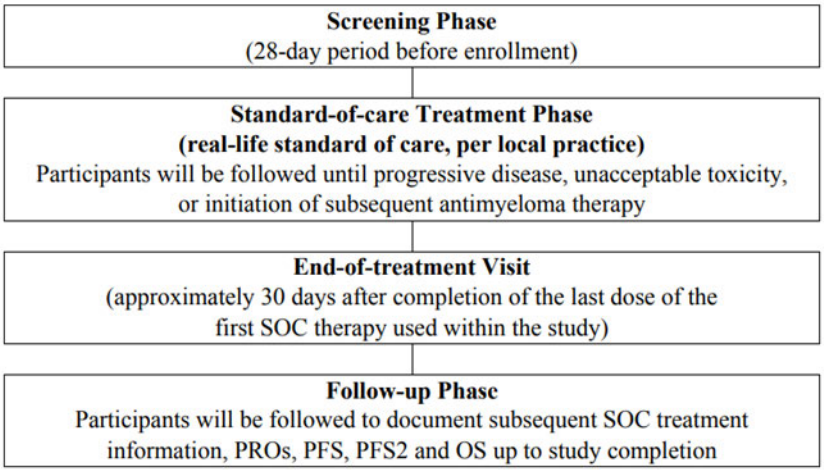
Source: [61]

7.1.2 LocoMMotion

7.1.2.1 Study design

The study design of LocoMMotion is shown in Figure 9. A screening phase, a SOC treatment phase, and a follow-up phase up to 24 months from Day 1, Cycle 1 of the first treatment used, were included. The follow-up phase continued until the end of the study. SoC are those treatments used in local clinical practice for the treatment of adult patients with RRMM. The minimum duration of a patient's participation in this study will be 24 months [68].

Figure 9. Study design (LocoMMotion)



Source: [68].

7.1.2.2 Inclusion and exclusion criteria

Key Eligibility Criteria was:

- Documented MM as per International Myeloma Working Group (IMWG) criteria
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Measurable disease at screening

- Received ≥3 prior line therapies or were double refractory to a PI and IMiD
- Received prior treatment with a PI, IMiD, and anti-CD38 mAb

7.1.2.3 Study endpoints

The primary endpoint was ORR, defined as the proportion of patients who achieved partial response or better according to the IMWG criteria, as assessed by a response review committee.

Key secondary objectives included, rates of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), DoR, progression-free survival (PFS), overall survival (OS), patient-reported outcomes and safety [68].

7.1.2.4 Baseline characteristics

At the data cut-off, May 21, 2021, 248 patients were enrolled between August 2019 and October 2020 with a median follow-up time of 11.0 months (range 0.1–19.2). Demographics and baseline characteristics are shown in Table 11 [68].

Table 11. Baseline characteristics LocoMMotion

Characteristic	n=248
Age, median (range) years	68.0 (41.0–89.0)
Male, n (%)	135 (54.4)
Geographic region	
US, n (%)	23 (9.3)
Europe, n (%)	225 (90.7)
Weight, kg (%)	**n= 208**
< 70	83 (39.9)
≥ 70	125 (60.1)
Mean (SD)	73.32 (16.314)
Median (range)	73.00 (37.0; 118.9)
Height, cm	n=196
Mean (SD)	167.21 (10.142)
Median (range)	167.00 (147.0; 193.0)
Body surface area (BSA), m2	**n=195**
Mean (SD)	1.8375 (0.24346)
Median (range)	1.8540 (1.274; 2.458)
Baseline ECOG score,[a] n (%)	
0	63 (25.5)
1	180 (72.9)
2	3 (1.2)
3	1 (0.4)
Time from initial MM diagnosis,[b] median (range) years	6.3 (0.3–22.8)
Number of prior lines of therapy, median (range)	4.0 (2.0–13.0)
Triple-class exposed,[c] n (%)	248 (100)
Refractory status, n (%)	
Any PI	197 (79.4)
Any IMiD	234 (94.4)
Any anti-CD38 mAb	228 (91.9)
Triple-class refractory	183 (73.8)

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Refractory to last line of prior therapy, n (%)	230 (92.7)

Note: a Screening ECOG scores were 0 or 1 only; b Out of 222 patients at the time of analysis; cPI, IMiD, and anti-CD 38 mA
Source: [68].

7.1.3 Overview of LEGEND-2

LEGEND-2 (NCT03090659) is an ongoing Phase 1, single-arm, open-label, multicenter study designed to evaluate the safety of Carvykti® and to provide initial proof-of-concept data to inform future clinical development. LEGEND-2 was conducted at four academic centers in China. It began on 2nd of October 2015 and completed enrolment in November 2017. In total, 74 patients with RRMM have received treatment with Carvykti® across the four centers, including 57 patients at the Xi'an site referred to as the all -treated. As of the clinical cut-off at May 25th, the median duration of follow-up was 47.8 months (range, 0.4-60.7) [70]. Table 12 below presents an overview of the LEGEND-2 study.

Table 12. Overview of LEGEND-2

Study	LEGEND-2
Sample size (n)	n=74
Study design	Phase 1, single-arm, open-label, multicentre study across four academic centres in China
Patient population	Age ≥18 years Documented MM according to IMWG criteria with clear BCMA expression detected on malignant plasma cells Refractory to at least three prior regimens, one of which must have contained bortezomib
Intervention(s)	Lymphodepletion using three doses of cyclophosphamide on Days -5, -4, and -3 was followed by infusion of cilta-cel. At the Xi'an, Ruijin, and Changzheng sites, the dose was split into three infusions administered over 7 days. In general, the number of CAR-T cells administered increased with each infusion. At the Jiangsu site, the dose was given as a single administration. Across all four sites, the median number of CAR-positive viable T-cells administered was 0.51×106 /kg (range 0.07–2.10×106 /kg).
Comparator(s)	N/A (Single armed trial)
Follow-up period	Median follow-up of 47.8 months at the May 2021 data cut-off
Is the study used in the health economic model?	No
Reasons for use / non-use of the study in model	LEGEND-2 reflected a long follow-up compared with published data for any BCMA-targeted CAR-T therapy for MM, as such, this study provided valuable data, which are used to validate extrapolations in the economic evaluation to reduce uncertainty around long-term survival extrapolation.
Primary endpoints reported* include results	Safety through assessment of AEs
Other outcomes reported * include results	• Response rates (ORR, CR, VGPR, PR) • Changes in aberrant immunoglobulin in serum and MM cells in bone marrow • BCMA expression • Number of cilta-cel CAR-T cells • PFS • OS • Median DoR

Abbreviations: AE = adverse event; BCMA = B-cell maturation antigen; CAR-T = chimeric antigen receptor T-cells; CR = complete response; CRS = cytokine release syndrome; CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; DoR = duration of response; IMWG

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= International Myeloma Working Group; ORR = overall response rate; OS = overall survival; PC = plasma cells; PCR = polymerase chain reaction; PFS = progression-free survival; PR = partial response; VGPR = very good partial response.
Source: [69, 70]

7.1.4 Efficacy and safety – results per study

7.1.5 CARTITUDE-1 efficacy results

The primary analysis population for all efficacy and safety summaries included all 97 subjects who received a Carvykti® infusion which is referred to as the all-treated population or the modified ITT (mITT). Some analyses were also conducted in the all-enrolled population or the ITT population which includes all 113 subjects who underwent apheresis. The efficacy will be presented based on the 11 January 2022 data cut-off with a median follow up of 27.7 months. Table 13 below provides a summary of the primary and secondary endpoints included in the study. The efficacy presented in the following section will be presented based on the 11 January 2022 data cut-off with a median follow up of 27.7 months.1

7.1.5.1 Overall response rate

As of the 11 January 2022 clinical cut-off, subjects had been followed for a median of 27.7 months from infusion. Table 13 below shows an overview of the overall best response results from CARTITUDE-1 for the all-enrolled (ITT population) and the all-treated (mITT population) at the 11 January 2022 data cut-off [66].

The ORR (PR or better) as assessed by the IRC based on IMWG criteria was:

- All-enrolled population (n = 113): 84.1% (95% CI: 76 to 90.3%)
- All-treated population (n=97): 97.6% (95% CI: 92.7% to 99.7%)

The stringent complete response (sCR) rate as assessed by the IRC based on IMWG criteria was:

- All-enrolled population (n=113): 80 (70.8%) (95% CI:61.5%, 79.0%)
- All-treated population (n=97): 80 (82.5%) (95% CI:73.4%, 89.4%)

The overall response of VGPR or better as assessed by the IRC based on IMWG criteria, was:

- All-enrolled analysis set (n=113): 81.4% (95% CI: 73.0% to 88.1%)
- All-treated analysis set (n=97): 94.8% (95% CI: 88.4% to 98.3%)

Table 13. Overall best response based on IRC mITT and ITT, data cut off 11 January 2022

Best response n (%) 95% CI	mITT n=97	ITT n=113
ORR (sCR + CR + VGPR + PR)	95 (97.9%) (92.7%, 99.7%)	95 (84.1%) (76.0%, 90.3%)
sCR	80 (82.5%) (73.4%, 89.4%)	80 (70.8%) (61.5%, 79.0%)
CR	0 (NE, NE)	0 (NE, NE)
VGPR	12 (12.4%) (6.6%, 20.6%)	12 (10.6%) (5.6%, 17.8%)
PR	3 (3.1%) (0.6%, 8.8%)	3 (2.7%) (0.6%, 7.6%)
VGPR or better (sCR + CR + VGPR)	92 (94.8%) (88.4%, 98.3%)	92 (81.4%) (73.0%, 88.1%)
CR or better (sCR + CR)	80 (82.5%) (73.4%, 89.4%	80 (70.8%) (61.5%, 79.0%)
MRD-negative CR/sCR[a]	42 (43.3%) (33.3%, 53.7%)	42 (37.2%) (28.3%, 46.8%)
Not evaluable (NE)	1 (1.0%) (0.0%, 5.6%)	17 (15.0%) (9.0%, 23.0%)
Did not received Carvykti®	-	16

a) 61 patients in total had an evaluable sample (i.e. subjects with identifiable clone at baseline and had sufficient cells to be tested at a sensitivity level of 10^{-5} in a post-treatment samples)

7.1.5.2 Duration of response (all-treated mITT population)

The median duration of response (DoR) for the all-treated, based on IRC review was not yet reached at the clinical cut-off of January 11, 2022 (95% CI [23.3 months, NE]), as in most responders, DoR data were censored at the time of clinical cut-off.

Of the 95 subjects comprising mITT, 53 subjects (55.8%) were censored. The probabilities of the responders in the mITT analysis set remaining in response at 9 months, 12 months and 18 months were 80.0% (95% CI:70.5% to 86.7%), 73.7% (95% CI: 63.6% to 81.4%) and 66.1% (95% CI: 55.6% to 74.7%), respectively.

7.1.5.3 Time to response (all-treated mITT population)

The median time to first response for the mITT population was 0.95 months (range 0.9 to 10.7 months). The median time to best response was 2.6 months (range 0.9 to 17.8 months). The median time to CR (or better) was 2.89 months (range 0.9 to 17.8 months).

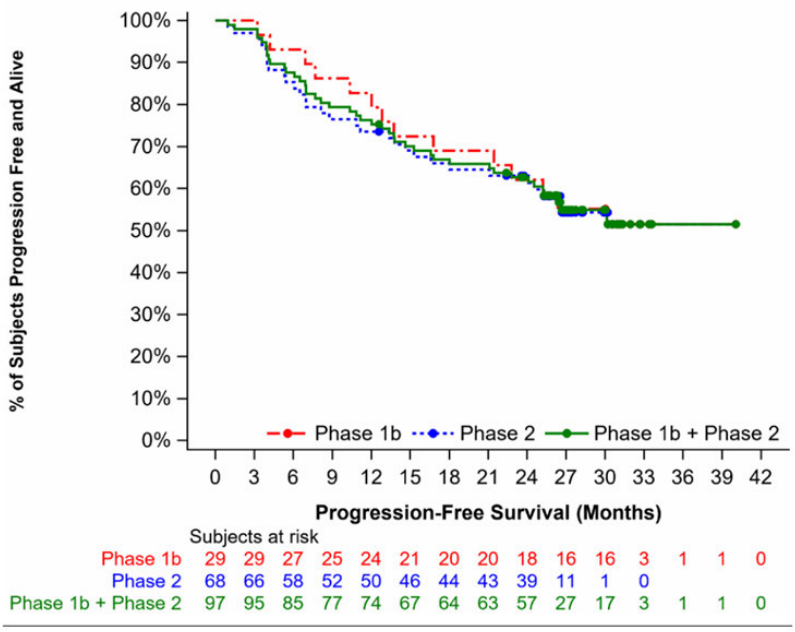
7.1.5.4 Progression free survival

For the January 11, 2022 update, with a median follow-up of 27.7 months, 54 subjects (55.7%) of the subjects in all-treated population (mITT) had their PFS data censored at the clinical cut-off. The overall median PFS (mPFS) based on the IRC response assessment was not reached (95% CI: 24.54, NE). The median mPFS for subjects who achieved CR/sCR was not reached. The 18-month PFS rates at the 11 January 2022 clinical cut-off are as follows:

- All-enrolled analysis set(n=113): [redacted]
- All-treated analysis set (n=97): 66.9% (95% CI: 56.5% to 75.3%)

The Kaplan-Meier plot for PFS for the mITT population is presented in Figure 10 below.

Figure 10. Kaplan-Meier plot for PFS based on IRC, all-treated analysis set (mITT)



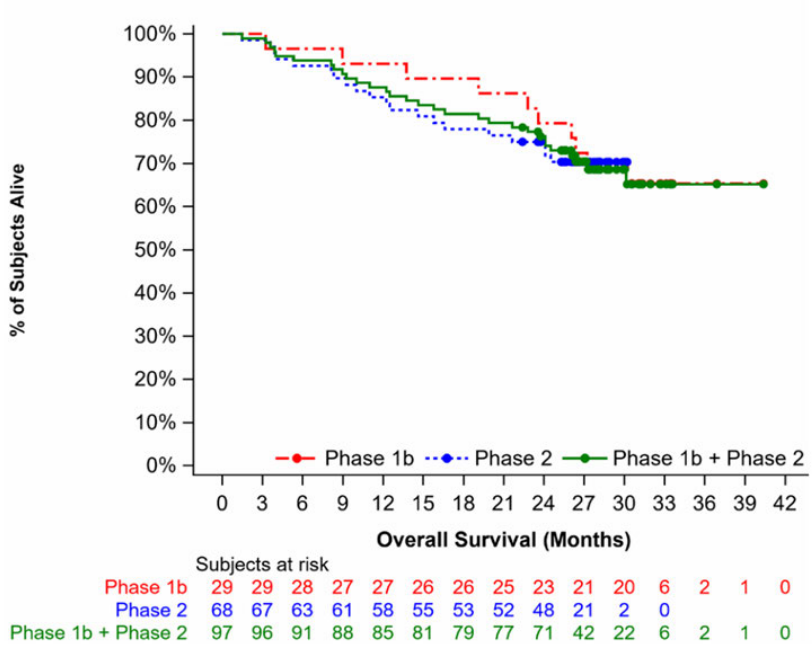
7.1.5.5 Overall survival

For the January 11, 2022 update, with a median follow-up of 27.7 months, 67 subjects (69.1%) in the all-treated group had their OS data censored. Further, 30 of the 97 subjects (30.9%) had died. With a median duration of follow-up of 27.7 months (range: 1.5 months [subject died] to 33.9 months) for the all-treated the mOS was not reached. The 18-months OS rate for the 11 January 2022 clinical cut-off was as follows:

- All-enrolled analysis set (n=113): [redacted]
- All-treated analysis set (n=97): 81.4% (95% CI: 72.2% to 87.9%)

The Kaplan-Meier plot for OS for the all-treated (mITT) population is presented in Figure 11 below.

Figure 11. Kaplan-Meier plot for OS based on IRC, all-treated analysis set (mITT)



7.1.5.6 MRD negativity

According to the IMWG definition, MRD is the persistence or re-emergence of very low levels of cancer cells in complete remission patients with about 1 tumour cell in at least 10^{-5} normal bone marrow cells [65]. The clinical implication of MRD within MM (both NDMM and RRMM) has been recognized; sustained MRD after treatment indicates that the tumour cells are not completely eradicated and a relapse in the near future is expected. Studies have shown that MRD negativity is a strong prognostic factor for both PFS and OS [20, 71, 72].

In CARTITUDE-1, at the time of the 11 January 2022 clinical cut-off, 96 subjects (99.0%) in the mITT population had bone marrow samples available for MRD evaluation. Of the 96 subjects 61 had evaluable samples for MRD (i.e., subjects with identifiable clone at baseline and had sufficient cells to be tested at sensitivity level of 10^{-5} in post treatment samples) 56 (91.8%) achieved MRD-negativity in bone marrow at a sensitivity level of 10^{-5}. Among the 80 subjects who achieved sCR/CR, 47 had evaluable samples. Of these subjects, 42 (89.4%) achieved MRD negativity at a sensitivity level of 10^{-5} [66].

PFS and OS was improved in patients with MRD-negativity (10^{-5}) sustained for ≥6 and ≥12 months (Figure 12 and Figure 13 respectively).

Figure 12. PFS by sustained MRD negativity status 10^{-5}

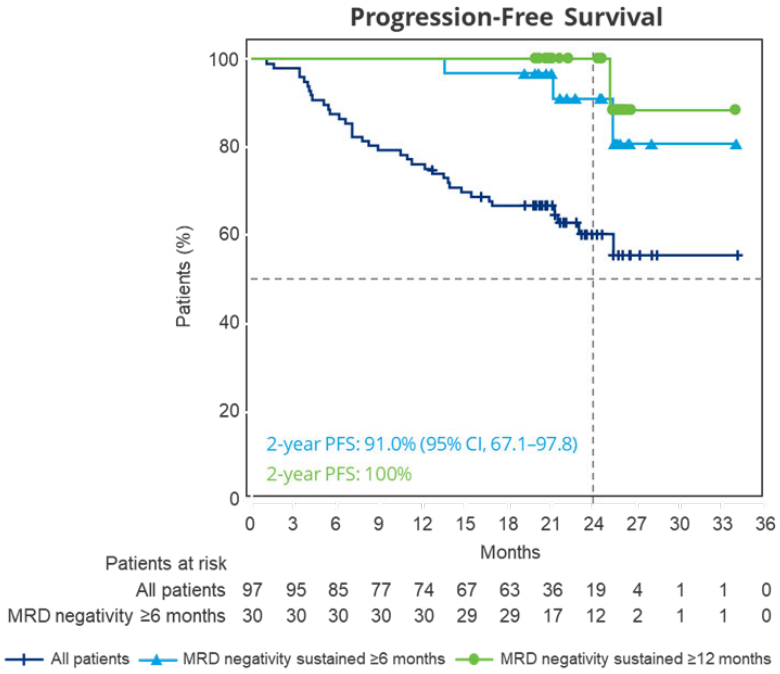
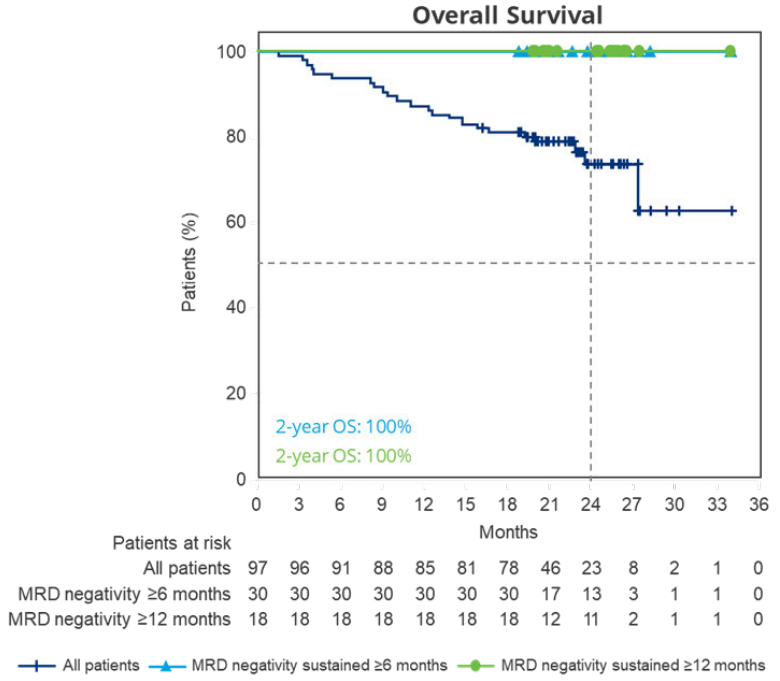
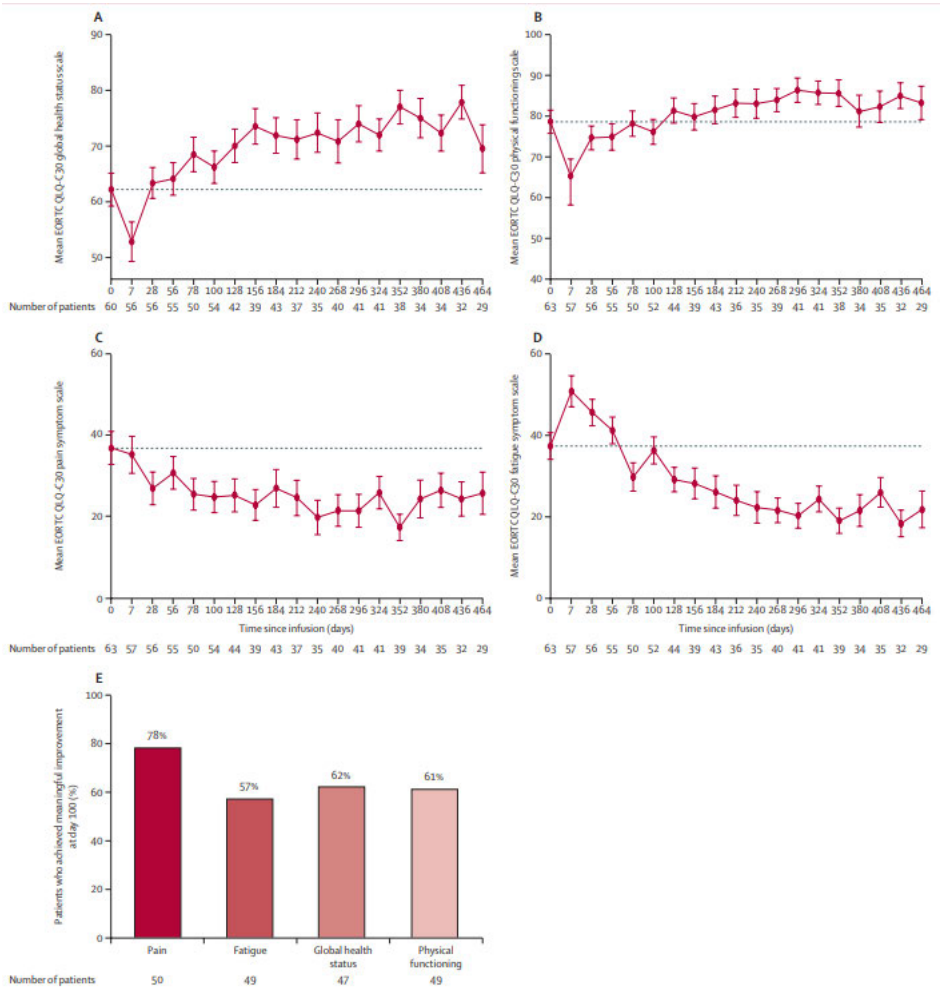


Figure 13. OS by sustained MRD negativity status at 10^{-5} threshold

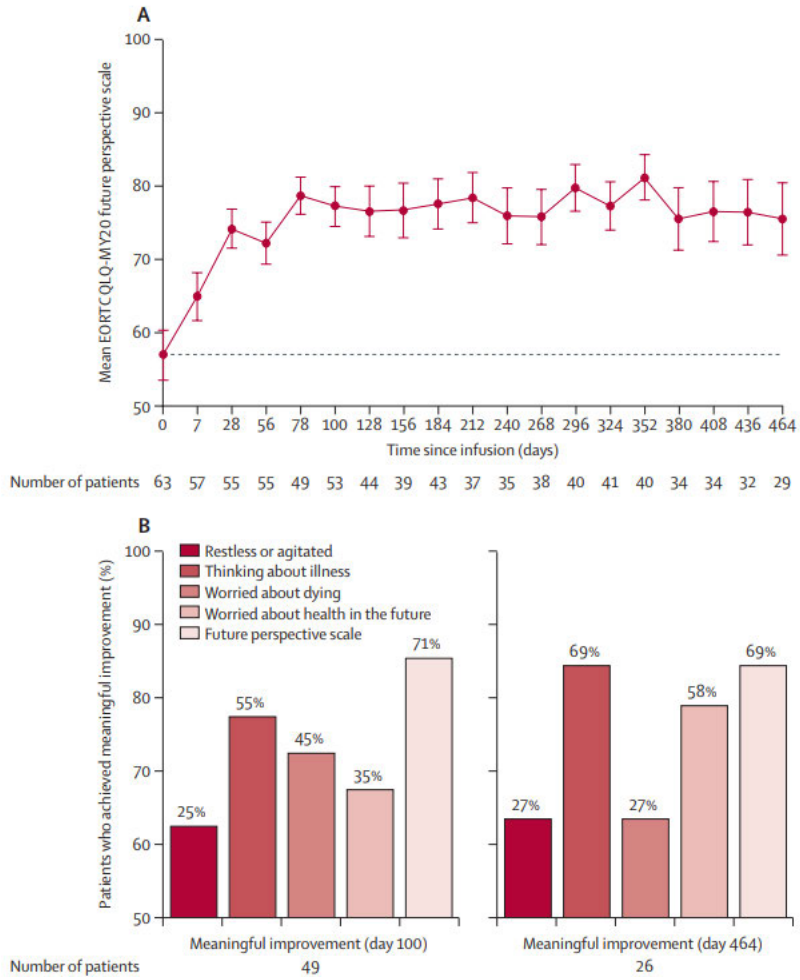


7.1.5.7 Health related quality of life

Despite an immediate decline in HRQoL after infusion in CARTITUDE-1, treatment with Carvykti® was associated improvements in GHS, physical functioning, emotional functioning scales. Furthermore, decreases were seen in symptom-based scores. The overall conclusion is that treatment with Carvykti is associated with clinically meaningful improvements of HRQoL, see Figure 14 and Figure 15 [73].



(A) Mean values for global health status, (B) Mean values for physical functioning, (C) Mean values for pain, (D) Mean values for fatigue, (E) Percentage of patients who had clinically meaningful improvement from baseline to day 100. For A-B, a higher score indicates better health. For for C-D, a higher score indicates greater symptom severity. Clinically meaningful changes were calculated using the PGIC as an anchor and estimated as the mean change score for the patients who improved by 1 point on the PGIC ("a little better now"). Error bars are standard error. Dashed lines represent score at baseline. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer health-related quality of life questionnaire. PGIC=Patient Global Impression of Change [73].



(A) Mean values for EORTC QLQ-MY20 future perspective scale. A higher score means better outcome, (B) Percentage of patients who had clinically meaningful improvement from baseline to day 100 or to day 464. Clinically meaningful changes were defined by literature-based minimal important differences of 10 points. Error bars indicate standard error. Dashed line represents score at baseline. EORTC QLQ-MY20=European Organisation for Research and Treatment of Cancer multiple myeloma health-related quality of life questionnaire [73].

See Appendix I Mapping of HRQoL data for more details on how the utility values relevant for Denmark were derived and used in the cost effectiveness analysis.

7.1.5.8 CARTITUDE-1 safety results

The safety findings for Carvykti® were consistent with expectations for CAR-Ts in MM, and AEs were effectively managed with available treatments [8, 74]. The most frequently observed treatment emergent adverse events (TEAEs) of any grade included neutropenia (95.9%), CRS (94.8%), anaemia (81.4%), and thrombocytopaenia (79.4%) (Table 14). Although CRS occurred in 94.8% of patients, less than 5% of these events were grade 3-5. The median time to onset of CRS was 7 days and the median duration was 4 days; CRS resolved in 98.9% of patients within 14 days of onset [8, 74].

Neurotoxicity events occurred in 20.6% of patients; 10.3% of the events were grade 3 or higher. Sixteen patients (16.5%) experienced neurotoxicities consistent with ICANS and 12 (12.4%) patients experienced other neurotoxicities [74, 75]. ICANS resolved in all patients; 50% of other neurotoxicities resolved. Infections of any grade were reported in 57.7% of patients; however, the incidence of grade 3 or 4 infections was low (19.6%) [8, 74]. Fourteen deaths occurred during the study: three were treatment-unrelated, six were treatment-related, and five were due to progressive disease [8, 74].

Table 14. Key safety outcomes in CARTITUDE-1 (phase 1b + 2)

Adverse Event (N = 97)	Result	
		Grade ≥3
Neutropenia	93 (95.9)	92 (94.8)
Febrile neutropenia	10 (10.3)	9 (9.3)
Anaemia	79 (81.4)	66 (68.0)
Thrombocytopaenia	77 (79.4)	58 (59.8)
Leukopaenia	60 (61.9)	59 (60.8)
Lymphopaenia	51 (52.6)	48 (49.5)
CRS n (%)	All Grade	Grade ≥3
CRS rate, n (%)	92 (94.8)	5 (4.1)
Median time to onset, days (range)	7 (1-12)	
Median duration, days (range)	4 (1-97)	
Neurotoxicity n (%)	**All Grade**	**Grade ≥3**
Total	21 (21.6)	11 (11.3)
ICANS	16 (16.5)	2 (2.1)
Other	13 (13.4)	9 (9.3)
Deaths (N = 97)		
Total number of deaths, n (%)	30 (30.9)	
Primary cause of death, n (%)		
Adverse event	15 (15.15.5)	
Progressive disease	14 (14.4)	
Other	1 (1)	
Number of patients who died within 30 days of infusion, n (%)	0	
Number of patients who died within 100 days of infusion, n (%)	2 (2.1)	

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome.
Source: [8, 74]

7.1.6 LocoMMotion efficacy results

The primary endpoint was ORR, defined as the proportion of patients who achieved partial response or better according to the IMWG criteria, as assessed by a response review committee.
Key secondary objectives included, rates of sCR, CR, PR, VGPR, VGPR or better, DoR, TTR, TTNT, PFS OS, patient-reported outcomes and safety [68].

At the time of the interim analysis, data-cut off May 21, 2021, the median response was evaluable in all patients in the all -treated population (n=248 patients). Table 15 gives an overview of the efficacy results for some of the main outcomes in LocoMMotion for the all -treated population (ITT).

As of clinical cut-off the ORR was 29.8%, with 12.5% of patients achieving VGPR or better. The median time for PFS was 4.63 months (95% CI: 3.88-5.62). The 12-month PFS rate was 19.9% (95% CI: 13.6%, 27.0%) (Table 15). Based on Investigator Assessment, 131 (52.8%) participants were censored. The median time for PFS was 6.47 months (95% CI: 5.59, 8.31). The 12-month PFS rate was 36.2% (95% CI: 27.9%,44.5%).

At the time of clinical cut-off, 107 (43.1%) participants had died. The median Kaplan-Meier estimate for OS was 12.39 months (95% CI: 10.28%, NE) (Table 15). The estimated OS rate (95% CI) at 12-month was 51.8% (95% CI: 44.1%, 58.8%).

Table 15. Overview of efficacy results, all-treated patients May

Median follow-up, months (range)	11 (0.1–19.2)
Response Rates n (%) 95% CI for %	n=248
ORR (sCR + CR + VGPR + PR)	74 (29.8) (24.2%-36.0%)
sCR	0 (0%) (NE-NE)
CR	1 (0.4%) (0.0%-2.2%)
VGPR	30 (12.1) (8.3%-16.8%)
PR	43 (17.3) (12.8%-22.6%)
VGPR or better (sCR + CR + VGPR)	31 (12.5) (8.7%-17.3%)
DoR, responders (PR or better)	n=74
Number of events (%)	36 (48.6%)
Number of censored (%)	38 (51.4%)
Median DoR, KM estimate, months (95% CI)	7.4 (4.7-12.5)
TTR (months), responders (PR or better)	n=74
Mean (SD)	2.24 (1.689)
Median (range)	1.87 (0.7-9.5)
TTNT VGPR or better, response evaluable 31	n=31
Number of events (%)	8 (25.8)
Number of censored (%)	23 (74.2)
Median TTNT, months (95% CI)	NE (11.96-NE)
TTNT Worse than VGPR, response evaluable	n=217
Number of events (%)	166 (76.5)
Number of censored (%)	51 (23.5)
Median TTNT, months (95% CI)	4.53 (4.04-5.36)
PFS	n=248
Number of events (%)	150 (60.5)
Number of censored (%)	98 (39.5)

Median PFS, months (95% CI)	4.63 (3.88–5.62)
6-month progression-free survival rate % (95% CI)	41.2 (34.2-48.0)
12-month progression-free survival rate % (95% CI)	19.9 (13.6-27.0)
18-month progression-free survival rate % (95% CI)	NE (NE-NE)
OS	n=248
Number of events (%)	107 (43.1)
Number of censored (%)	141 (56.9)
Median OS, months (95% CI)	12.39 (10.28–NE)
6-month overall survival rate % (95% CI)	73.4 (67.3-78.5)
12-month overall survival rate % (95% CI)	51.8 (44.1-58.8)
18-month overall survival rate % (95% CI)	42.7 (33.2-51.8)

Source: [68]

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7.1.8 Comparative analyses of efficacy and safety

7.1.8.1 Method of Synthesis

An external control arm for CARTITUDE-1 was constituted from triple-class exposed RRMM patients treated with physician's choice SoC therapies from the LocoMMotion prospective cohort study. In the adjusted analysis the physician's choice cohort is referred to as the real-world clinical practice (RWCP)-cohort. Individual patient data (IPD) were available for CARTITUDE-1 (clinical cut-off January 2022) and LocoMMotion (clinical cut-off May 2021).

The ITT treatment group was comprised of the all-enrolled population and consisted of 113 patients that were enrolled and who underwent apheresis within the CARTITUDE-1 study. The apheresis date was the index date. The comparator group was comprised of all patients that received RWCP SoC treatments of physician's choice derived from LocoMMotion and included subjects 248 who were enrolled in the study.

Co-analyses considered a mITT group from CARTITUDE-1 which was comprised of 97 patients who received infusion at the target dose of Carvykti® in CARTITUDE-1 (all treated). The infusion date was the index date. For LocoMMotion it was required to align the patients with the CARTITUDE-1 mITT cohort. The cohort consisted of 170 subjects from the all-enrolled population that were alive and had not progressed within the number of days equal to the mean duration from apheresis to Carvykti® infusion as observed in CARTITUDE-1, after the start of treatment.

Naïve comparisons of outcomes between two interventions of interest based on non-randomized study typically introduce bias from confounding due to differences in baseline patient demographic and clinical factors, which may be associated both with the treatment exposure and the outcomes. In such circumstances, analyses that involve propensity

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score (PS) methods and multivariable regression are often used to estimate relative treatment effects while adjusting for observed differences between the comparator populations.

Adjusted comparisons were performed to balance patients in terms of prognostic factors. These factors were selected considering both prognostic value and imbalances between data sources and were evaluated and ranked by clinical opinion. Through inverse probability weighting (IPW) and regression, characteristics known to be associated with participation in the trial and the outcomes of interest (i.e., confounding factors) were sought to be balanced. IPW uses the PS to derive weights and recreate a pseudo-population where the distribution of prognostic factors is balanced across groups being compared. The estimated propensity scores were then used to derive weights for each patient using estimand-specific weighting formulas. The analysis estimated the average treatment effect on the treated population (ATT), and the weights for patients in the comparative cohort. In addition, an alternative weighting formula for deriving the average treatment effect for the overlap population (ATO) was also considered as a sensitivity analysis.

Patients were weighted on the following factors: refractory status, ISS stage, time to progress on last regimen, extramedullary disease, number of prior LOTs, years since MM diagnosis, average duration of prior lines of therapy LOTs, age, haemoglobin, LDH, creatinine clearance, ECOG performance status, sex, and MM type. The analysis includes adjusted comparison for OS, PFS assessed by a review committee, TTNT and evaluated measures of treatment response (ORR; VGPR; ≥CR) in both all the all enrolled (ITT) population and all treated population (mITT). This assessment will focus on the ITT (all enrolled patients) comparison.

The full methodology is described in F Comparative analysis of efficacy and safety.

7.1.8.2 Results from the comparative analysis

7.1.8.2.1 Balance of study populations IPW-ATT analysis

Prior to weighting, differences (as reflected by values of SMD >0.2 which is an acceptable effect size [64]) existed between the Carvykti® and physician's choice groups for 9/14 (64.3%) covariates, with the exceptions of extramedullary disease, years since diagnosis, haemoglobin, LDH and gender. The Carvykti® group consisted of more patients who were penta-refractory; were of ISS Stage I; had experienced disease progression in <3 months on prior treatment line; had received 4+ prior LOTs; had a duration of prior treatment line <8.14 months; were <65 years of age; had creatinine clearance >90 mL/min; had ECOG PS of 0 (versus 1); were of IgG MM type (see Appendix F).

Following application of IPW-ATT weights to re-weight the LocoMMotion population, the degree of differences between the Carvykti® and physician's choice groups was reduced, and no imbalances with an SMD > |0.2| remained. The differences in propensity score distributions between groups were quite different prior to reweighting and became very similar afterward. Similar findings as for the ITT analysis regarding balance of population characteristics were observed for the mITT population. Following application of IPW-ATT weights to re-weight the LocoMMotion population, the degree of differences between the Carvykti® and physician's choice groups was reduced, though one imbalance with SMD >|0.2| still remained (extramedullary disease). As observed for the ITT population, the distribution of PS again shifted from being very different before reweighting to very similar after reweighting (see Appendix)

Sensitivity analysis using IPW-ATO reweighting again achieved perfect balance between groups. When the additional variables of race, history of prior transplant and cytogenetic risk were added to propensity score estimation for IPW-ATT analysis, balance between groups was again reduced compared to the main analyses (Appendix F Comparative analysis of efficacy and safety).

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7.1.8.2.2 Response outcomes

Table 17 presents an overview of results across the four outcome measures of ORR, ≥VGPR, ≥CR and MRD negativity in both the ITT and mITT populations, including IPW-ATT adjusted rates of response in the physician's choice group for each outcome as well as corresponding OR and RR estimates following adjustment (where feasible). Of note for both ≥CR and MRD negativity, very few responders in the physician's choice group were observed, and this precluded the ability to perform adjusted analyses for these endpoints. Overall, for all outcomes, findings demonstrated significant benefits with Carvykti® in terms of increased likelihood of response to treatment. For detailed information on results for the response outcomes see Appendix F.

Table 17. Summary of observed and adjusted comparisons for response outcomes

Outcome	Observed Response (unadjusted)		Adjusted physician's choice % Response (95% CI)	Observed OR (95% CI) (unadjusted)	IPW-ATT Adjusted OR (95% CI)	Response-Rate Ratio (95% CI) (adjusted)
	Carvykti®[a]	Physician's choice[b]				
ITT Population						
ORR	84.1%	29.8%	19.0% (13%, 27%)	12.41 (7.00, 22.00)	22.00 (11.14, 43.35)	4.34 (2.69, 6.00)
≥VGPR	81.4%	12.5%	10.0% (6%, 17%)	30.67 (16.74, 56.17)	39.08 (18.19, 83.98)	8.08 (3.63, 12.53)
≥CR	70.8%	0.4%	NE	NE	NE	NE
MRD-	NE[c]	0%[d]	NE	NE	NE	NE
mITT Population						
ORR	97.9%	42.9%	31% (23%, 41%)	63.12 (15.06, 264.53)	103.87 (24.17, 446.37)	3.12 (2.24, 4.00)
≥VGPR	94.8%	17.6%	17% (11%, 25%)	85.87 (32.14, 229.39)	91.55 (32.63, 256.89)	5.67 (3.25, 8.08)
≥CR	82.5%	0.6%	NE	NE	NE	NE
MRD-	91.8%[e]	NE	NE	NE	NE	NE

Observed and adjusted data comparing rates of clinical response between Carvykti® and physician's choice are shown. Adjusted comparisons account for the effects of refractory status, ISS stage, time to progression on prior line, presence of EMD, number of prior LOTs, years since MM diagnosis, average duration of prior LOTs, patient age and sex, haemoglobin at index date, lactate dehydrogenase at index date, creatinine clearance at index date, ECOG PS, and MM type. a denotes N = 113 for ITT population, and N = 97 for mITT population; b denotes N = 248 for ITT population, and N = 170 for mITT population; c As two bone marrow samples must be available for the evaluation, the base for the calculation cannot be estimated for the ITT population; d measured at a sensitivity level of 10-5, only 2 subjects had an MRD evaluable sample, at the sensitivity level of 10-4, 1 of the 2 samples was MRD negative; e measured at a sensitivity level of 10-5, 61 subjects had an MRD evaluable sample, of these 56 were MRD negative (for more details, please check the CSR)

Abbreviations: ATT, average treatment effect in the treated population; CR, complete response; IPW, inverse probability weighting; MRDN, minimal residual disease negativity; NE, not estimable; OR, odds ratio; ORR, overall response rate;; VGPR, very good partial response.

7.1.8.2.3 Progression free survival from adjusted IPW-ATT comparison analyses

Findings for IPW-ATT analyses are presented in Figure 18 (Panel A for ITT population, Panel B for mITT population). First, unadjusted results are shown. Then, additional variables are cumulatively included in the analyses until finally all variables are included in the model. Across all analyses, results were consistently favouring Carvykti®, with slight shifts in summary estimates observed dependent upon the number of covariates included in the propensity score.

Findings from the unweighted analysis produced HR estimates of [redacted] and 0.19 (95% CI: 0.12, 0.29) in favour of Carvykti® within the ITT and mITT populations, respectively. IPW-ATT analyses accounting for all covariates produced estimates of treatment effect for Carvykti® that remained strong in both the ITT [redacted] and mITT (HR 0.15, 95% CI: 0.08, 0.29) populations. The largest changes in the adjusted comparison were associated with refractory status, while the inclusion of additional factors produced smaller shifts in the summary estimate of effects.

[redacted]

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7.1.8.2.4 Progression free survival from additional analysis

Additional analyses were performed using different statistical models (IPW-ATO and multivariable Cox proportional hazards regression modelling) and including additional variables (race, history of prior transplant, cytogenetic risk). Results from these analyses are presented alongside findings from the IPW-ATT analysis (Figure 19).

The additional analyses were confirmatory of the IPW-ATT analysis and demonstrated a significantly longer survival when patients received treatment with Carvykti® compared to physician's choice. Related details for these analyses are provided in Appendix F (for multivariable regression analyses and cumulative regression and IPW-ATO analyses) as well as (for evaluation of group balance after additional forms of IPW re-weighting). Analyses for the related outcome of TTNT are presented in Appendix F and were confirmatory of findings for PFS.

[redacted]

7.1.8.2.5 Kaplan Meier estimated progression free survival

Unweighted and weighted Kaplan-Meier estimated PFS results for ITT are presented in table 18. In the unweighted ITT patient population, the median PFS for physician's choice was 4.63 months (95% CI: 3.88, 5.62). After re-weighting patients from the physician's choice cohort using IPW-ATT weights, the median PFS was 4.07 months (95% CI 2.86, 5.09). Compared to the physician's choice group, Carvykti® [redacted]

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Results in the mITT population (Figure 20 and Table 19) were similar. In the unweighted mITT patient population, median PFS for the physician's choice group was 4.34 months (95% CI: 3.65, 5.55). After reweighting patients from the physician's choice group using IPW-ATT weights, the median OS was 2.73 months (95% CI: 2.37, 4.76). The median PFS associated with Carvykti® was not reached (95% CI: 24.54, NE).

The unweighted ITT PFS rates at 12 and 15 months were [redacted] were 19.88% and 17.31% for physician's choice, respectively. For the reweighted physician's choice group, the PFS rate at 12 months was 14.25% using IPW-ATT weights; the corresponding rate at 15 months was 13.77%. Similar results were observed in the mITT population, as the unweighted PFS rates were 76.29% and 70.03% for Carvykti® at 12 and 15 months, respectively; the PFS rates at these timepoints were 18.69% and 18.58% in the reweighted physician's choice cohort.

[redacted]

Study/Analysis	Median PFS (months) (95% CI)	12-Month PFS Rate (%)	15-Month PFS Rate (%)
Unadjusted			
CARTITUDE-1	[redacted]	[redacted]	[redacted]
LocoMMotion	4.63 (3.88, 5.62)	19.88 (13.65, 26.97)	17.31 (11.19, 24.53)
Adjusted using IPW-ATT weights			
CARTITUDE-1	[redacted]	[redacted]	[redacted]
LocoMMotion	4.07 (2.86, 5.09)	14.25 (4.57, 29.23)	13.77 (4.18, 28.99)

Note: Adjusted results correspond to the fully adjusted scenario which adjusted for refractory status, ISS stage, time to progress on last regimen, extramedullary disease, number of prior LOTs, years since MM diagnosis, average duration of prior LOTs, age, haemoglobin, LDH, creatinine clearance, ECOG performance status, sex, and MM type. Abbreviations: ATT, average treatment effect in the treated population; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; NE, not estimable; PFS, progression-free survival, RWCP, real world clinical practice

Figure 20. Unadjusted and Adjusted Kaplan–Meier Estimated PFS for the mITT Population

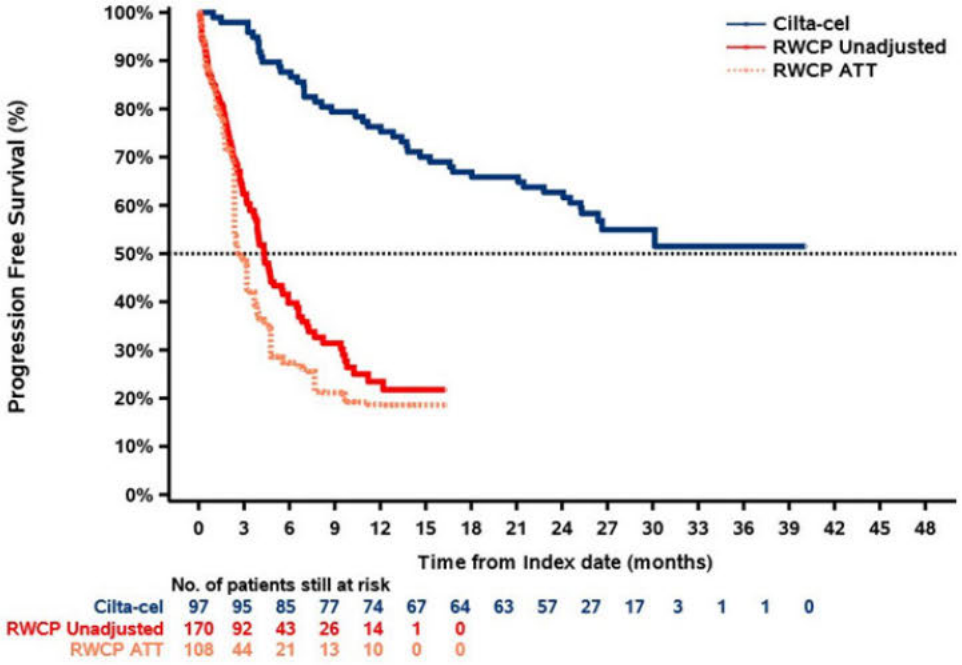

Table 19. Unadjusted and Adjusted Kaplan–Meier Estimated PFS for the mITT Population

Study/Analysis	Median PFS (months) (95% CI)	12-Month PFS Rate (%)	15-Month PFS Rate (%)
Unadjusted			
CARTITUDE-1	NE (24.54, NE)	76.29 (66.51, 83.56)	70.03 (59.83, 78.11)
LocoMMotion	4.34 (3.65, 5.55)	23.43 (15.68, 32.10)	21.76 (14.07, 30.54)
Adjusted using IPW-ATT weights			
CARTITUDE-1 ATT	NE (24.54, NE)	76.29 (66.51, 83.56)	70.03 (59.83, 78.11)
LocoMMotion ATT	2.73 (2.37, 3.68)	18.69 (5.22, 38.57)	18.58 (5.13, 38.53)

Note: Adjusted results correspond to the fully adjusted scenario which adjusted for refractory status, ISS stage, time to progress on last regimen, extramedullary disease, number of prior LOTs, years since MM diagnosis, average duration of prior LOTs, age, haemoglobin, LDH, creatinine clearance, ECOG performance status, sex, and MM type. Abbreviations: ATT, average treatment effect in the treated population; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; mITT, modified intention-to-treat; NE, not estimable; PFS, progression-free survival, RWCP, real-world clinical practice.

7.1.8.2.6 Overall survival from adjusted IPW-ATT comparison analyses

Findings for IPW-ATT analyses are presented in Figure 21 (Panel A for ITT population, Panel B for mITT population). First, unadjusted results are shown. Then, additional variables are cumulatively included in the analyses until finally all variables are included in the model. Across all analyses, results were consistently favouring Carvykti®, with slight shifts in summary estimates observed dependent upon the number of covariates included in the propensity score.

Findings from unweighted analyses produced HR estimates of [redacted] and 0.28 (95% CI: 0.16, 0.49) in favour of Carvykti® within the ITT and mITT populations, respectively. IPW-ATT analyses accounting for all covariates produced estimates of treatment effect for Carvykti® that remained strong in both the [redacted] and mITT (HR 0.20, 95% CI: 0.09, 0.41) populations. The largest changes in the adjusted comparison were associated with ISS stage and refractory status, while the inclusion of additional factors produced smaller shifts in the summary estimate of effects.

[redacted]

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7.1.8.2.7 Overall survival from additional analysis

Additional analyses were performed using different statistical models (IPW-ATO and multivariable Cox proportional hazards regression modelling) and including additional variables (race, history of prior transplant, cytogenetic risk). Results from these analyses are presented alongside findings from primary analyses in Figure 22. All additional analyses were confirmatory of primary findings and demonstrated a significantly longer survival when patients received treatment with Carvykti® compared to physician's choice. Related details for these analyses are provided in Appendix F.

[redacted]

7.1.8.2.8 Kaplan-Meier estimated overall survival

Unweighted and weighted Kaplan-Meier estimated OS results for ITT are presented table 20. In the unweighted ITT patient population, the median OS for physician's choice was 12.39 months (95% CI: 10.28, NE). After re-weighting patients from the physician's choice cohort using IPW-ATT weights, the median OS was 11.76 months (95% CI 7.16, NE). Compared to the physician's choice group, Carvykti® was associated with a longer median [redacted] Results in the mITT population (Figure 21 and

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Table 21) were similar. In the unweighted mITT patient population, median OS for the physician's choice group was not reached (95% CI: 12.12, NE). After reweighting patients from the physician's choice group using IPW-ATT weights, the median OS was 11.33 months (95% CI: 5.45, NE). The median OS associated with Carvykti® was also not reached (95% CI: NE, NE).

The unweighted ITT OS rates at 12 and 15 months were [redacted] Carvykti® and were 51.75% and 45.36% for physician's choice, respectively. For the reweighted physician's choice group, the OS rates at 12 and 15 months were 49.05% and 44.00% using IPW-ATT weights. Similar results were observed in the mITT population (Figure 23), as the OS rates were 87.63% and 83.51% for Carvykti® at 12 and 15 months, respectively; the OS rates at these timepoints were 44.91% and 44.63% in the reweighted physician's choice cohort.

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Figure 23. Unadjusted and Adjusted Kaplan–Meier Estimated OS for mITT Population

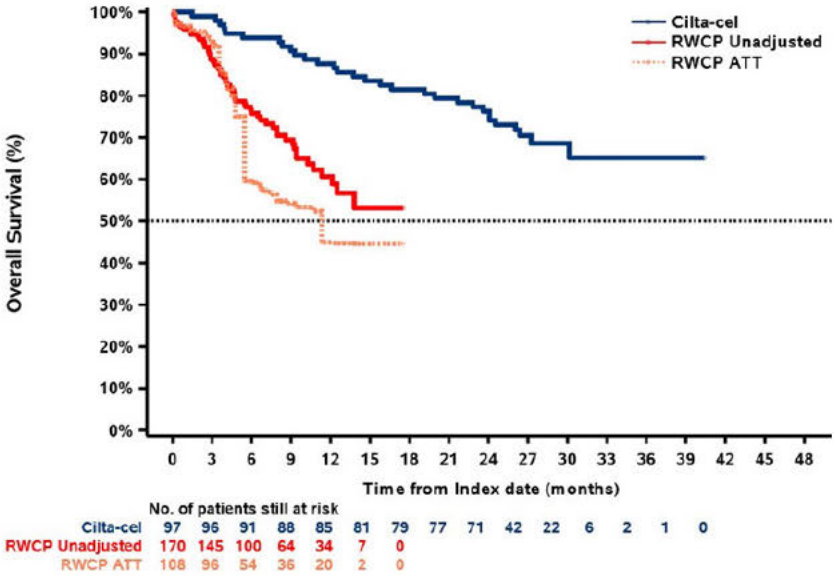

Table 21. Unadjusted and Adjusted Kaplan–Meier Estimated OS for mITT Population

Study/Analysis	Median OS (months) (95% CI)	12-Month OS Rate (%)	15-Month OS Rate (%)
Unadjusted			
CARTITUDE-1	NE (NE, NE)	87.63 (79.24, 92.78)	83.51 (74.5, 89.55)
LocoMMotion	NE (12.12, NE)	60.64 (50.93, 69.01)	53.13 (40.99, 63.87)
Adjusted using IPW-ATT weights			
CARTITUDE-1	NE (NE, NE)	87.63 (79.24, 92.78)	83.51 (74.5, 89.55)
LocoMMotion	11.33 (5.45, NE)	44.91 (21.11, 66.24)	44.63 (20.81, 66.06)

Note: Adjusted results correspond to the fully adjusted scenario which adjusted for refractory status, ISS stage, time to progress on last regimen, extramedullary disease, number of prior LOTs, years since MM diagnosis, average duration of prior LOTs, age, haemoglobin, LDH, creatinine clearance, ECOG performance status, sex, and MM type. Abbreviations: ATT, average treatment effect in the treated population; CI, confidence interval; HR, hazard ratio; mITT, modified intention-to-treat; NE, not estimable; OS, overall survival, RWCP, real-world clinical practice.

7.1.8.2.9 Safety outcomes

Detailed safety findings for CARTITUDE-1 [67] and LocoMMotion [76] have been previously reported. Unadjusted comparison of all AEs shows higher rates of AEs were observed for Carvykti® vs. physician's choice across organ classes. All patients treated with Carvykti® experienced at least one AE, while 83.5% of patients treated with physician's choice had at least one AE. This was also the case for grade 3/4 events (93.8% vs. 49.2%, Table 22). Of note, due to the observational nature of the LocoMMotion study, AEs were described as being underreported for physician's choice. Six (6.2%) patients treated with Carvykti® and nineteen (7.7%) patients with physician's choice experienced an adverse event with an outcome of death. Cytokine release syndrome and CAR-T cell related neurotoxicites only occurred in CARTITUDE-1, as no CAR-T cell therapy was reported in LocoMMotion.

Table 22. Summary of Adverse Events Observed with Incidence >25% and of special interest

	Carvykti®, n/ N (%)		Physicians choice1, n/ N (%)	
Type of Event	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Hematologic AEs ≥25%				
Neutropenia	95.9%	94.8%	15.7%	13.3%
Anaemia	81.4%	68.0%	25.8%	10.9%
Thrombocytopenia	79.4%	59.8%	23.0%	17.7%
Leukopenia	61.9%	60.8%	7.3%	4.8%
Lymphopenia	53.6%	50.5%	6.5%	5.6%
Nonhematologic AEs ≥25% and AEs of special interest				
Cytokine release syndrome	94.8%	4.1%	n/a[3]	n/a[3]
Total CAR-T cell Neurotoxicities	21.6%	10.3%	n/a[3]	n/a[3]
ICANS	16.5%	2.1%	n/a[3]	n/a[3]
Other CAR-T cell Neurotoxicities[2]	13.4%	9.3%	n/a[3]	n/a[3]
Metabolism and nutrition disorders				
Hypocalcaemia	32.0%	3.1%	1.2%	0.4%
Hypophosphataemia	30.9%	7.2%	0.4%	0.0%
Decreased appetite	28.9%	1.0%	2.4%	0.4%
Hypoalbuminaemia	27.8%	1.0%	0.4%	0.0%
Gastrointestinal disorders				
Diarrhoea	29.9%	1.0%	15.3%	0.8%

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Nausea	27.8%	1.0%	9.3%	1.2%
Other				
Fatigue	37.1%	5.2%	12.1%	0.8%
Cough	35.1%	0.0%	3.2%	0.0%
AST increased	28.9%	5.2%	1.2%	0.4%
ALT increased	24.7%	3.1%	1.6%	1.2%

Note: 1 denotes adverse events underreported for physicians' choice; 2 denotes events not reported as ICANS in CARTITUDE-1 (i.e., onset after a period of recovery from CRS and/or ICANS); 3 denotes no CAR-T treatments used in LocoMMotion. AEs ≥25% and of special interest (CRS, CAR-T cell Neurotoxicities) are reported for Carvykti® and physician's choice for any grade and for grade 3/4 events.
Abbreviations: AEs: adverse events; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ICANS: Immune effector cell-associated neurotoxicity syndrome; N: total sample.

See Appendix F for detailed information on the comparative analysis of efficacy and safety

7.1.8.3 Strengths and limitations of the methodology

Certain strengths and limitations of the methods should be noted. Covariates for adjusted comparison analyses are often selected post hoc and in a haphazard manner. However, in this submission, covariates were selected based on strength of the prognostic factor and degree of balance between studies, assessed using prior evidence, study data, and clinician consultation. Covariates were ranked in order from most to least likely to influence the outcome of interest, and these covariates were used for adjustment. As with all observational studies, inferences from these methods hinge on adequate adjustment for factors that differ across trials. As with all non-randomized studies, the potential for residual confounding for unobserved patient characteristics cannot be ruled out. However, in the current analyses the prospective collection of covariates was broad and included key clinical measures.

A sequential approach to inclusion of covariates both for IPW and regression analyses was used, and secondary analyses involving different approaches related to population (ITT and mITT) and IPW approach (ATT and ATO) were performed. While unavailability of complete information for certain variables from the LocoMMotion cohort was noted as per above, the collection of risk factors adjusted for was otherwise highly thorough. While three baseline characteristics (race, history of SCT, cytogenetic risk) were not adjusted for in main analyses, they were included in sensitivity analyses that showed consistent results. While cytogenetic risk is known to be a relevant predictive factor [77], missingness in LocoMMotion was high (37.9%), which reflects that cytogenetic testing is not routinely performed in clinical practice. As its testing cannot be mandated in a non-interventional study, missingness could not be reduced. Similar challenges were also described for recording of adverse events. Comparison of incidence rates between investigator reported and laboratory derived data showed two-fold higher TEAE for grade 3/4 cytopenia when asses by laboratory values. Thus, actual differences might be smaller than observed in the current analysis.

7.1.9 Conclusion on the adjusted comparison

We have assessed the comparative effectiveness of Carvykti® (as assessed in CARTITUDE-1) versus physicians' choice therapies used in real-world clinical as observed in patients from the LocoMMotion prospective cohort. The set of analyses presented in this section demonstrate evidence of the clinical benefits of Carvykti® as a novel, clinically meaningful therapy for this patient population, in the absence of comparative data from randomized controlled trials. While certain differences in population characteristics were noted between the Carvykti® and physician's choice groups,

findings from a multitude of approaches to analysis (including using both ITT and mITT populations, using both IPW-ATT and IPW-ATO weights, and applying a multivariable regression approach) produced highly similar estimates of effect that supported the presence of clinically important benefits of Carvykti®. The consistency of findings across analytic approaches lends considerable strength to the clinical findings and based on these results, Carvykti® compared to physician's choice showed clinical benefits for patients with triple-class exposed RRMM. These results reinforce findings from other recent studies presenting findings for similar adjusted comparisons related to the effectiveness of Carvykti® (as assessed in CARTITUDE-1) derived using other external sources of control patients [78-81] (see section 7.1.10 below), and also present evidence for additional outcomes that could not be assessed when using other sources of an external control group.

7.1.10 Other external data sources for indirect comparison of Carvykti® vs. Physicians' choice

There are several possible data sources, identified by Janssen, for a comparative analysis between CARVYKTI® and SoC therapy; An overview of the comparative outcomes with different sources for the efficacy of SoC are presented in Table 23; more information is available on request. Over all data sets, improved outcomes are seen with CARVYKTI® and these results additionally suggest that CARVYKTI® is associated with better clinical outcomes than SoC therapy.

[redacted]

8. Health economic analysis

For the health economic analysis of Carvykti®, a cost-utility analysis was conducted, comparing Carvykti® with physician's choice (a basket of treatments containing PCd, Pd, Vd, VCd, KRd, Kd, IRd, ERd, DRd, DVd, D and venetoclax),from a Danish limited societal perspective. The outcomes of the analysis include total and incremental costs as well as quality adjusted life years (QALYs) and life years (LYs) gained. The main model outcome is an ICER defined as the incremental cost per incremental QALY gained.

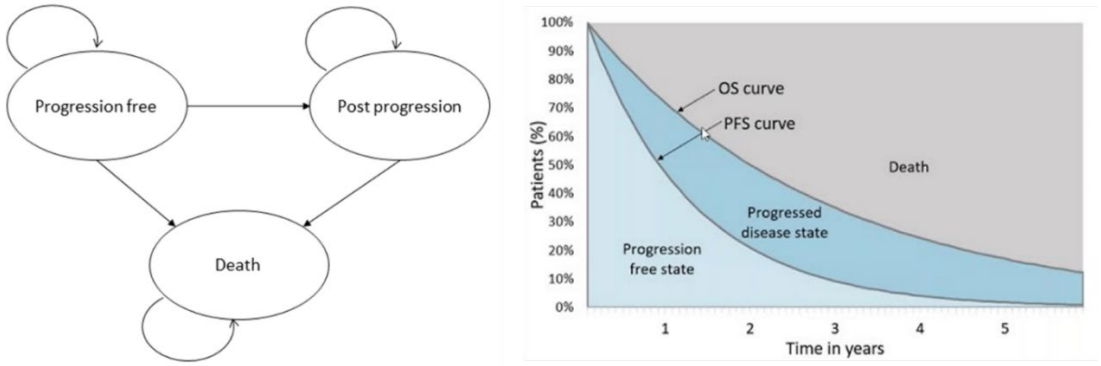
The base case analysis included a Danish limited societal perspective that included both direct treatment costs, healthcare utilization costs and non-medical costs (i.e., transportation costs and time spent in connection with treatment [patient and caregiver]).

8.1 Model

A *de novo* cost-effectiveness (CEM) model was previously developed to conduct a cost-effectiveness analysis for Carvykti®, applicable to a general European setting. The CEM was developed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task force on Good Modelling Practices [82]. This CEM was subsequently adapted to fit the Danish setting and a 'Standard analysis' according the method guide for new assessment of drugs set by Medicinrådet [83].

A partitioned survival model (PSM) structure was used for the cost-utility analysis. In this model structure, the proportions of patients in each health state are derived directly from the OS and PFS projections using the area under the curve approach. A visual representation of the model structure is presented in Figure 24. This type of model is commonly used to model oncology treatments and RRMM [84-87].

Figure 24. PSM structure



Three health states are included in the model: progression-free, post-progression and death, which are defined by overall survival (OS) and progression-free survival (PFS). All patients start with stable disease or response to therapy in the PFS health state, patients that progress in their disease (as defined in CARTITUDE-1) enter the post-progression state [9]. Following progression, patients are unable to transitions back to the progression free state. At any time point in the model, a patient can be alive with non-progressed disease (progression-free), alive with progressed disease (post-progression) or dead. Upon disease progression, a proportion of patients (52.6%) are assumed to receive subsequent anticancer treatment, based on a study by Djebbari and colleagues [88]. Patients enter the PSM at the time of apheresis in the Carvykti® arm, and at the start of the first treatment cycle in the physician's choice arm.

The model structure captures the expected patient pathway from treatment initiation to death and reflects the differences in costs and outcomes among patients receiving two different treatments for tri-exposed RRMM. As the proportion of patients in each state is derived directly from the OS and PFS analysis, variation in the risk of progression and death over time is allowed in this structure. A model cycle length of one week was selected to provide precision in the tracking of the number of patients in each health states over time. This cycle length was selected as it allows capturing of the varied dosing schedules of therapies that make up the physician's choice comparator. A half-cycle correction is applied to the calculation of costs and health effects accrued throughout each cycle, to account for the

transition of patients from one health state to another happening in a continuous process, representing an average transition of halfway through a cycle (i.e., not at the beginning or end of a cycle).

8.1.1 Outcomes

Costs and health-related utilities are allocated to each health state and multiplied by the number of patients in each health state to calculate costs and QALYs per cycle. Costs considered in the analysis included pre-treatment drug costs (apheresis, bridging therapy and conditioning therapy), drug acquisition costs, drug administration costs, monitoring costs, cost of managing adverse events (AEs), end-of-life costs and non-medical costs. Health-related utilities were applied differently according to each health state. The utility in the progression-free state is considered the same for both the Carvykti® and physician's choice treatment arms, as health-state utility values are considered disease dependent (rather than treatment dependent).

A utility decrement is applied to the Carvykti® arm only, to account for the effect of AEs. No AE disutility was applied to the physician's choice arm as the heterogenous mix of different regimens makes this difficult to account for. Thus, this conservative assumption was made.

8.1.2 Time Horizon

The time horizon set in the base case analysis was 40 years. Carvykti® represents a new innovative treatment option for patients with RRMM with the potential to significantly reduce the risk of disease progression extend survival, thus a time horizon long enough to capture all the significant differences in health gains and costs between the treatment alternatives is required [83]. This corresponds with a lifetime perspective for the modelled cohort and is long enough to ensure that all costs and benefits associated with the treatments are captured.

8.1.3 Discounting

Costs and benefits were discounted at the following rates: 3.5% per annum for years 0 to 35, 2.5% for years 36 to 70 and 1.5% for years >70. These rates were applied in line with the current guidelines of the DMC and Danish Ministry of Finance [83, 89].

8.1.4 Model Validation

A Danish clinician provided validation of the model structure, clinical trial characteristics for both Carvykti® and physician's choice, comparator (regimens and frequency of use), as well as pre-treatments and subsequent therapies. A Nordic clinician provided validation on the survival distributions used for the OS and PFS analysis.

Upon completion of model programming, a rigorous and comprehensive quality check of the model was conducted to ensure the completed model contained no errors and worked as intended. A series of tests and checks were also conducted on the model engine. Among other reviews, the validator:

- Confirmed that all model inputs were correctly linked to the engine.
- Checked all cells with "IF logic" in detail, confirming that the statements provided the correct value for each condition.
- Traced all links between the calculation sheets and results sheet to make sure that the proper outputs were displayed in the correct location.
- Thoroughly reviewed and debugged all Visual Basic for Applications (VBA) code.
- Searched for common Microsoft Excel® errors (e.g., !#REF errors, unused named ranges, broken links, links to external workbooks, copy/paste errors) and resolved them as needed.
- Checked all text and formatting to ensure that there were no typographical errors or formatting irregularities.

- Finally, an extreme-value sensitivity analysis was conducted on all applicable model inputs. While conducting the analysis, the validator noted the direction and magnitude of change for each extreme value tested and confirmed that this aligned with the expected result (e.g., if all drug cost inputs are set to 0, the model should output total drug costs of 0 as well). The model validation process uncovered minimal discrepancies and no impactful model calculation errors. Feedback from the validation was addressed in the model, and the refined post-validation model was used to generate the results included in this report.

8.1.5 Key model assumptions

The key model assumptions made in the base case analysis are presented in Table 24 below. The assumptions have been validated by a Nordic clinical expert to be relevant for the Danish setting [59].

Table 24. Summary of key model assumptions

Parameter/Variable	Assumption
Clinical Effectiveness	The patient population on which the model is based is representative of the Danish RRMM patient population.
HRQoL	Among patients who receive Carvykti® infusion and remain progression-free, HRQoL at week 30 remains stable thereafter and is only impacted by ageing.
	Grade <3 AEs are captured by the EQ-5D health state utility values. Grade ≥3 AEs are not and are therefore modelled separately by applying an AE-specific utility decrement (applicable only to the Carvykti® arm).
	No AEs decrements are assumed for the comparator.
	The disutility associated with grade ≥3 CRS and neurotoxicity renders a conservative utility value of 0 for the duration of the event.
	Bridging therapy in Denmark consists of pomalidomide plus dexamethasone.
	52.6% of patients receive subsequent therapy [88].
	Conditioning therapy in Denmark comprises fludarabine and cyclophosphamide
	Carvykti® patients receive subsequent therapy for a mean duration of 5.77 months, reflecting the mean duration of fifth-line treatment for patients with RRMM (based on Yong et al. [90]) The same applied to the comparator arm.

8.1.6 Model limitations

The costs, resource use and PPS HSUV included in the analysis were primarily based on assumptions, other literature sources and clinical expert opinion. This could reduce the robustness of the results. Additionally, CARTITUDE-1 was a non-comparative study, thus an adjusted comparison was used to assess comparative effectiveness. The comparator, physician's choice, comprised a basket of the most commonly administered RRMM treatments overall. Thus, a level of uncertainty on the match of the comparator to the intervention exists. Furthermore, the long-term extrapolation of OS and PFS from short-term clinical trials is always subject to uncertainty. Ideally, the extrapolation should be validated

against long-term data from other sources, but in this case, it is difficult due to the lack of real-world evidence for the current patient population.

8.1.7 Presentation of input data used in the model and how they were obtained

The input data used for the base case analysis was primarily derived from the pivotal trial CARTITUDE-1 for Carvykti®, and the matched LocoMMotion study for physician's choice. Additional literature sources were for other model parameters. A summary of the inputs regarding clinical effect, adverse events and HSUV are presented in Table 25 below.

Table 25. Input data used in the model (clinical effect, AEs and HSUV)

Variable	Input/Value	Source
Survival parametrisation (Carvykti®)		
OS	Loglogistic	CARTITUDE-1
PFS	Lognormal	CARTITUDE-1
Survival parametrisation (physician's choice)		
OS	Loglogistic	LocoMMotion
PFS	Lognormal	LocoMMotion
Adverse events * (costs)		
Anaemia	41,278.00 DKK	DRG_Takster 2022 (DRG 16MA05)
AST increased	44,127.00 DKK	DRG_Takster 2022 (DRG 07MP10)
Asthenia and fatigue	7,619.00 DKK	DRG_Takster 2022 (DRG 49SP01)
CRS, Grade 1-2*	3,107.84	Assumption, DRG 18MA04 divided by Trimpunkt 6; DRG Takster 2022
CRS, Grade 3**	33,310.48 DKK	Assumption
Diarrhoea	26,019.00 DKK	DRG_Takster 2022 (DRG 06MA14)
Febrile neutropenia	18,926 DKK	DRG_Takster 2022 (DRG 49PR07)
Gamma-glutamyltransferase	28,762.00 DKK	DRG_Takster 2022 (DRG 07MA14)
Hyperglycaemia	6,224.00 DKK	DRG_Takster 2022 (DRG 23MA05)
Hypertension	16,630.00 DKK	DRG_Takster 2022 (DRG 05MA11)
Hypokalemia	6,224.00 DK	DRG_Takster 2022 (DRG 23MA05)
Hyponatremia	6,224.00 DKK	DRG_Takster 2022 (DRG 23MA05)
Hypophosphataemia	6,224.00 DKK	DRG_Takster 2022 (DRG 23MA05)
Leukopenia	14,836.00 DKK	DRG_Takster 2022 (DRG 17MA05)
Lymphopenia	14,836.00 DKK	DRG_Takster 2022 (DRG 17MA05)

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Neutropenia	18,926.00 DKK	DRG_Takster 2022 (DRG 49PR07)
Pneumonia	40,070.00 DKK	DRG_Takster 2022 (DRG 04MA13)
Sepsis	45,361.00 DKK	DRG_Takster 2022 (DRG 18MA01)
Thrombocytopenia	38,408.00 DKK	DRG_Takster 2022 (DRG 16MA03)
Adverse reactions (occurrence) Carvykti®		
Anaemia	68.0%	CARTITUDE-1 (ITT population)
AST increased	5.2%	
Asthenia and fatigue	5.2%	
CRS only, Grade 1-2	89.7%*	
CRS only, Grade	5.2%**	
Diarrhoea	1.0%	
Febrile neutropenia	9.3%*	
Gamma-glutamyltransferase	6.2%*	
Hypertension	6.2%*	
Hypokalemia	2.1%	
Hyponatremia	4.1%	
Hypophosphataemia	7.2%	
Leukopenia	60.8%	
Lymphopenia	50.5%	
Neutropenia	94.8%	
Pneumonia	10.3%	
Sepsis	5.2%	
Thrombocytopenia	59.8%	
Adverse reactions (occurrence) Physician's Choice	0%	Assumption
Adverse reaction (utility loss) Carvykti®		
Anaemia	-0.31	Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
AST increased	-0.07	Assumed lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
Asthenia and fatigue	-0.12	Lloyd 2006[92]
CRS only, Grade 1-2	-0.11	Assumed to be equal in magnitude to the utility value in the progression-free health state, per Hettle 2017 [93]and Yescarta NICE submission for DLBCL [94]
CRS only, Grade 3+	-0.0506	Assumed to be equal in magnitude to the utility value in the progression-free health state, per Hettle 2017 [93] and Yescarta NICE submission for DLBCL
Diarrohea	-0.10	Lloyd 2006 [92]
Febrile neutropenia	-0.39	TA510 (based on Launois 1996) [95]
Gamma-glutamyltransferase	-0.07	Assumed lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014) [91]

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Hypertension	0	TA573 (assume no QoL impact, controlled by medication) [96]
Hypokalemia	-0.2	TA510 (based on clinical opinion) [95]
Hyponatremia	-0.07	Assumed to be the same as hypokalemia
Hypophosphataemia	-0.15	TA559 (2018) [97]
Leukopenia	-0.07	Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
Lymphopenia	-0.07	Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
Neutropenia	-0.15	Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
Pneumonia	-0.19	Brown 2013/Partial Review TA171(Bacelar 2014) [91]
Thrombocytopenia	-0.31	Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
HSUV		
Carvykti® (PFS off treatment)	0.8435	CARTITIDE-1 (CARTITUDE-1 pre-infusion baseline utility))
Physician's choice (PFS on treatment)	0.8435	PFS utility on treatment (CARTITUDE-1 pre-infusion baseline utility)
PPS	0.717	Calculated based on the ICARIA-MM trial difference, used in the IsaPd NICE submission

Abbreviations: AE = adverse event; AST = aspartate aminotransferase; cilta-cel = ciltacabtagene autoleucel; CRS = cytokine release syndrome; d = dexamethasone; P = pomalidomide; Pan = panobinostat; USPI = United States prescribing information; V = bortezomib

*Incidence, duration and cost of CRS, Grade 1-2 is assumed to include neurotoxicity, Grade 1 – 2.

**Incidence, duration and costs of CRS, Grade 3+ is assumed to include neuotoxicity, Grade 3+
***Event rates based on CARTITUDE-1 data on file, not per publication
Sources: [98, 99]

8.1.8 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.1.8.1 Patient population

The eligible patient population in Denmark is constituted by adult patients with RRMM, who have received ≥3 prior lines of therapy (triple-exposed) or including an IMiD, a PI and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy. The patient population is based on the pivotal clinical trial for Carvykti®, CARTITUDE-1. The patient population was assumed to be representative of the Danish setting based on validation by a Danish clinical expert [59].

The baseline characteristics of the patient population are presented in Table 26 below.

Table 26. Overview of baseline characteristics of the patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
Age, mean (SD)	61.7 (9.1) [67]	61.7 [59, 67]	61.7 [59, 67]

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
Body weight, mean (SD) (kg)	80.7 (17.1) [67]	80.7 [59, 67]	80.7 [59, 67]
Body surface area, mean (SD) (m^2)	1.91(0.22) [67]	1.91 [59, 67]	1.91 [59, 67]

8.1.8.2 Intervention

Intervention as expected in Danish clinical practice

Mode of action

Carvykti® is a genetically modified autologous CAR-T therapy that targets B-cell maturation antigen (BCMA), a molecule highly expressed on the surface of late-stage B cells, plasma cells and malignant B-lineage cells such as myeloma cells [1, 2]. Its mechanism of action is similar to that of cytotoxic T-cells, allowing it to kill malignant cells and thereafter, potentially maintain ongoing anti-tumour surveillance [3]. A patient's own T-cells are genetically engineered to express a CAR construct, which contains an external target-binding domain responsible for recognising BCMA-expressing myeloma cells, and an internal activating domain, which initiates T-cell activation, thereby inducing malignant cell death [4, 5]. The extracellular binding domain of Carvykti® consists of two VHH domains, that are directed against two distinct BCMA epitopes [6]. These domains enable high-avidity binding to BCMA and distinguish Carvykti® from other CAR-T cell therapies, which typically only have one BCMA binding domain.

Form of administration:

Carvykti® is administered as a single intravenous infusion. Each dose of Carvykti® is specifically tailored to, and manufactured for, an individual patient using the patient's own blood cells, representing a personalised approach to the manufacturing, logistic and administration of treatment.

Dosage

Carvykti® is provided as a single dose for intravenous infusion. The dose is 0.5-1.0 x 10^6 CAR-positive viable T-cells per kg of body weight, with a maximum dose of 1 x 10^8 CAR-positive viable T-cells per single infusion [7].

Treatment Plan

The process begins with apheresis, which is the collection of the patient's T-cells. During apheresis, blood is withdrawn from the patient's body and the blood is separated using a centrifuge. Peripheral blood mononuclear cells are collected, which include T-cells, and then the remaining blood is returned to the body. The T-cells are then frozen and sent to a manufacturing facility to be transduced with the CAR-T lentiviral vector and expanded before being returned to the hospital where they are being treated. In the time between apheresis and infusion, a bridging therapy is administered to a proportion of patients for which it is clinically indicated to stabilize their disease until the CAR-T cells are ready for infusion. In the analysis, it was assumed that 77% of patients would receive bridging therapy based on the CARTITUDE-1 clinical study. Further, bridging therapy was assumed to be composed of a basket of the most commonly administered treatments in CARTITUDE-1. The next step in the treatment plan is to administer a conditioning, or lymphodepleting, regimen to enhance treatment efficacy by eliminating regulatory T cells and competing elements of the immune system. This helps to prevent rejection of the treatment and is initiated five – seven days before the infusion of Carvykti® [100]. Conditioning therapy was formulated to consist of three days of fludarabine 30 mg/m^2 and 3 days of cyclophosphamide 300 mg/m^2, per the CARTITUDE-1 protocol, and validated by a Danish clinical expert [59]. Additionally, the proportion of patients with apheresis receiving conditioning therapy was assumed to be 89.4% based on CARTITUDE-1 data, and

also validated by a Danish clinical expert [59]. Finally, in the event of disease progression, patients receive subsequent anti-cancer therapy (see 8.4.1). An overview of the treatment plan is presented in Figure 25.

Figure 25. Carvykti® patient treatment pathway

Abbreviations: CAR-T = chimeric antigen receptor T-cell.
Source: [75]

Monitoring

The model captured routine monitoring costs during the 100 days post-infusion period, PFS and PPS state. The types and frequencies of resources were based on the CARTITUDE-1 protocol for pre-progression and post-infusion. For post-progression frequency of resource use was based on Danish clinical practice. These were validated by a Danish clinical expert.

Position in existing Danish clinical practice

Carvykti® is expected to be positioned in the fourth- or subsequent line of therapy in MM treatment practice. It is expected to supplement treatments in this line of therapy. Carvykti® is indicated for adult patients with RRMM, who have received ≥3 prior lines of therapy (triple-exposed) or including an IMiD, a PI and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy.

Intervention as in clinical practice

The key clinical documentation in the health economic analysis is the pivotal clinical trial CARTITUDE-1, and LocoMMotion. See section 6 and section 7 for further information.

Intervention as in the health economic analysis

Inputs used the analysis are primarily informed by the clinical trial CARTITUDE-1, LocoMMotion and clinical literature in combination with input from a Danish clinical expert. In the model treatments were administered according to a cycle length of one week. Administration and dosing of Carvykti®, pre-infusion treatments and subsequent treatments were set according the CARTITUDE-1 protocols and clinical expert input.

Table 27 below presents an overview of the intervention (Carvykti®) and associated pre- and subsequent treatments.

Table 27. Overview of intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	**Carvykti®** 0.5-1.0 x 10^6 CAR-positive viable T-cells per kg of body weight, (maximum dose of 1 x 10^8 CAR-positive viable T-cells per single infusion) [67]. **Bridging therapy** Patient specific treatments [67]. (See section 8.4.1) **Conditioning therapy** Fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 [67] **Subsequent therapy** Patient specific treatments [67].	**Carvykti®** 0.5-1.0 x 10^6 CAR-positive viable T-cells per kg of body weight, (maximum dose of 1 x 10^8 CAR-positive viable T-cells per single infusion). **Bridging therapy** Treatment Basket of most commonly used regimens in CARTITUDE-1 [100]. (See section 8.4.1) **Conditioning therapy** Fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 **Subsequent therapy** Pomalidomide 4 mg/day P.O. and cyclophosphamide 500 mg IV and dexamethasone 40 mg/week P.O. OR Carfilzomib 20 mg/m^2 IV (biw) in week one of treatment cycles , thereafter 56 mg/m^2 IV (biw) and dexamethasone 20 mg P.O. (biw). The model assumed that 50% of progressed patients receive PCd and 50% receive Kd [59].	**Carvykti®** 0.5-1.0 x 10^6 CAR-positive viable T-cells per kg of body weight, (maximum dose of 1 x 10^8 CAR-positive viable T-cells per single infusion) [59]. **Bridging therapy** Treatment Basket of different regimens commonly used to treat RRMM [100]. (See section 8.4.1) **Conditioning therapy** Fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 [59]. **Subsequent therapy** Pomalidomide 4 mg/day P.O. and cyclophosphamide 500 mg IV and dexamethasone 40mg/week P.O. OR Carfilzomib 20 mg/m^2 IV (biw) in week one of treatment cycles , thereafter 56 mg/m^2 IV (biw) and dexamethasone 20mg P.O. (biw). The model assumed that 50% of progressed patients receive PCd and 50% receive Kd [59].
Length of treatment (time on treatment) (mean/median)	**Carvykti®** Provided as a single dose for intravenous infusion [67]. **Bridging therapy**	**Carvykti®** Provided as a single dose for intravenous infusion [67] **Bridging therapy**	**Carvykti®** Provided as a single dose for intravenous infusion [67] **Bridging therapy**

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Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
	9.94 days [100]	9.94 days	9.94 days
	Conditioning therapy	**Conditioning therapy**	**Conditioning therapy**
	Three days [100]	Three days [59, 101].	Three days [59, 101].
	Subsequent therapy	**Subsequent therapy**	**Subsequent therapy**
	Patient specific treatment duration [67].	5.77 months [59, 90]	5.77 months [59, 90]
Criteria for discontinuation	Not applicable	Not applicable	Not applicable
The pharmaceutical's position in Danish clinical practice	Fourth- or subsequent therapy for the treatment of adult patients with RRMM who have had at least three prior therapies comprising the following: PI, IMiD and anti-CD38 mABs	Fourth- or subsequent therapy for the treatment of adult patients with RRMM who have had at least three prior therapies comprising the following: PI, IMiD and anti-CD38 mABs	Fourth- or subsequent therapy for the treatment of adult patients with RRMM who have had at least three prior therapies comprising the following: PI, IMiD and anti-CD38 mABs

8.1.8.3 Comparators

Comparator in Danish clinical practice

In Denmark, evidence-based treatment guidelines for MM are provided by The Danish Medicines Council (DMC) and The Danish Myeloma Study Group (DMSG) [55, 56]. The guidelines prepared by the DMC provide treatment recommendations for the first three lines of therapy (primary treatment, first relapse and second relapse) as well as fourth and subsequent treatment lines [57]. At fourth and subsequent treatment lines, the same treatment offer as patients with disease progression during or after third-line therapy are recommended, which include treatment with Pd, PCd or PVd. Additionally, these guidelines recommend that participation in clinical trials (protocol treatments) may be considered The DMSG provides treatment guidelines specifically for relapsed disease [55]. Treatments at first and second relapse could include different combinations regimens of lenalidomide, daratumumab, carfilzomib and pomalidomide, and choice of treatment depend on previous treatment received and the refractory status [55].

Comparator in the clinical documentation

CARTITUDE-1 (the pivotal trial for Carvykti®) is a single-arm study with no active control arm. Thus, an external control arm for CARTITUDE-1 was constituted from the LocoMMotion study (NCT04035226), a prospective efficacy and safety study of real-life SoC in triple-class exposed patients with RRMM who have received at least three prior lines of therapy. LocoMMotion includes several combination treatment regimens that include drugs from three SoC classes: PIs, IMiDs and anti-CD38 mABs, representing physician's choice.

Comparator in the health economic analysis

In the health economics analysis physician's choice was modelled as a blended comparator for Carvykti®. The efficacy and treatment durations, pharmaceutical form, posology and mode of administration were informed by the study LocoMMotion. LocoMMotion was the most relevant comparative data source for Denmark as it was designed to be a synthetic control arm for CARTITUDE-1, and had a prospective trial design.

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Cost-wise, the regimens included and proportion of use were based on a survey of the treatment market for MM, that included 12 haematologists from several regions in Denmark [58]. These were validated by a Danish clinical expert who is currently treating RRMM patients in Denmark [59].

Please see Table 28 for an overview of the comparator information.

Table 28. Comparator

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	**PCd**	**PCd**	**PCd**
	-P: 4 mg/day P.O.	-P: 4 mg/day P.O.	-P: 4 mg/day P.O.
	-C: 400 mg/m²/week IV	-C: 400 mg/m²/week IV	-C: 400 mg/m²/week IV
	-d: 40 mg/week P.O.	-d: 40 mg/week P.O.	-d:40 mg/week P.O.
	Pd	**Pd**	**Pd**
	-P:4 mg/day P.O.	-P:4 mg/day P.O.	-P:4 mg/day P.O.
	-d: 40 mg/week P.O.	-d: 40 mg/week P.O.	-d: 40 mg/week P.O.
	Vd	**Vd**	**Vd**
	-V: 1.3 mg/m² S.C.	-V: 1.3 mg/m² S.C.	-V: 1.3 mg/m² S.C.
	-d: 20 mg P.O. (once)	-d: 20 mg P.O. (once)	-d: 20 mg P.O. (once)
	VCd	**VCd**	**VCd**
	-V: 1.5 mg/m²/week S.C.	-V: 1.5 mg/m² /week S.C.	-V: 1.5 mg/m² S.C.
	- C: 300mg/m²/kg/week IV	- C: 300mg/m²/kg/week IV	- C: 300mg/m2/kg/week IV
	-d: 40 mg/week P.O.	-d: 40 mg/week P.O.	-d: 40 mg/week P.O.
	KRd	**KRd**	**KRd**
	- K: 20/27 mg/m² (biw) IV	- K: 20/27 mg/m² (biw) IV	- K: 20/27 mg/m² (biw) IV
	- R: 25 mg/day P.O.	- R: 25 mg/day P.O.	- R: 25 mg/day P.O.
	- d: 40 mg/week P.O.	- d: 40 mg/week P.O.	- d: 40 mg/week P.O.
	Kd	**Kd**	**Kd**
	- K – 20-70 mg/m² /week IV	- K – 20-70 mg/m² /week IV	- K – 20-70 mg/m² /week IV
	- d -40 mg/week P.O.	- d -40 mg/week P.O.	- d -40 mg/week P.O.
	IRd	**IRd**	**IRd**
	- I: 4 mg/week P.O.	- I: 4 mg/week P.O.	- I: 4 mg/week P.O.
	-R: 25 mg/day P.O.	-R: 25 mg/day P.O.	-R: 25 mg/day P.O.
	- d: 40 mg/week P.O.	- d: 40 mg/week P.O.	- d: 40 mg/week P.O.
	ERd	**ERd**	**ERd**
	-E: 10 mg/kg/week IV	-E: 10 mg/kg/week IV	-E: 10 mg/kg/week IV

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Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
	-R: 25 mg/day P.O. -d: 28/40mg/week P.O. **DVd** - D: 1800mg/kg/week S.C - V: 1.3mg/m^2 biw S.C - d: 20mg/week P.O. **D mono** - D: 1800mg/kg/week S.C **Venetoclax** -Venetoclax: 1200mg/day P.O. for 3 weeks, followed by 1200mg/week P.O	-R: 25 mg/day P.O. -d: 28/40mg/week P.O. **DVd** - D: 1800 mg/kg/week S.C - V: 1.3 mg/m^2 biw S.C - d: 20 mg/week P.O. **D mono** - D: 1800mg/kg/week S.C **Venetoclax** -Venetoclax: 1200mg/day P.O. followed by 1200mg/week P.O	-R: 25 mg/day P.O. -d: 28/40mg/week P.O. **DVd** - D: 1800 mg/kg/week S.C - V: 1.3 mg/m^2 biw S.C - d: 20 mg/week P.O. **D mono** - D: 1800mg/kg/week S.C **Venetoclax** -Venetoclax: 1200mg/day P.O. for 3 weeks followed by 1200mg/week P.O
Length of treatment	Patient specific treatment duration	Patient specific treatment duration	Patient specific treatment duration
The comparator's position in the Danish clinical practice	Fourth- and subsequent line of therapy for RRMM	Fourth- and subsequent line of therapy for RRMM	Fourth- and subsequent line of therapy for RRMM

Abbreviations. P: pomalidomide, V: velcade, d: dexamethasone, C: cyclophosphamide, R: Revlimid, K: carfilzomib, Ixa: Ixazomib, E: elotuzumab, Sources: [58, 59, 76]

8.1.8.4 Relative efficacy outcomes

Relative efficacy outcomes used to compare Carvykti® with physician's choice were PFS and OS. Data from and adjusted comparison between Carvykti® (CARTITUDE-1) and physician's choice (LocoMMotion) were used as the basis for relative efficacy outcomes. Both PFS and OS endpoints were included in CARTITUDE-1 and LocoMMotion.

The available treatment guidelines for MM aim to ensure that treatment is optimal and focus on improving outcomes such a OS, PFS and HRQoL. Survival is an essential metric for assessing the efficacy of anti-cancer treatments [102]. Along with safety and tolerability, efficacy represents a relevant factor regarding treatment decisions in Denmark. Thus, these relative efficacy outcomes are relevant for Danish clinical practice.

The health economic analysis utilized a PSM to assess the cost effectiveness of Carvykti® in Denmark. The model was populated with key outcomes from the CARTITUDE-1 and LocoMMotion studies using the all enrolled populations (ITT). Table 29 presents the model values for PFS and OS, and the median valued from CARTITUDE-1 and LocoMMotion. Table 30 presents a summary of the relevance of the clinical outcomes in Danish clinical practice.

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[redacted]

Table 30. Summary of relevance

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
PFS	Defined as time from date of initial infusion of Carvykti® to date of first documented disease progression or death due to any cause, whichever occurs first. IMWG criteria for PD.	PFS represents a relevant outcome measure with regards to treatments for RRMM in Denmark	Relevant
OS	Measured from the date of the initial infusion of Carvykti® to the date of the participant's death	OS represents a relevant outcome measure with regards to treatments for RRMM in Denmark.	Relevant

Abbreviations: OS (overall survival), PFS (progression-free survival), MRD (minimal residual disease), PD (progressed-disease)

8.1.8.5 Adverse reaction outcomes

Clinical documentation:

The number of participants with AEs and their severity was the primary outcome of the phase 1b portion of CARTITUDE®. Adverse events included anaemia, AST increased, asthenia and fatigue, CRS Grades 1 – 2 and 3, neurotoxicity, diarrhoea, febrile neutropenia, Gamma-glutamyltransferase increased, hypertension, hypokalemia, hypophosphatemia, leukopenia, lymphopenia, neutropenia, pneumonia and thrombocytopenia.

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Health economic analysis:

In the health economic analysis, the impact of AEs on both costs and HRQoL for patients in the Carvykti® arm were included. Grade 3 or 4 AEs were included if they occurred in at least 5% of patients in the intervention arm. Additionally, grade 1 and 2 cytokine release syndrome (CRS) and neurotoxicity were included to capture AEs specific to CAR-T therapy. When considering CRS and neurotoxicity events, CRS events (grade 3+) were considered on their own and CRS and neurotoxicity events that occurred concurrently were considered, to capture the associated costs and disutility's most appropriately. Carvykti® AE-rates were based on CARTITUDE-1.

The effect of AEs on the costs and HRQoL for patients in the physician's choice arm were not included. The rationale behind this exclusion is that the composition of physician's choice is likely to be subject to change, from the clinical input and HTA discussions. This exclusion removes the uncertainty around the choice of comparator dataset. Additionally, AEs are not key drivers of the analysis and their exclusion from the comparator arm should have minimal impact on the results of the analysis.

Please see Table 31 below for an overview of the AEs

Table 31. Adverse events (AEs) (All enrolled patients (ITT))

Adverse reaction	Frequency (clinical documentation)	Frequency (used in the model (numerical value))
Anaemia	68.0% [101, 103]	68.0% [101, 103]
AST increased	5.2% [101, 103]	5.2% [101, 103]
Asthenia & Fatigue	5.2% [101, 103]	5.2% [101, 103]
CRS only , grade 1-2*	89.7%[101, 103]	89.7% [101, 103]
CRS only, grade 3+**	5.2% [101, 103]	5.2% [101, 103]
Diarrhoea	1.0% [101, 103]	1.0% [101, 103]
Febrile neutropenia	9.3% [101, 103]	9.3% [101, 103]
Gamma-glutamyltransferase increased	6.2% [101, 103]	6.2% [101, 103]
Hypertension	6.2% [101, 103]	6.2% [101, 103]
Hypokalaemia	2.1% [101, 103]	2.1% [101, 103]
Hyponatremia	4.1% [101, 103]	4.1% [101, 103]
Hypophosphatemia	7.2% [101, 103]	7.2% [101, 103]
Leukopenia	60.8% [101, 103]	60.8% [101, 103]
Lymphopenia	50.5% [101, 103]	50.5% [101, 103]
Neutropenia	94.8% [101, 103]	94.8% [101, 103]

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Adverse reaction	Frequency (clinical documentation)	Frequency (used in the model (numerical value))
Sepsis	9.3% [101, 103]	9.3% [101, 103]
Pneumonia	10.3% [101, 103]	10.3% [101, 103]
Thrombocytopenia	59.8% [101, 103]	59.8% [101, 103]

*Incidence of CRS, Grade 1-2 is assumed to include neurotoxicity, Grade 1 – 2 .**Incidence of CRS, Grade 3+ is assumed to include neuotoxicity, Grade 3+

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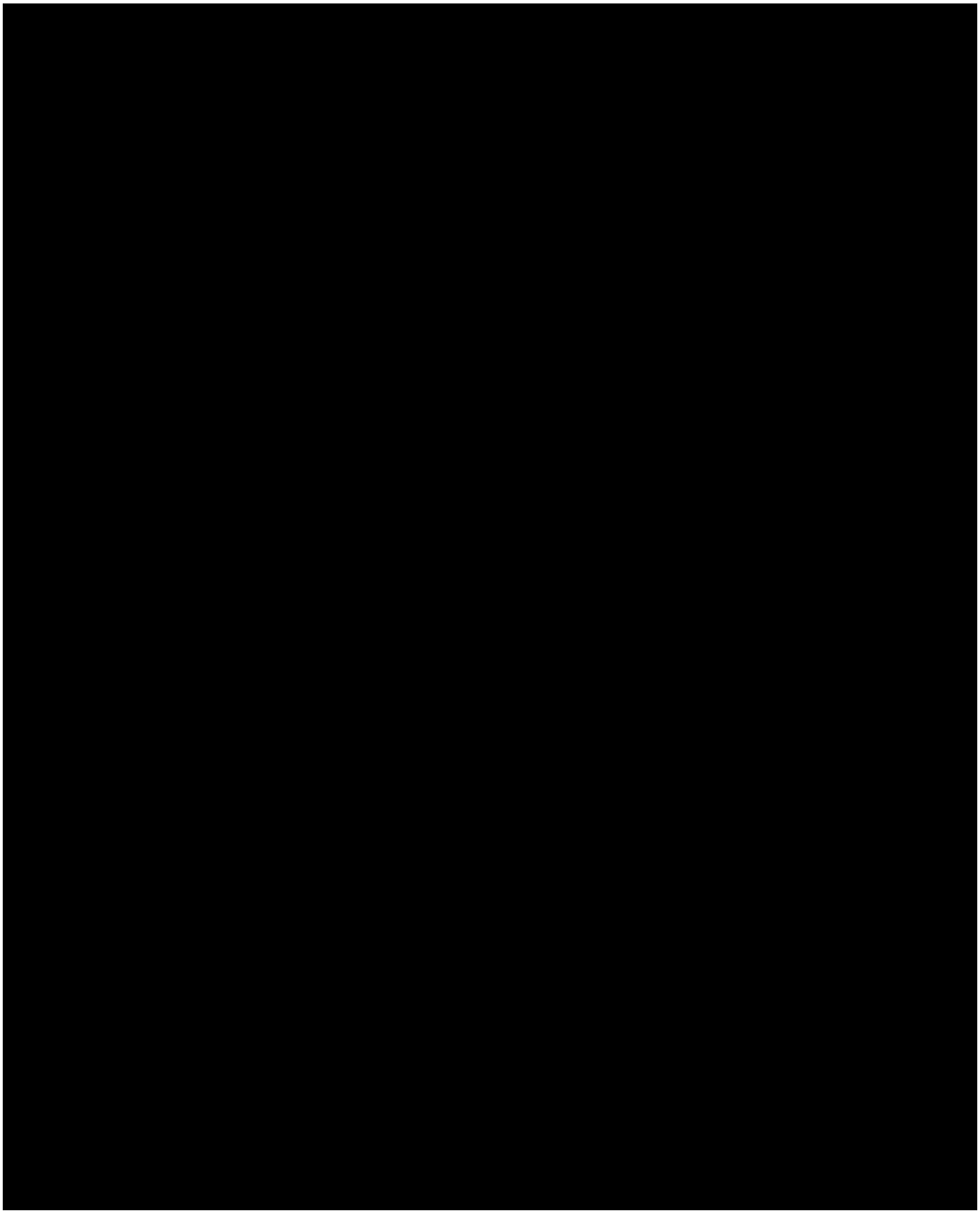

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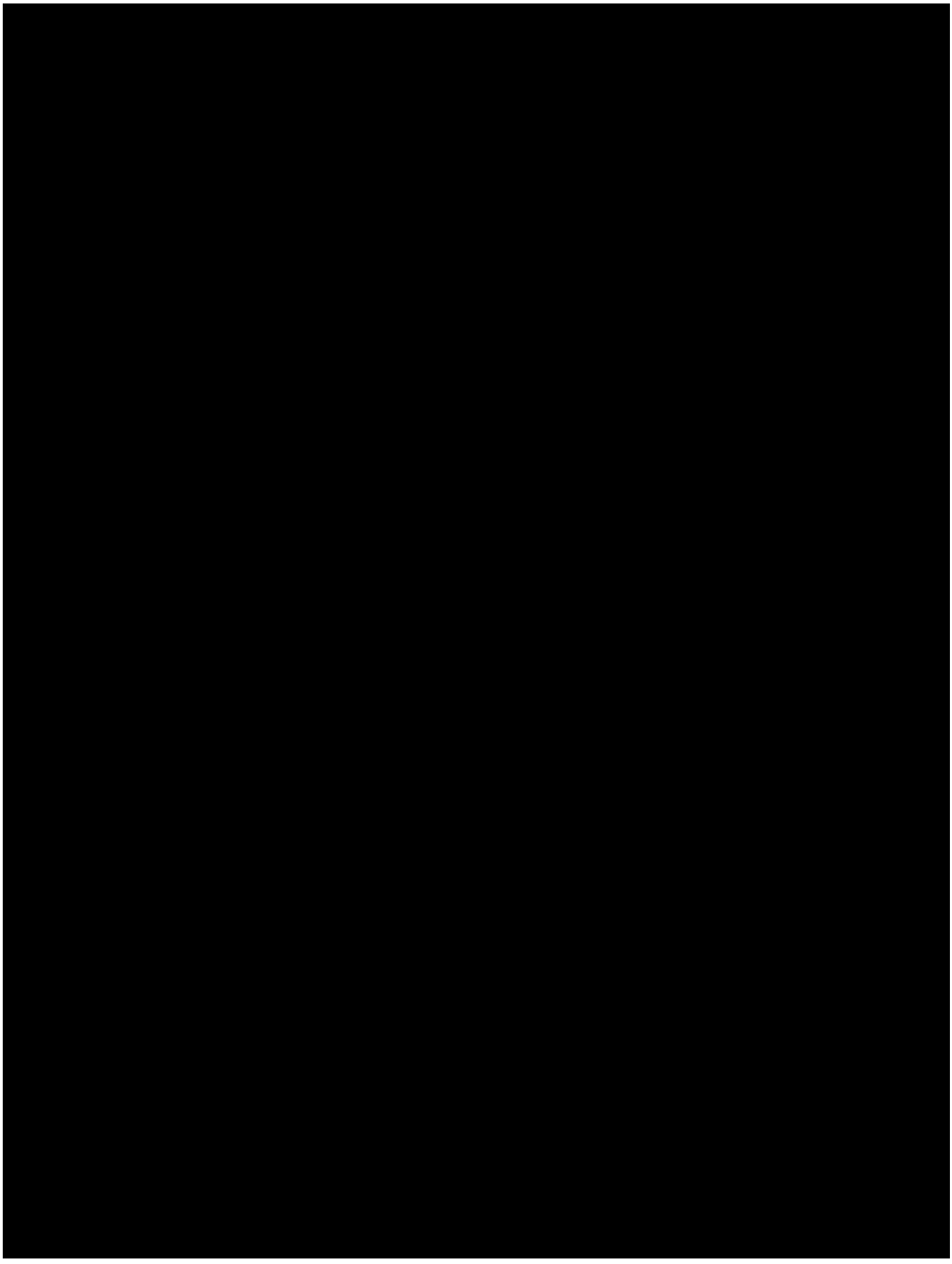

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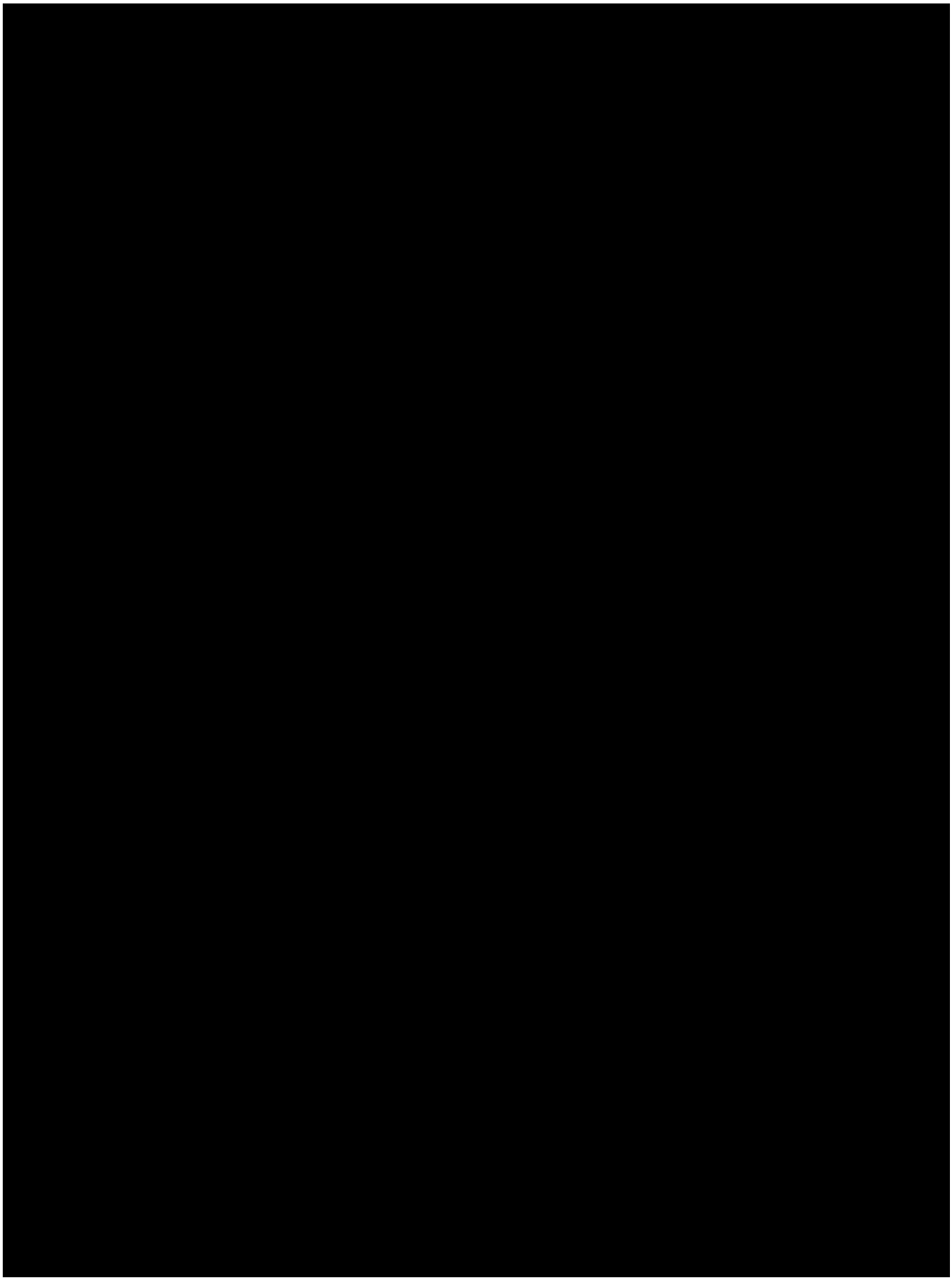

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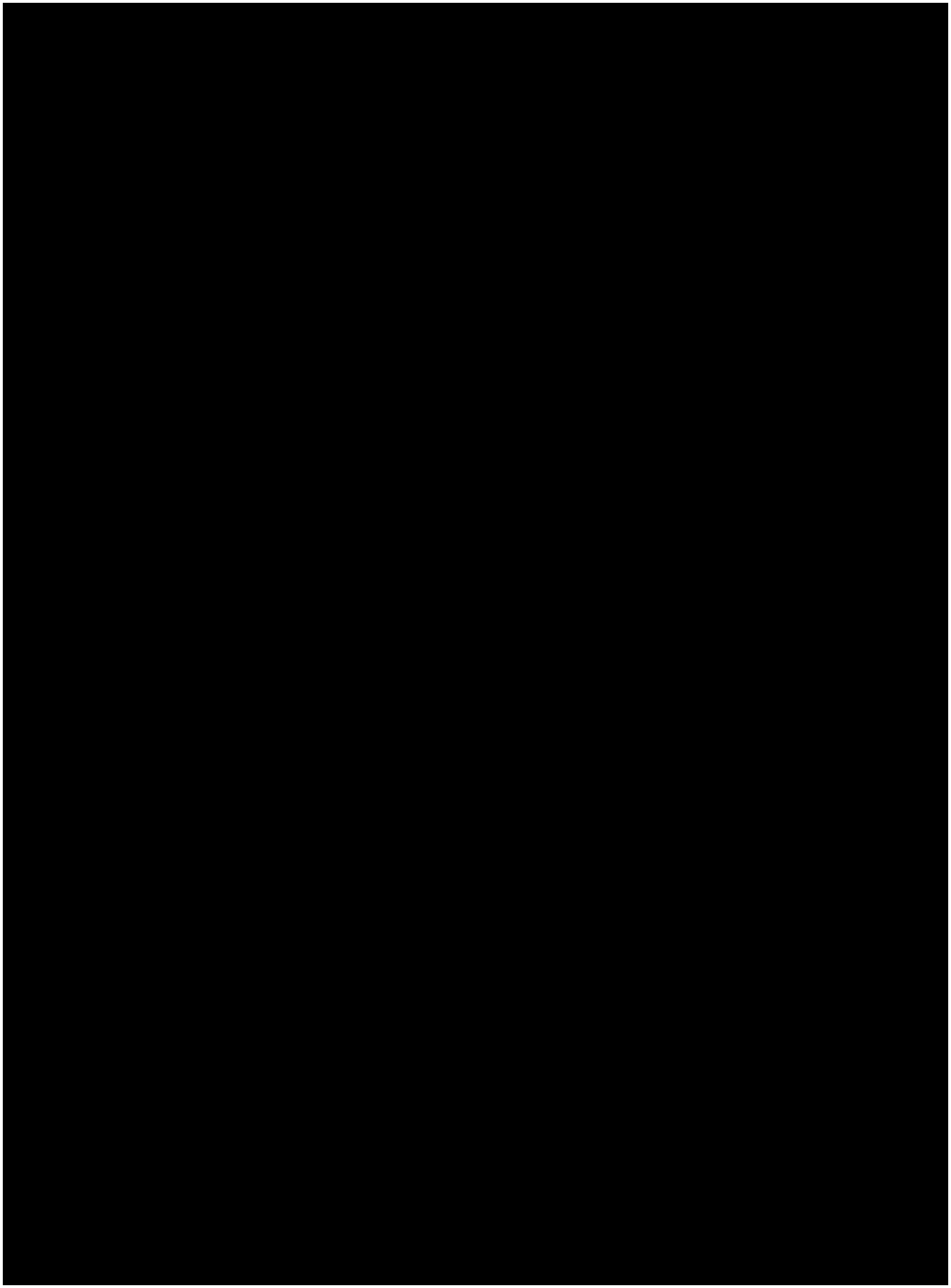

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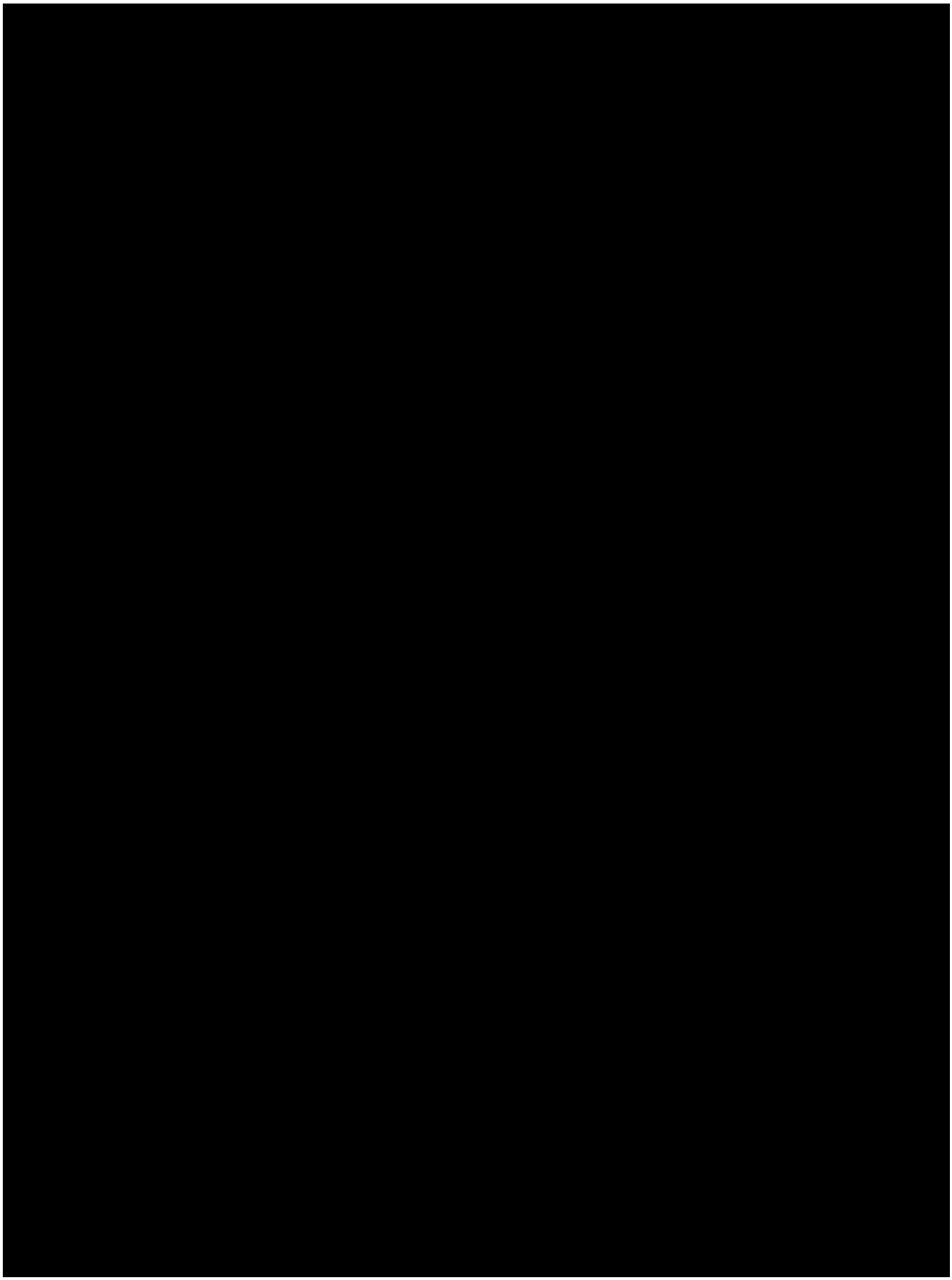

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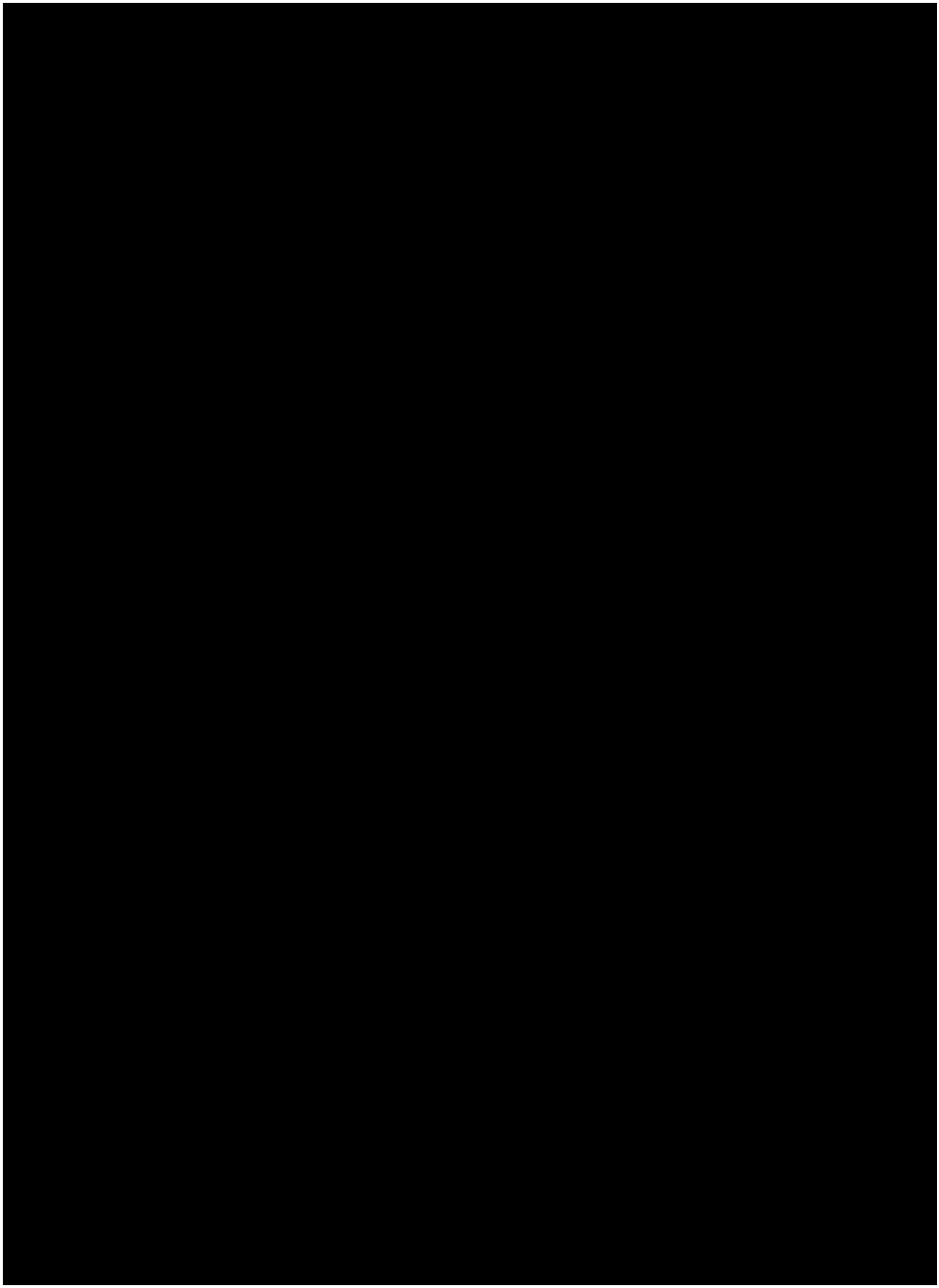

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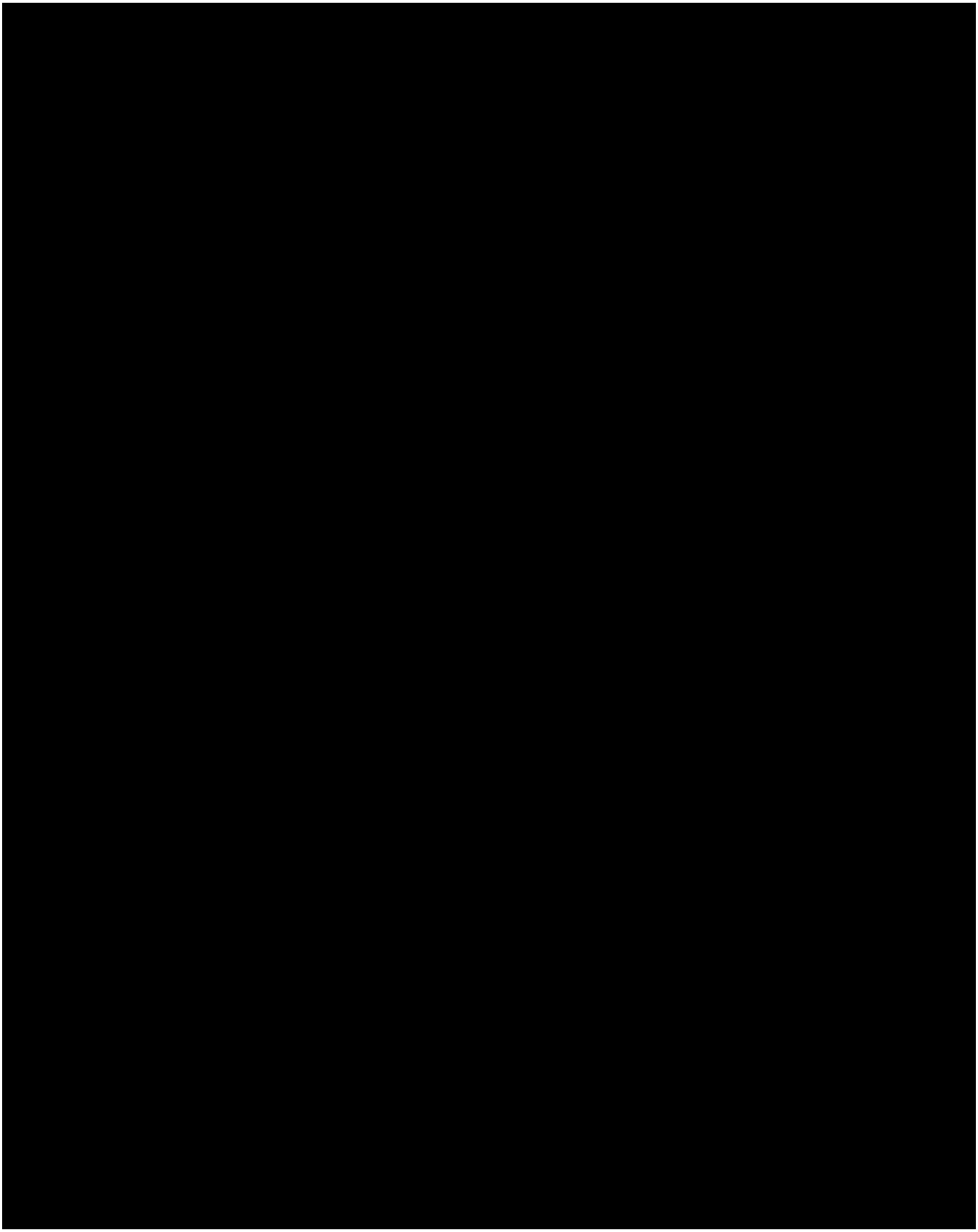

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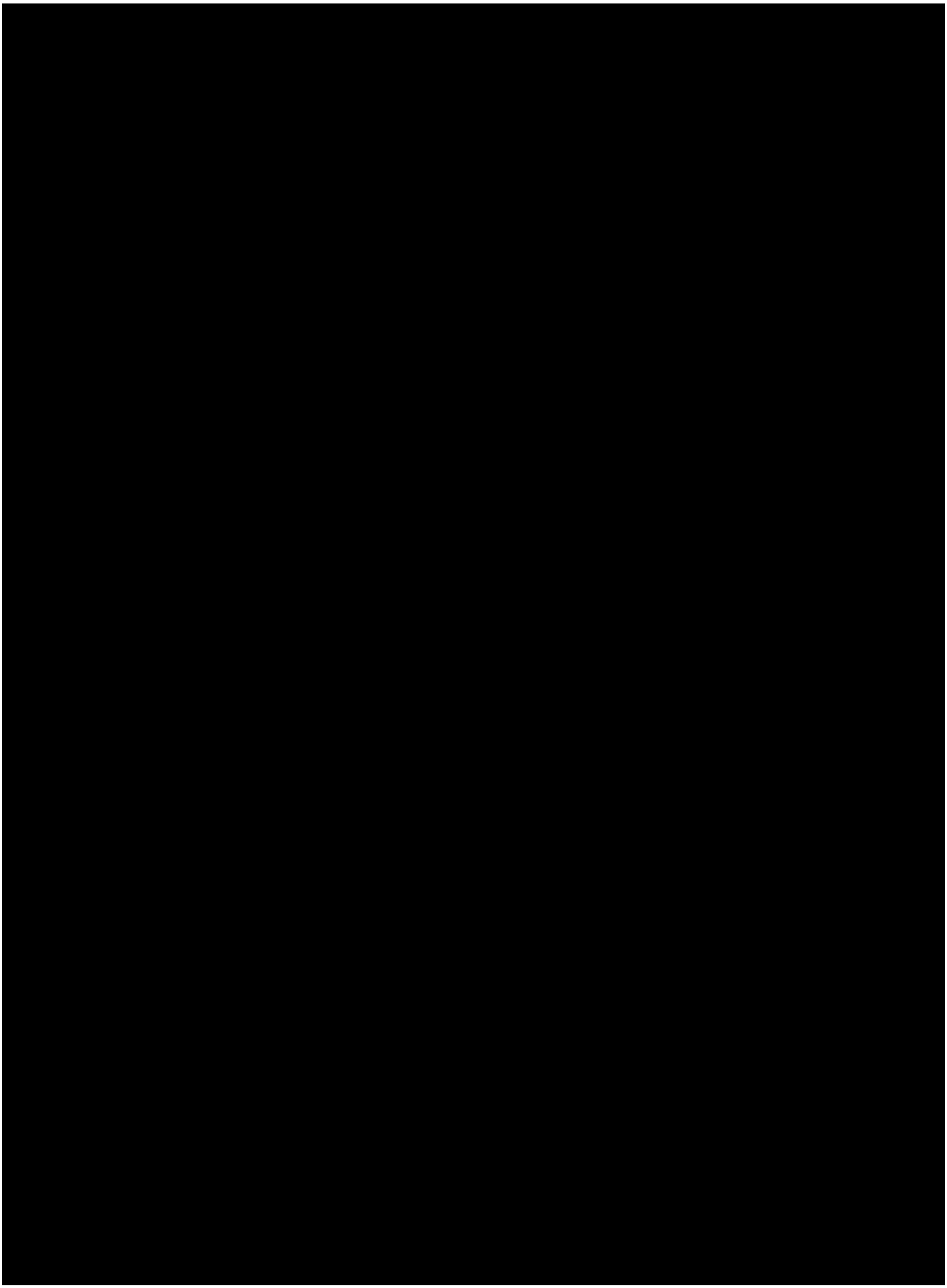

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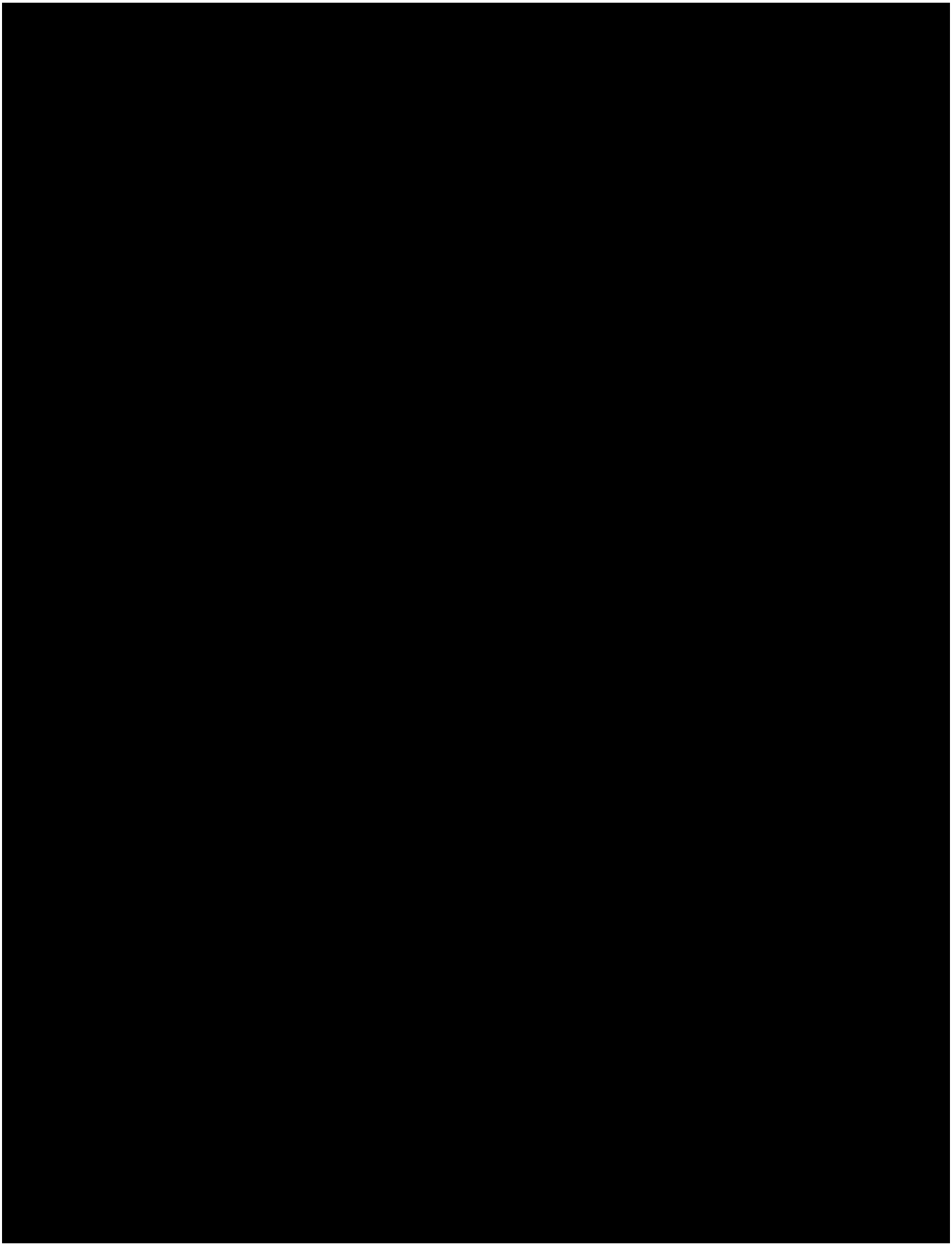

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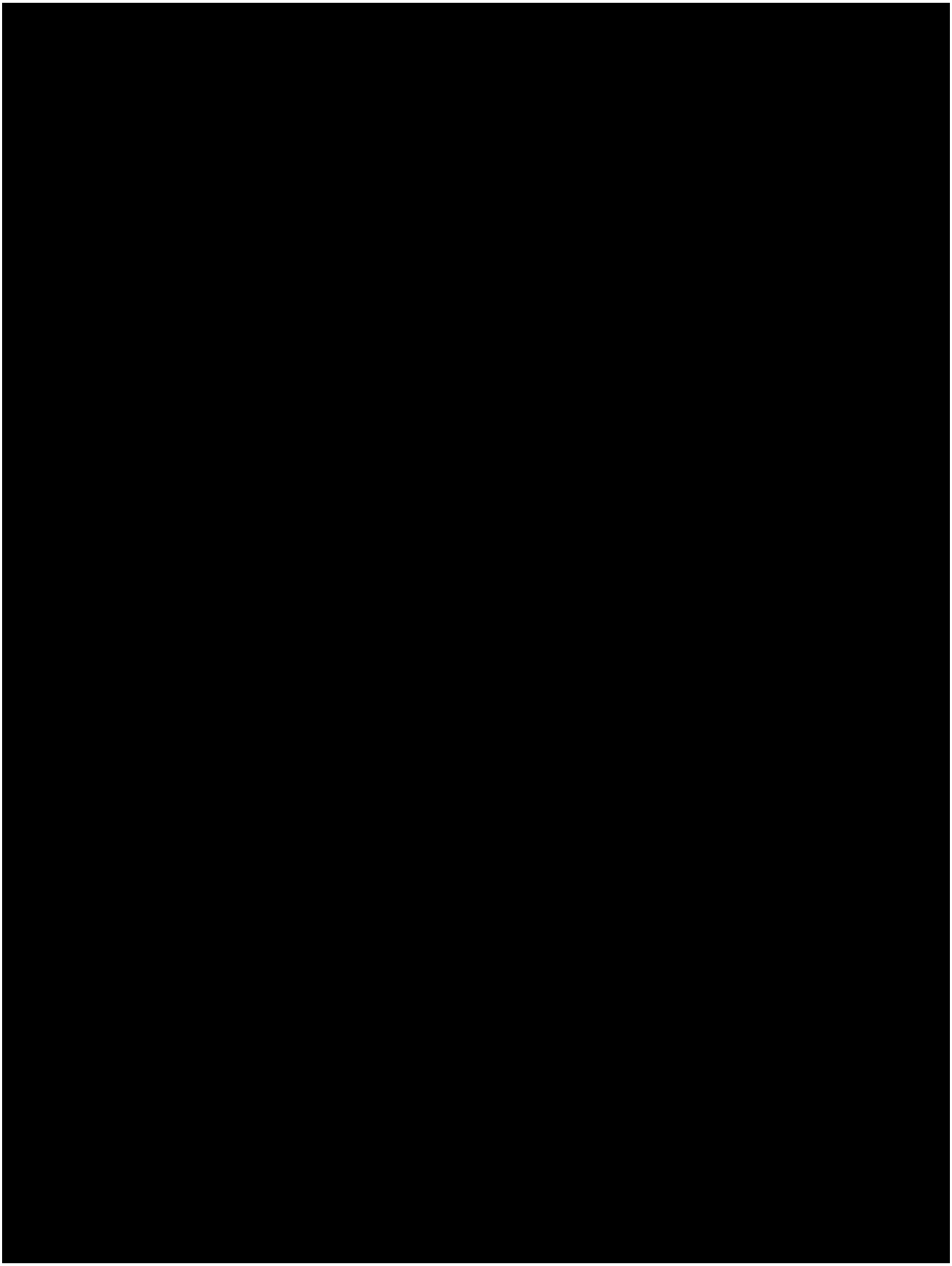

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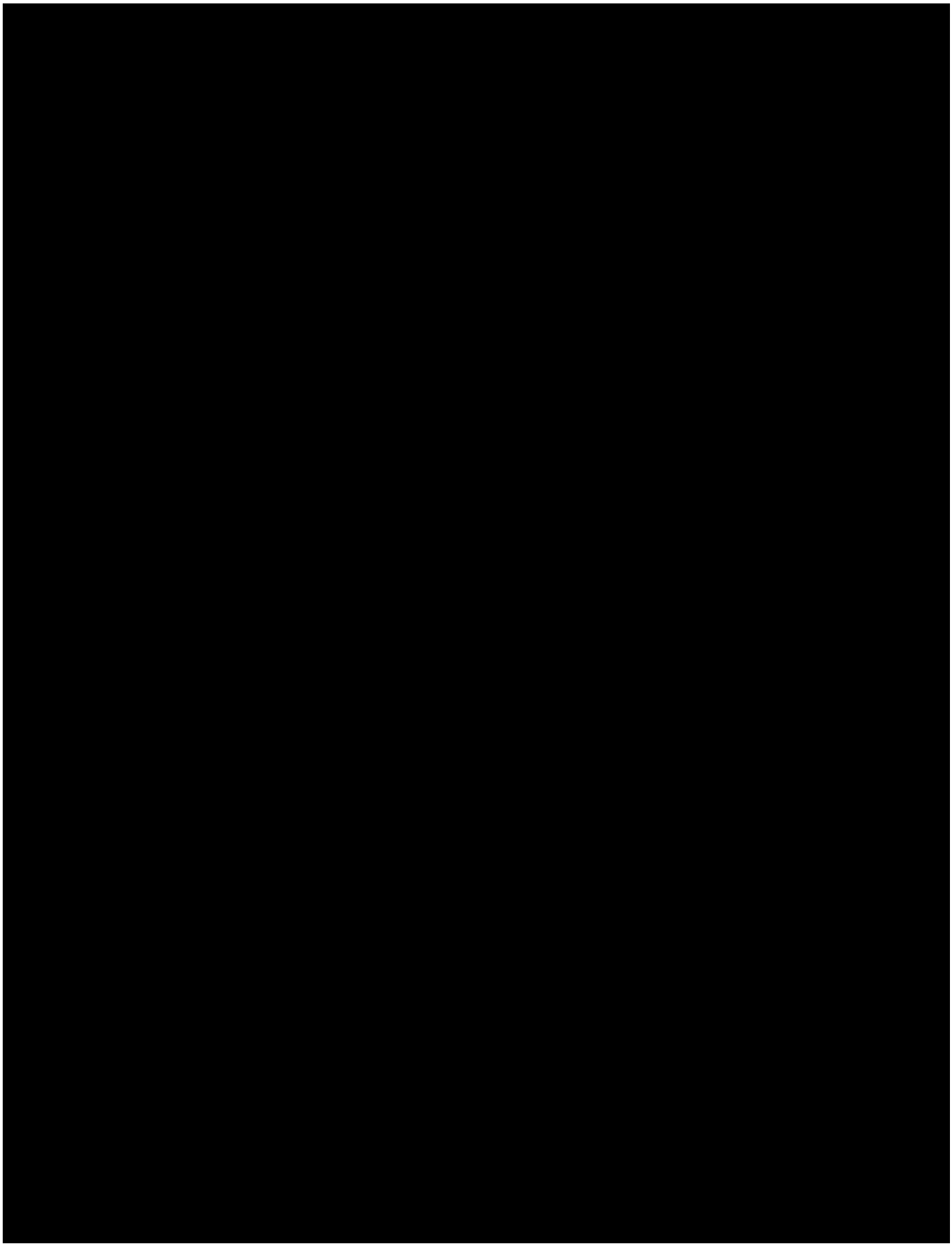

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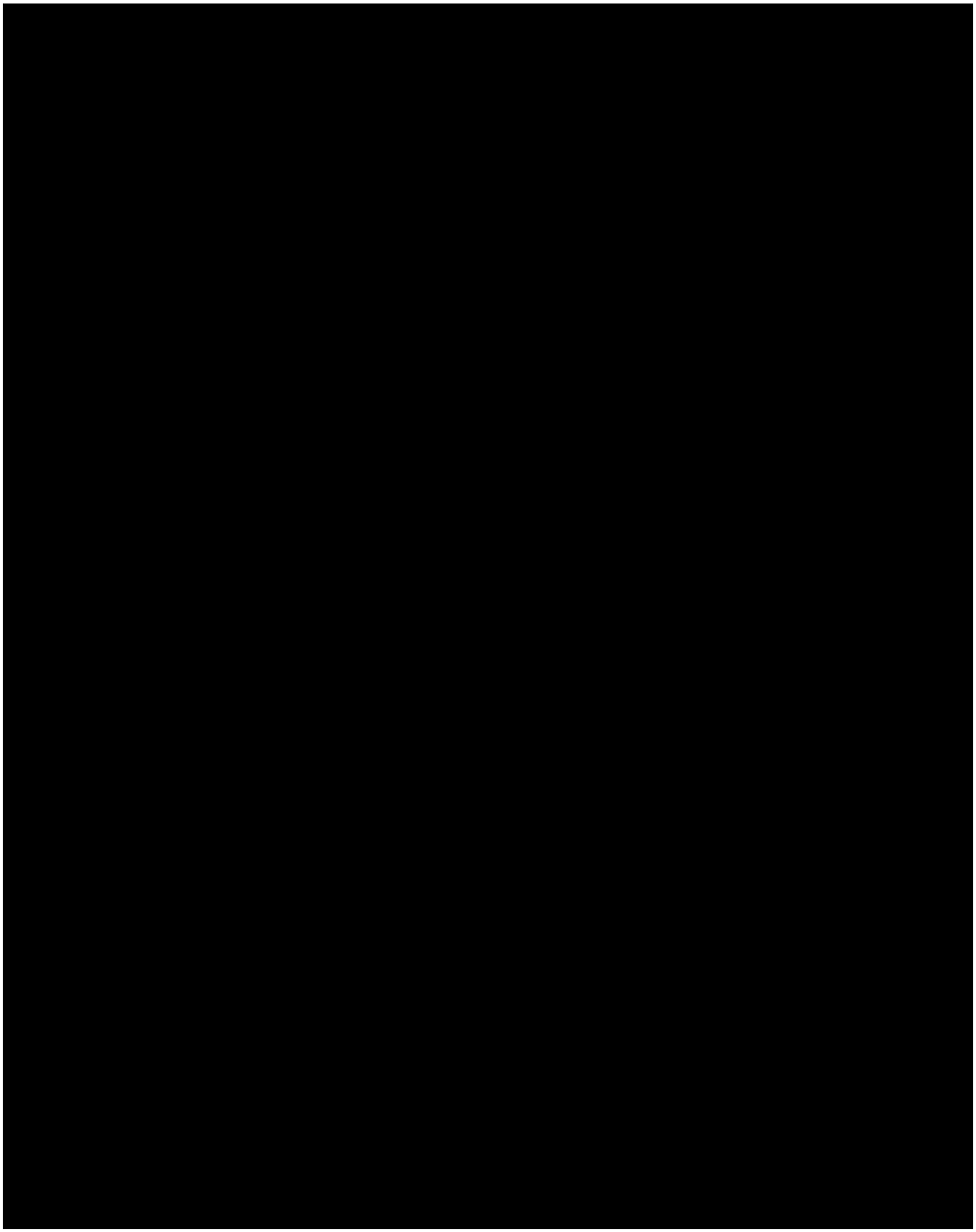

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8.3 Documentation of health-related quality of life (HRQoL)

8.3.1 Overview of health state utility values (HSUV)

Utility data were obtained from the analysis of CARTITUDE-1 EuroQoL Five-Dimension (EQ-5D-5L) data, with Danish utility weights applied (for details see Appendix I Mapping of HRQoL data). Two utility analyses were conducted, according to two different analysis sets, where the Adverse Event-free EQ-5D-5L Analysis Set was a subset of the EQ-5D-5L Analysis Set. The predicted health state utility results were comparable for the two analysis sets; that is, the overall mean utilities for the 1) progression-free and 2) progression-free and adverse event-free health states were similar. Therefore, the impact of treatment-related adverse events on patients' average quality of life in the progression-free health state was minimal, as measured by the EQ-5D instrument.

However, only progression-free observations were analysed in this analysis, due to the limited number of observed progression events; therefore, in order to determine the quality of life in the post-progression health state, subsequent analyses of additional data would be required. Therefore, health state utility values from the ICARIA-MM trial were utilised to calculate the most appropriate value for patients in PPS. The trial population from the ICARIA-MM trial was deemed to be most similar to the CARTITUDE-1 population, compared to other trials in RRMM, as they have a similar number of prior therapies (despite the fact that they are not triple class exposed). In the ICARIA-MM trial, isatuximab + pomalidomide + dexamethasone (IsaPd) was compared with pomalidomide + dexamethasone (Pd) (respectively, the intervention and comparator). The utility values were extracted from the IsaPd NICE submission (TA658) [107].

The PPS utility value applied in this analysis was calculated as follows:

- Firstly, the average of the intervention and comparator PFS utility values was calculated.

- Secondly, to determine the utility decrement between the PFS and PPS health states, the difference between the utility values was calculated (0.718 – 0.611).
- Thirdly, to determine the relative decrease in the utility value from PFS to PPS, the proportion by which this value decreases was calculated (0.107/0.718).

The resulting value was 0.15. This proportion was then applied to the PFS utility value derived from CARTITUDE-1 (0.843) to determine the relative utility value of the PPS state used in this analysis. The PPS value used in the cost-effectiveness analysis of Carvykti® as a result of the calculation was 0.717.

See Table 34 below for an overview of the PPS utility value calculations.

Table 34. Steps for the calculation of the PPS HSUV

Step	Formulae	Value	Justification
Step 1: Average PFS value (IsaPd and Pd)	(0.719 + 0.717)/2	0.718	Health state utility values are disease specific
Step 2: Calculate utility decrement between PFS and PPS	0.718 – 0.611	0.107	-
Step 3: Calculation of relative decrease in utility value between health states	(0.107/0.718)	0.15 (15%)	-
Step 4: Calculation of PPS utility value	0.8435 – (0.15 * 0.8435)	0.7170	Compared to the absolute decrease, the relative decrease in health state utility values allows for a more accurate PPS value to be derived (when estimating HSUV from other RRMM trials)

Source: [107]

Table 35 below presents an overview of the utility values for each health state.

Table 35. Overview of HSUV derived from CARTITUDE-1 and mapping

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
PFS (Carvykti®)				
CARTITUDE-1	0.8435 [0.8.24, 0.8746]	EQ-5D-5L	DK	CARTITUDE-1, predicted Mean Danish utility score
PFS (Physician's choice)				
CARTITUDE-1	0.8435 [0.8124, 0.8746]	EQ-5D-5L	DK	CARTITUDE-1, predicted Mean Danish utility score
PPS				

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	Results [95% CI]	Instrument	Tariff (value set) used	Comments
CARTITUDE-1 and ICARI-MM trial NICE submission	0.717	EQ-5D-5L	DK	To capture the decrease in HRQoL expected upon disease progression, a relative decrease in utility value was applied based on the ICARIA-MM trial [107]

Utility decrements due to AEs were sourced from publications and previous HTA submissions from NICE (see Table 36). The duration of utility decrements were based on CARTITUDE-1 data (see Table 37) [100]. All inputs and sources are presented in Table 35. Decrements for AEs were applied for a specified duration as a one-off upon the start of the PFS health state for Carvykti® i.e. as one-time decrements of baseline utility value at the start of the model cycle. Conservatively the effect of AEs for physician's choice was not included in the cost effectivness model. (Table 36).

Table 36. Summary of adverse events associated disutility (derived from literature)

Adverse event	Utility decrement	Source/comment
Anaemia	-0.31	Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
AST increased	-0.07	Assumed lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
Asthenia and fatigue	-0.12	Lloyd 2006
CRS (grade 1-2)*	-0.11	-
CRS (grade 3+)**	-0.804	Assumed to be equal in magnitude to the utility value in the progression-free health state, per Hettle 2017[93] and Yescarta NICE submission for DLBCL [94]
Diarrhoea	-0.10	Lloyd 2006 [92]
Febrile neutropenia	-0.39	TA510 (based on Launois 1996) [95]
Gamma-glutamyl-transferase increased	-0.07	Assumed lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
Hypertension	0.00	TA573 (assume no QoL impact, controlled by medication)[96]
Hypokalaemia	-0.65	Bacelar 2014 [91]
Hypophosphatemia	-0.15	TA559 (2018) [97]
Leukopenia	-0.07	Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
Lymphopenia	-0.07	Assume lowest in range, Brown 2013/Partial Review TA171 (Bacelar 2014) [91]
Neutropenia	-0.15	Brown 2013/Partial Review TA171 (Bacelar 2014) [91]

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Pneumonia	-0.19	Brown 2013/Partial Review TA171(Bacelar 2014) [91]
Sepsis	-0.20	TA510 (based on Tolley 2013) [108]
Thrombocytopenia	-0.31	Brown 2013/Partial Review TA171 (Bacelar 2014) [91]

*Utility decrement of CRS, Grade 1-2 is assumed to include neurotoxicity, Grade 1 – 2.

**Utility decrement of CRS, Grade 3+ is assumed to include neuotoxicity, Grade 3+

Type of adverse event	Duration of adverse event (days)	Source
Anemia	15.1	CARTITUDE-1
AST increased	5.0	
Asthenia and fatigue	12.0	
CRS, Grade 1-2	4.4	
CRS, Grade 3+	23.2	
Neurotoxicity Grade 1-2	14.3	
Neurotoxicity Grade 3+	55.2	
Diarrhea	2.0	
Febrile neutropenia	7.6	
Gamma-glutamyltransferase increased	19,5	
Hypertension	5,8	
Hypokalemia	2.0	
Hyponatremia	3,5	
Hypophosphatemia	6.0	
Leukopenia	25,6	
Lymphopenia	85,8	
Neutropenia	38,1	
Pneumonia	15,5	
Pyrexia	38,1	
Sepsis	7.0	
Thrombocytopenia	51,1	

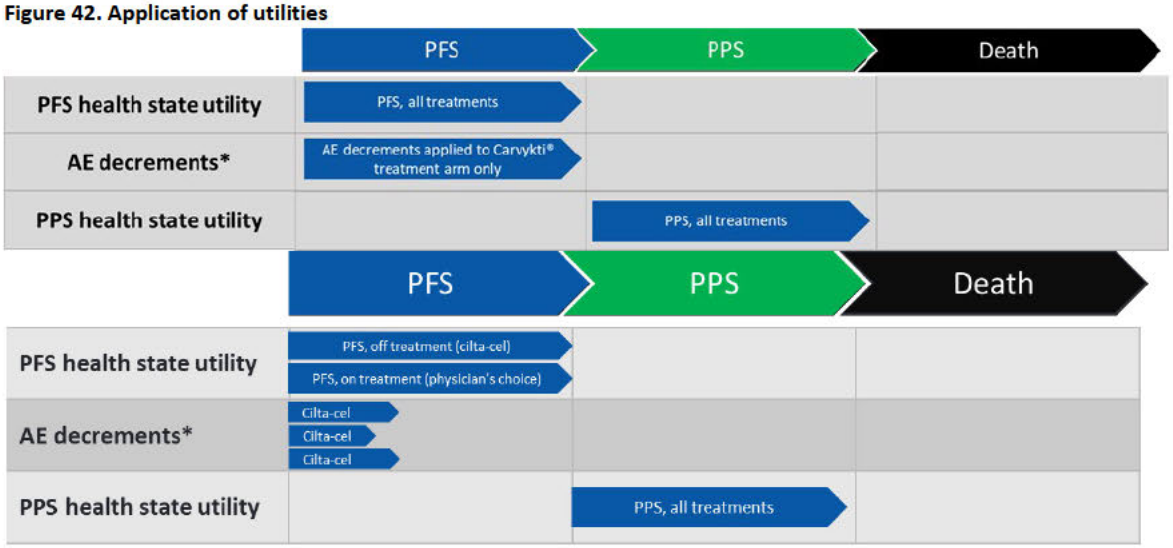
8.3.2 Health state utility values used in the health economic model

In the model, a utility value of 0.8435 was applied to both treatment arms in the PFS state. This was based on the assumption that utility values are disease specific rather than treatment specific.

The disutilities for adverse events is applicable to the Carvykti® treatment arm only. No adverse event disutility was applied to the physician's choice treatment arm as this value is difficult to estimate based on the heterogeneous mix of

different treatment regimens that comprise it. Additionally, adverse event related disutilities were included if they were observed in at least 5% of patients. A single PPS utility value is assigned to all patients in the post-progression health state. Decrements for AEs are applied for a specified duration once-off, upon the start of the PFS health state. The total AE disutility applied in the model was 0.0663. Figure 42 presents the application of utilities in the model.

Figure 42. Application of utilities



* A decrement for each AE is applied for a specified duration; applied as a one-off upon the start of the PFS health state
Abbreviations: AE = adverse event; PFS = progression-free survival; PPS = post-progression survival; PSM = partitioned survival model

Justifications:

HSUV for PFS (Carvykti®)

Utility value are considered disease specific.

HSUV for PFS (off treatment)

Utility value are considered disease specific. No AE utility decrement was applied to the difficulty in estimating this value with the heterogenous mix of treatment regimens.

HSUV for PPS

The trial population from the ICARIA-MM trial was deemed to be most similar to the CARTITUDE-1 population, compared to other trials in RRMM, as they have a similar number of prior therapies.

Table 38. below presents an overview of HSUV used in the model.

Table 38. Summary of HSUV used in the model

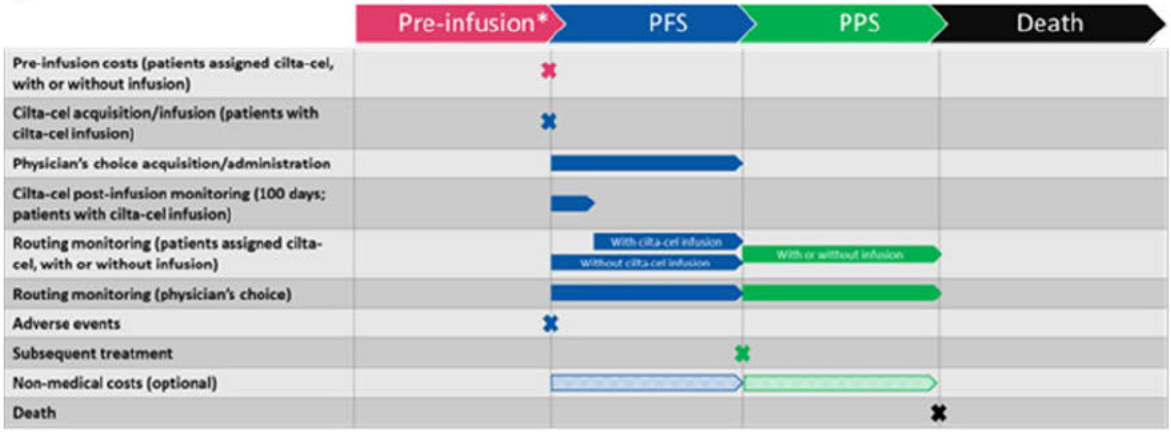
Health state	HSUV (mean value)	Justification	Source (literature search, study, ITC, etc.)
PFS (baseline/on treatment)	0.8435	HSUV are disease specific	Assumed equal to CARTITUDE-1 pre-infusion baseline utility [67]

Health state	HSUV (mean value)	Justification	Source (literature search, study, ITC, etc.)
PFS (off treatment)	0.8435	HSUV are disease specific	Assumed equal to CARTITUDE-1 pre-infusion baseline utility[67]
PPS	0.717	To capture the decrease in HRQoL expected upon disease progression, a relative change in utility was calculated from the ICARIA-MM trial-	Assumption based on Pd arm of the ICARI-MM trial, used in the IsaPd NICE submission [107]

8.4 Resource use and costs

Costs considered in the analysis include pre-treatment drug costs, drug acquisition cost, drug administration costs, monitoring cost, cost of managing AEs, end of life costs and non-medical cost. All costs are reported in DKK and were sourced from latest available public price list from 2022 [99, 109]. Figure 43 presents the application of costs in the model.

Figure 43. Cost and resource use



Abbreviations: cilta-cel = ciltacabtagene autoleucel; PFS= progression-free survival; PPS= post-progression survival

8.4.1 Pre-treatment costs

Pre-treatment costs included the cost of apheresis, bridging therapy, and conditioning therapy. These costs were applied to user-defined proportions of patients originally assigned to receive Carvykti® (100%, 77% and 89% respectively).

8.4.1.1 Apheresis

Apheresis was costed as an inpatient procedure and the cost was assumed to apply to all patients assigned to receive Carvykti® (100%). The costs for apheresis was sourced from the 2022 Diagnosis Related Group (DRG) codes - rates list available from Sundhedsdatastyrelsen [99]. The DRG cost represents the entire care episode for the apheresis procedure per patient. The value used in the analysis is 18,391 DKK. See Table 39.

Table 39. Apheresis

Item	Value	Source
Apheresis (cost per patient)	18,391 DKK	[99] (DRG 16MP05)
% receiving apheresis	100%	Assumption based on CARTITUDE-1
Time spent/procedure	8 hours	Assumption – one day for apheresis

8.4.1.2 Bridging Therapy

The analysis assumes that 77% of patients receive bridging therapy, between time of apheresis and infusion, based on CARTITUDE-1. Since bridging therapy was patient-specific, the regimen composition was assumed to be composed of a basket of the most commonly administered treatments in CARTITUDE-1. The proportions of each regimen are presented Table 40 below. The Unit costs for the drug included in the bridging therapy regimens are presented in Table 41. The total cost applied in the analysis is 48,243 DKK.

Table 40. Bridging therapy

Regimens	Proportions (%)	Source
DRd	8.16	CARTITUDE-1
DVd	14.74	CARTITUDE-1
DPd	8.48	CARTITUDE-1
Pd	6.01	CARTITUDE-1
IsaPd	6.01	CARTITUDE-1
Kd	7.41	CARTITUDE-1
KPD	9.71	CARTITUDE-1
IxaRd	6.36	CARTITUDE-1
IxaPd	6.68	CARTITUDE-1
Bendamustine	0.64	CARTITUDE-1
Melfuflen	1.34	CARTITUDE-1
PVd	14.57	CARTITUDE-1
DKd	9.89	CARTITUDE-1
Total	100	CARTITUDE-1

Abbreviations: Pd=Pomalidomide plus dexamethasone; PCd=Pomalidomide plus cyclophosphamide plus dexamethasone; Kd=Carfilzomib plus dexamethasone; Kcd= Carfilzomib plus cyclophosphamide plus dexamethasone; KRd= Carfilzomib plus lenalidomide plus dexamethasone; DVd= Daratumumab plus bortezomib plus dexamethasone

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Table 41. Bridging therapy drug unit costs

Drug	Pack size	Strength	Price per pack (DKK)	Source
Daratumumab (S.C)	1	1800 mg	3,8901	Medicinpriser.dk varenummer: 185054
Lenalidomide (P.O.)	21	25 mg	38,829	Medicinpriser.dk varenummer: 096515
Dexamethasone (P.O.)	100	4 mg	229	Medicinpriser.dk varenummer: 579043
Velcade (SC)	1	3.5 mg	1,940	Medicinpriser.dk varenummer: 179371
Pomalidomide (P.O.)	21	1 mg	55,581	Medicinpriser.dk varenummer: 179371
Isatuximab (IV)	1	20 mg	1,130	Medicinpriser.dk varenummer: 187406
Carfilzomib (IV)	1	10 mg	1,372	Medicinpriser.dk varenummer: 542915
Ixazomib (P.O.)	3	2.3 mg	48,000	Medicinpriser.dk varenummer: 590825
Bendamustine (IV)	125	2.5 mg	1,174	Medicinpriser.dk varenummer:
Melfuflen (P.O.)	25	2 mg	330	Medicinpriser.dk varenummer: 131603

Abbreviations: IV: intravenous, P.O.: Per oral S.C.: Subcutaneous

8.4.1.3 Conditioning therapy

Conditioning therapy consists of three days of fludarabine (30 mg/m²) and cyclophosphamide (300 mg/m²), per the CARTITUDE-1 protocol, and validated by a Danish clinical expert [59]. The duration of conditioning therapy was expressed as 0.43 weeks per model cycle in the model. Additionally, the proportion of patients with apheresis receiving conditioning therapy was assumed to be 89.4% based on the proportion in CARTITUDE-1, validated to be transferable to Denmark by a Danish clinical expert [59]. An administration cost was applied to account for the mode of IV administration. The unit costs for the drugs included in conditioning therapy are presented Table 42 below. The total cost applied in the analysis was 9,454 DKK

Table 42. Conditioning therapy

Item	Pack size	Strength	Price per pack (DKK)	Source
Fludarabine (IV)	1	50 mg	1,310.10	Laegemiddelstyrelsen [110] varenummer: 187406
Cyclophosphamide (IV)	1	500 mg	61.50	Laegemiddelstyrelsen [110] varenummer: 020242
Total unit cost (DKK)			1,371.60	

8.4.2 Treatment costs – Carvykti®

The treatment cost for Carvykti® was applied as a one-off cost at the time of infusion for the proportion of patients receive Carvykti®, based on what was observed in CARTITUDE-1 (86%). The company price for Carvykti®, applied in the analysis for Denmark was 3,124,215.19 DKK. Pre-medication was added to the pre-infusion period according to the SmPC [60]. For the pre-medication, it was assumed an average dose of 825 mg of an antipyretic and a 37.5 mg dose of antihistaminic. For both, oral administration was assumed. See Table 43 for details on pre-medications.

Table 43. Pre-medication costs

	Dose per infusion	Administration	Cost per infusion	Cost per administration	Total costs
Antipyretic	825 mg	Oral	1.92 DKK	0 DKK	1.92 DKK
Antihistamine	37.5 mg	Oral	11.90 DKK	0 DKK	11.90 DKK

Table 44 below presents an overview of the intervention related treatment costs.

Table 44. Intervention related treatment costs

	Cost (DKK)
CAR-T acquisition cost	3,124,215.19
% patients infused with CAR-T	86%*
CAR-T acquisition cost of the cohort	**2,681,813.24 ****
	CAR-T acquisition cost * % patients infused with CAR-T
Cost of OOS	35.19***
CAR-T infusion cost	**51,756.8**
	% patients infused with CAR-T * total cost of CAR-T infusion
CAR-T retreatment cost	**1,347.07**
	% patients infused with CAR-T * total cost of CAR-T infusion * % patients retreated
Apheresis costs	**18,391.00**
	Cost of apheresis * % patients receiving apheresis
Bridging therapy costs	**74,649.09**
	(% patients receiving bridging therapy) * (total bridging drug cost + total bridging administration cost)
Conditioning therapy costs	**16,025.99**
	(% patients receiving CAR-T) * cost of conditioning therapy + (% patients receiving CAR-T) * cost of administrating conditioning therapy
Total	**2,845,728.05**

*% minus patients infused with OOS
**The cost is based on the acquisition cost multiplied by the 86% of patients who receive the infusion.
*** Calculated based on the 4.1% patient who received OOS products for which a cost of 1,000 DKK has been added in place of the company price of Carvykti®.

Note: There was 1 patient who was re-treated with cilta-cel after disease progression in CARTITUDE-1.
Note: total bridging/conditioning costs are explained above.

8.4.2.1 Out-of-specification cost

The model includes an option for a cost associated with out-of-specification (OOS) products. A small proportion of manufactured products (assumed to be 4.1% based on CARTITUDE 1) is expected to be OOS yet clinically permissible for patient administration, as the benefit of administering such products is thought to outweigh the risk of a delay to

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receive a new product, or a switch to less effective pharmacological therapy. If the option is selected a cost of DKK 1,000 is applied per OOS product (i.e., 4.1%). The cost is a payment from the payer to Janssen; if the product(s) had been within specification, the size of the payment would have been of DKK 3,124,215.19 DKK rather than of DKK 1,000.

8.4.3 Treatment costs – Comparator

Physician's choice constitutes the comparator for Carvykti® in the health economic analysis. The treatment mix and corresponding proportions were based on a market dynamics survey which collated input from 12 haematologists in Denmark on the treatment market for MM [58]. These proportions were further validated by a Danish clinical expert (Table 45) [59].

The total cost of the comparator was calculated by adding the following.

- Drug acquisition cost
- Drug administration costs

Table 45. Physician's choice regimens in Denmark

Regimen	Proportion	Source
PCd	13%	[58]
Pd	13%	[58]
Vd	4%	[58]
KRd	4%	[58]
Kd	21%	[58]
IRd	8%	[58]
ERd	8%	[58]
DVd	4%	[58]
D	4%	[58]
VCd	18.9%	[58, 59]
Venetoclax	2.1%	[58, 59]

Abbreviations. P: pomalidomide, V: velcade, d: dexamethasone, C: cyclophosphamide, R: Revlimid, K: carfilzomib, Ixa: Ixazomib, E: elotuzumab

Table 46 presents an overview of the unit costs and modes of administration for all drugs included in physician's choice.

Table 46. Physician's choice overview

Drug	Mode of administration	Strength	Price per pack (DKK)	Source
Bortezomib	SQ	3.5mg	1,940	Laegemiddelstyrelsen [110] Varenummer: 179371
Carfilzomib	IV	10mg	1,371	Laegemiddelstyrelsen [110] Varenummer: 542915

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Cyclophosphamide	P.O	50 mg	906.61	Laegemiddelstyrelsen [110] Varenummer: 575916
Daratumumab	S.C.	1800 mg	38,901.18	Laegemiddelstyrelsen [110] Varenummer: 185054
Dexamethasone	IV	4 mg	1,401	Laegemiddelstyrelsen [110] Varenummer: 08682
Lenalidomide	P.O	25mg	38,829	Laegemiddelstyrelsen [110] Varenummer: 096515
Pomalidomide	P.O.	4 mg	55,580	Laegemiddelstyrelsen [110] Varenummer: 455325
Venetoclax	P.O.	10mg	487	Laegemiddelstyrelsen [110] Varenummer: 461441

8.4.4 Drug administration costs

The cost of drug administration was applied to each of the drug included in the regimens of physician's choice. Dosage and administrations information was provided by a Danish clinical expert [59]. The Interactive DRG by Sunhetsdatastyrelsen [111] was used to identify the cost of administration, using the DRG 17MA88: Diagnose (DC900) Myelomatose and procedure (BWAA31) Medicingivning ved subkutan injection and (BWAA62) Medicingivning ved intravenøs infusion, for subcutaneous and intravenous administration respectively. For oral drug administration no additional cost was assumed. A cost of 3,225 DKK respectively was assumed based on the code 17MA88.

Table 47 presents an overview of the drug administration costs.

Table 47. Drug administration costs

Resource	Unit cost (DKK)	Source
IV administration	3,225	Sunhetsdatastyrelsen Interactive DRG[111]
Each SC administration	3,225	Sundhetsdatastyrelsen Interactive DRG[111]
Oral drug initiation	0	Assumption

8.4.5 Concomitant medication

Concomitant medications offered orally were not applied for the comparator arm as it was assumed they would be paid for by the patient as out-of-pocket payments, in the limited societal perspective. However, concomitant medications offered intravenously were kept (e.i., saline solution, and LMHeparin). For the Carvykti arm, all concomitant medications were included. The aforementioned approach is a conservative approach, since it will overestimate the treatment costs of Carvykti, in relation to the costs of the comparator.

The unit costs for concomitant medication are presented in Table 48 below. All drug costs were sourced from Laegemiddelstyrelsen [110].

Table 48. Concomitant medication unit costs

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Drug	Units	Strength	Price per pack (DKK)	Source
Paracetamol (acetaminophen)	20	1,000 mg	47	Paracetamol, V.nr. 476964, Scanpharm (Laegemiddelstyrelsen)
Diphenhydramine	24	8 mg	70	Benadryl, V.nr. 412205, McNeil Denmark (ApoPro & Webapoteket)
Saline solution	20	450 mg	168	Natriumklorid B. Braun , V.nr. 420079 , B. Braun Medical (Laegemiddelstyrelsen)
LMHeparin	25	2,500 mg	533	Fragmin, V.nr.001004 , Pfizer (Laegemiddelstyrelsen)

8.4.6 Subsequent treatment

The cost of subsequent treatment is captured in the PPS health state and applied as a one-off cost at disease progression to a specified proportion of patients (52.5%) in both arms based on Djebbari (2020) [112]. The composition of subsequent treatment was provided by a clinical expert currently treating MM in Denmark. As per the clinical expert input, the regimens comprising subsequent therapy were pomalidomide-cyclophosphamide-dexamethasone (PCd) and carfilzomib-dexamethasone (Kd). The mean duration of subsequent treatment was 5.77 months, based on Yong et al., and validated by the clinical expert to be representative of Danish clinical practice[59, 90]. The treatment duration reflects the mean duration of fifth-line treatments in patients with RRMM.

The unit cost for subsequent therapy is presented in Table 49 below. The total cost of subsequent treatment applied in the analysis was DKK.

Table 49. Subsequent treatment

Drug	Unit cost (DKK)	Pack size	Source
Pomalidomide (P.O.)	55,581	**21**	www.medicinpriser.dk. Varenummer: 455325
Cyclophosphamide (P.O.)	907	**100**	www.medicinpriser.dk. Varenummer: 575916
Carfilzomib (IV)	1,372	**1**	www.medicinpriser.dk. Varenummer: 542915
Dexamethasone (P.O)	229	**20**	www.medicinpriser.dk. Varenummer: 579403

8.4.7 Monitoring costs

The model captured routine monitoring costs during the 100 days post-infusion period, and for the PFS and PPS state. The types and frequencies of resources were based on the CARTITUDE-1 protocol for the 100-days post infusion [113]. The pre-progression and post-progression frequency of resource use were based on inputs from a clinical expert currently treating MM in Denmark [59]. Table 50 presents the resource use for monitoring costs.

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Table 50. Monitoring costs - resource use

Weekly resource use for routine follow-up care by health state	100 days post-infusion*	Pre-progression (non-CAR-T)**	Pre-progression (CAR-T)**	Post-progression**
Haematologist visit	0.77	0.25	0.25	0.25
Full blood count	0	0.25	0.25	0.25
Biochemistry	0.77	0.25	0.25	0.25
Protein electrophoresis	0.28	0.25	0.25	0.25
Quantitative immunoglobulin	0.28	0.25	0.25	0.25
Urinary light chain excretion	0.56	0.25	0.25	0.25
Vital signs, including oxygen saturation		0.56	0	0 0
Serum calcium corrected for albumin		0.28	0	0 0

Source: *CARTITUDE-1 protocol **Danish KOL [6, 59].

The costs for monitoring were sourced from the latest available price list from Laegemiddelstyrelsen (Takstkort, October 2021) and haematology visit from Laegeforeningen, the lab test were calculated by multiplying the rate with the price adjustment for 2022 [99, 109]. Table 51 presents the monitoring unit costs.

Table 51. Monitoring unit costs

Resource	Cost (DKK)	Source
Haematologist visit	1049	Ledende overlaeger/professor, Værdisætning af Enhedsomkostninger [114]
Full blood count	21	Laegemiddelstyrelsen Takstkort 29A Ydelsesnummer: 7110 [109]
Biochemistry	21	Laegemiddelstyrelsen Taktskort 29A Ydelsesnummer: 7110 [109]
Protein electrophoresis	21	Laegemiddelstyrelsen Taktskort 29A Ydelsesnummer: 7110 [109]
Quantitative immunoglobulin	21	Laegemiddelstyrelsen Taktskort 29A Ydelsesnummer: 7110 [109]
Urinary light chain excretion	29	Laegemiddelstyrelsen Taktskort 29A Ydelsesnummer: 7116 [109]
Vital signs, including oxygen saturation	187.44	Laegemiddelstyrelsen Taktskort 29A Ydelsesnummer: 7117 [109]
Serum calcium corrected for albumin	86.50	Laegemiddelstyrelsen Taktskort 29A Ydelsesnummer: 7119/7120 [109]

The above mentioned frequencies and unit costs for monitoring costs were applied in the model. For Carvykti® monitoring was divided between the period up top 100 days following infusion, for which total cost was 11,229 DKK and the monitoring post that period, in PFS was 97,795 DKK and in PPS 38,101 DKK respectively. For physician's choice only monitoring costs in PFS and PPS were incurred corresponding to 8,564 DKK and 16,425 DKK respectively.

8.4.8 Adverse events costs

The incidence rates of AEs for Carvykti® were based on CARTITUDE-1. However, AEs were excluded from the physician's choice arm in the analysis. The rationale behind this exclusion is that the composition of physician's choice is likely to be subject to change, from the clinical input and HTA discussions. This exclusion removes the uncertainty around the choice of comparator dataset. Additionally, AEs are not key drivers of the analysis and their exclusion from the comparator arm should have minimal impact on the results of the analysis. The incidence rates are presented in Table 52 below.

Table 52. Incidence rates of AEs

AE (Grade 3-4 Unless Otherwise Specified)	Carvykti®
Anaemia	68.0%
AST increased	5.2%
Asthenia and fatigue	5.2%
CRS only, Grade 1-2*	89.7%
CRS only, Grade 3+**	5.2%
Neurotoxicity, Grade 1-2	10.3%
Neurotoxicity, Grade 3+	11.3%
Diarrhoea	1.0%
Febrile neutropenia	9.3%
Gamma-glutamyltransferase increased	6.2%
Hypertension	6.2%
Hypokalaemia	2.1%
Hyponatremia	4.1%
Hypophosphatemia	7.2%
Leukopenia	60.8%
Lymphopenia	50.5%
Neutropenia	94.8%
Pneumonia	9.3%
Sepsis	5.2%
Thrombocytopenia	59.8%

Costs of adverse events were sourced based on conversion of the international classification of disease version 10 (ICD-10) codes to relevant Danish diagnosis related group (DRG) codes. The costs were sourced from the 2022 Diagnosis Related Group (DRG) codes - rates list available from Sundhedsdatastyrelsen [99]. The costs of AEs are presented in Table 53 below.

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Table 53. Costs of AEs

Adverse event	Cost (DKK)	Source
Anemia	22,545	Sundhedsdatastyrelsen – DRG takster DRG 16MA0
AST increased	25,512	Sundhedsdatastyrelsen – DRG takster DRG 07MP10
Asthenia & fatigue	7,364	Sundhedsdatastyrelsen – DRG takster DRG 49SP01
CRS, Grade 1-2	3,107.83	Assumption Fever, DRG 18MA04 divided by Trimpunkt 6, DRG_Takster 2022
CRS, Grade 3+	33,310	Sundhedsdatastyrelsen – DRG takster
Neurotoxicity, Grade 1-2	11,538	Sundhedsdatastyrelsen – DRG takster DRG 21MA05
Neurotoxicity, Grade 3+	26,083	Sundhedsdatastyrelsen – DRG takster DRG 21MA04
Diarrhoea	22,789	Sundhedsdatastyrelsen – DRG takster DRG 06MA14
Febrile Neutropenia	18,926	Sundhedsdatastyrelsen – DRG takster DRG 49PR07
Gamma-glutamyltransferase increased	25,512	Sundhedsdatastyrelsen – DRG takster DRG 07MA14
Hypertension	14,155	Sundhedsdatastyrelsen – DRG takster DRG05MA11
Hypokalemia	6,016	Sundhedsdatastyrelsen – DRG takster DRG 23MA05
Hyponatremia	6,016	Sundhedsdatastyrelsen – DRG takster DRG 23MA05
Hypophosphatemia	6,016	Sundhedsdatastyrelsen – DRG takster DRG 23MA05
Leukopenia	25,761	Sundhedsdatastyrelsen – DRG takster DRG 17MAO5
Lymphopenia	25,761	Sundhedsdatastyrelsen – DRG takster DRG 17MAO5
Neutropenia	20,622	Sundhedsdatastyrelsen – DRG takster DRG 49PR07
Pneumoniae	25,695	Sundhedsdatastyrelsen – DRG takster DRG 04MA13
Sepsis	42,770	Sundhedsdatastyrelsen – DRG takster DRG 18MA01
Thrombocytopenia	96,963	Sundhedsdatastyrelsen – DRG takster DRG 16MA03

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8.4.9 End of life cost

An end-of-life total cost from was sourced from the Sundheddatasryrelsen DRG Takster 2022 list.

A end-of-of life cost of 71,612 DKK was applied in the analysis. See Table 54 below.

Table 54. End-of-life cost for Denmark

Cost item	Cost (DKK)	Comment/reference
End of life (Denmark)	71,612	DRG 16MP48, Sundhedsdatastyrelsen Takster 2022 [99]

8.4.10 Non-medical costs

Non-medical costs were derived for patients, by estimating the time spent (e.g. four hours) due to treatment (i.e., based on sources such as physician's visits and medical tests) and transportation costs (round trip).

Patient and transportation costs were sourced from the Danish Medicines Council's valuation of unit costs Danish [114]

The costs and resource use presented were applied in the analysis. See Table 55 for an overview of non-medical costs.

Table 55. Non-medical costs per health state

Health state	Patient				Transport			Total
	Frequency	Hours spent	Cost/hour	Total cost	Frequency	Cost/hour	Total cost	
PFS (on treatment)	0.25	4	181 DKK	181 DKK	0.25	140 DKK	35 DKK	216 DKK
PFS (off treatment)	0.25	4	181 DKK	181 DKK	0.25	140 DKK	35 DKK	216 DKK
PPS	0.25	4	181 DKK	181 DKK	0.25	140 DKK	35 DKK	214 DKK

8.5 Results

8.5.1 Base case overview

The base case settings are presented in Table 56.

Table 56. Base case overview

Comparator	Physician's choice
Type of model	Partitioned survival model (PSM)
Time horizon	40 years (life time)
Treatment line	4th- or subsequent treatment line
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in study CARTITUDE-1 [103]Danish population weights were used to estimate health-state utility values

Included costs	Pharmaceutical costs (Carvykti® costs, apheresis, bridging therapy, conditioning therapy, physician's choice costs, subsequent treatment cost) Healthcare utilisation costs Costs of adverse events Non-medical costs (patient and travel costs)
Dosage of pharmaceutical	Based on weight (0.5-1.0 x 10^6 CAR-positive viable T cells per kg of body weight)
Average time on treatment	Intervention: one-time infusion Comparator: Until progression
Parametric function for PFS	Intervention: Lognormal Comparator: Lognormal
Parametric function for OS	Intervention: Loglogistic Comparator: Loglogistic

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8.5.2 Base case results

The base case results showed that Carvykti® was associated with 5.28 additional LY and 4.20 additional QALYs compared to physician's choice. Treatment with Carvykti® led to incremental cost of DKK 2,345,652 and was resulting in an ICER of DKK 558,527 per QALY gained over a lifetime Danish limited societal perspective. The LYs and QALYs gained as well as the total costs are presented for each treatment arm as well as the increment is presented in Table 57 below. Table 58 presents the discounted disaggregated results.

Table 57. Base case results

	Carvykti®	Physician's choice	Increment
Total life years (LYs)	6.82	1.54	5.28
Total quality adjusted life years (QALYs)	5.37	1.17	4.20
Total cost	3,282,638	936,986	2,345,652.34
ICER			**558,527**

Table 58. Disaggregated results (discounted)

	Carvykti®	Physician's choice	Increment
Life Years			
PFS	5.06	0.56	4.51
PPS	1.75	0.98	0.77
total	6.82	1.54	5.28
QALYs			
PFS	4.21	0.47	3.74
PPS	1.23	0.70	0.53
Disutility	-0.07	0.00	-0.07
total	5.37	1.17	4.20
Costs			
PFS			
Cost of CAR-T	2,681,813		2,681,813
CAR-T infusion costs	51,637		51,637
CAR-T retreatment costs	1,371		1,371
Apheresis costs	18,391		18,391
Bridging therapy costs	74,649		74,649
Conditioning therapy costs	16,026		16,026
CAR-T total costs	**2,843,887**		**2,843,887**
Cost of physician's choice		427,847	-427,847

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Physician's choice administration		211,111	-211,111
Physician's choice total		**638,958**	**-638,958**
Monitoring/disease management	73,165	8,461	64,704
CAR-T infusion monitoring	10,998	0	10,998
Total follow-up	84,163	8,461	75,702
Adverse events	108,973	0	108,973
Travel costs	10,821	4,358	6,463
Patient time	73,908	22,537	51,370
Total non-medical	**84,729**	**26,895**	**57,833**
PPS			
Monitoring/Disease management	26,541	14,960	11,581
CAR-T infusion monitoring	308	0	308
Total follow-up	**26,849**	**14,960**	**11,889**
Subsequent treatment	53,335	153,572	-100,237
End of life cost	55,935	69,039	-13,104
Travel costs	4,013	4,067	-54
Patient time	20,754	21,033	-279
Total non-medical	24,767	21,033	3,734
Total cost	**3,282,638**	**936,986**	**2,345,652**

8.6 Sensitivity analyses

A one-way deterministic one-way sensitivity analysis (OWSA) was conducted. Input values were varied by 20% for both lower and upper bound. Table 59 Shows the results of the OWSA including the 10 values which had the largest impact on the ICER when being varied. The tornado diagram in Figure 44 shows the ten most sensitive values. The PFS utility had the largest impact on the ICER.

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8.6.1 Deterministic sensitivity analyses

Table 59. OWSA

Parameter	Lower bound	Upper bound	Lower bound (kr)	Upper bound (kr)	Absolute difference (kr)
PFS utility (off treatment)	0.08	0.21	602,873	504,963	97,910
% patients discontinuing treatment prior to CAR-T infusion - Cilta-cel	0.81	0.87	580,482	539,666	40,816
PPS utility	0.57	0.85	573,598	546,217	27,381
% of Kd	0.14	0.29	570,304	544,995	25,308
PFS utility (on treatment)	1.48	2.34	568,758	546,793	21,965
Body surface area (mean)	0.12	0.27	548,575	570,148	21,573
% of VCd	4.64	6.90	566,347	550,707	15,641
Duration of subsequent treatment - Physician's choice	0.42	0.63	565,715	551,416	14,299
% taking subsequent treatment - Physician's choice	0.02	0.11	553,980	564,932	10,952
CAR-T bridging therapy composition: Cilta-cel - IsaPd	0.01	0.09	554,787	564,485	9,698

Figure 44. Tornado Diagram

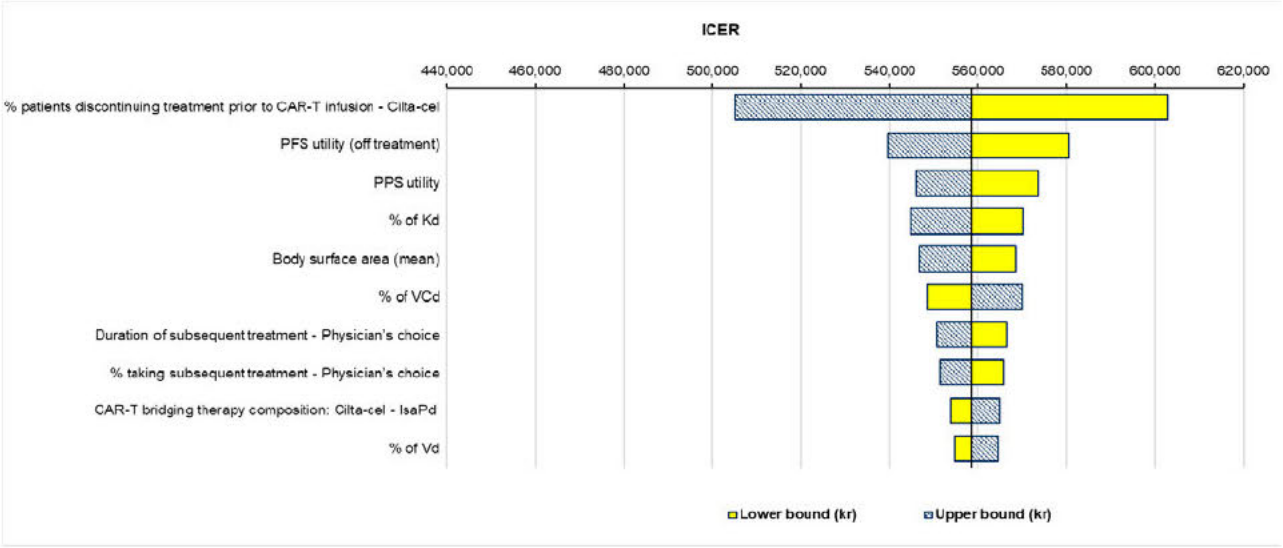

Table 60 presents the results of ICER exploration in relation to different discounts applied to the acquisition unit cost of Carvykti®. With a discount of 100%, the ICER is dominant.

Table 60. Results of exploration of the ICER in relation to the drug price

Discount for pack price	ICER – Base case (no discount)	ICER – Discount applied	Difference
	558,527		
10%		494,669	-63,858
20%		430,811	-127,716

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30%	366,953	-191,574
40%	303,095	-255,432
50%	239,237	-319,290
60%	175,380	-383,148
70%	111,522	-447,005
80%	47,664	-510,863
90%	Dominant	-
100%	Dominant	-

Table 61 presents the results of the scenario analyses conducted for key model variables.

Table 61. Scenario Analyses

Parameter	Base case	Scenario	Incremental cost (DKK)	Incremental QALY	ICER (DKK/QALY)
Base case			**2,345,652**	**4.20**	**558,527**
Perspective	Limited societal	Payer	2,288,152	4.20	544,836
	OOS Cost for OOS products included-No	Yes	2,345,652	4.20	558,527
Starting age	Starting age – 61	71	2,329,913	3.69	631,710
Time horizon	40 years	5 years	2,232,630	1.48	1,510,931
		10 years	2,277,899	2.62	869,502
		15 years	2,305,831	3.31	697,158
		20 years	2,323,642	3.74	621,095
		30 years	2,342,034	4.14	566,046
LocoMMotion & Cartitude PFS distribution	Lognormal	Loglogistic	2,320,629	4.17	556,502
		Weibull	2,429,805	4.01	605,332
		Exponential	2,414,352	3.98	606,705
		Generalised gamma	2,274,003	4.20	540,787
		Gompertz	2,341,633	4.29	546,456
LocoMMotion & Cartitude OS distribution	Loglogistic	Lognormal	2,365,577	4.57	517,990
		Weibull	2,316,916	3.34	692,918
		Exponential	2,284,309	2.61	873,884

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		Generalised gamma	2,262,031	2.02	1,121,621
		Gompertz	2,376,770	4.36	545,292
Discount rates	Discount rates costs and QALYs/LYs 3.5%, 3.5%	Costs 0%; QALYs/LYs 0%	2,415,969	5.94	407,030
Drug wastage	Yes	No	2,331,636	4.20	555,190
Age-dependent utilities	Yes	No	2,345,652	4.29	547,321
Reimbursement for OOS products	No	Yes	2,345,652	4.20	558,527
Data source PC's choice	LocoMMotion	MAMMOTH	2,526,819	4.28	590,767
Disutility considered by	AE related disutility	Treatment related disutility	2,345,652	4.26	551,249
		No AE-related or treatment related disutility	2,345,652	4.27	549,828

8.6.2 Probabilistic sensitivity analyses

In order to evaluate uncertainty associated with parameter precision, probabilistic sensitivity analyses were conducted to establish the impact of such uncertainty. Probabilistic sensitivity analyses included all model parameters; estimates of uncertainty were based on the uncertainty in the source data where data availability permitted this. In those cases, exact data were used to capture the upper and lower bounds; in instances of a lack of data, 20% variability from mean values was applied.

A second-order Monte Carlo simulation was run for 1,000 iterations including the simultaneous variation of all parameters. Multiple sets of parameter values were sampled from predefined probability distributions to characterize the uncertainty associated with the precision of mean parameter values.

Figure 45 presents the cost-effectiveness plane, which showed that all of the 1,000 iterations were in the North-East quadrant. This means that Carvykti® resulted in more QALYs and higher costs compared to physician's choice.

Figure 46 presents the cost-effectiveness acceptability curve (CEAC). The CEAC showed that Carvykti®'s probability of being cost-effective is 50% at a willing-to-pay of DKK 600,000-650,000.

Figure 45. Cost-effectiveness plane

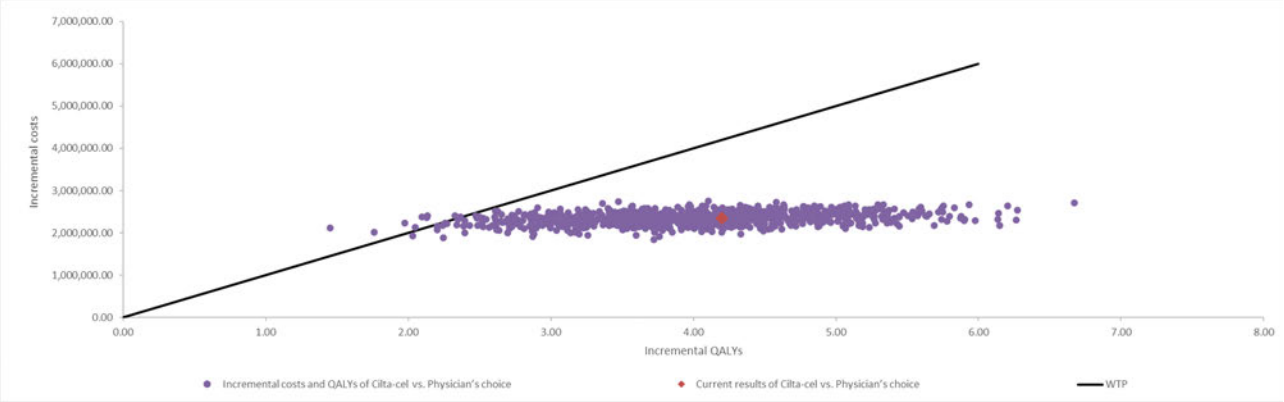
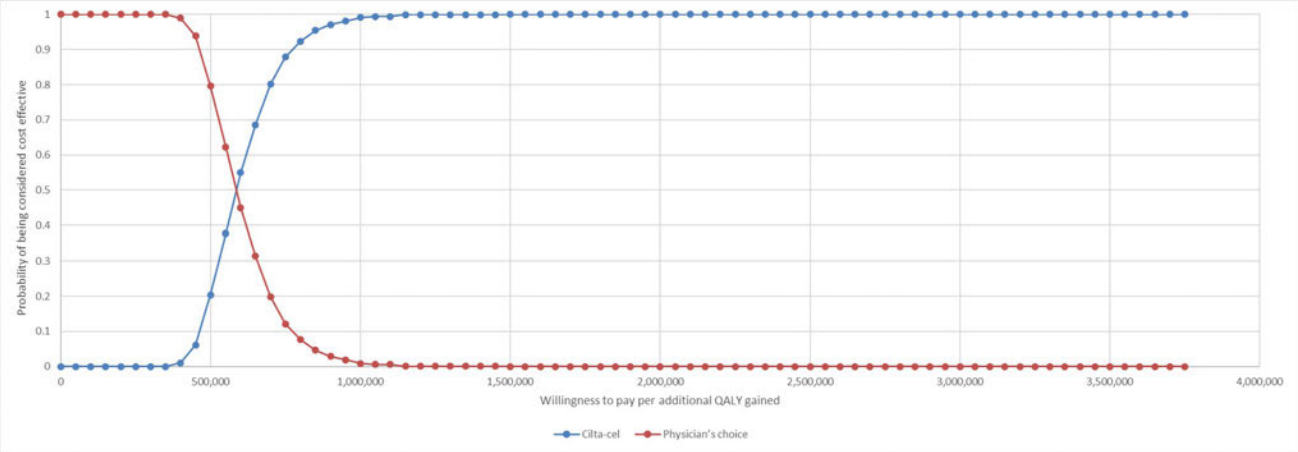


Figure 46. Cost-effectiveness acceptability curve (CEAC)



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9. Budget impact analysis

Based on the prevalence and incidence of triple class exposed patients with RRMM, Janssen Pharmaceuticals is assuming 20 patients to be treated with Carvykti® in the first year after the therapy is introduced, followed by 22 in the second year and onwards. A constant prevalence and incidence rate was assumed over the five-year period of 70 eligible patients, that is approximate 12% of the MM incidence. The numbers presented in
Table 62 and Table 63 represent the number of patients expected to be treated with Carvykti® if the intervention is introduced and if the intervention is not introduced.

9.1 Number of patients

Table 62. Number of patients over the next five-year period (Carvykti® introduced)

	Year 1	Year 2	Year 3	Year 4	Year 5
Carvykti®	20	22	22	22	22
Physician's choice	50	48	48	48	48

Table 63. Number of patients over the next five-year period (Carvykti® not introduced)

	Year 1	Year 2	Year 3	Year 4	Year 5
Carvykti®	0	0	0	0	0
Physician's choice	70	70	70	70	70

Drug expenditure is presented for two scenarios. Introduction of Carvykti® into SoC is presented in scenario one (Table 64). No introduction of Carvykti® into SoC is presented in scenario 2 (Table 65).

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9.2 Expenditure per patient

Table 64. Costs per year if Carvykti® is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Carvykti®	3,011,336	31,700	22,081	16,725	14,509
Physician's choice	720,562	109,305	32,446	13,822	6,978

Table 65. Costs per patient if Carvykti® is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Carvykti®	-	-	-	-	-
Physician's choice	720,562	109,305	32,446	13,822	6,978

9.3 Budget impact

The budget impact of the introduction of Carvykti® into SoC is presented in Table 66 below.

Table 66. Expected budget impact of introduction Carvykti® at the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	95,338,500	107,882,934	109,733,688	110,729,101	111,373,287
Of which: Drug costs	73,720,499	83,212,157	83,737,308	83,975,597	84,093,869
Of which: Administrative costs	8,745,746	9,520,074	9,844,784	9,986,101	10,056,242
Of which: Hospital costs	1,027,006	1,528,286	1,855,254	2,109,971	2,339,208
Of which: Adverse reaction costs	2,135,880	2,441,006	2,441,006	2,441,006	2,441,006
Of which: Subsequent treatment	7,665,630	7,979,210	8,187,384	8,298,712	8,367,864
Of which: End of life cost	2,043,739	3,202,201	3,667,952	3,917,714	4,075,098
Minus: The pharmaceutical under consideration is NOT recommended	50,439,328	58,090,652	60,361,860	61,329,402	61,817,849
Of which: Drug costs	24,972,663	28,483,331	29,407,745	29,790,059	29,975,564
Of which: Administrative costs	12,146,870	13,897,151	14,445,375	14,672,106	14,782,120
Of which: Hospital costs	844,319	1,196,142	1,361,619	1,455,458	1,515,679
Of which: Adverse reaction costs	-	-	-	-	-
Of which: Subsequent treatment	9,996,701	10,584,779	10,704,842	10,747,517	10,766,325
Of which: End of life cost	2,478,776	3,929,249	4,442,278	4,664,262	4,778,161

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Budget impact of the recommendation	**44,899,172**	**49,792,282**	**49,371,828**	**49,399,700**	**49,555,439**

10. Discussion on the submitted documentation

Patients with RRMM have a poor prognosis with high mortality, especially seen in triple-class exposed patients. Triple-class-exposed RRMM emerges after all effective therapies have failed; therefore, patients have an acute and very high unmet medical need. As MM progresses, each subsequent line of treatment is associated with a shorter PFS along with poor overall survival. In Denmark, the currently avaible SoC is a mix of therapies and the choice of treatement is based on previously received treatments together with patient preference.

Carvykti®, a CAR-T theraphy studied in CARTITUDE-1, demonstrated important clinical benefits for patients with triple-class exposed RRMM. CARTITUDE-1 was a single armed trial but results from the adjusted comparison of Carvykti® versus a cohort of patients in a prospective study LocoMMotion, representative of SoC in Denmark showed a substantial improvement in key endpoints: ORR, PFS, and OS.

A cost utility analysis was performed, assessing the value of Carvykti® compared to physciand choice in Denmark. The anlysis was perfomed using a previously developed cost-effectivness model adapted to a Danish setting. The model structure consisted of a PSM and the analysis was based on the ATT population from CARTITUDE-1 compared to a the matched cohort from the study LocoMMotion, representing pysician's choice.

To reduce uncertainty in long-term extrapolation based, the analysis was validated with external data and clinical expert opinion. Results of the base case analysis were shown to be robust in multiple scenario analyses. The ICERs were assessed for LY gained and QALYs gained. Carvykti® was shown to be more costly DKK 2,345,652 and more effective 4.20 QALYs compared to SoC (pysician's choice). The ICER was DKK 558,527 per QALY gained over a lifetime Danish limited societal perspective.

Carvykti® is a highly efficacious CAR-T, with a one-time administration that provides sustained treatment-free PFS. Carvykti® was shown to be well tolerated and represents an innovative treatment offering a cost-effective treatment of patients with triple-calss exposed RRMM in Denmark.

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Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

Janssen would like to emphasize that in our view there is no doubt that LocoMMotion is the most relevant source to estimate the efficacy of standard of care, because of its prospective trial design as well as having similar eligibility criteria as CARTITUDE-1; a prospective trial design should be deemed preferable to a retrospective. However, Janssen has carried out a systematic literature review (SLR) with the following objective:

- The objective of this study was to conduct systematic literature reviews (SLRs) of clinical, health-related quality of life (HRQoL), and economic evidence investigating therapeutic regimens in patients with RRMM to support health economics and outcomes research (HEOR) and market access activities for the novel CAR-T therapy cilta-cel. The clinical SLR focused on the triple-class exposed population, while the economic and HRQoL looked at RRMM overall given the limited literature for triple-class exposed patients for these topics.

Janssen_CAR-T RRMM SLR R.pdf

Appendix B Main characteristics of included studies

Table 67. Main characteristics of CARTITUDE-1

Trial name: CARTITUDE-1	NCT number: NTC03548207
Objective	The primary objectives were to characterize the safety of cilta-cel and confirm the RP2D (Phase2b) and to evaluate the efficacy of cilta-cel (phase 2)
Publications – title, author, journal, year	1. Berdeja, J. G., Madduri, D., Usmani, S. Z., Jakubowiak, A., Agha, M., Cohen, A. D., Stewart, A. K., Hari, P., Htut, M., & Lesokhin, A. (2021). Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. The Lancet, 398(10297), 314-324. 2. Usmani, S. Z., Berdeja, J. G., Madduri, D., Jakubowiak, A. J., Agha, M. E., Cohen, A. D., Hari, P., Yeh, T.-M., Olyslager, Y., & Banerjee, A. (2021). Ciltacabtagene autoleucel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy, in relapsed/refractory multiple myeloma (R/R MM): Updated results from CARTITUDE-1. In: Wolters Kluwer Health. 3. Martin, T., Usmani, S. Z., Berdeja, J. G., Jakubowiak, A., Agha, M., Cohen, A. D., Hari, P., Avigan, D., Deol, A., & Htut, M. (2021). Updated Results from CARTITUDE-1: Phase 1b/2Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen-Directed Chimeric Antigen Receptor T Cell Therapy, in Patients With Relapsed/Refractory Multiple Myeloma. Blood, 138, 549. Janssen data on file
Study type and design	CARTITUDE-1 was a Phase 1b-2, single-arm, pen label study.
Sample size (n)	mITT=97 ITT=113
Main inclusion and exclusion criteria	Inclusion Criteria: • Have documented diagnosis of multiple myeloma according to International Myeloma Working Group (IMWG) diagnostic criteria • Have measurable disease at Screening as defined by any of the following a) Serum monoclonal paraprotein (M-protein) level more than or equal to (>=) 1.0 gram per deciliter(g/dL) or urine M-protein level >=200 milligram per 24 hours (mg/24hr); or b) Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain 10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio • Have received at least 3 prior multiple myeloma treatment lines of therapy or are double refractory to an immunomodulatory drug (IMiD) and proteasome inhibitor (PI) (refractory multiple myeloma as defined by IMWG consensus criteria). Note: induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single lines of therapy a) Undergone at least 1 complete cycle of treatment for each line of therapy, unless progressive disease (PD) was the best response to the regimen

	• Have received as part of previous therapy a PI, an IMiD, and an anti-CD38 antibody • Participant must have documented evidence of progressive disease based on investigator's determination of response by the IMWG criteria on or within 12 months of their last line of therapy. Confirmation may be from either central or local testing. Also, participants with documented evidence of progressive disease (as above) within the previous 6 months and who are refractory or non-responsive to their most recent line of therapy afterwards are eligible • Have Eastern Cooperative Oncology Group (ECOG) Performance Status grade of 0 or 1 Exclusion Criteria: • Have received prior treatment with chimeric antigen receptor T (CAR-T) therapy directed at any target • Have received any therapy that is targeted to B-cell maturation antigen (BCMA) • Have following cardiac conditions: a) New York Heart Association (NYHA) stage III or IV congestive heart failure b) Myocardial infarction or coronary artery bypass graft (CABG) less than or equal to (<=) 6 months prior to enrollment c) History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration d) History of severe non-ischemic cardiomyopathy e) Impaired cardiac function (left ventricular ejection fraction [LVEF] less than [<]45%) as assessed by echocardiogram or multiple-gated acquisition (MUGA) scan (performed less than or equal to (<=) 8 weeks of apheresis) • Received a cumulative dose of corticosteroids equivalent to >= 70 mg of prednisone within the 7 days prior to apheresis • Have received either of the following: a) An allogenic stem cell transplant within 6 months before apheresis. Participants who received an allogeneic transplant must be off all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease (GVHD) b) An autologous stem cell transplant less than or equal to (<=) 12 weeks before apheresis • Have known active, or prior history of central nervous system (CNS) involvement or exhibits clinical signs of meningeal involvement of multiple myeloma
Intervention	Ciltacabtagene-autoleucel (cilta-cel [JNJ-68284528]) administered at a dose of 0.5 x 10^6 CAR-positive viable T-cells per kg of body weight, with a maximum dose of 1 x 10^8 CAR-positive viable T-cells per single infusion. Cilta-cel was administered as a single intravenous infusion. In total, 97 subject received the infusion.
Comparator(s)	N/A
Follow-up time	Median duration of follow-up for all treated subjects was 27.7 months (range 1.5 – 40.4)
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	Endpoints included in this application: The primary endpoint was overall response rate (ORR), defined by the proportion of subjects who achieved a partial response (PR) or better according to the IMWG response criteria, as assessed by the IRC. Secondary endpoints were assessment of a very good partial response (VGPR[or better]) rate, duration of response (DoR), minimal residual disease (MRD), negativity rate, time to response (TTR), progression-free survival (PFS) and overall survival (OS).
Method of analysis	E.g.: Efficacy analyses were ITT analyses, mITT analysis was also included as supportive evidence.
Subgroup analyses	No subgroup analysis is presented
Other relevant information	-

Table 68. Main characteristics of LocoMMotion

Trial name: LocoMMotion	**NCT number: NTC**
Objective	To evaluate the overall response rate (ORR9 of real-life SIC treatments in patients with relapsed/refractory MM
Publications – title, author, journal, year	
Study type and design	Prospective, non-interventional
Sample size (n)	225
Main inclusion and exclusion criteria	Inclusion criteria: • Have a documented diagnosis of multiple myeloma according to the International myeloma working group (IMWG) diagnostic criteria • Received at least 3 prior line of therapy or are double refractory to a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) (induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single regimen). Patients will have undergone at least 1 complete cycle of treatment for each regimen (unless progressive disease was the best response) • Must have documented evidence of progressive disease based on study physician's determination of response by the IMWG response criteria on or after the last regimen. Patients with documented evidence of progressive disease within the previous 6 months and who are refractory or nonresponsive to their most recent line of treatment afterwards are also eligible. • Have an Eastern Cooperative Oncology Group (ECOG) Performance Status grade of 0 or 1 • Must not be pregnant or must not plan to become pregnant within the study period
Intervention	Standard of Care treatment

Comparator(s)	-
Follow-up time	24 months
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	The primary endpoint was ORR, defined as the proportion of patients who achieved a partial response or better according to the IMWG criteria, as assessed by a response review committee. Key secondary endpoints included: rates of stringent complete response, complete response, very good partial response (VGPR), partial response, duration of response, progression-free survival and overall survival, patient-reported outcomes and safety.
Method of analysis	-
Subgroup analyses	-
Other relevant information	-

Table 69. Main characteristics of LEGEND-2

Trial name: LEGEND-2	**NCT number: NTC**
Objective	The primary objective was to investigate the safety of using LCAR-B38M CAR-T cells in a clinical study. The secondary objective was to investigate antimyeloma response to LCAR-B38M CAR-T cell treatment.
Publications – title, author, journal, year	
Study type and design	Phase 1, single-arm, open-label, multicentre study across four academic centres in China
Sample size (n)	74
Main inclusion and exclusion criteria	Inclusion criteria: • Patients must have a confirmed prior diagnosis of active multiple myeloma as defined by the updated IMWG criteria • Patients with relapsed or refractory multiple myeloma. Clear BCMA expression must be detected on malignant plasma cells from either bone marrow or a plasmacytoma by flow cytometry or immunohistochemistry • Refractory disease: 1) resistant to at least 3 prior regimens, which must at least have contained bortezomib or thalidomide; or 2) other circumstances identified by clinical doctors • Relapse criteria in national Comprehensive Cancer Network /NCCN) clinical practice guidelines in Oncology: Multiple Myeloma (2016.V2) Exclusion criteria: • Women of child-bearing potential or who are pregnant or breastfeeding. • Have any active and uncontrolled infection: hepatitis B, hepatitis C, HIV, or other fatal viral or bacterial infection.

	• Systemic corticosteroid therapy of greater than 5 mg/day of prednisone or equivalent dose of another corticosteroid and are not allowed within 2 weeks prior to either the require leukapheresis or the initiation of the conditioning chemotherapy regimen. • Patients with any uncontrolled intercurrent illness or serious uncontrolled medical disorder. • Patients with CNS metastases or symptomatic CNS involvement (including cranial neuropathies or mass lesions and spinal cord compression). • History of allogeneic stem cell transplantation. • Patients with active autoimmune skin diseases such as psoriasis or other active autoimmune diseases such as rheumatoid arthritis
Intervention	Lymphodepletion using three doses of cyclophosphamide on Days -5, -4, and -3 was followed by infusion of cilta-cel. At the Xi'an, Ruijin, and Changzheng sites, the dose was split into three infusions administered over 7 days. In general, the number of CAR-T cells administered increased with each infusion. At the Jiangsu site, the dose was given as a single administration. Across all four sites, the median number of CAR-positive viable T-cells administered was 0.51×106 /kg (range 0.07–2.10×106 /kg).
Comparator(s)	N/A (Single armed trial)
Follow-up time	Median follow-up of 30.4 months and a maximum follow-up of 42.8 months at the November 2019 cut-off
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Primary endpoints was safety through assessment of AEs Secondary endpoints were response rates (ORR, CR, VGPR, PR), Changes in aberrant immunoglobulin in serum and MM cells in bone marrow, BCMA expression, Number of cilta-cel CAR-T cells, PFS, OS, Median DoR

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 70. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	CARTITUDE-1		LocoMMotion
	Phase 1b + 2 All-treated mITT (n = 97)	Phase 1b +2 All enrolled ITT (n =113)	All enrolled ITT (n =248)
Age, years			
Mean (SD)	62 (8.38)	61.7 (9.11)	-
Median (range)	61 (43-78)	-	68.0 (41.0 – 89.0)
Age category (%)			
<65 years	63.9	61.9	-
65 – 75 years	27.8	30.1	-
> 75 years	8.2	8.0	-
Male, n (%)	58.8%	57.5%	135 (54.4)
Weight, kg			**(n = 208)**
Mean (SD)	79.2 (16.69)		73.32 (16.314)
Median (range)	78.3 (39-126)		73.00 (37.0 ; 118.9)
Height, cm			**(n = 196)**
Mean (SD)	169.7 (9.2)		167.21 810.143)
Median (range)	170.2 (150-188)		167.00 (147.0; 193.0)
Body surface area, m2			(n=195)
Mean (SD)	1.92 (0.231)		1.8375 (0.24346)
Median (range)	1.94 (1.3-2.5)		1.8540 (1.274; 2.458)
ECOG score prior to infusion, n (%)a			**(n= 247)**
0	40.2	48.7	63 (25.5)
1	55.7	51.3	180 (72.9)
2	4.1	0.0	3 (1.2)
3	-	-	1 (0.4
ISS disease stage (%)			
I	62.9	55.2	-
II	2.7	36.2	
III	14.4	8.6	
Cytogenetic profile*, n/N (%)			-
Standard risk	70.1	61.9	-
High risk*	23.7	24.8	
Unknown	6.2	13.3	
Tumour BCMA expression (%),			
mean	76.3	76.3	
≥50%	91.9	91.9	
Median time since initial diagnosis (range), years	5.94 (1.6 – 18.2)	5.73 (1.0 – 18.2)	6.3 (0,3 – 22.8)
Refractory to last line of therapy, n (%)	96 (99.0%)		230 (92.7)

Refractory status, n (%)		
PI + IMiD + anti-CD38 antibody	85 (87.6%)	-
Any PI	87 (89.7%)	197 (79.4)
Any IMiD	95 (97.9%)	234 (94.4)
Any anti-CD38 antibody	96 (99.0%)	228 (91.9)
≥2 PIs + ≥2 IMiDs + anti-CD38 antibody	41 (42.3%)	-
Refractory to, n (%)		
Bortezomib	66 (68.0%)	-
Carfilzomib	63 (64.9%)	
Ixazomib	27 (27.8%)	
Lenalidomide	79 (81.4%)	
Pomalidomide	81 (83.5%)	
Thalidomide	8 (8.2%)	
Daratumumab	94 (96.9%)b	
Isatuximab	7 (7.2%)	
TAK-079c	1 (1.0%)	
Elotuzumab	19 (19.6%)	
Panobinostat	8 (8.2%)	

Comparability of patients across studies

As previously have been described, an external control arm for CARTITUDE-1 was constituted from triple-class exposed RRMM patients treated with physician's choice SoC therapies from the LocoMMotion prospective cohort study where the ITT treatment group was comprised of the all enrolled population and consisted of 113 patients that were enrolled and who underwent apheresis within the CARTITUDE-1 study and the comparator group was comprised of all patients that received physician's choice derived from LocoMMotion and included subjects 248 who were enrolled in the study. These patients are considered to be comparable. In the adjusted comparison, main analyses weighted patients on all of the following factors: refractory status, ISS stage, time to progress on last regimen, extramedullary disease, number of prior LOTs, years since MM diagnosis, average duration of prior LOTs, age, haemoglobin, LDH, creatinine clearance, ECOG performance status, sex, and MM type. Appendix 0 presents the population differences between CARTITUDE-1 and the LocoMMotion for each of the ranked factors before and after weighting. Following application of IPW-ATT weights to re-weight the LocoMMotion population, the degree of differences between the Carvykti® and RWCP groups was reduced, and no imbalances with an SMD > |0.2| remained, where 0.2 is an accepted difference.

Comparability of the study populations with Danish patients eligible for treatment

The CARTITUDE-1 ITT study population is assessed to be comparable with the Danish patients eligible for treatment. The target patient population for this assessment consist of adult Danish patients with relapsed and refractory multiple myeloma (RRMM), who have received at least three prior therapies, including IMiD, a PI and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy and is in line with the expected indication of Carvykti®. Key patient characteristics and efficacy was based on CARTITUDE-1, the pivotal clinical trial for Carvykti®, which correspond well to Danish patients with triple class exposed RRMM eligible for CAR-T therapy.

Baseline characteristics of patients LocoMMotion used for the comparative analysis of efficacy and safety (LocoMMotion), is also considered comparable to the Danish patients eligible for treatment and reflects eligible population. The mean age of 61 at treatment initiation in CARTITUDE-1 was assumed to be representative for the Danish patient population relevant for CAR-T and the median age in CARTITUDE-1 is considered representative for the patients that will be treated with

Carvykti®, since they are expected to be slightly younger than the overall median age for MM in Denmark, which is tested in a scenario analysis with the health economic analysis.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 71 below presents the study endpoints and definitions in CARTITUDE-1.

Table 71. Study endpoints in CARTITUDE-1

Endpoint	Description
Primary Endpoints	
Number of participants with AEs (Phase 1b only)	An AE is any untoward medical event that occurs in a participant administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product
Number of participants with AEs by severity (Phase 1b only)	An assessment of severity grade will be made according to the NCI CTCAE, with the exception of CRS, and ICANS. CRS and ICANS should be evaluated according to the ASTCT consensus grading
ORR (Phase 2 only)	Defined as the proportion of participants who achieve PR or better according to IMWG criteria as assessed by the Independent Review Committee
Secondary Endpoints	
Number of participants with AEs (Phase 2 only)	An AE is any untoward medical event that occurs in a participant administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product
PFS	Defined as time from date of initial infusion of Carvykti® to date of first documented disease progression or death due to any cause, whichever occurs first. IMWG criteria for PD: • Increase of 25% from lowest response value in any one of the following: serum M-component (absolute increase must be ≥0.5 g/dL, urine M-component (absolute increase must be ≥200 mg/24 hours), • Participants without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)

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	• Participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC % (absolute percentage must be ≥10%), definite development of new bone lesions or soft tissue plasmacytomas, or increase in size of bone lesions or tissue plasmacytomas
OS	Measured from the date of the initial infusion of Carvykti® to the date of the participant's death
Percentage of participants with negative MRD	Defined as the proportion of participants who achieve MRD negative status by the respective time point. MRD negativity will be evaluated as a potential surrogate for PFS and OS in MM treatment
Levels of BCMA expressing cells and soluble BCMA	Levels of expression of BCMA-expressing plasma cells in the bone marrow as well as the level of soluble BCMA in blood will be reported
Systemic cytokine concentrations	Serum cytokine concentrations (IL-6, IL-15, IL-10, and interferon [IFN-g]) will be measured for biomarker assessment
Level of CAR-T cells	CAR-T cell markers including, but not limited to, CD4+, CD8+, CD25+, and central memory, effector memory cells will be reported. An evaluation of cell populations may be performed by flow cytometry or cytometry by time of flight or both and correlated with response
Level of cilta-cel T-cell expansion (proliferation) and persistence	Levels of Carvykti® T-cell expansion (proliferation) and persistence via monitoring CAR-T positive cell counts and CAR transgene level will be reported
Number of participants with anti-cilta-cel antibodies	Number of participants exhibiting anti-drug antibodies for Carvykti® will be reported
VGPR or better rate	The VGPR or better rate (sCR + CR + VGPR), defined as the percentage of participants achieving VGPR or better response according to IMWG criteria during or after the study treatment. IMWG criteria for: • VGPR: serum and urine M-component detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours, • CR: negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas, and <5% PC in bone marrow. • sCR: CR plus normal FLC ratio and absence of clonal PCs by immunohistochemistry, immunofluorescence, or 2- to 4-colour flow cytometry.
Percentage of participants who achieve CBR	Clinical benefit rate is CR + VGPR + PR + MR based on IMWG defined response criteria

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DoR	Calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of PD, as defined in the IMWG criteria.
TTR	Defined as the time between date of the initial infusion of Carvykti® and the first efficacy evaluation that the participant has met all criteria for PR or better
Change from baseline in HRQoL as measured by EORTC QLQ-C30 (Phase 2 only)	Subscale and single item scores are reported on a 0-100 scale, with higher scores representing better global health status, better functioning, and worse symptoms.
Change from baseline in HRQoL as measured by EORTC QLQ-MY20 (Phase 2 only)	Subscale and single item scores are reported on a 0-100 scale, with higher scores representing better global health status, better functioning, and worse symptoms.
Change from Baseline in Participant-reported Health Status Measured by EQ-5D-5L (Phase 2 only)	A total utility score is reported based on the health status, ranging from 0 to 1, where higher values indicate better health utility. The visual analogue scale ranges from 0 to 100, where higher values indicate better overall health status.
Change from Baseline in GHS Using PGIC Scale (Phase 2 only)	A single verbal rating scale ranges from 1 (a lot better now) to 7 (a lot worse now)
Change from Baseline in Pain Measured by PGIS Scale (Phase 2 only)	A single item to assess pain severity. The 5-point verbal rating scale ranges from 1 (none) to 5 (very severe).

Abbreviations: AE = adverse event; ASTCT = Autologous Stem Cell Transplant ; BCMA = B-cell maturation antigen; CBR = clinical benefit rate; CR = complete response; CRS = cytokine release syndrome; DoR = duration of response; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-5L = EuroQol Group 5-dimension, 5 level; FLC = free light chain; GHS = global health status; ICANS = immune effector cell-associated neurotoxicity syndrome; IMWG = International Myeloma Working Group; MM = multiple myeloma; MR = minimal response; MRD = minimal residual disease; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OS = overall survival; PC = plasma cell; PD = progressive disease; PFS = progression-free survival; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PR = partial response; QLQ-C30 = Quality of Life Questionnaire Core-30; QLQ-MY20 = Quality of Life Questionnaire – Multiple Myeloma; TTR = time to response; VGPR = very good partial response.

Regarding the study LocoMMotion, The primary endpoint was ORR, defined as the proportion of patients who achieved partial response or better according to the IMWG criteria, as assessed by a response review committee. Key secondary objectives included, rates of sCR, CR, PR, VGPR, VGPR or better, DoR, TTR, TTNT, PFS OS, patient-reported outcomes and safety

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Results per study

Table 72. Results of CARTITUDE-1

Best response n (%) 95% CI	mITT n=97	ITT n=113
ORR (sCR + CR + VGPR + PR)	95 (97.9%) (92.7%, 99.7%)	95 (84.1%) (76.0%, 90.3%)
sCR	80 (82.5%) (73.4%, 89.4%)	80 (70.8%) (61.5%, 79.0%)
CR	0 (NE, NE)	0 (NE, NE)
VGPR	12 (12.4%) (6.6%, 20.6%)	12 (10.6%) (5.6%, 17.8%)
PR	3 (3.1%) (0.6%, 8.8%)	3 (2.7%) (0.6%, 7.6%)
VGPR or better (sCR + CR + VGPR)	92 (94.8%) (88.4%, 98.3%)	92 (81.4%) (73.0%, 88.1%)
CR or better (sCR + CR)	80 (82.5%) (73.4%, 89.4%	80 (70.8%) (61.5%, 79.0%)
MRD-negative CR/sCR[a]	42 (43.3%) (33.3%, 53.7%)	42 (37.2%) (28.3%, 46.8%)
Not evaluable (NE)	1 (1.0%) (0.0%, 5.6%)	17 (15.0%) (9.0%, 23.0%)
Did not received Carvykti®	-	16

Table 73. LocoMMotion: overview of efficacy results (all treated population)

	May 21, 2021 cut-off n=248
Median follow-up, months (range)	11 (0.1–19.2)
Response Rates n (%) 95% CI for %	n=248
ORR (sCR + CR + VGPR + PR)	74 (29.8%) (24.2%-36.0%)
sCR	0 (0%) (NE-NE)
CR	1 (0.4%) (0.0%-2.2%)
VGPR	30 (12.1%) (8.3%-16.8%)
PR	43 (17.3%) (12.8%-22.6%)
VGPR or better (sCR + CR + VGPR)	31 (12.5%) (8.7%-17.3%)
DoR, responders (PR or better)	n=74
Number of events (%)	36 (48.6%)
Number of censored (%)	38 (51.4%)
Median DoR, KM estimate, months (95% CI)	7.4 (4.7-12.5)
TTR (months), responders (PR or better)	n=74
Mean (SD)	2.24 (1.689)
Median (range)	1.87 (0.7-9.5)
TTNT VGPR or better, response evaluable 31	n=31
Number of events (%)	8 (25.8)
Number of censored (%)	23 (74.2)
Median TTNT, months (95% CI)	NE (11.96-NE)
TTNT Worse than VGPR, response evaluable	n=217
Number of events (%)	166 (76.5)
Number of censored (%)	51 (23.5)
Median TTNT, months (95% CI)	4.53 (4.04-5.36)
PFS	n=248
Number of events (%)	150 (60.5)
Number of censored (%)	98 (39.5)
Median PFS, months (95% CI)	4.63 (3.88–5.62)
6-month progression-free survival rate % (95% CI)	41.2 (34.2-48.0)
	19.9 (13.6-27.0)

12-month progression-free survival rate % (95% CI)	NE (NE-NE)
18-month progression-free survival rate % (95% CI)	
OS	n=248
Number of events (%)	107 (43.1)
Number of censored (%)	141 (56.9)
Median OS, months (95% CI)	12.39 (10.28–NE)
6-month overall survival rate % (95% CI)	73.4 (67.3-78.5)
12-month overall survival rate % (95% CI)	51.8 (44.1-58.8)
18-month overall survival rate % (95% CI)	42.7 (33.2-51.8)

Source: [8]

* The lesser number of participants indicated low clinical relevance of MRD in real-life clinical practice for heavily pre-treated RRMM participants.

Appendix E Safety data for intervention and comparator(s)

In CARTITUDE-1, the following safety definitions were followed:

- Adverse event: An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]) [8] any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. The AE does not necessarily have to have a causal relationship with the treatment.
- Serious adverse event: A serious adverse event based on ICH and European Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose: results in death, Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity , is a congenital anomaly/birth defect , is a suspected transmission of any infectious agent via a medicinal product, is medically Important [8]
- Adverse reaction: If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study treatment and the event (e.g., death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality) [8]

In LocoMMotion, the following safety definitions were used:

- Adverse event: An adverse event is any untoward medical occurrence in a patient administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavourable and unintended sign (including an abnormal finding or lack of expected pharmacological action), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational)All adverse events and special situations following exposure to the first primary SOC antimyeloma therapy used within the study were systematically recorded in eCRF and participant's source records, regardless of seriousness or causality [8]
- Serious adverse event: A serious adverse event, based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is any untoward medical occurrence any ADR that at any dose: results in death, is life-threatening (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe), requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, is a congenital/birth defect, is a suspected transmission of any infectious agent via a medicinal product, is medically important [8]
- Adverse drug reaction: An adverse drug reaction (ADR) is defined as a response to a medicinal (investigational or non-investigational) product that is noxious and unintended. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is possible, probable or very likely. An ADR, in contrast to an adverse event, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All adverse events

judged by either the reporting physician or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs [8]

An overview of safety information according to section 4.2 of the guidelines is presented in Table 74 below.

Table 74. Presentation of Safety data for intervention and comparator

	Intervention: CARTITUDE-1 (n)	Comparator: LocoMMotion (n)
Patients with at least one adverse event	97 [8]	207 [115]
Patients with at least one serious adverse event	53 [8]	84 [115]
Patients with at least one adverse reaction	53 [8]	84 [61] [115]
Patients who discontinued treatment (any reason)	31 [8]	19 [115]
Patients who discontinued treatment due to adverse events/effects	0 [75] [8]	0 [115]

Note: In both CARTITUDE-1 and LocoMMotion only treatment emergent adverse events (TEAEs) were captured and are thus reported. All available information on AEs are reported in the table above.

For the comparative evidence for adverse events see section 7.1.8.2.9.

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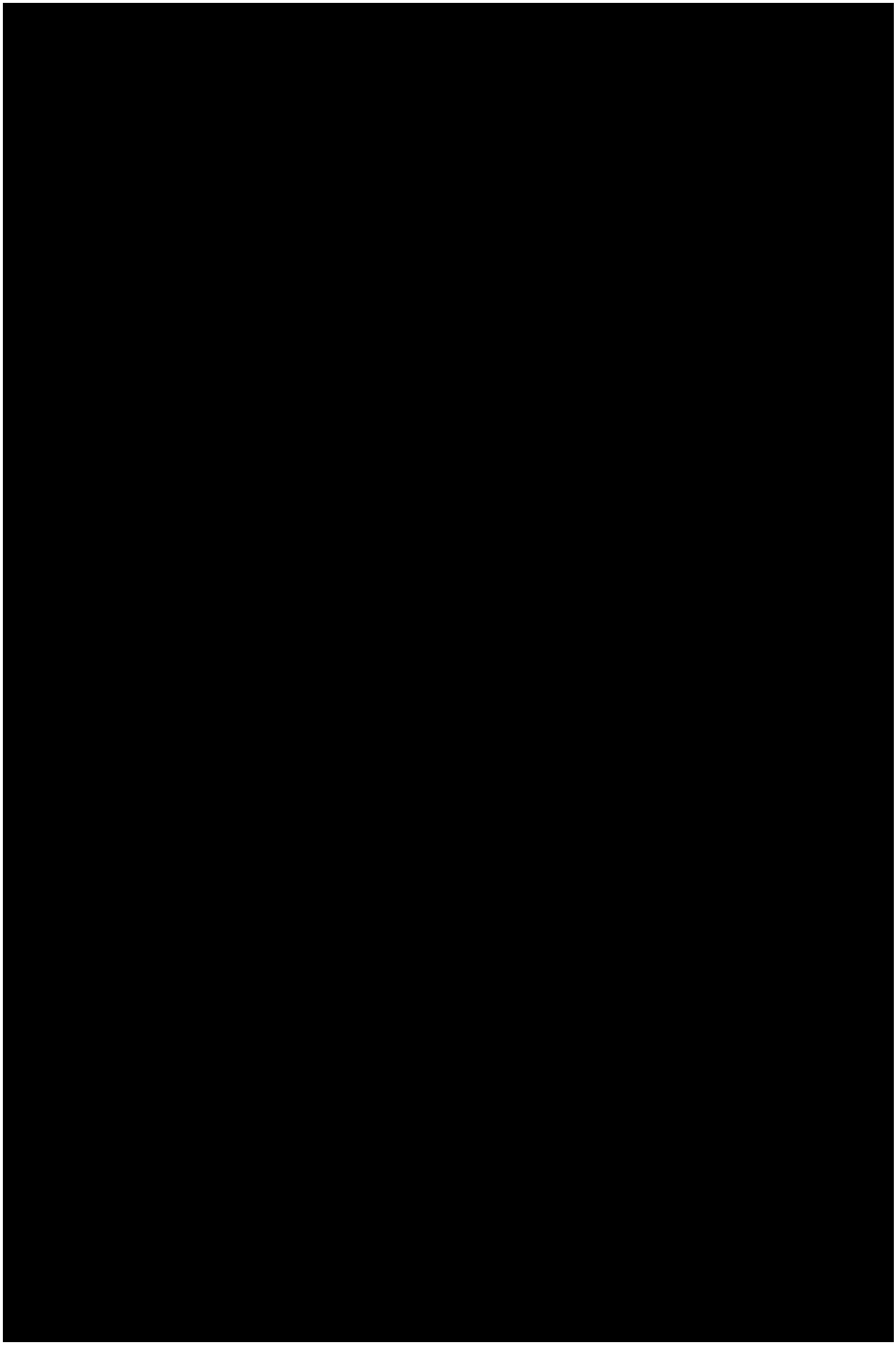

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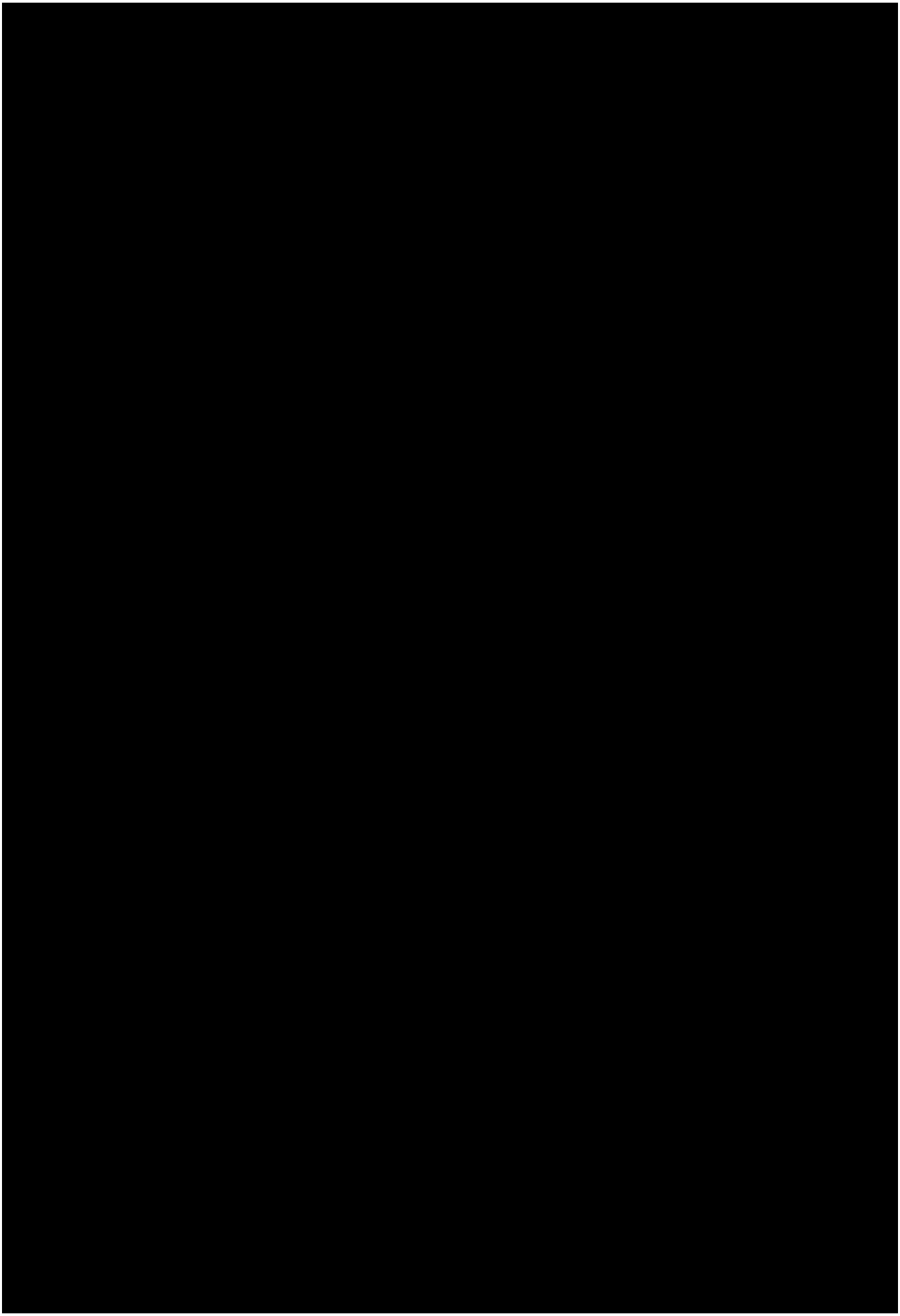

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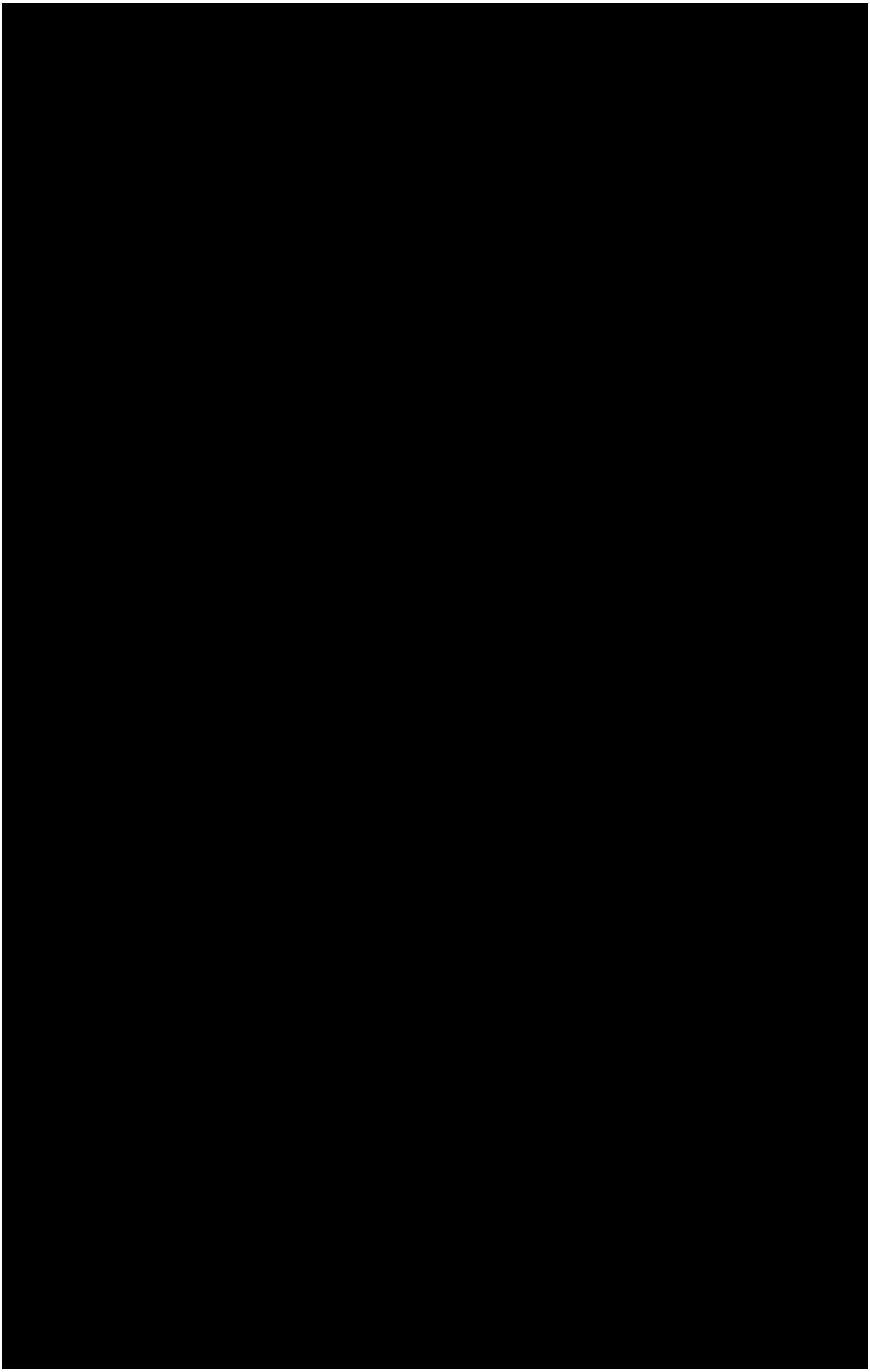

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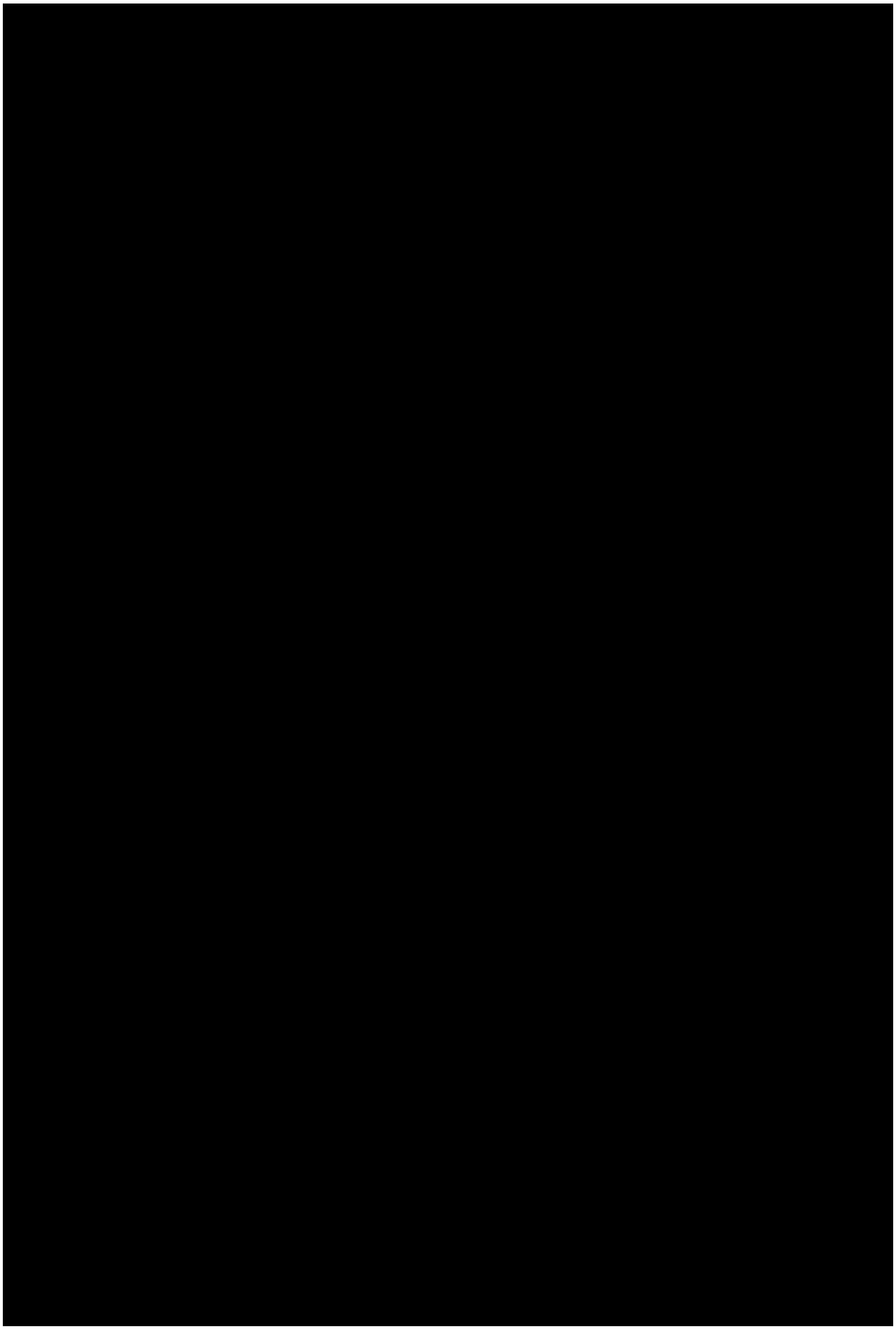

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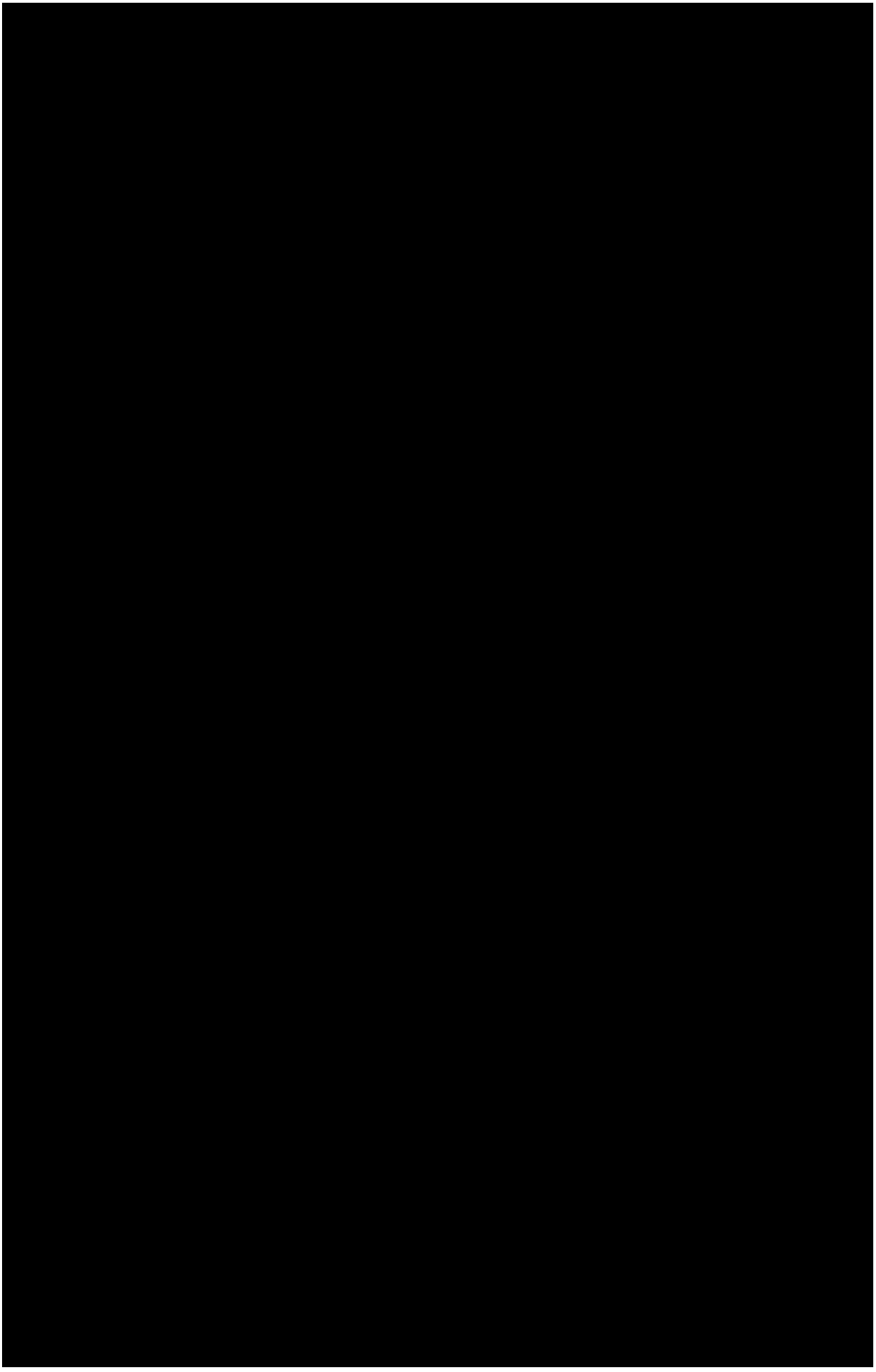

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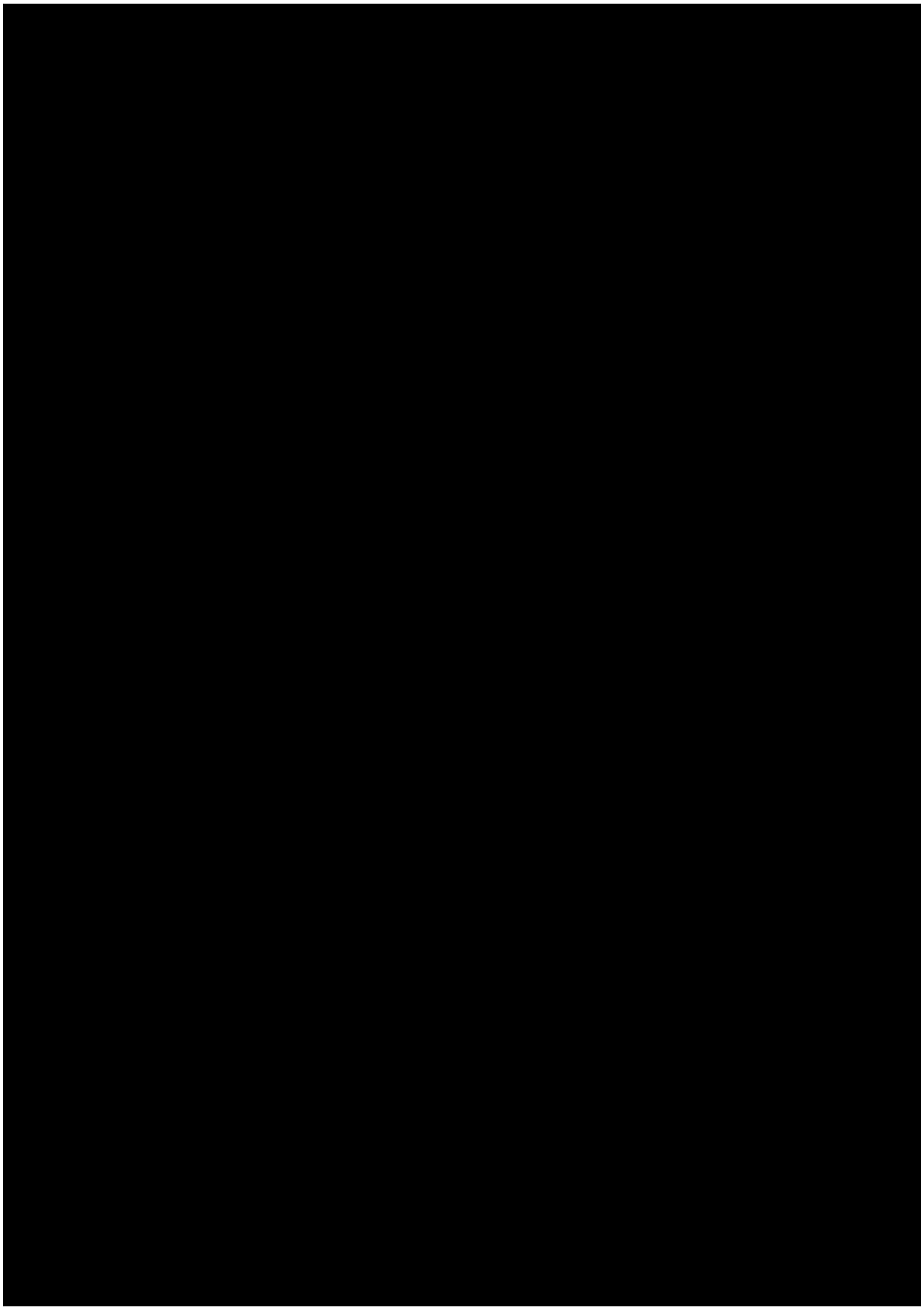

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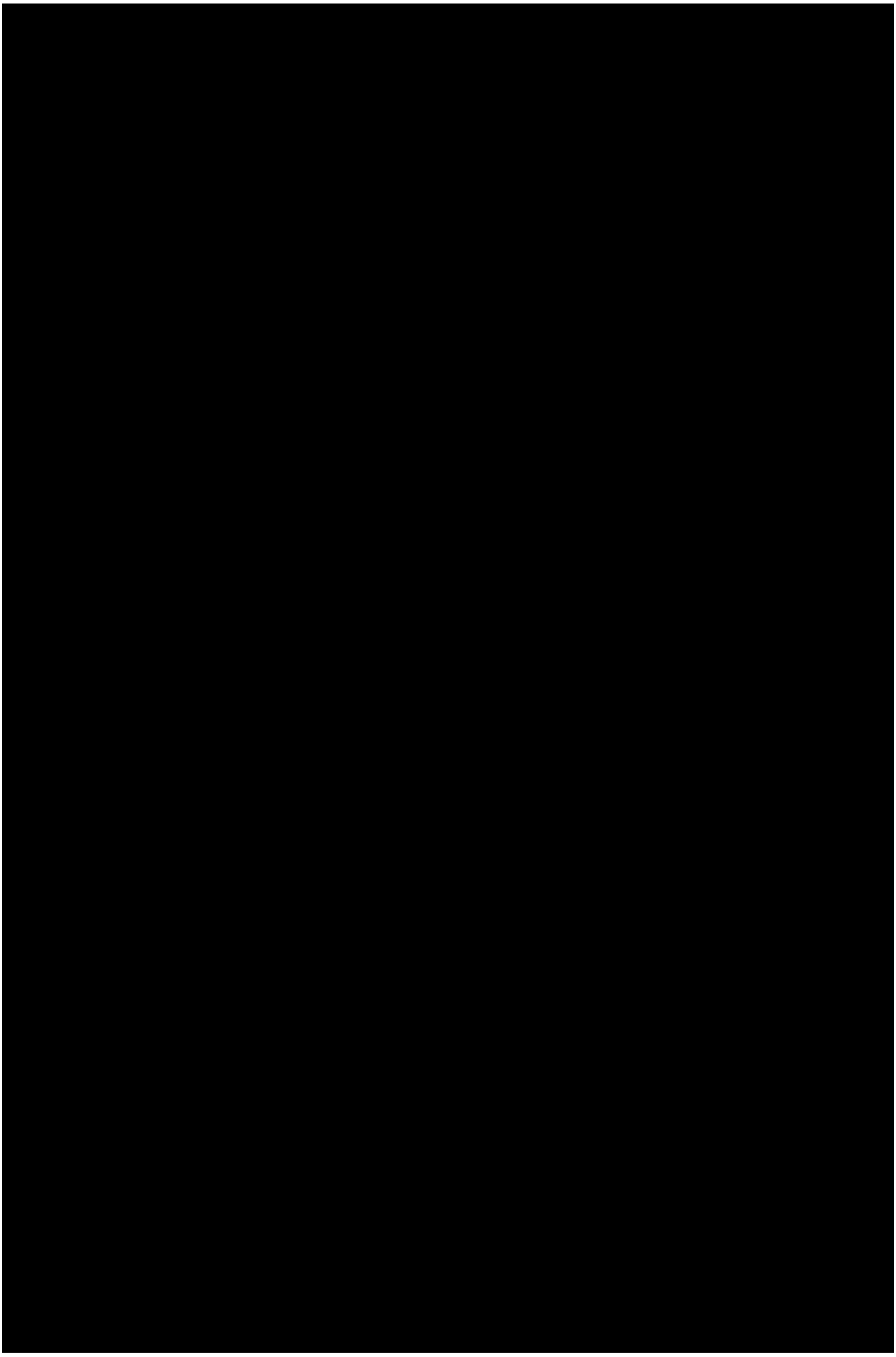

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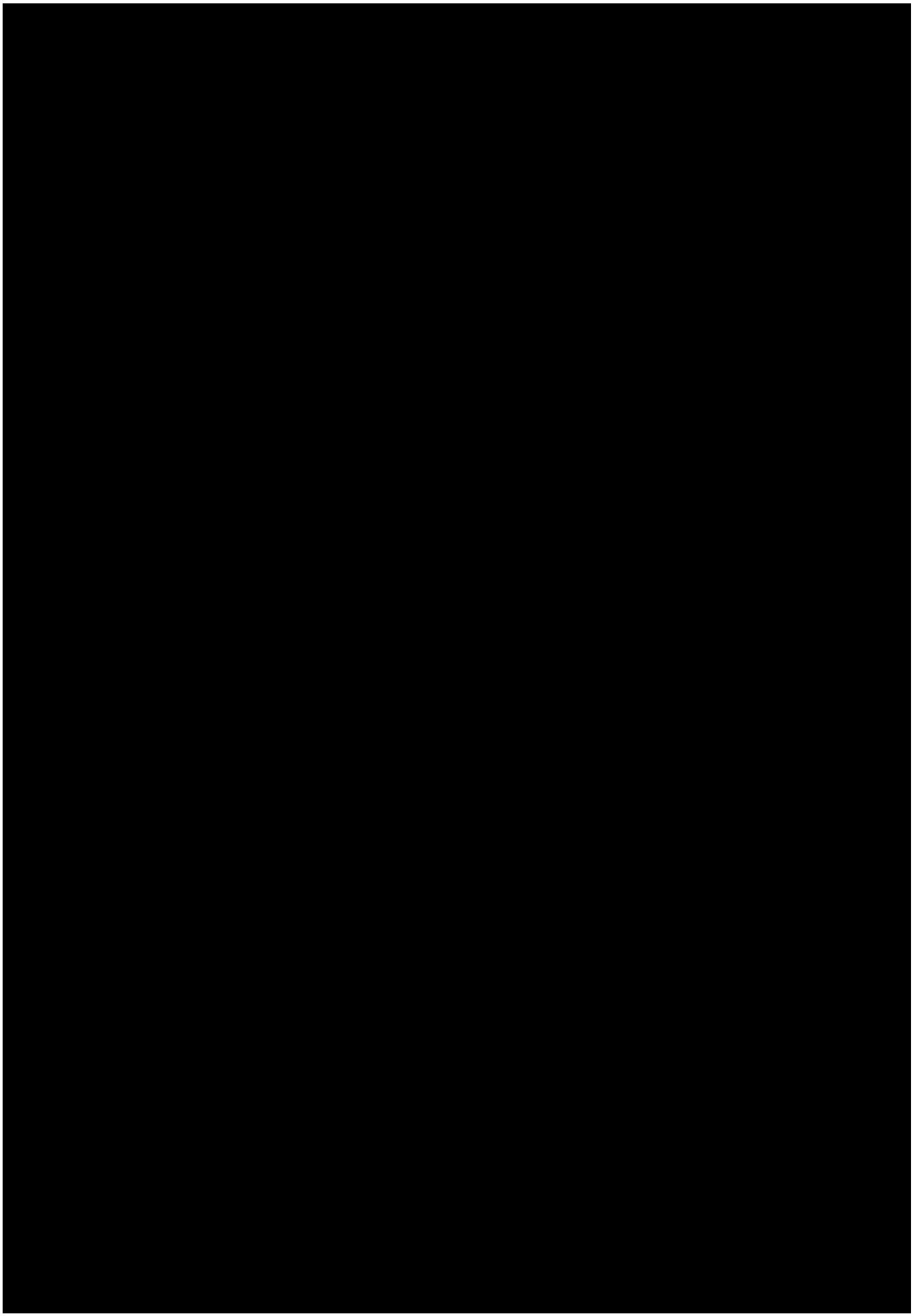

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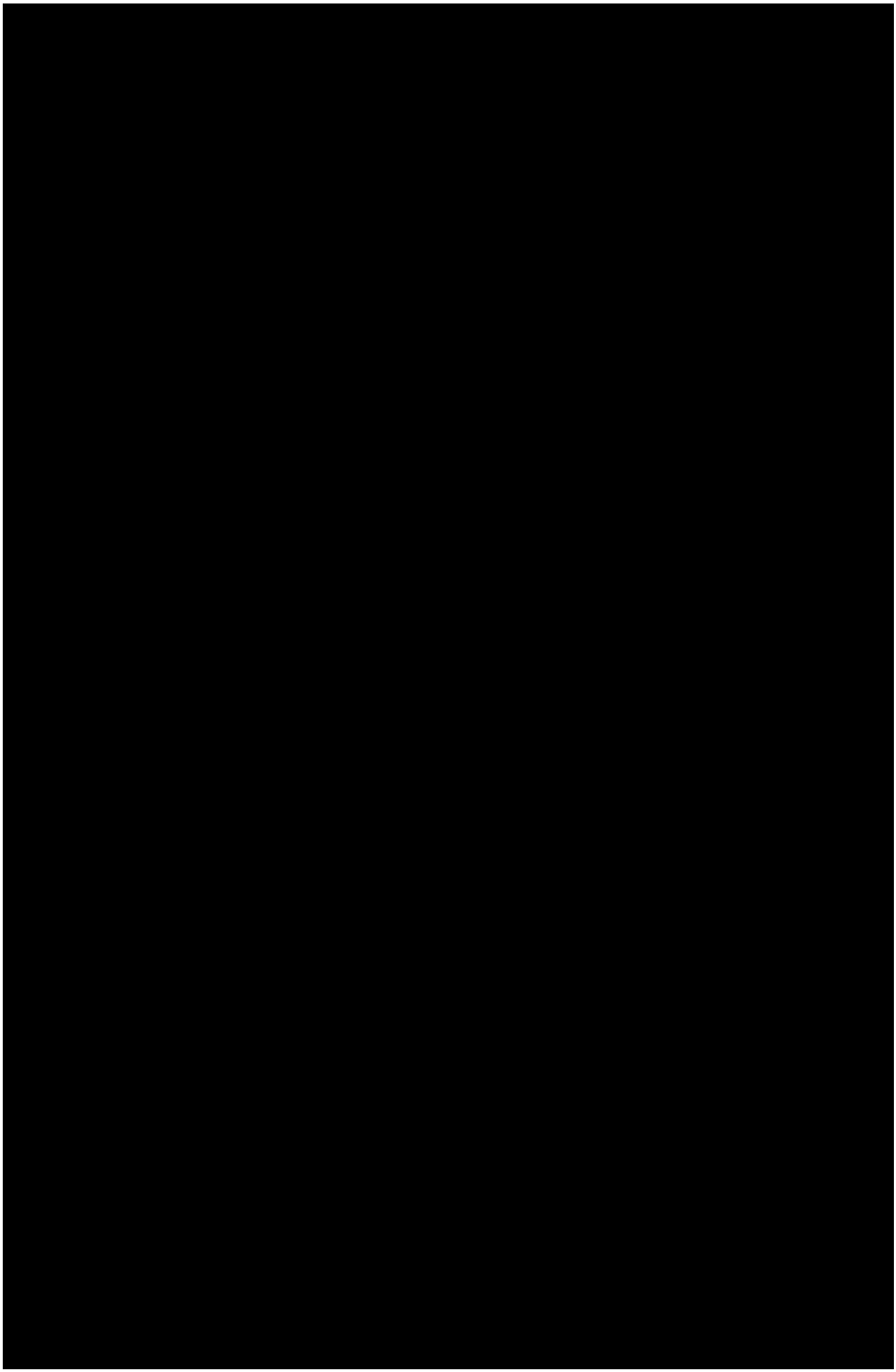

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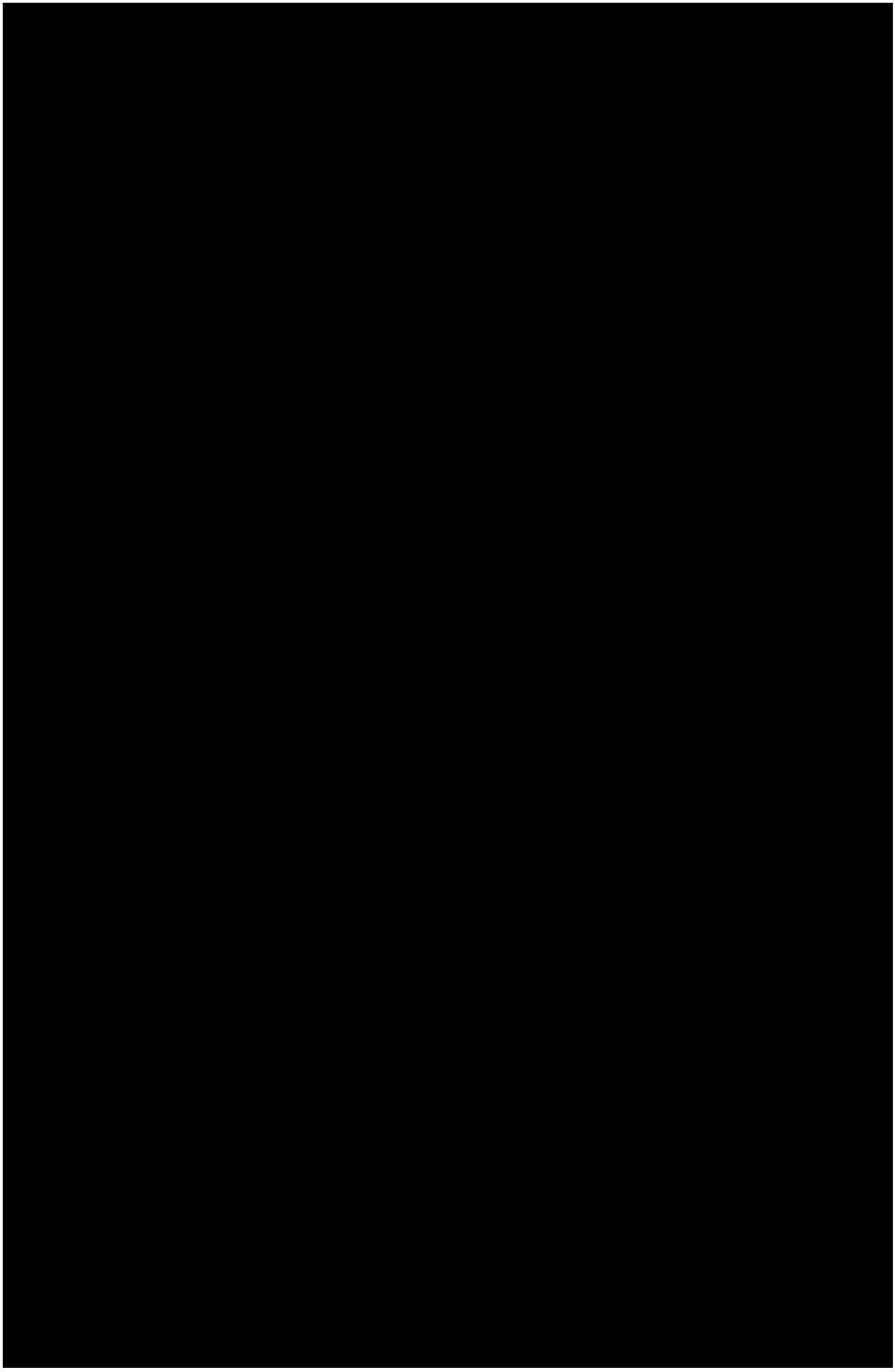

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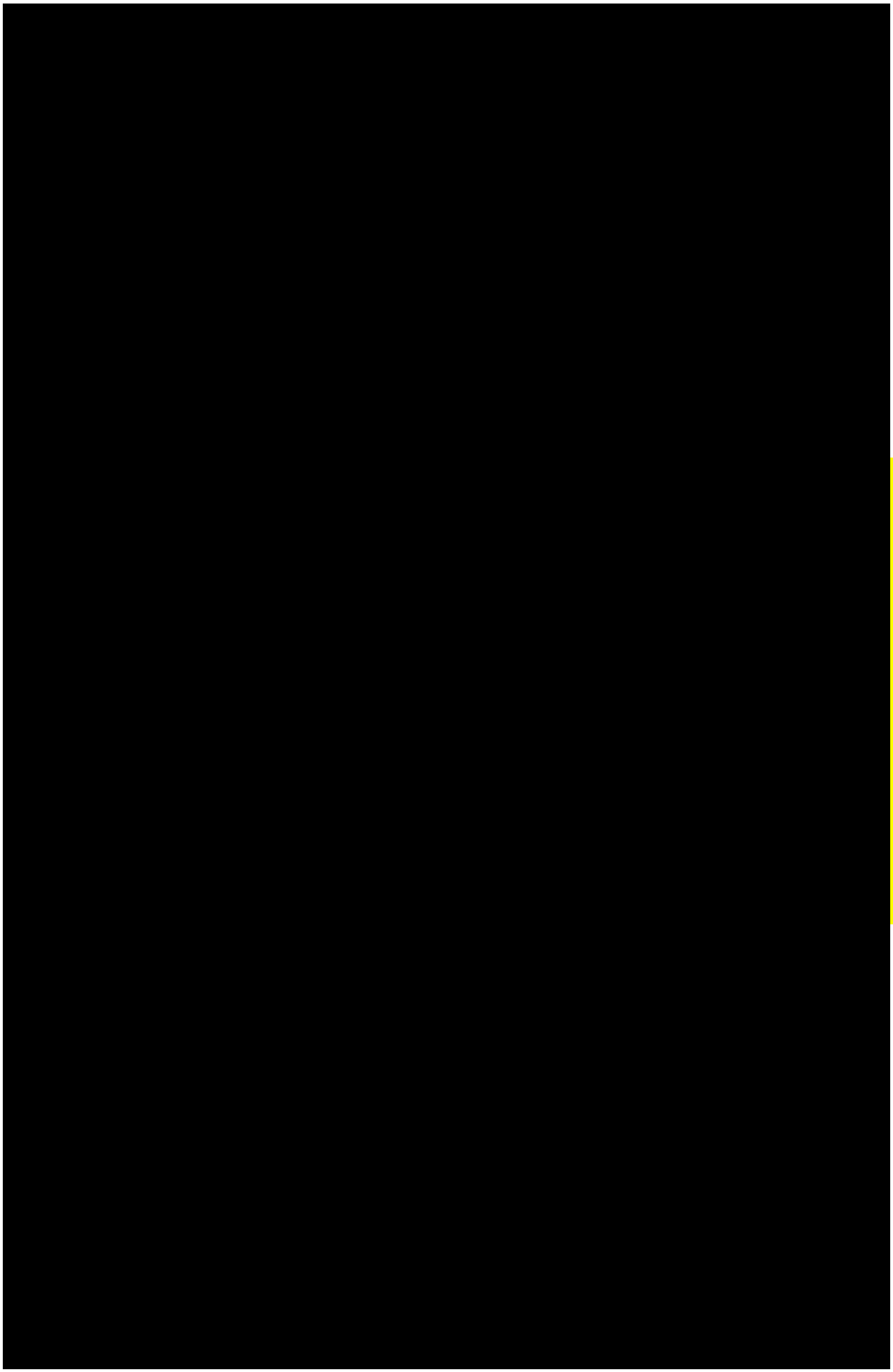

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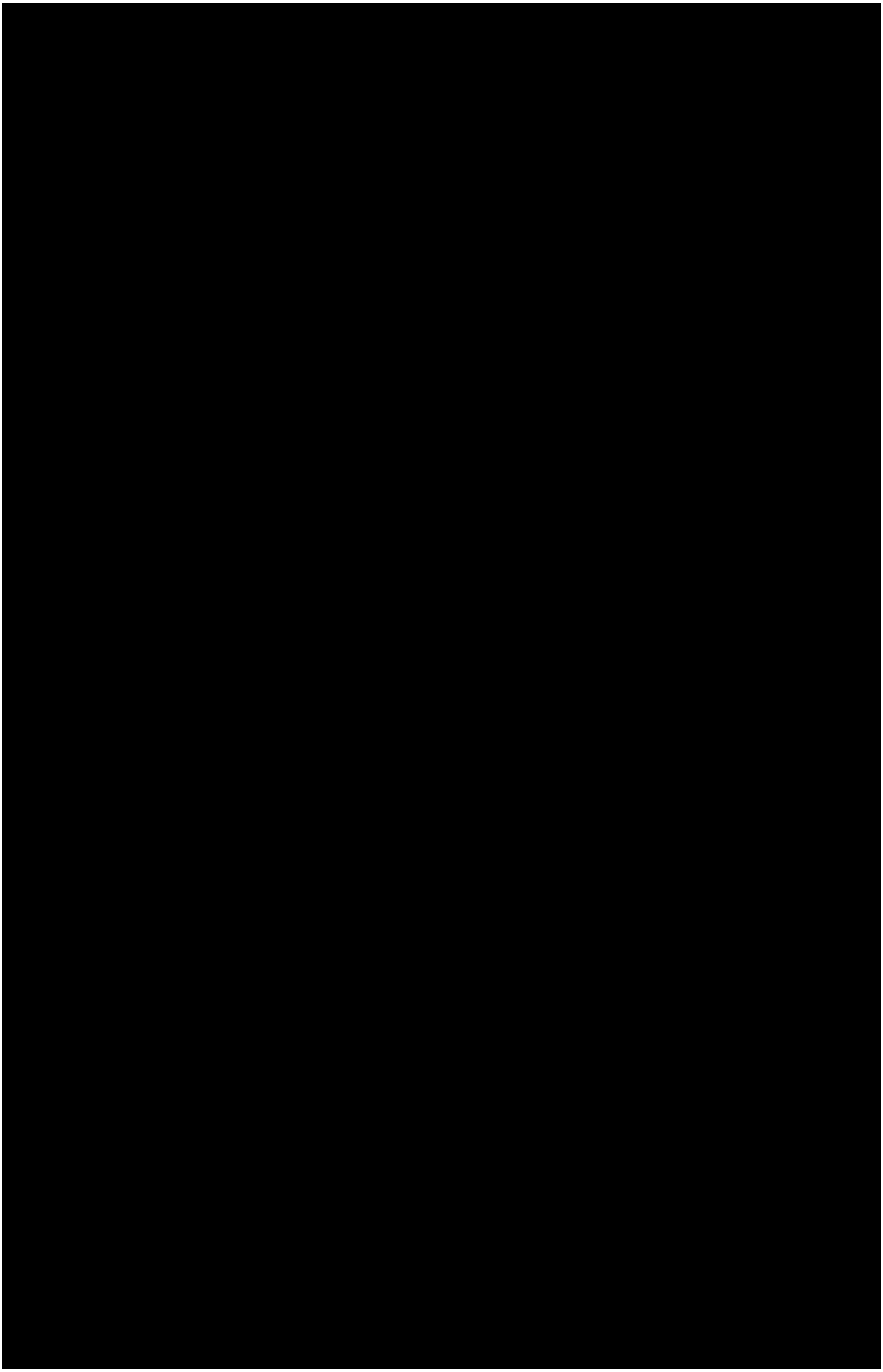

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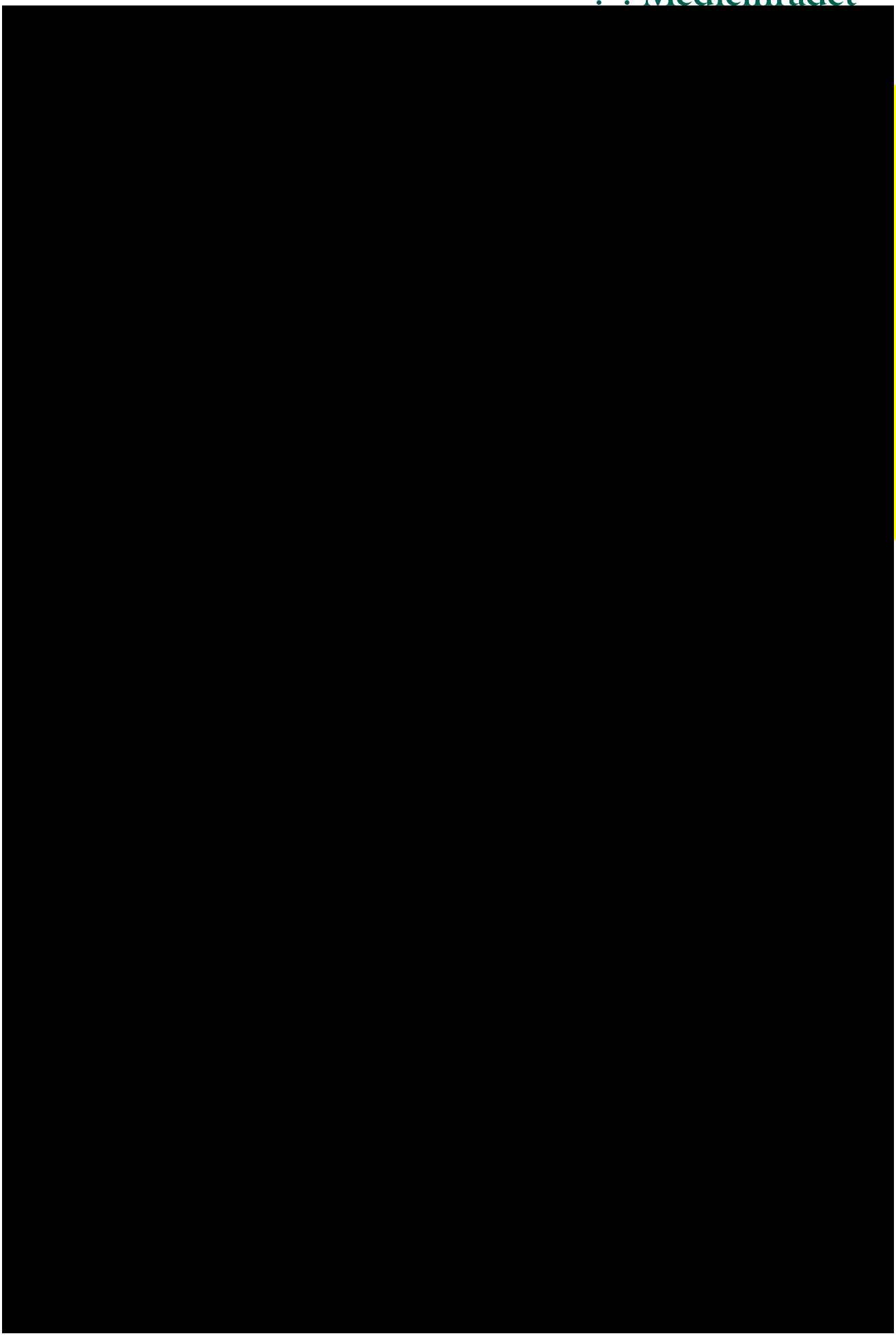

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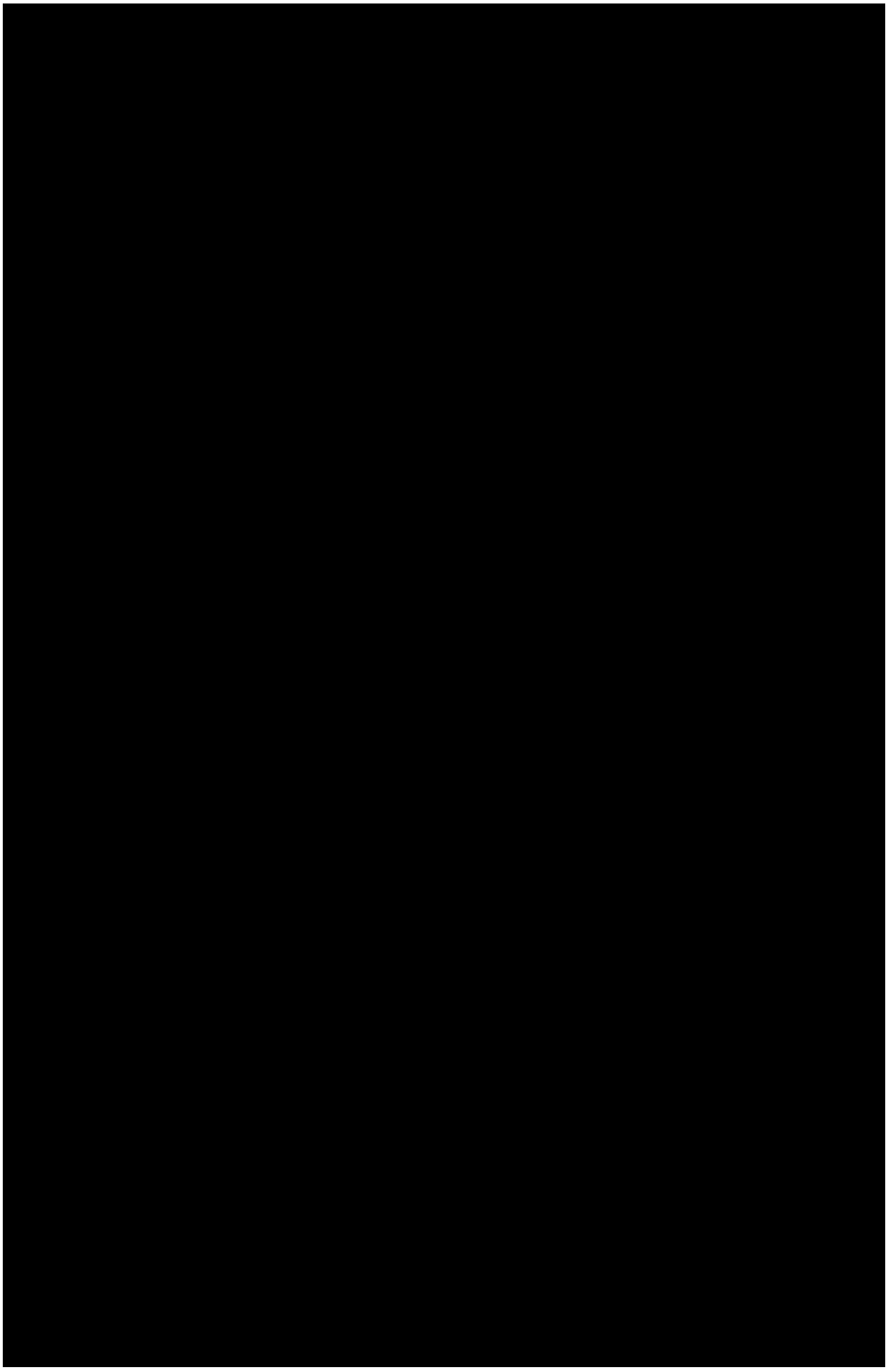

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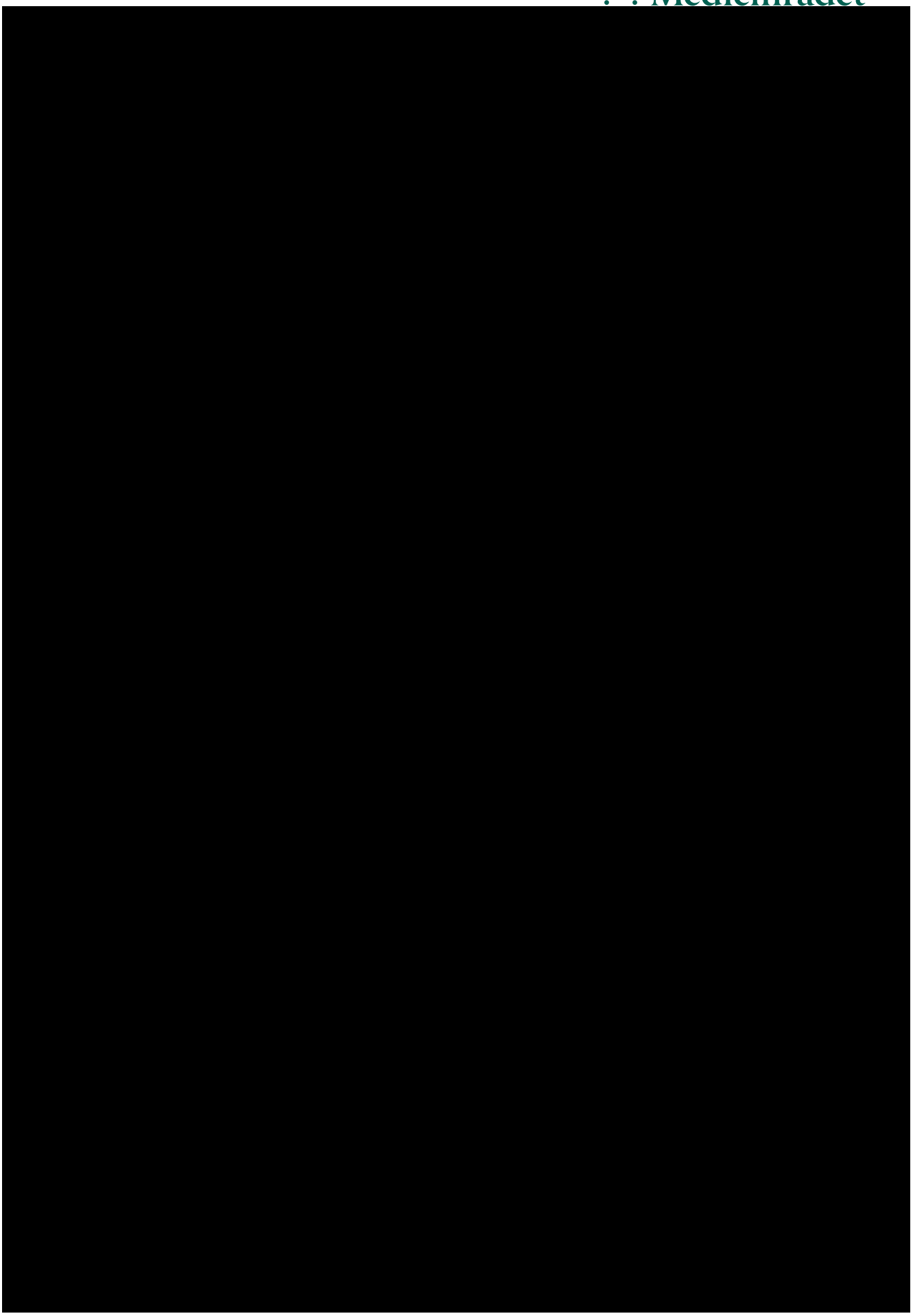

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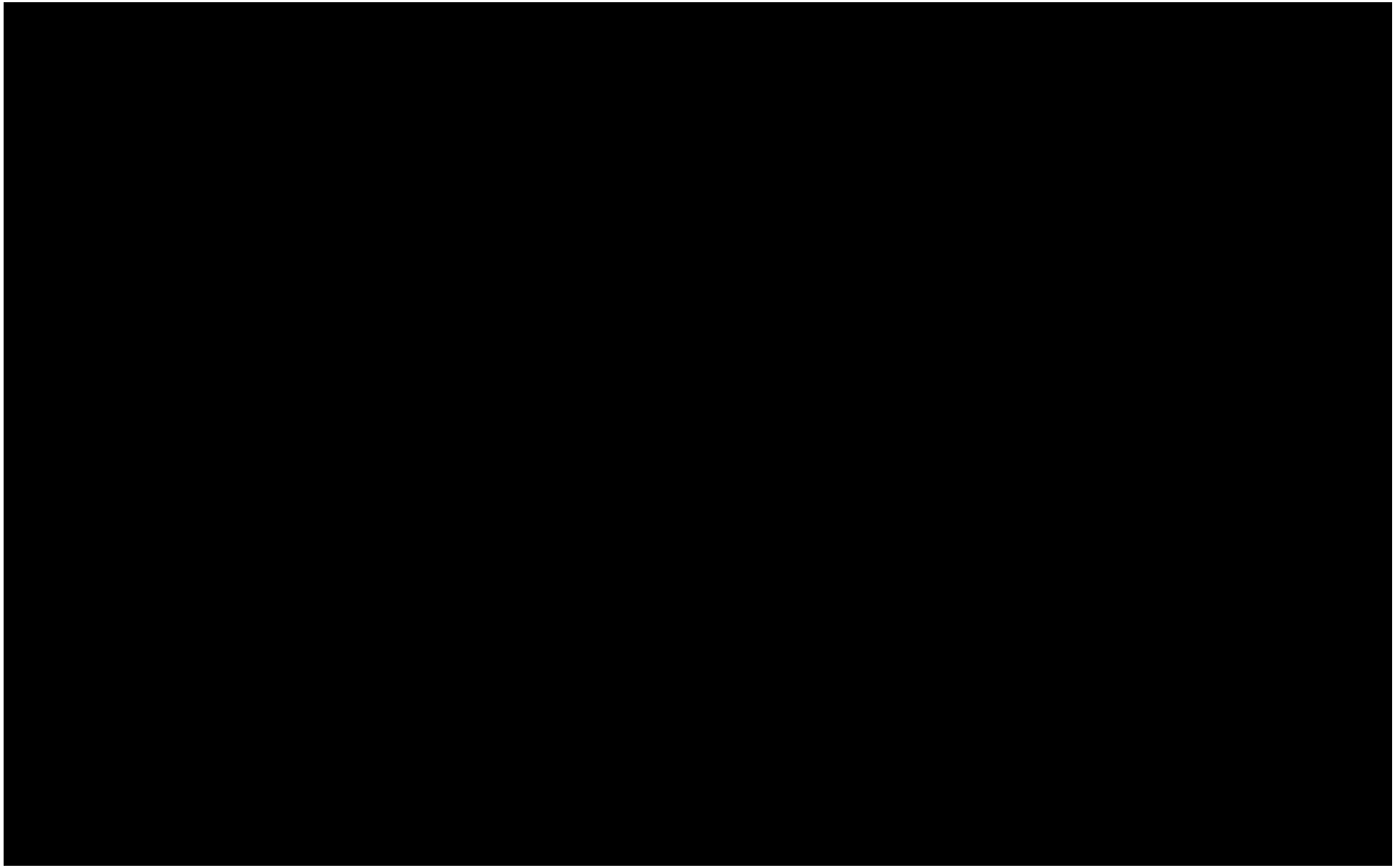

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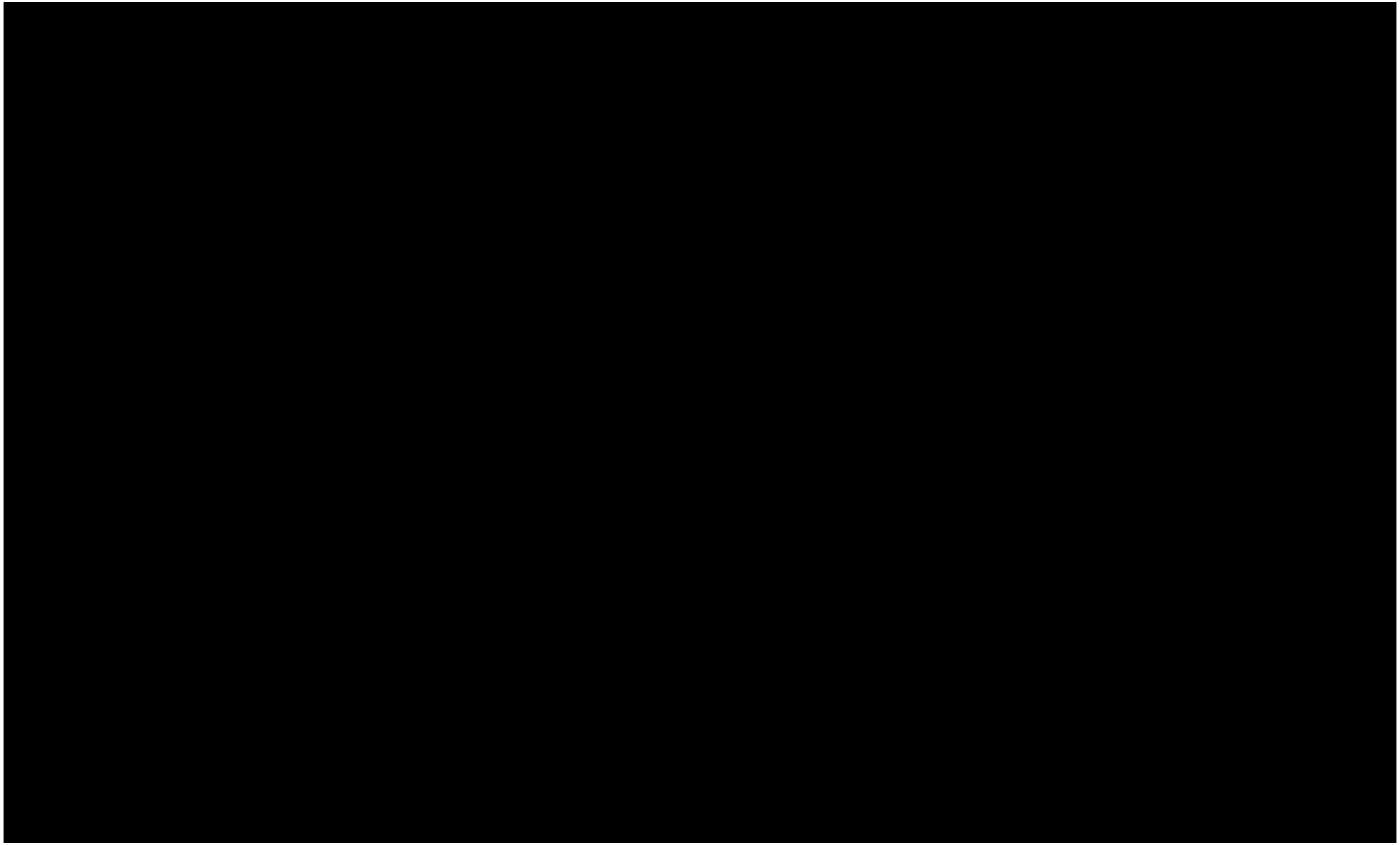

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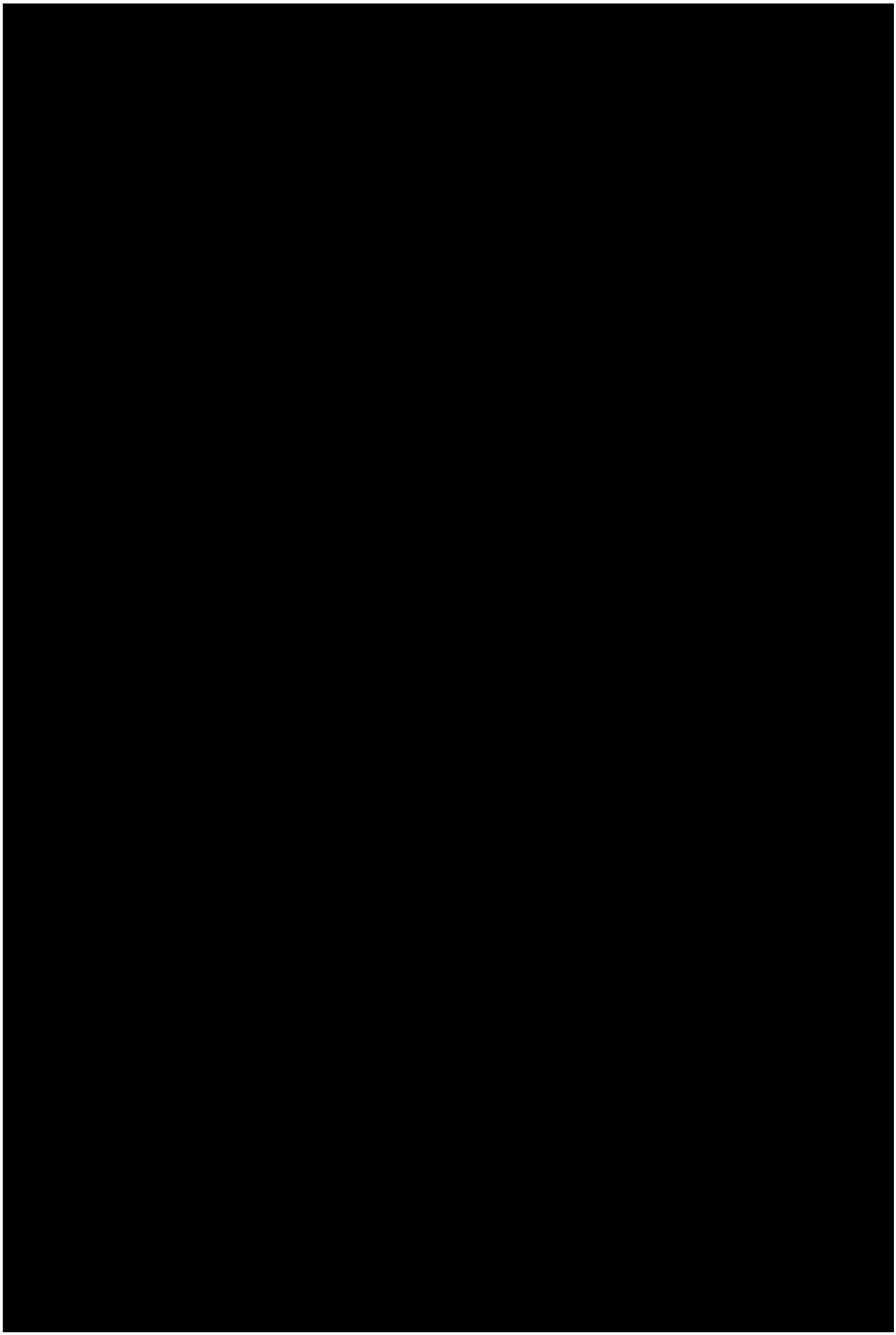

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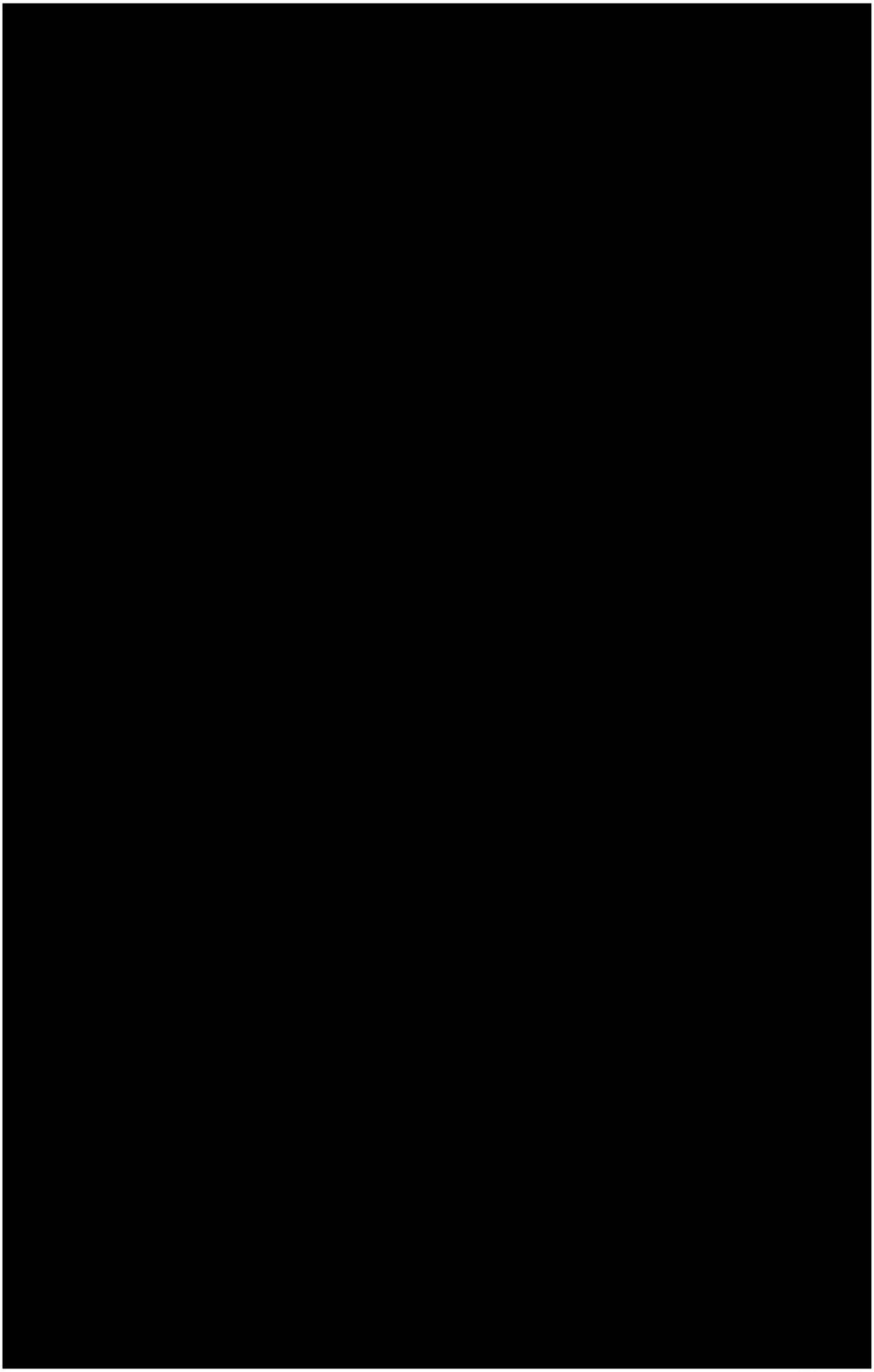

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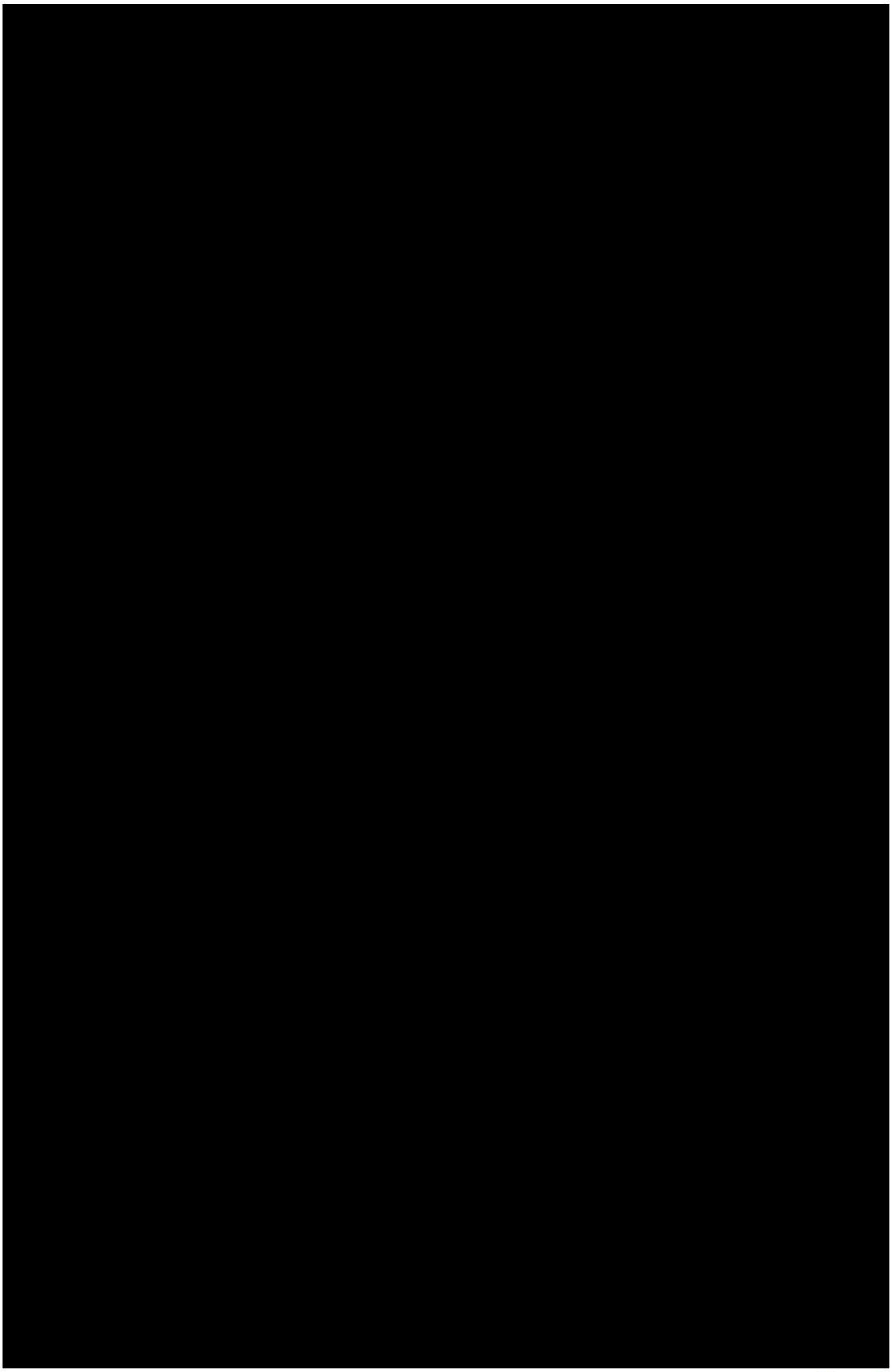

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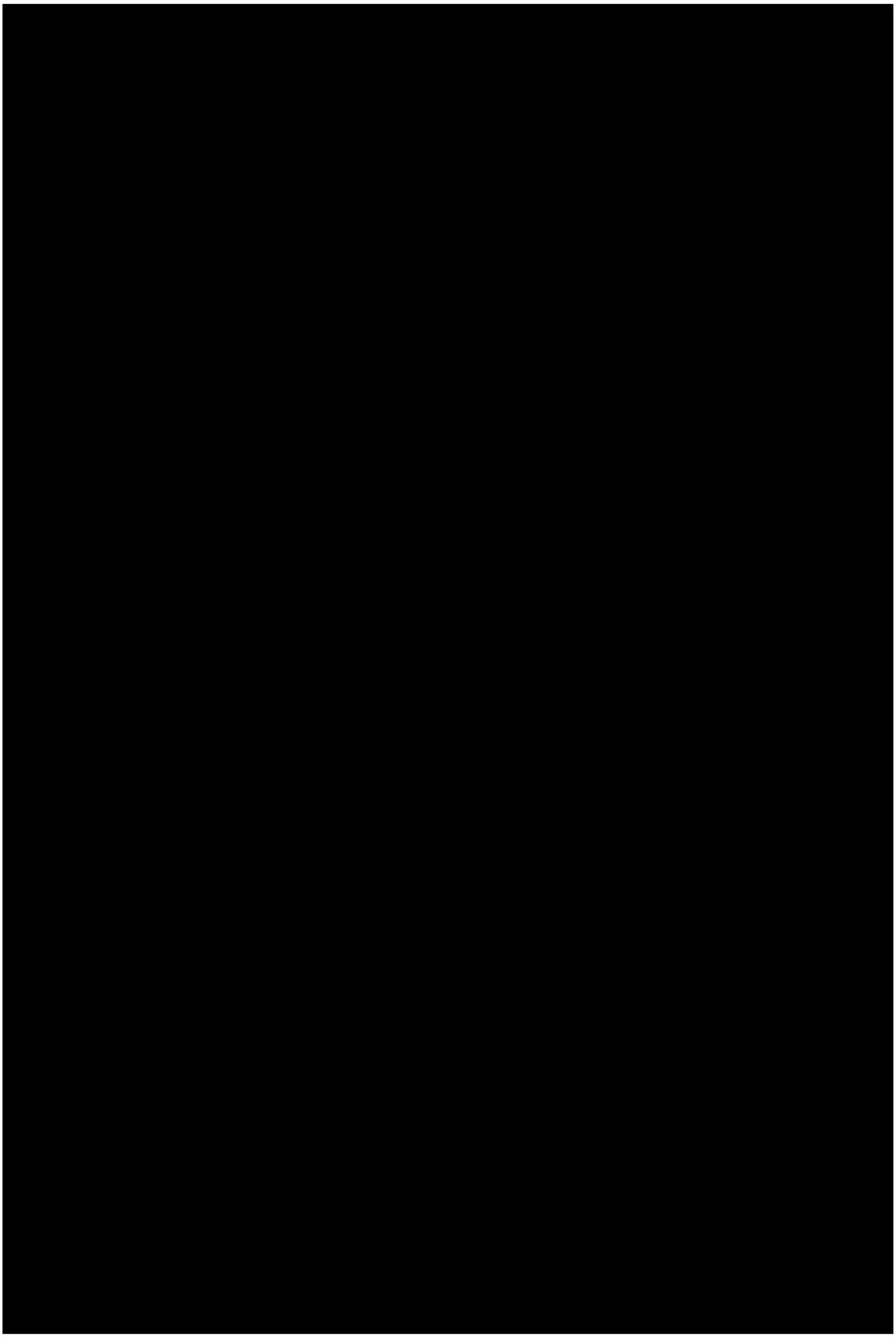

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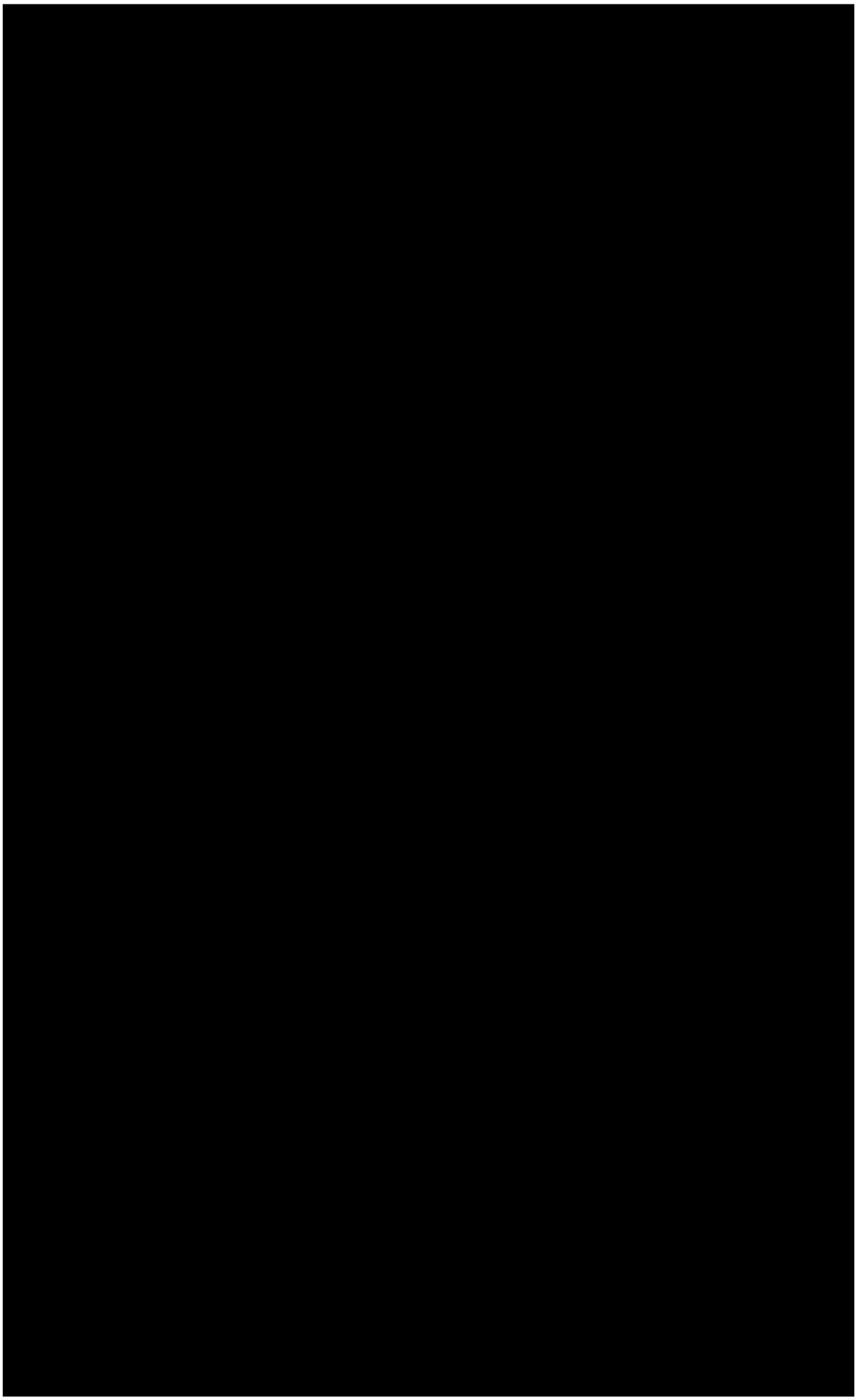

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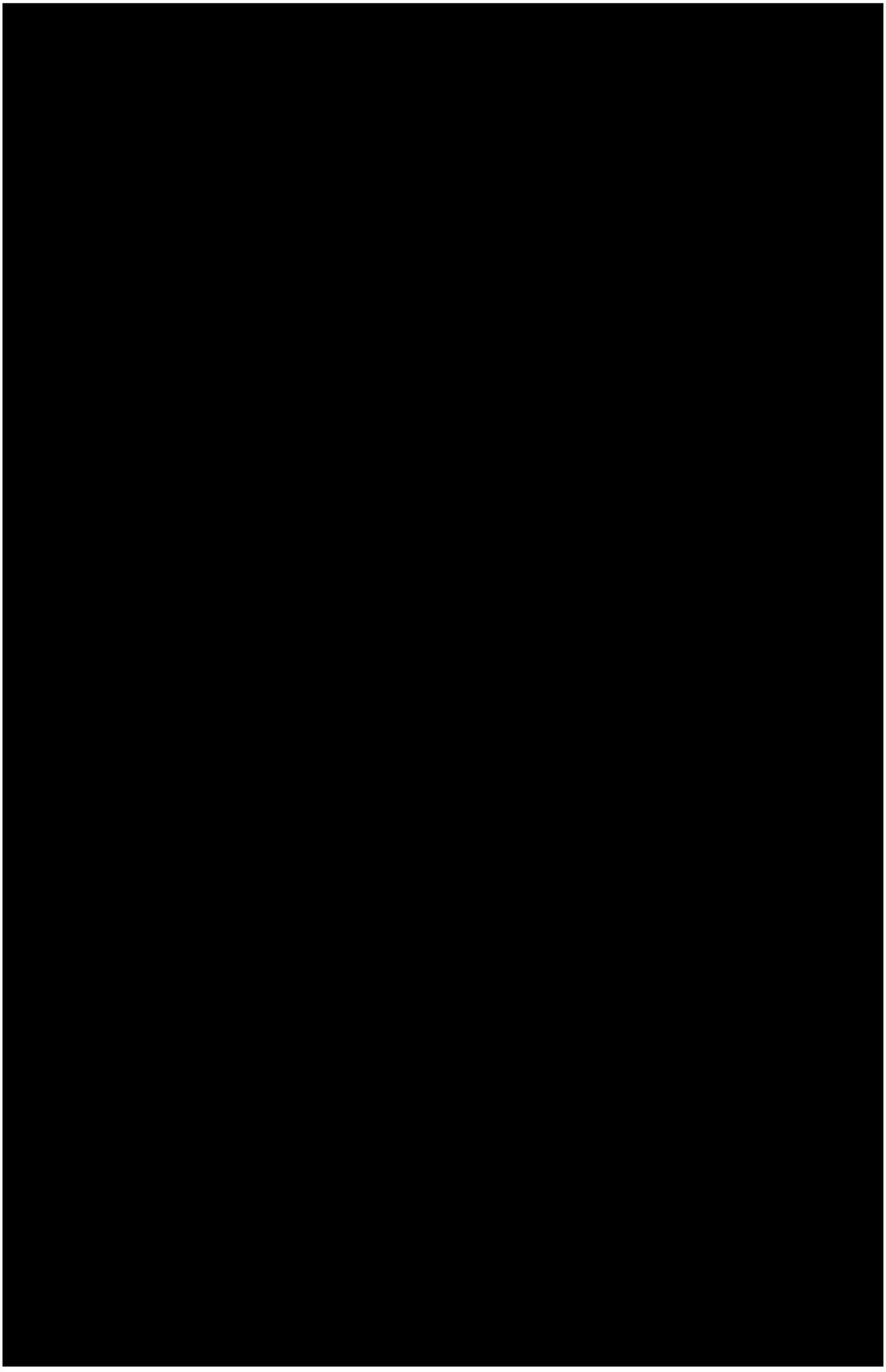

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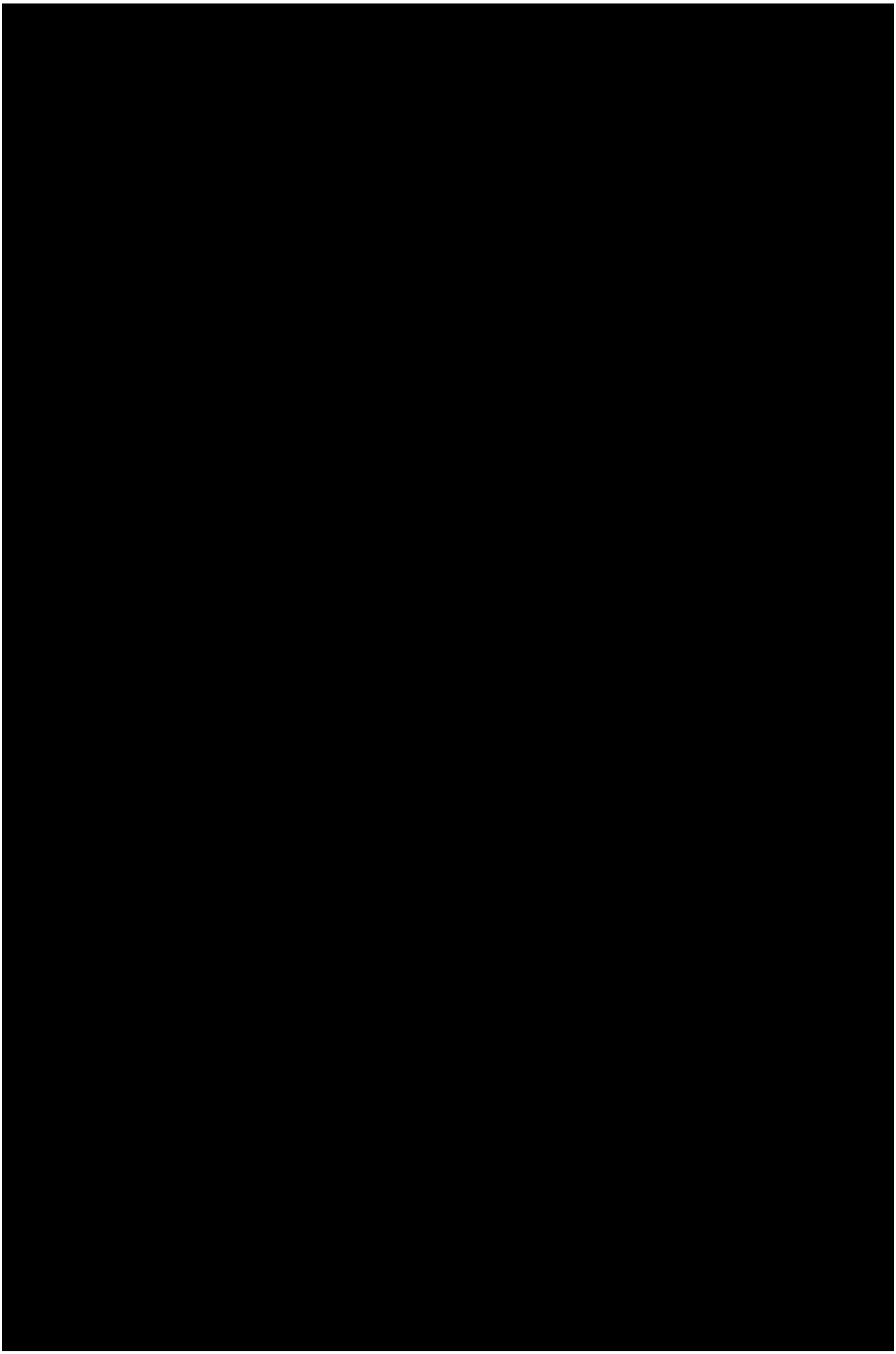

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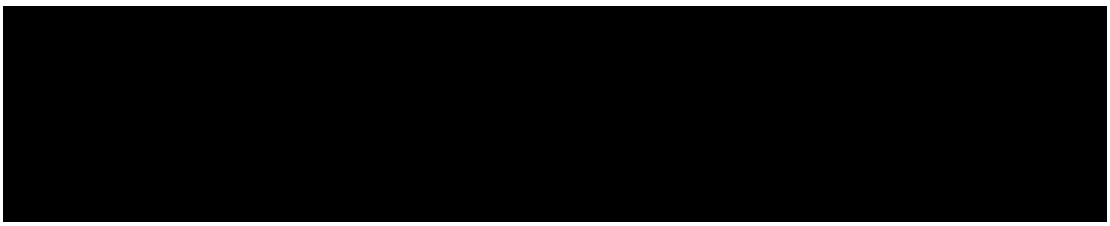

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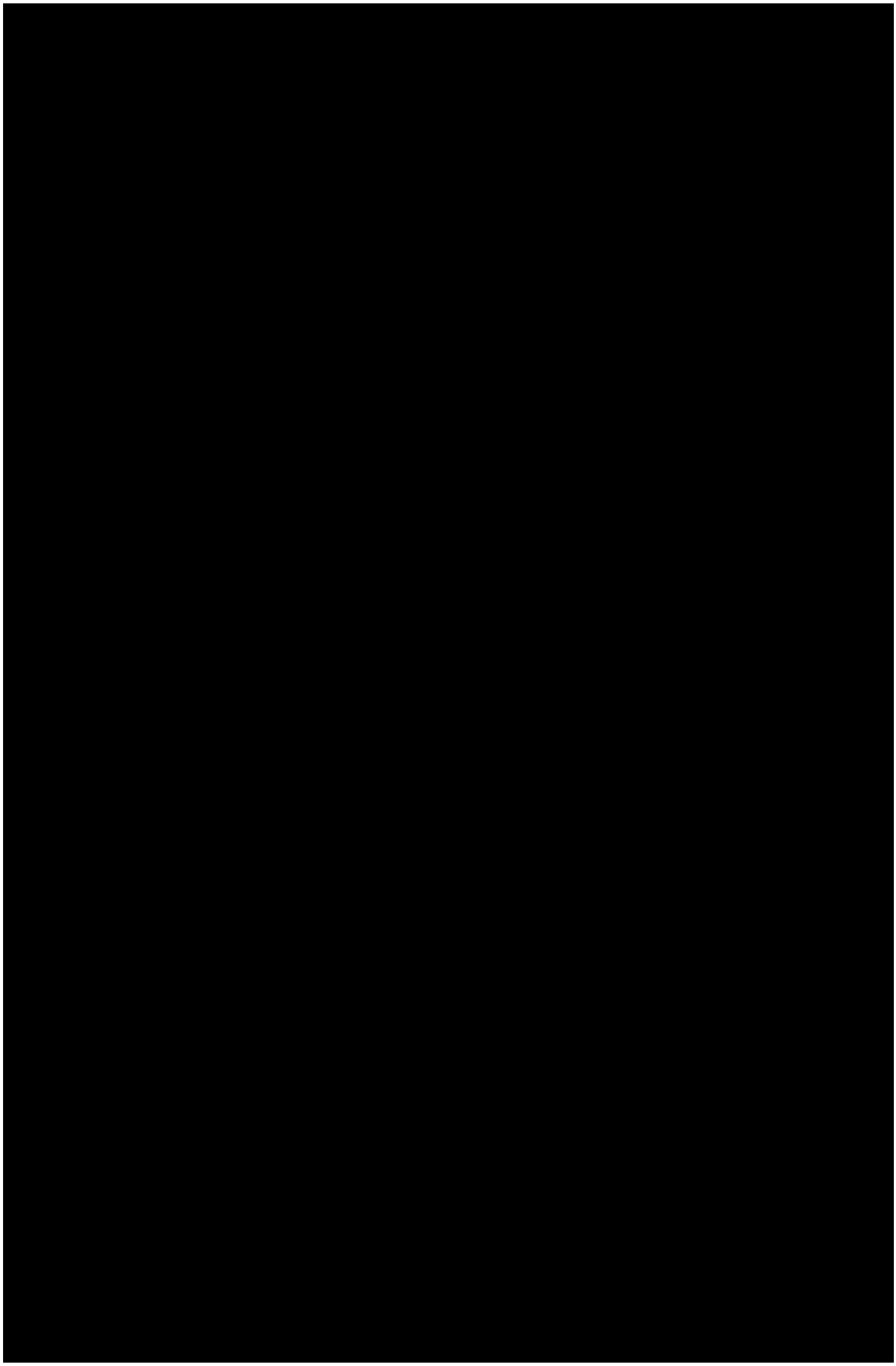

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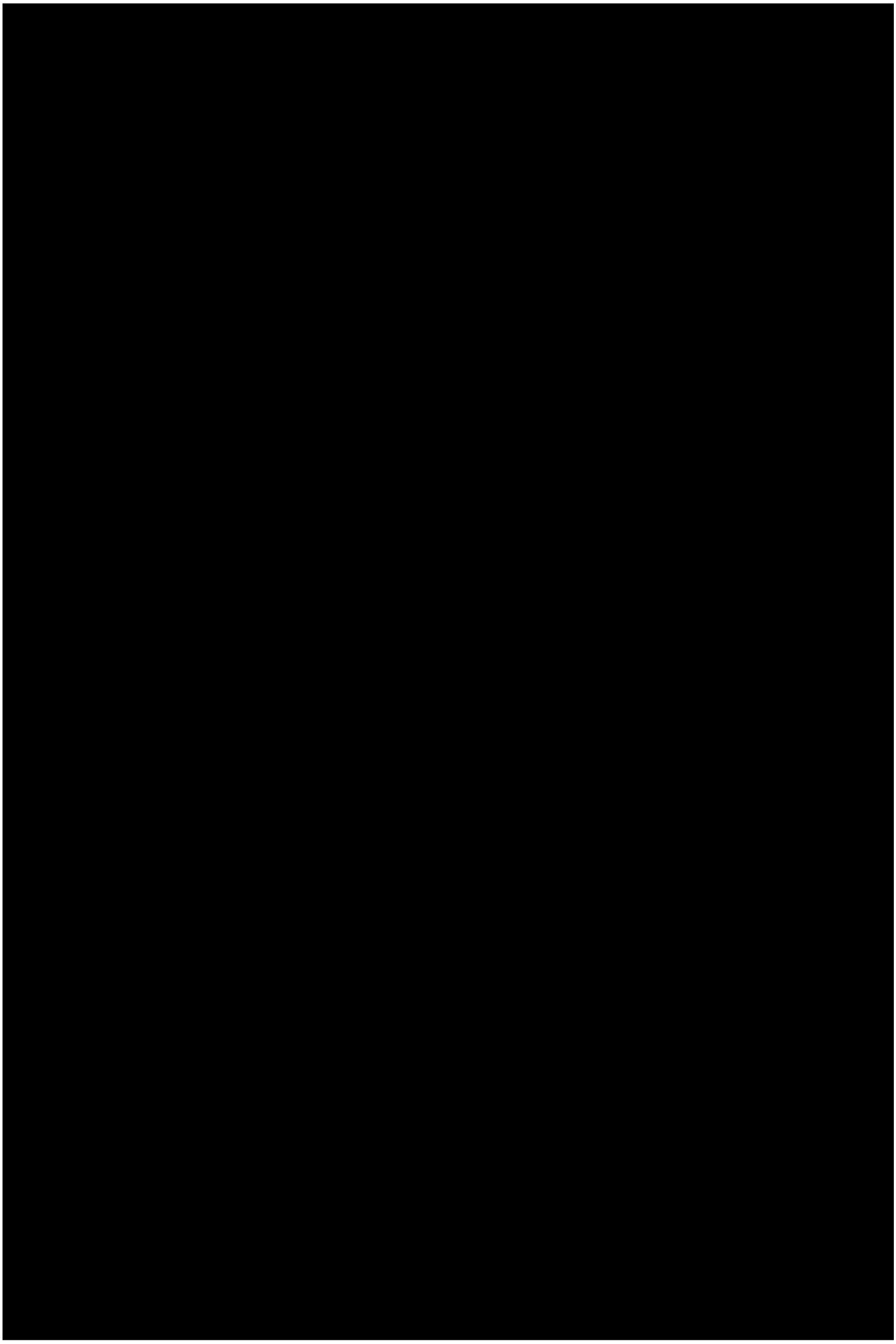

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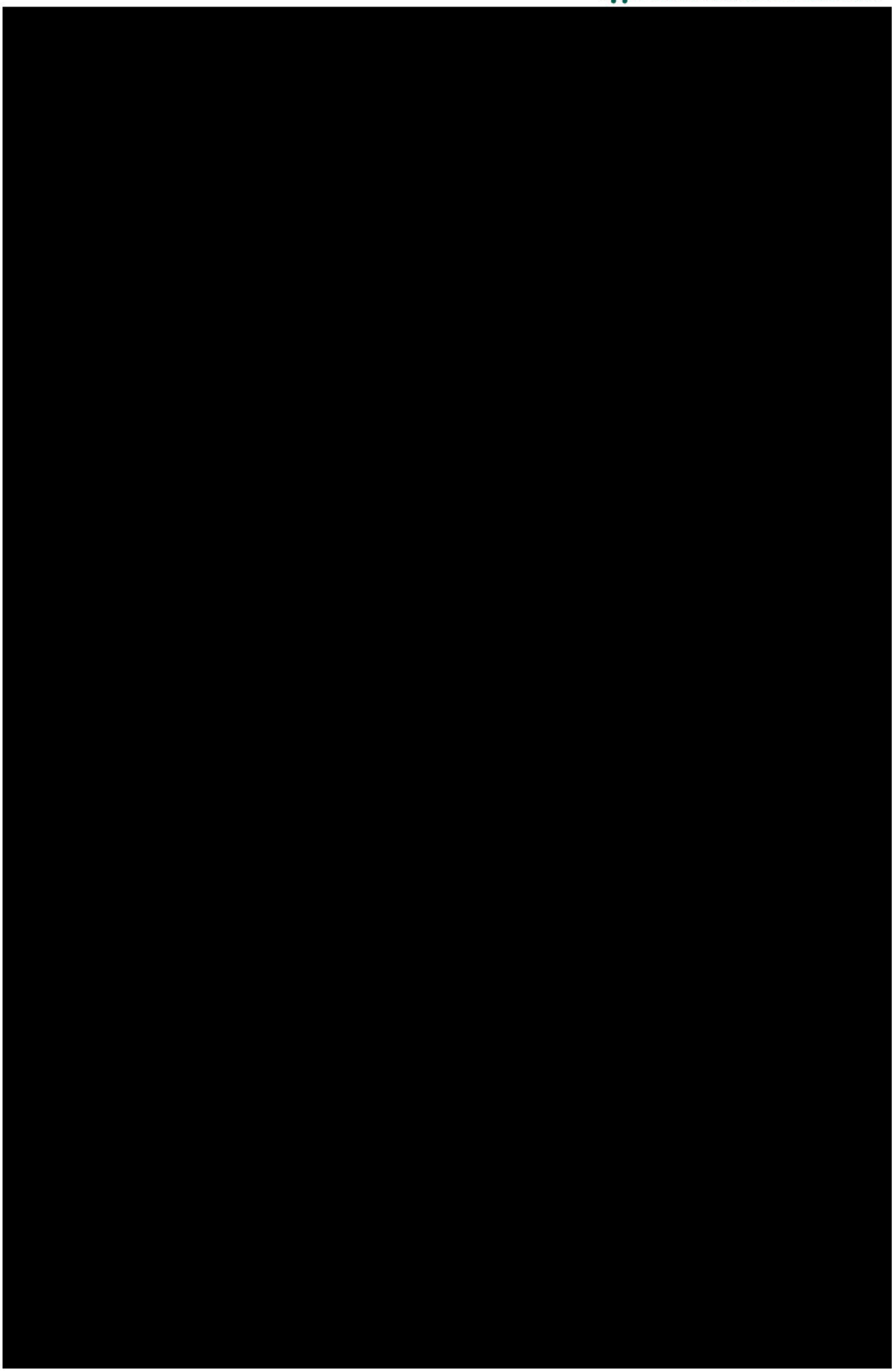

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Appendix H – Literature search for HRQoL data

See Appendix A.

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Appendix I Mapping of HRQoL data

A unique EQ-5D-5L health state was derived by concatenating the levels, or response options, from each of the five dimensions included in the questionnaire. Responses to the five items were then converted to a health state. Various established methods exist for computing utility index scores for use in cost-effectiveness analyses according to EQ-5D-5L responses extracted from the CARTITUDE-1 trial, where EQ-5D-5L utility scores were computed according to the recently published EQ-5D-5L value set for Denmark. If one or more questions were not answered on the five dimensions of the EQ-5D-5L, the health utility score was set to missing.

The utility analysis consisted of EQ-5D assessments completed while patients were progression-free. That is, if the date of the patient-reported outcome (PRO) visit occurred on or after the progression date, then the observation was excluded from the analysis set. In CARTITUDE-1, progression-free survival (PFS) was defined as the time from the date of the initial infusion of JNJ 68284528 to the date of first documented disease progression, as defined in the International Myeloma Working Group (IMWG) criteria, or death due to any cause, whichever occurs first. Independent review committee (IRC)-assessed PFS was used to derive progression-free status in order to define the analysis population. Post-progression observations were excluded due to the limited number of progression events observed in the EQ-5D analysis set of CARTITUDE-1. Therefore, due to a lack of events, it was not possible to estimate a mean utility value for the post-progression health state.

EQ-5D values that were collected post-censoring for PFS were excluded from analyses, because in these cases the patients' progression status cannot be determined after the censoring date for progression. That is, it was unknown whether patients were still progression-free during these post-censoring assessments.

Mixed-Effect Model Repeated Measure (MMRM) models were developed to estimate Danish EQ-5D-5L utility scores. The MMRM approach specifies a correlated residual error structure to account for repeated utility measurements over time. The response variable was defined as actual utility score (i.e., raw outcomes as opposed to change scores), and EQ-5D data across all assessments were analysed via MMRM. All analyses were adjusted for baseline utility as a continuous fixed effect, to consider between patient differences in utilities at baseline. Although visit was identified as a significant predictor in prior analyses, it was excluded from the MMRM to align with the structure of the CEM. No random effects were included in the MMRM. Autoregressive, compound symmetric, Toeplitz, and unspecified covariance structures were tested and the covariance structure with the lowest fit statistics (i.e., Akaike's Information Criteria [AIC] and Bayesian Information Criteria [BIC]) in the regression model was selected for the analysis.

The EQ-5D-5L, time-to-event (i.e., PFS), and adverse event data from CARTITUDE-1 were available as of the September 2021 data cut-off. Statistical analyses to derive the MMRM models were conducted using SAS version 9.4.

The Danish Medicines Council cites EQ-5D-5L as the preferred instrument for measuring life quality, and responses to the questionnaire should be used to subsequently derive associated utility inputs for use in a cost-effectiveness analyses (version 1.2 of methods guide). Furthermore, the guidelines specify that the Jensen et al., 2021 Danish preference weights representative of the general public should be used for converting EQ-5D health states into utility indexes. In particular, Jensen et al., 2021 studied a combination of composite time trade-off and discrete choice experiment techniques to estimate Danish-specific social tariffs for converting EQ-5D-5L responses into utility indexes. Data was collected over a period from May 2018 to September 2020 for 1,014

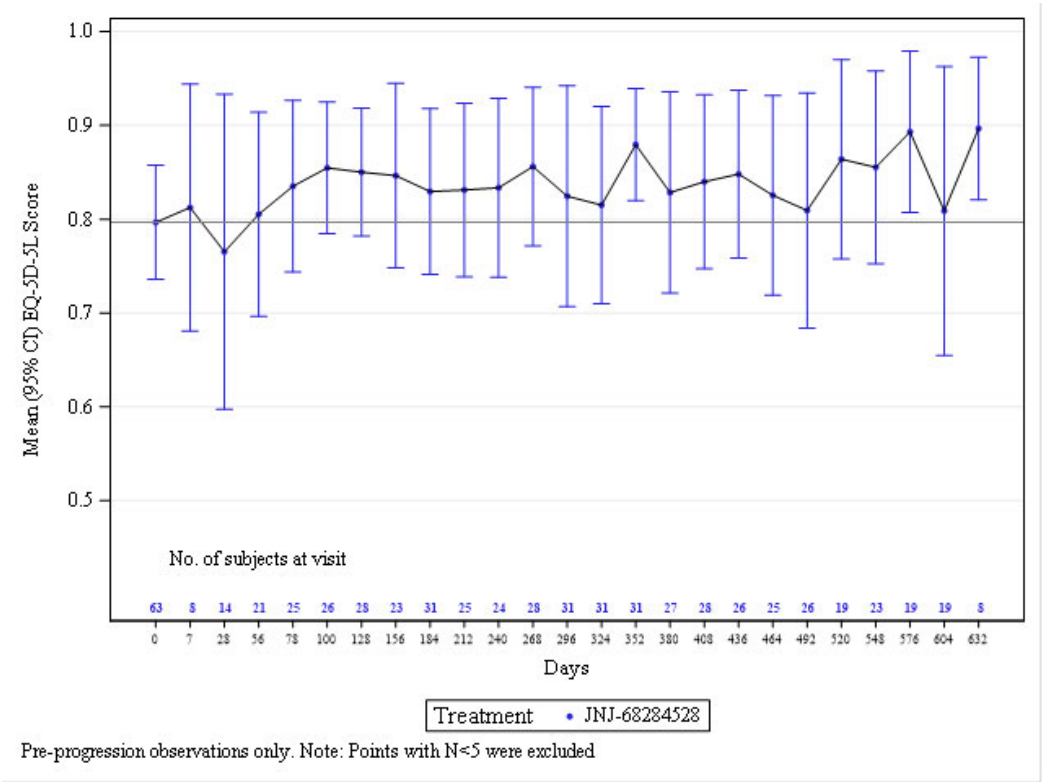
participants, representative of the Danish population according to age, gender, geographic region, marital status, region, education, annual income, and employment status. Several linear mixed effects models were fit and evaluated by the researchers, and the final recommended model was implemented in the analyses described herein.

Results

Two utility analyses were conducted, according to two different analysis sets, where the Adverse Event-free EQ-5D-5L Analysis Set was a subset of the EQ-5D-5L Analysis Set. The predicted health state utility results were comparable for the two analysis sets; that is, the overall mean utilities for the 1) progression-free and 2) progression-free and adverse event-free health states were similar. Therefore, the impact of treatment-related adverse events on patients' average quality of life in the progression-free health state was minimal, as measured by the EQ-5D instrument. However, only progression-free observations were analysed in this analysis, due to the limited number of observed progression events; therefore, in order to determine the quality of life in the post-progression health state, subsequent analyses of additional data would be required.

The observed mean EQ-5D-5L utilities along with the associated 95% confidence intervals are presented in Figure 63.

Figure 63. Observed plot for EQ-5D-5L utility analysis



Two of the four covariance structures tested failed to converge, and thus could not be used for the final model fitting (i.e., unstructured and Toeplitz). The first-order autoregressive (i.e., AR[1]) covariance structure resulted in the lowest AIC and BIC fit statistic and was used for the final regression model fitting. The final model for EQ-5D-5L is summarized in Table 85.

Table 85. MMRM model for EQ-5D-5L utility values

Effect	Estimate	SE	DF	t Value	Pr > |t|
Intercept	0.4315	0.05154	84.6	8.37	<.0001
Baseline EQ-5D-5L utility score	0.5162	0.06251	83.9	8.26	<.0001

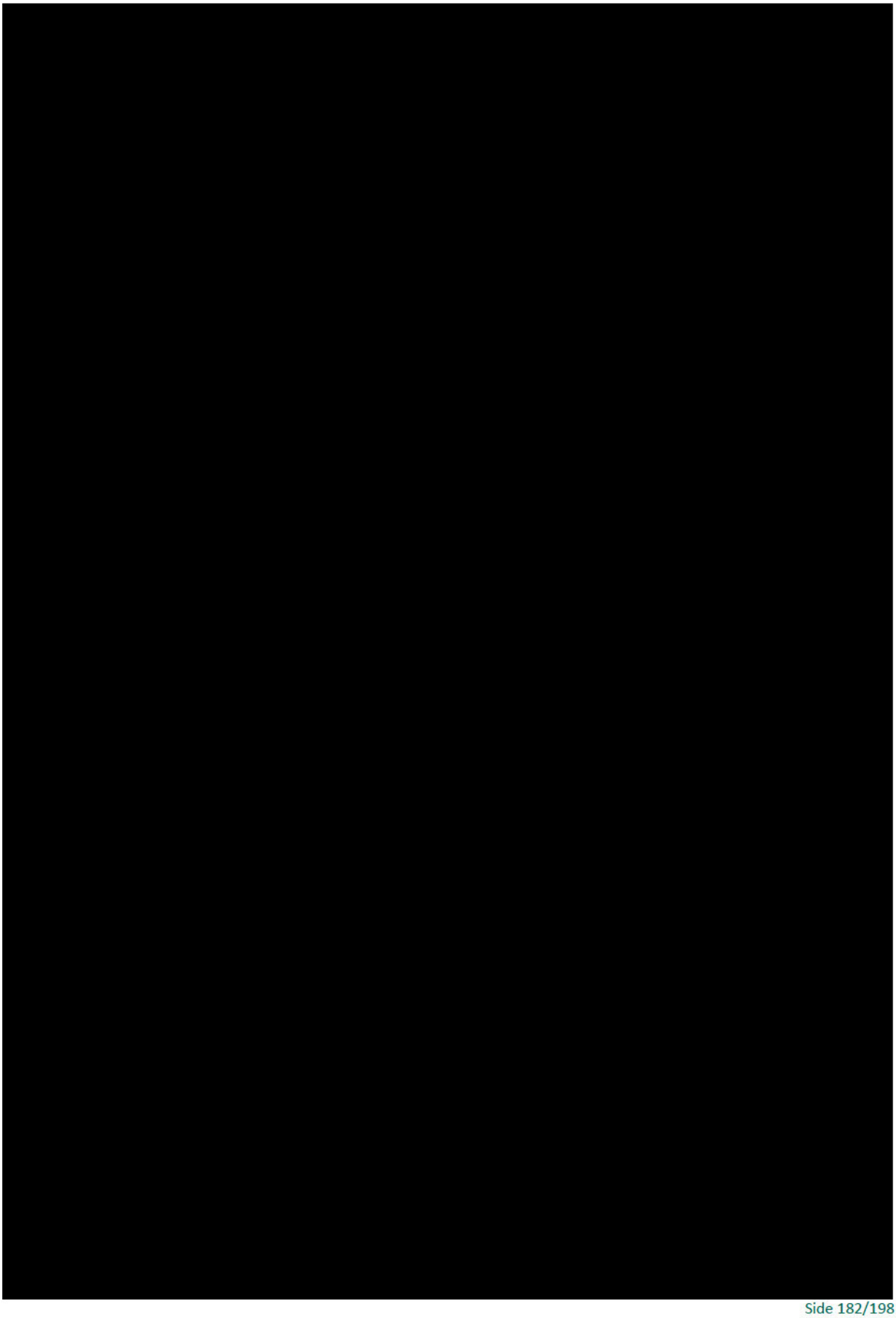
The mean health state utility was estimated according to the EQ-5D-5L model and compared against the observed mean utility scores (Table 86). The predicted progression-free health state utility was comparable to the observed average.

Table 86. Predicted and observed mean Danish EQ-5D-5L utility scores

	Mean PF Utility	SE	Lower 95% CL	Upper 95% CL
Observed	0.8373	0.009973	0.8177	0.8569
Predicted	0.8435	0.01565	0.8124	0.8746

Missingness

The EQ-5D consists of 5 domains/questions. If a response was missing for any of the 5 domains, then the utility score was set to missing and this observation was removed from the final analysis set. No imputation was performed. Furthermore, the EQ-5D utility analyses considered all individuals from the mITT analysis set with complete response to EQ-5D questionnaire at baseline (non-missing), at least one follow-up EQ-5D utility (i.e., after the baseline assessment), and progression-free at the time of EQ-5D assessment. Overall, 6 patients were missing a response to one domain of EQ-5D across 9 total observations (none were missing >1 domain). Additionally, 5 patients were missing baseline EQ-5D and were removed. Linear mixed-effects models were used to predict health state utilities for the CEM, which assumes the data are missing at random (MAR). This relaxes the assumption of missing completely at random (MCAR) required by some of the other statistical methods used to analyze repeated measures, such as generalized estimating equations (GEE).



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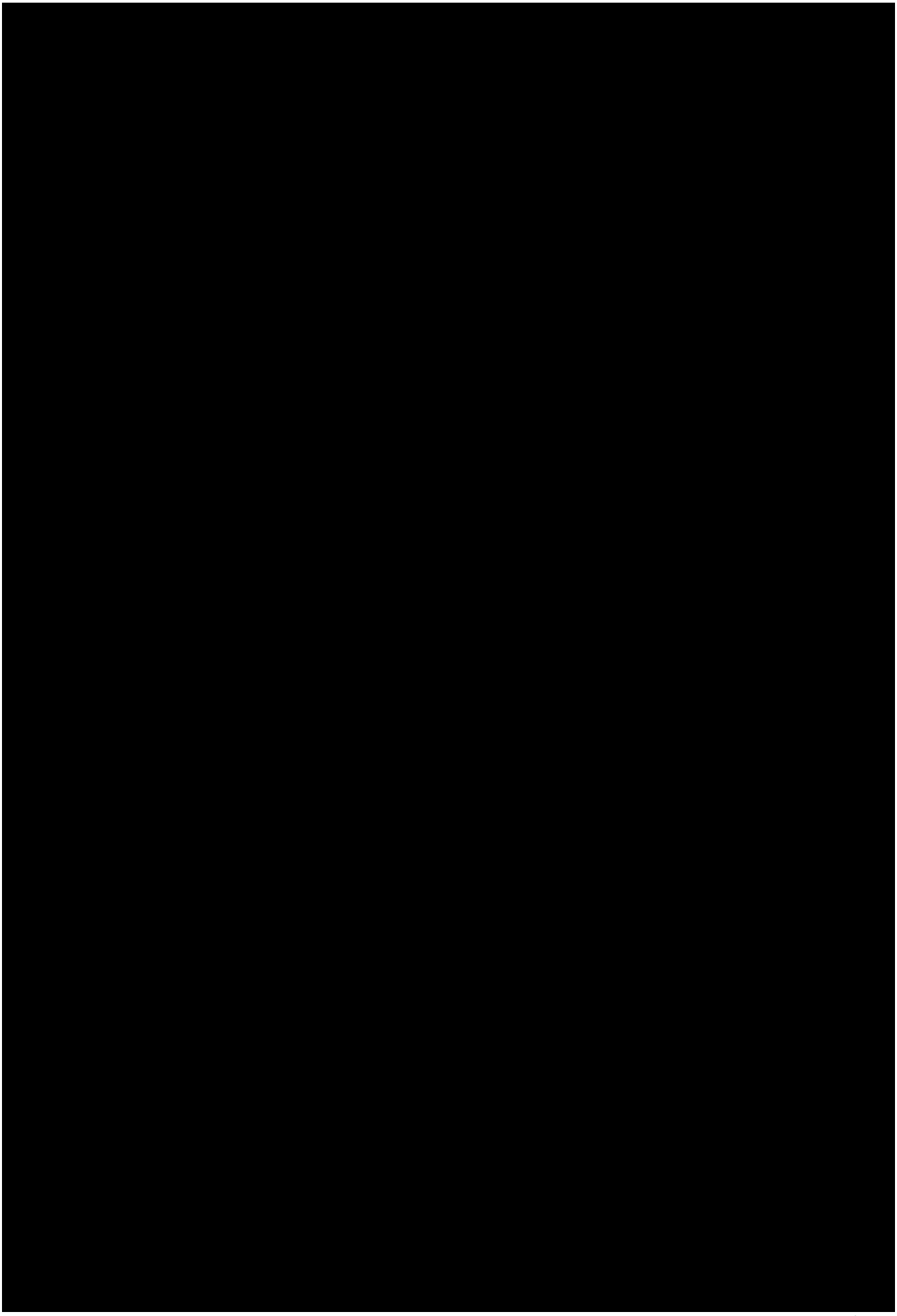

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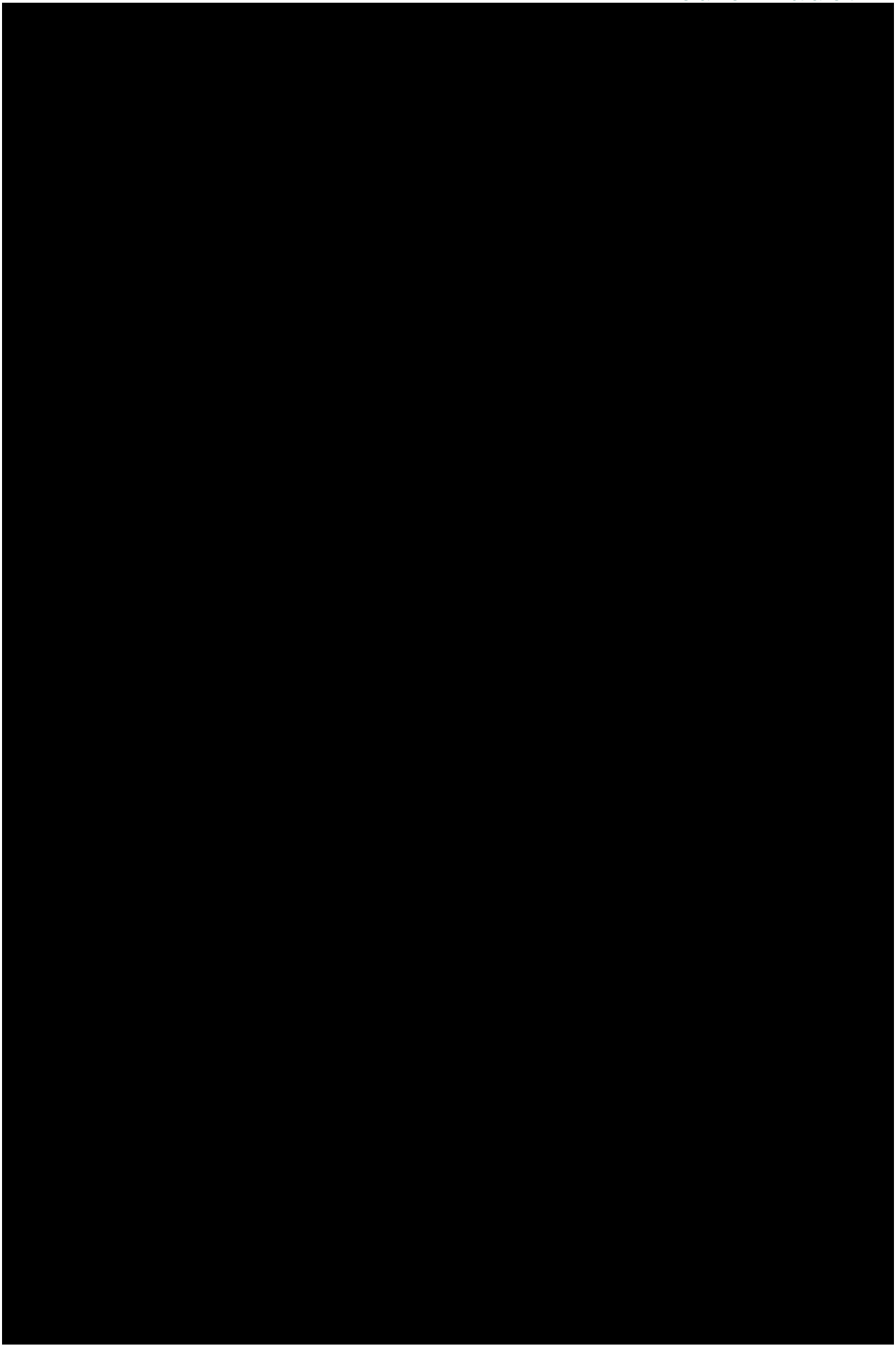

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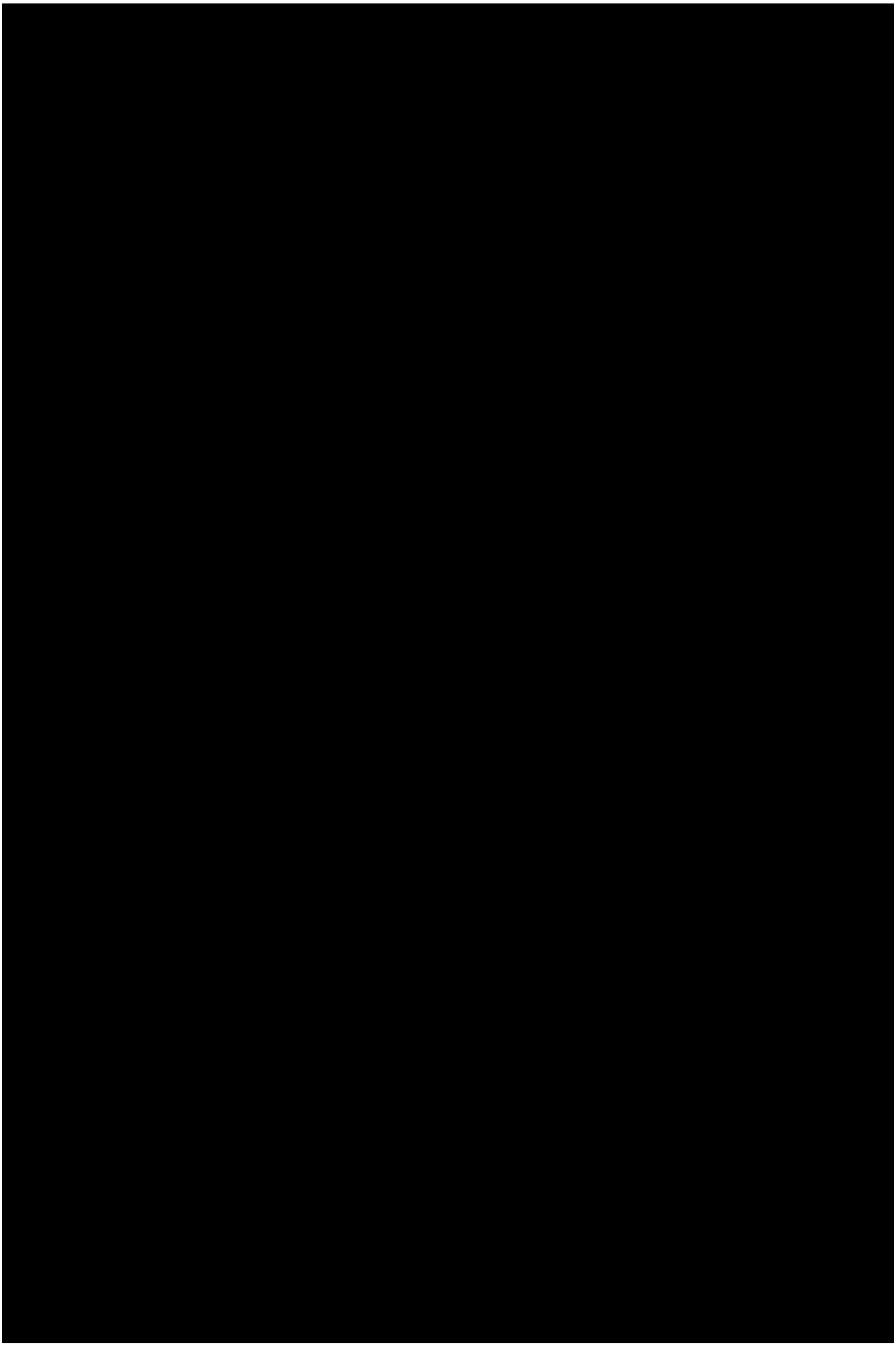

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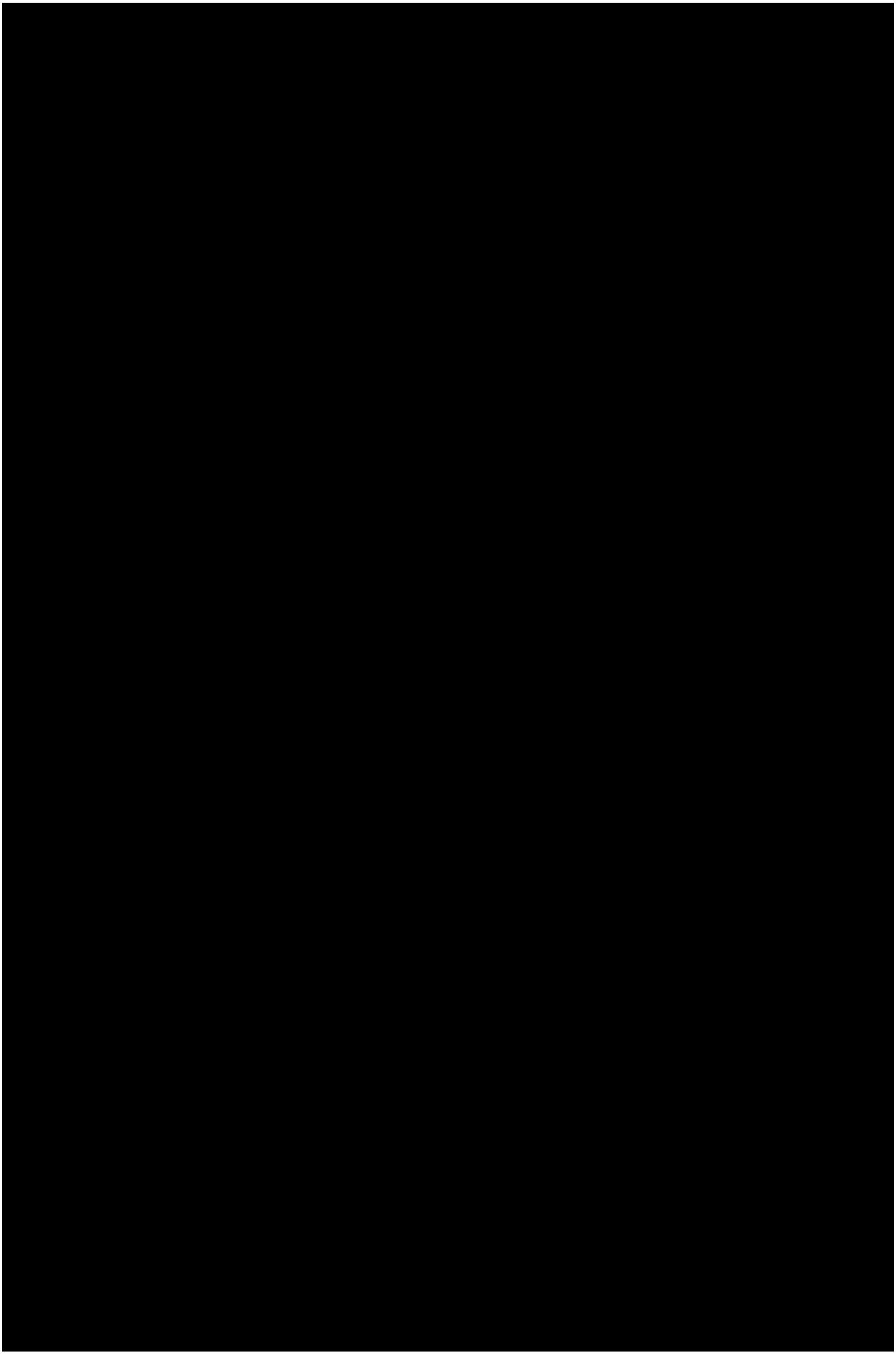

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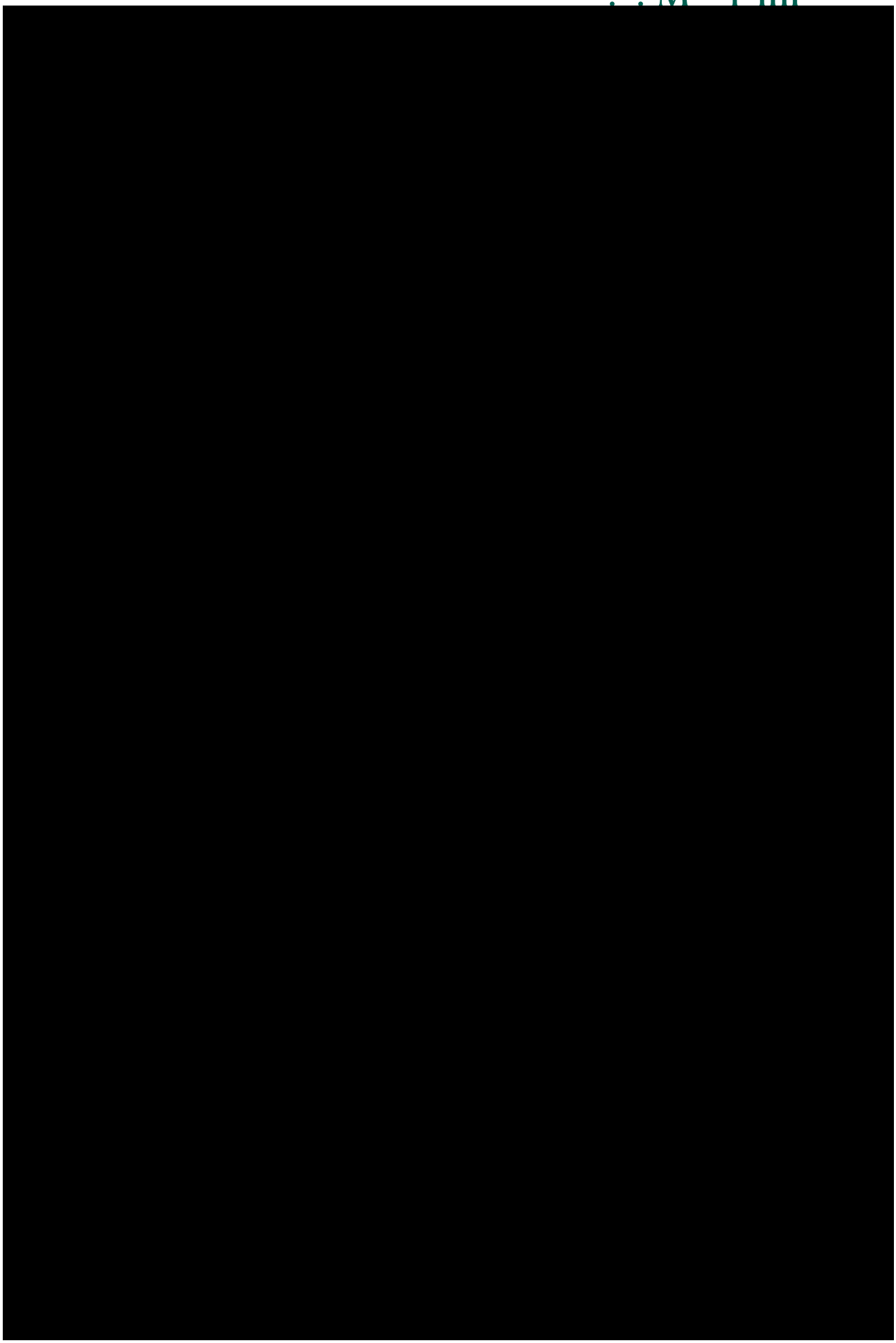

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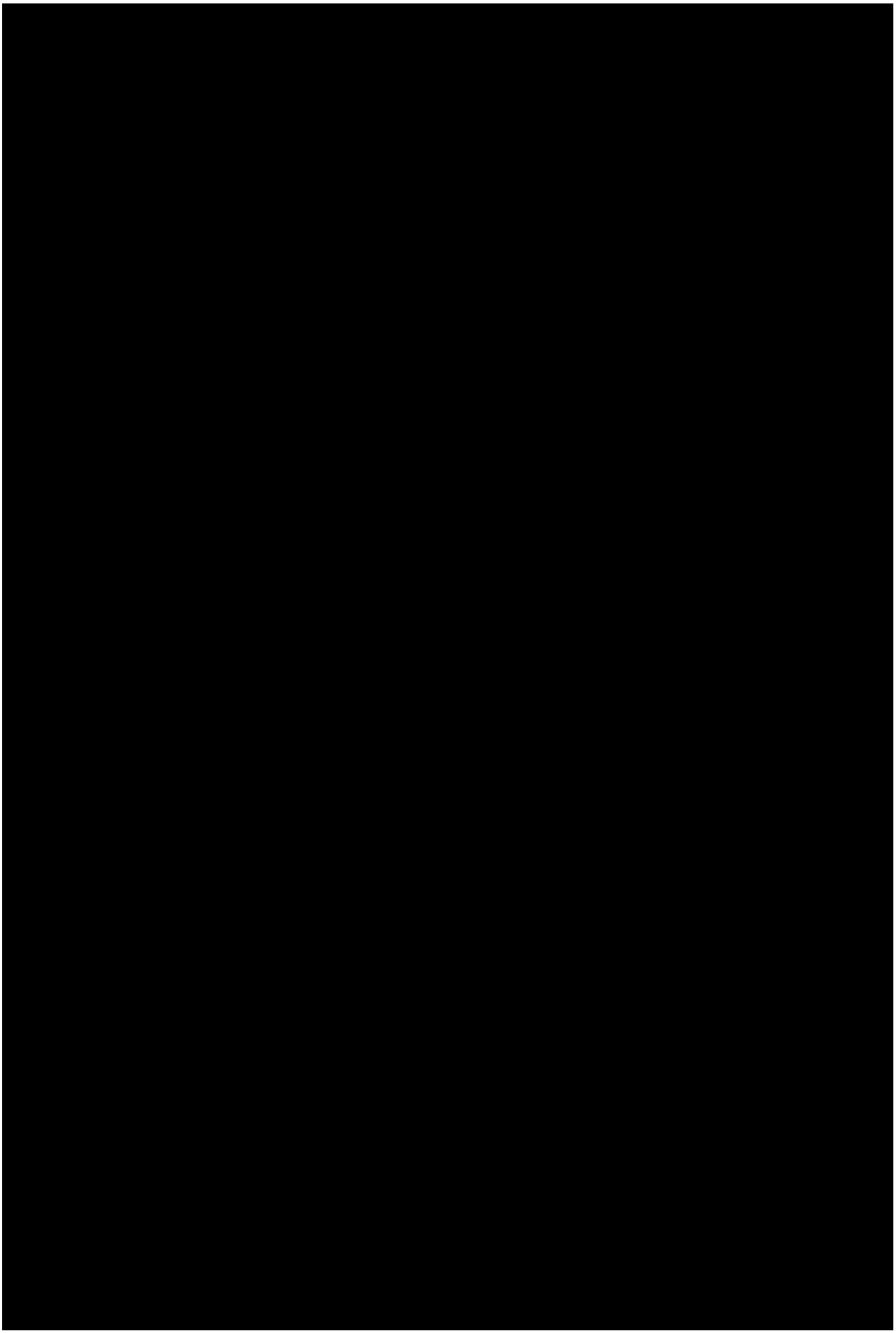

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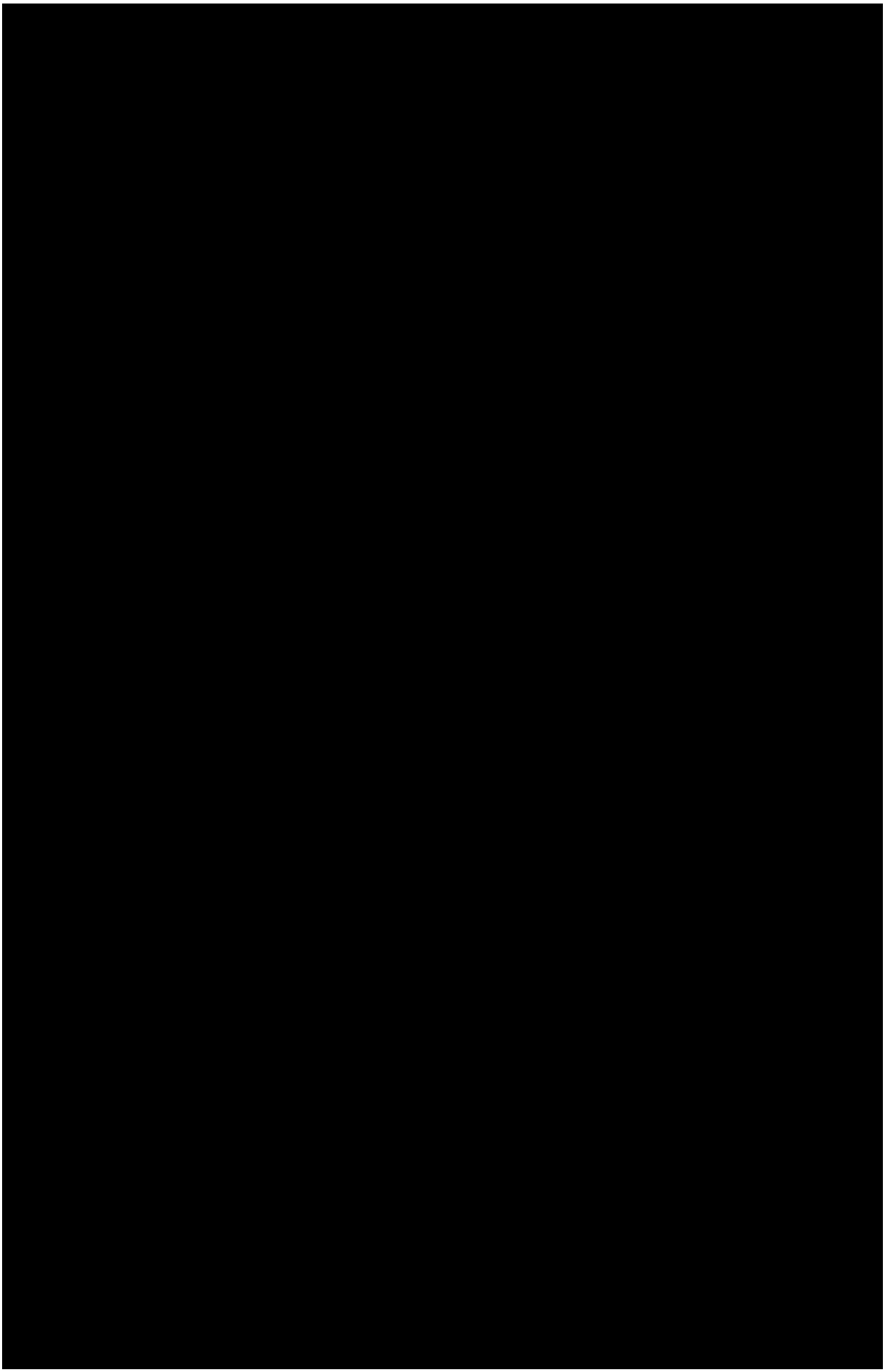

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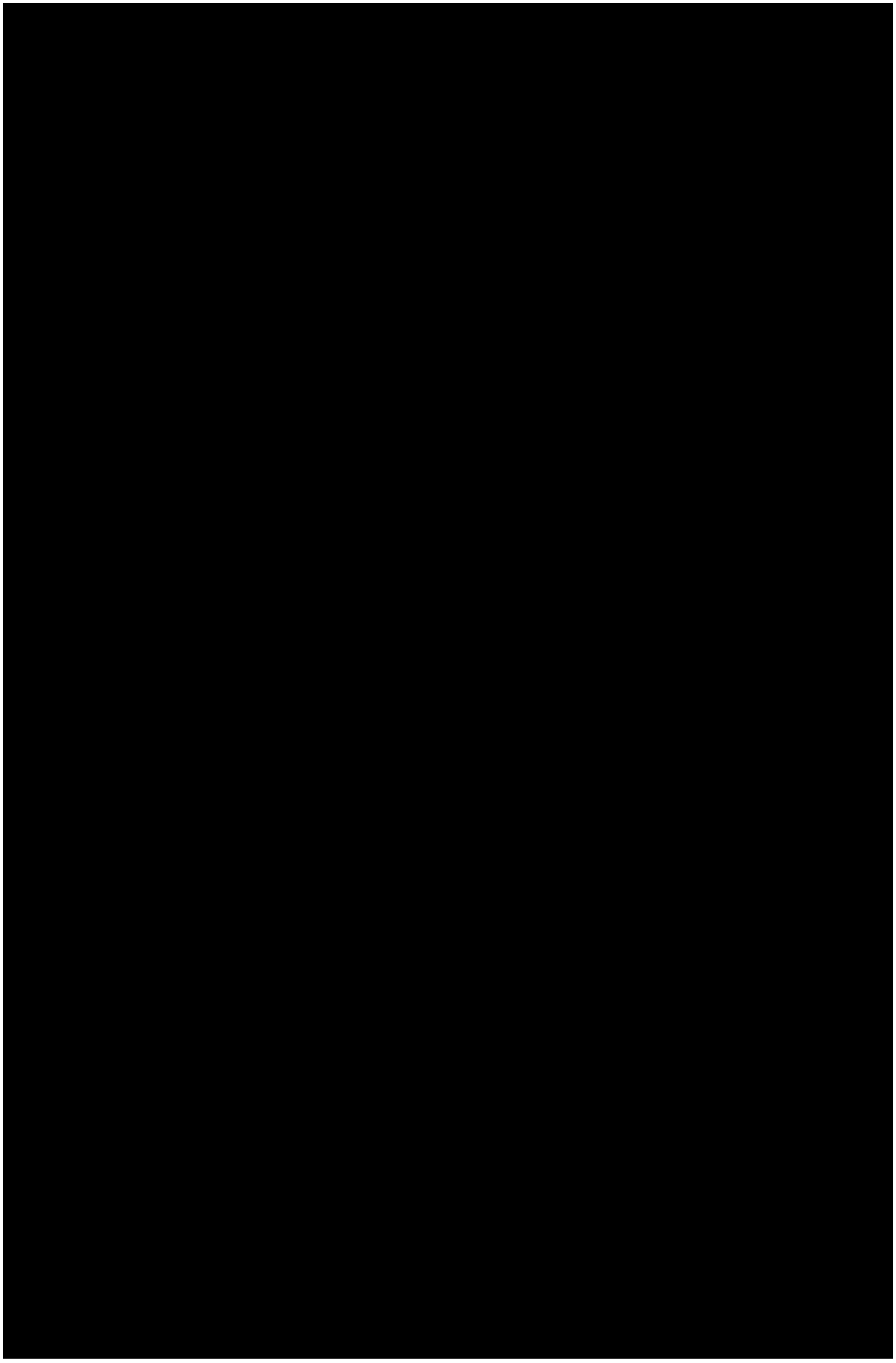

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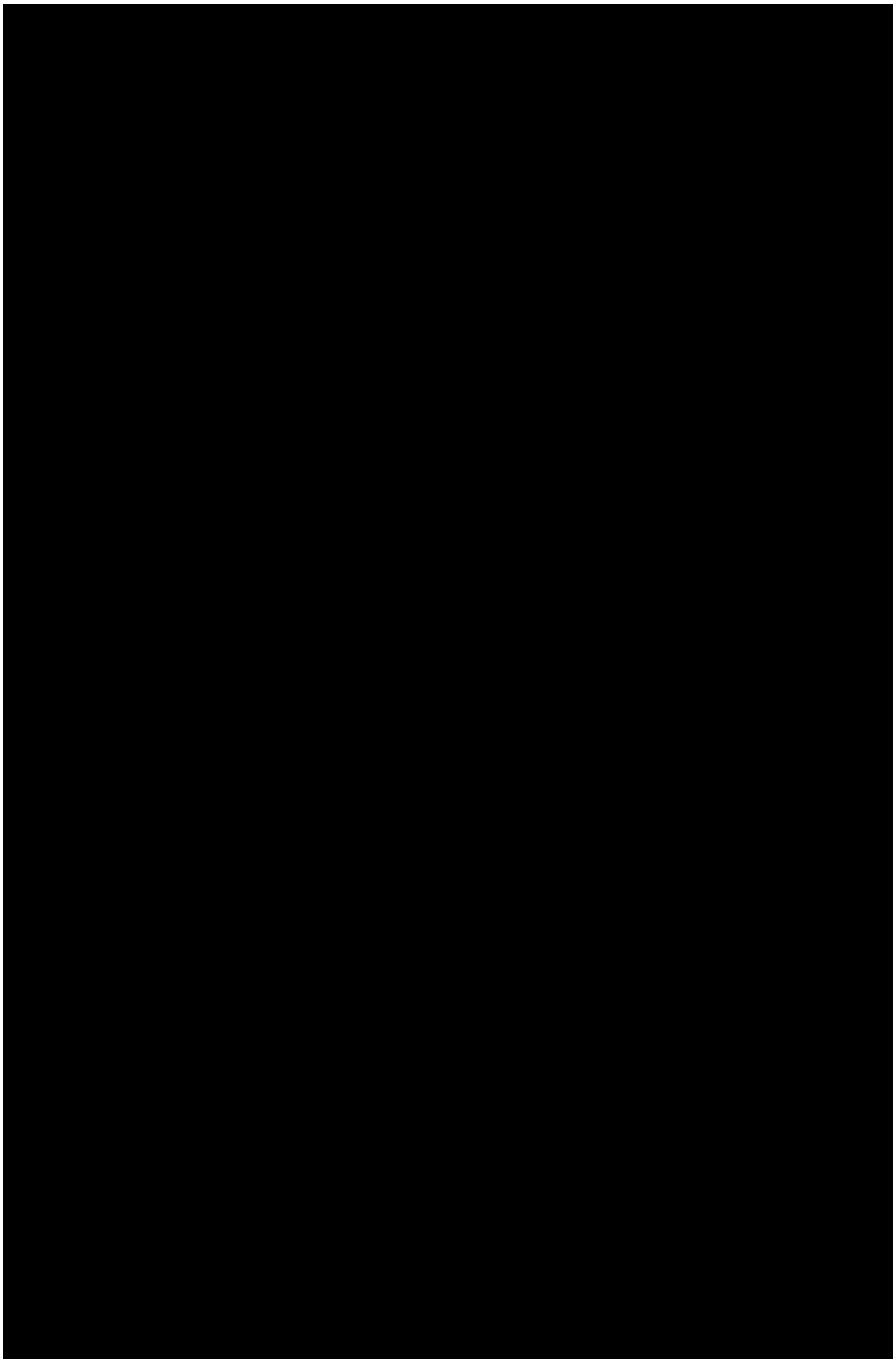

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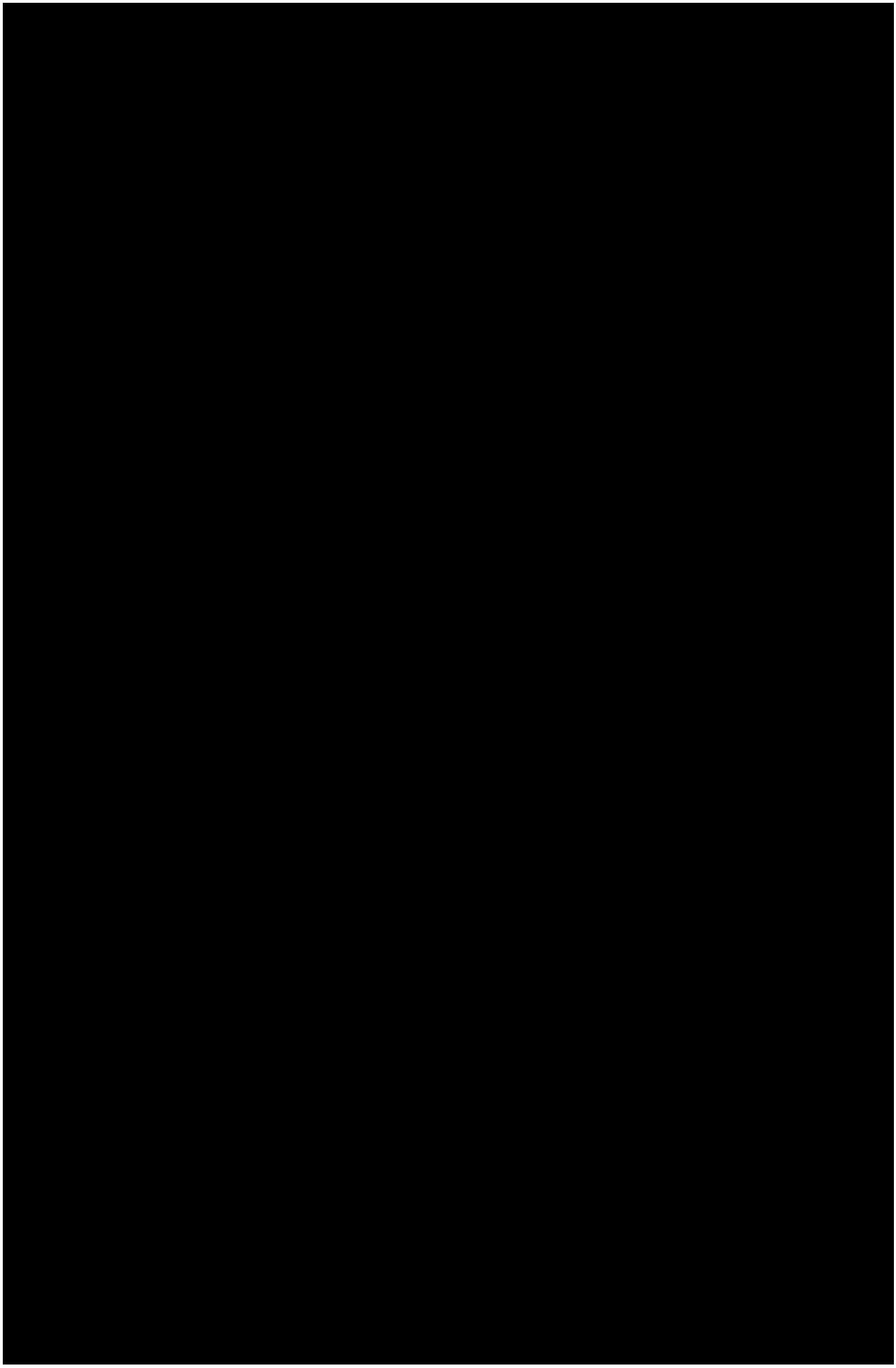

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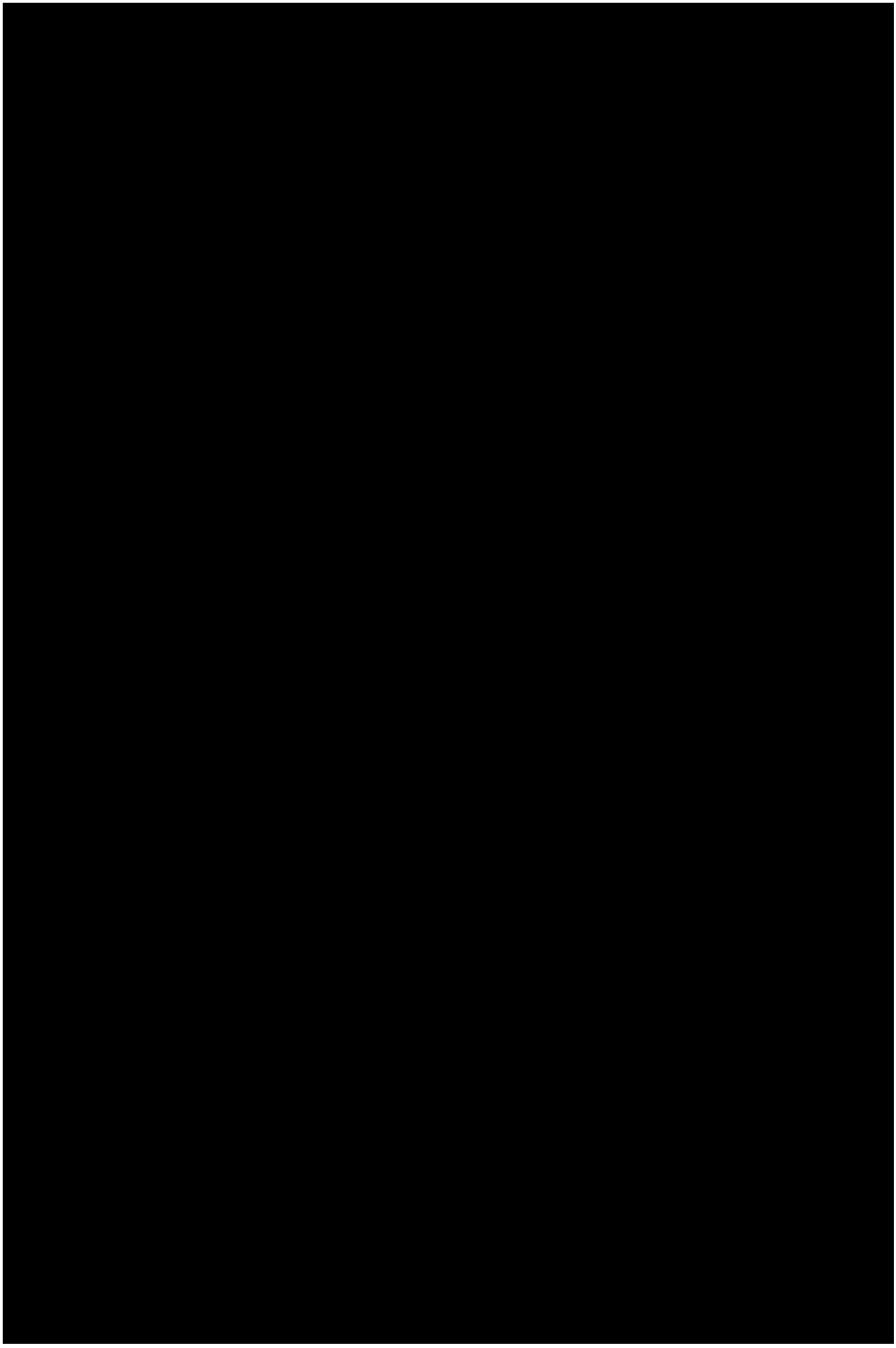

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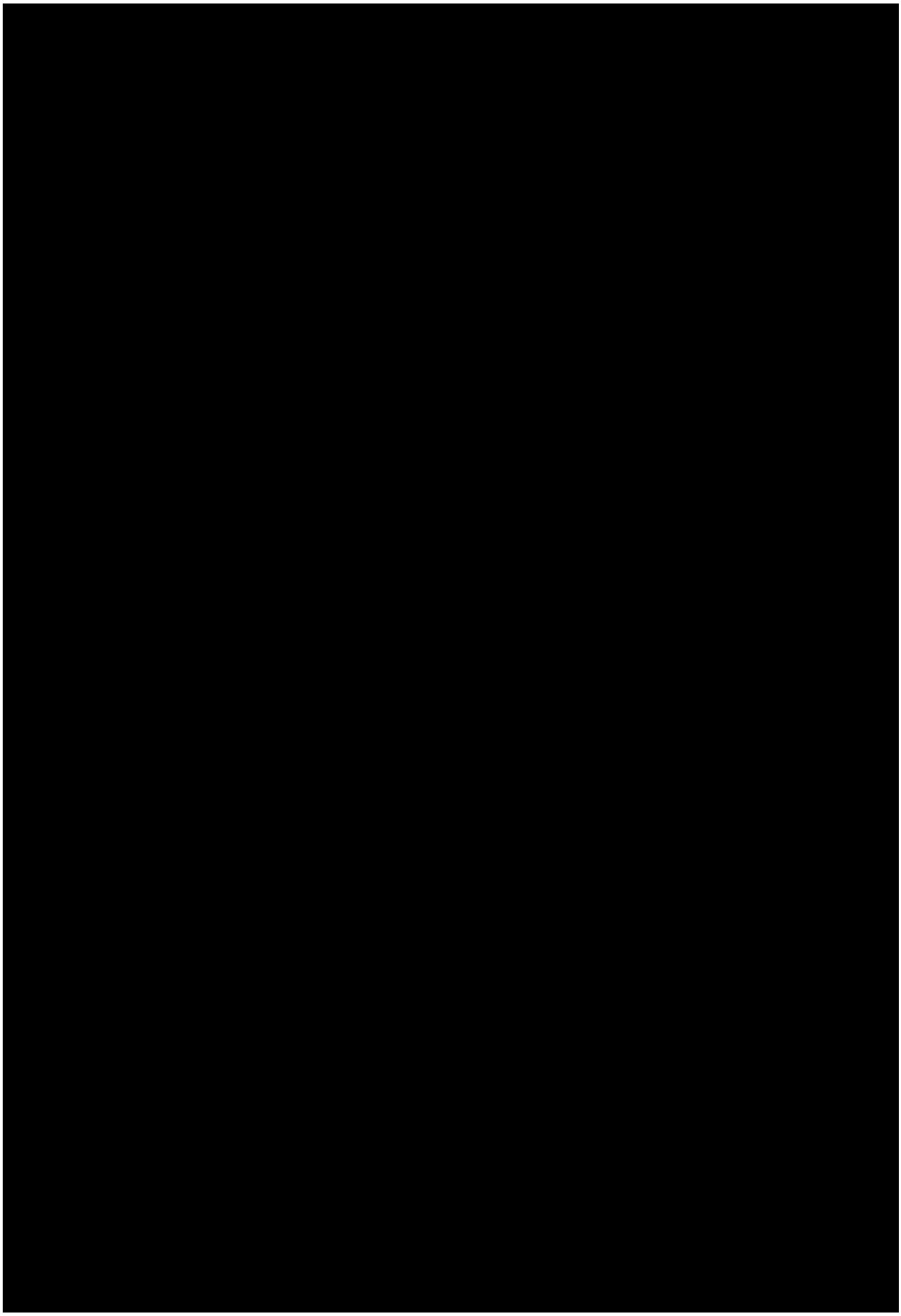

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Appendix K Treatments in LocoMMotion

The following treatment were given in LocoMMotion.

Table 88. Standard of care treatments in LocoMMotion

Treatment Regimen	Frequency (number)	Frequency proportion
Carfilzomib-Dexamethasone	32	12.9%
Pomalidomide-Cyclophosphamide-Dexamethasone	27	10.9%
Pomalidomide-Dexamethasone	24	9.7%
Ixazomib-Lenalidomide-Dexamethasone	13	5.2%
Panobinostat-Bortezomib-Dexamethasone	11	4.4%
Carfilzomib-Cyclophosphamide-Dexamethasone	7	2.8%
Bortezomib-Bendamustine-Dexamethasone	6	2.4%
Elotuzumab-Pomalidomide-Dexamethasone	6	2.4%
Bortezomib-Doxorubicin-Dexamethasone	5	2.0%
Carfilzomib-Pomalidomide-Dexamethasone	5	2.0%
Lenalidomide-Dexamethasone	5	2.0%
Belantamab Mafodotin	4	1.6%
Bendamustine-Prednisone	4	1.6%
Cyclophosphamide-Dexamethasone	4	1.6%
Daratumumab-Bortezomib-Dexamethasone	3	1.2%
Bortezomib-Lenalidomide-Dexamethasone	3	1.2%
Bortezomib-Dexamethasone-Venetoclax	3	1.2%
Daratumumab-Carfilzomib-Cisplatin-Cyclophosphamide-Etoposide	3	1.2%
Daratumumab-Carfilzomib-Dexamethasone	3	1.2%
Carfilzomib-Lenalidomide-Dexamethasone	3	1.2%
Cisplatin-Cyclophosphamide-Doxorubicin-Etoposide-Dexamethasone	3	1.2%
Daratumumab-Pomalidomide-Dexamethasone	3	1.2%
Elotuzumab-Lenalidomide-Dexamethasone	3	1.2%
Melphalan-Dexamethasone	3	1.2%
Bendamustine	2	0.8%

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Bortezomib-Cisplatin-Cyclophosphamide-Doxorubicin-Etoposide	2	0.8%
Daratumumab-Bortezomib-Cyclophosphamide	2	0.8%
Bortezomib-Cyclophosphamide-Dexamethasone	2	0.8%
Cisplatin-Cyclophosphamide-Doxorubicin-Etoposide	2	0.8%
Cyclophosphamide	2	0.8%
Daratumumab-Lenalidomide-Dexamethasone	2	0.8%
Ixazomib-Dexamethasone	2	0.8%
Ixazomib-Pomalidomide-Dexamethasone	2	0.8%
Melphalan	2	0.8%
Melphalan-Prednisone	2	0.8%
Bortezomib-Belantamab Mafodotin-Dexamethasone	1	0.4%
Belantamab Mafodotin-Dexamethasone	1	0.4%
Bortezomib-Bendamustine	1	0.4%
Ixazomib-Bendamustine-Dexamethasone	1	0.4%
Bendamustine-Dexamethasone-Prednisone	1	0.4%
Bendamustine-Rituximab	1	0.4%
Bortezomib-Cisplatin-Cyclophosphamide-Etoposide-Dexamethasone	1	0.4%
Bortezomib-Thalidomide-Cisplatin-Doxorubicin	1	0.4%
Bortezomib-Cyclophosphamide	1	0.4%
Bortezomib-Cyclophosphamide-Doxorubicin-Etoposide-Dexamethasone	1	0.4%
Bortezomib-Thalidomide-Cyclophosphamide-Etoposide-Dexamethasone	1	0.4%
Daratumumab-Bortezomib-Pomalidomide-Doxorubicin-Dexamethasone	1	0.4%
Bortezomib-Pomalidomide-Dexamethasone	1	0.4%
Bortezomib-Melphalan-Prednisone	1	0.4%
Melphelan-Busulfan-Dexamethasone	1	0.4%
Carfilzomib	1	0.4%
Carfilzomib-Thalidomide-Cisplatin-Cyclophosphamide-Etoposide	1	0.4%
Carfilzomib-Cyclophosphamide	1	0.4%
Daratumumab-Carfilzomib-Cyclophosphamide-Dexamethasone	1	0.4%
Carfilzomib-Thalidomide-Cyclophosphamide-Dexamethasone	1	0.4%

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Daratumumab-Carfilzomib-Pomalidomide-Dexamethasone	1	0.4%
Daratumumab-Carfilzomib-Selinexor-Dexamethasone	1	0.4%
Daratumumab-Carfilzomib-Doxorubicin	1	0.4%
Panobinostat-Carfilzomib-Dexamethasone	1	0.4%
Carfilzomib-Venetoclax-Dexamethasone	1	0.4%
Carmustine-Cyclophosphamide-Melphalan-Vincristine-Prednisone	1	0.4%
Thalidomide-Cisplatin-Cyclophosphamide-Etoposide-Dexamethasone	1	0.4%
Daratumumab-Lenalidomide-Doxorubicin-Cyclophasphamide-Dexamethasone	1	0.4%
Daratumumab-Lenalidomide-Cyclophasphamide	1	0.4%
Cyclophosphamide-Doxorubicin-Vincristine-Dexamethasone	1	0.4%
Ixazomib-Cyclophosphamide-Dexamethasone	1	0.4%
Ixazomib-Pomalidomide-Cyclophosphamide-Dexamethasone	1	0.4%
Thalidomide-Cyclophosphamide-Dexamethasone	1	0.4%
Isatuximab-Cyclophosphamide	1	0.4%
Pomalidomide-Cyclophosphamide	1	0.4%
Pomalidomide-Cyclophosphamide-Prednisone	1	0.4%
Cyclophosphamide-Prednisone	1	0.4%
Lenalidomide-Melphalan-Dexamethasone	1	0.4%
Lenalidomide-Melphalan-Dexamethasone-Prednisone	1	0.4%
Venetoclax-Dexamethasone	1	0.4%
Pomalidomide	1	0.4%
Selinexor-Prednisone	1	0.4%
Venetoclax	1	0.4%

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