Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende sacituzumab govitecan til behandling af lokalt fremskreden eller metastatisk triple-negativ brystkræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. sacituzumab govitecan til behandling af lokalt fremskreden eller metastatisk triple-negativ brystkræft
2. Forhandlingsnotat fra Amgros vedr. sacituzumab govitecan til behandling af lokalt fremskreden eller metastatisk triple-negativ brystkræft
3. Ansøgers endelige ansøgning vedr. sacituzumab govitecan til behandling af lokalt fremskreden eller metastatisk triple-negativ brystkræft

From Gilead Sciences

To Danish Medicines Council

28.09.2022

Gilead comments to draft DMC report Trodelvy mTNBC

Dear Andreas Willerslev-Olsen and colleagues,

Thanks to you and your colleagues for sending the draft DMC assessment report for Trodelvy in mTNBC, and for our opportunity to come with our inputs to the report by 28th September 2022.

We have reviewed the report, and generally we find the draft report thorough and well written.

We have therefore focused our comments on two aspects of the report;

1. The decision to set QALY net gains to zero vs comparator in the progression free state.
2. The choice of distribution model for survival estimation.

Ad 1

ASCENT data on QoL is the best information available to compare Trodelvy with TPC in this patient population, and a significant difference in favor of Trodelvy has been demonstrated.

The assessment overrules this documented benefit by saying that there is some uncertainty due to a sum of arguments consisting of open label design, lower completion rates in the TPC arm, uncertainty stemming from mapping and uncertainty stemming from use of British utility weights. In the Discussion chapter 5 however, you state that it is not documented that there is a considerable **difference** in QoL between the two treatments, i.e. that there may be a difference, which Gilead would agree to.

Lower completion rates in the comparator arm in such studies is to our knowledge common, as these study participants typically has a shorter time to event. It is furthermore standard practice to use mapping from a disease specific and very much used tool like EORTC. British utility weights is also

standard practice to use in HTA evaluations. Real world evidence is increasingly used to support decision-making, in spite of the fact that it is by definition open label.

We would therefore argue that it is too conservative to set the benefit to zero, and would pragmatically propose that the QALY benefit for Trodelvy is set between the DMC estimate and the estimate resulting from using treatment specific QALY weights in the PFS state as per our submission.

Ad 2

We take note that you on the basis of our submission based on the primary data cut (Bardia et al. 2021, NEJM) have decided to use Weibull distribution for the estimation of survival, on the basis of statistical fit and what you see as evidence from current clinical practice in Denmark.

[redacted]

[redacted]

Summary

1. Using a Weibull distribution model does not provide the best estimations of OS when you take the the secondary data cut into account
2. Log-logistic distribution is in our opinion the best model choice, both from a visual inspection of the curves and from an AIC/BIC perspective
3. The use of Trodelvy for mTNBC would change clinical practice with increased survival, and there is already now documented evidence of long time survivors among these patients. Hence, the use of Weibull distribution is in our opinion too conservative.
4. We therefore pragmatically propose to use a log-logistic distribution model with a ten year time horizon to more accurately reflect the added benefit of Trodelvy in this patient group.

Enclosures

- Large size plots ppt format
- Mougalian et al 2018, Cancer Medicine
- Loibl et al (abstract); Health-related quality of life (HRQoL) in the ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC)
- Loibl et al (abstract); Assessment of health-related quality of life by clinical response from the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC)

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28.10.2022
MGK/ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.11.2022
Leverandør	Gilead Sciences
Lægemiddel	Trodelvy (sacituzumab govitecan)
Ansøgt indikation	Trodelvy (sacituzumab govitecan) er som monoterapi indiceret til behandling af voksne patienter med ikke-resektabel eller metastatisk triple-negativ brystkræft (mTNBC), som har fået to eller flere tidligere systemiske behandlinger, herunder mindst en af dem ved fremskreden sygdom.

Forhandlingsresultat

Amgros har opnået følgende pris på Trodelvy (sacituzumab govitecan):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Trodelvy (sacituzumab govitecan)	200 mg	1 stk.	6.976	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen lægemidler i direkte konkurrence. Tabel 2 nedenfor viser de årlige lægemiddeludgifter for Trodelvy (sacituzumab govitecan).

Tabel 2: Årlige lægemiddeludgifter

Lægemiddel	Dosering/ dispenseringsform	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år*	Årlige lægemiddeludgift SAIP pr. år (DKK)
Trodelvy (Sacituzumab govitecan)	10 mg/kg på dag 1 og af 8 i 21-dages behandlingsserier/ IV	200 mg	[redacted]	~129	[redacted]

*74,3 kg

Status fra andre lande

Norge: Under vurdering [1]
Sverige: Anbefalet[2]
England: Anbefalet[3]

Konklusion

[redacted].

[1] Sacituzumab govitecanm (Trodelvy) (nyemetoder.no)
[2] https://janusinfo.se/download/18.1d01de9d181a12740df8ca3c/1656586450540/Trodelvy-220630.pdf
[3] https://www.nice.org.uk/guidance/ta819/chapter/1-Recommendations

Medicinrådet

Application for the assessment of sacituzumab govitecan (Trodelvy®) for the treatment of patients with unresectable or metastatic triple-negative breast cancer (mTNBC)

January 10th, 2022

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	Trodelvy®
Generic name	Sacituzumab govitecan
Marketing authorization holder in Denmark	Gilead Sciences Ireland UC, Carrigtohill, County Cork, T45 DP77, Ireland
ATC code	L01FX17
Pharmacotherapeutic group	Other antineoplastic agents, monoclonal antibodies
Active substance(s)	Sacituzumab govitecan

Overview of the pharmaceutical	
Pharmaceutical form(s)	Powder for concentrate for solution for infusion
Mechanism of action	Sacituzumab govitecan is a Trop-2-directed antibody-drug conjugate. Sacituzumab is a humanized antibody that recognizes Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker. Sacituzumab govitecan binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.
Dosage regimen	The recommended dose of sacituzumab govitecan is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles. Continue treatment until disease progression or unacceptable toxicity.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Sacituzumab govitecan as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, including at least one of them for advanced disease.
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Monotherapy. No co-medication.
Packaging – types, sizes/number of units, and concentrations	1 vial of powder containing 200 mg sacituzumab govitecan. After reconstitution, one mL of solution contains 10 mg sacituzumab govitecan.
Orphan drug designation	No

2. Abbreviations

1L	First line
2L	Second line
3L	Third line
ACS	American Cancer Society
AE	Adverse events
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
BC	Breast Cancer
BIC	Bayesian information criterion
BM	Brain metastases
BM-ve	Brain Metastasis negative population in ASCENT study
CBR	Clinical benefit rate

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CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
CNS	Central nervous system
CT	Computed tomography
CUA	Cost-utility analysis
DBCG	Danish Breast Cancer Group
DMC	Danish Medicines Council (Medicinrådet)
DOR	Duration of response
DPD	Dihydropyrimidine dehydrogenase
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
EQ-5D-5L/3L	EuroQoL 5 dimensions, 5 levels/3 levels
ER	Estrogen receptor
GP	General practitioner
HER2	Human epidermal growth factor 2
HR	Hazard ratio
HRQoL	Health related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
IRC	Independent review committee
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KOL	Key Opinion Leader
LA	Locally advanced
LY	Life years
mBC	Metastatic breast cancer
mTNBC	Metastatic triple negative breast cancer
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall survival
OWSA	One way sensitivity analysis
PD	Progressed disease
PD-1	Programmed cell-death protein 1
PD-L1	Programmed death-ligand 1
PF	Progression free
PFS	Progression free survival
PR	Progesterone receptor
QALY	Quality of adjusted life years
QLQ-C-30	Quality of Life Questionnaire of Cancer Patients, version 3.0

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QoL	Quality of life
RCT	Randomized Controlled Trial
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RR	Response rate
SAE	Serious adverse event
SD	Standard deviation
SG	Sacituzumab govitecan (TRODELVY®)
TEAE	Treatment-emergent adverse event
TNBC	Triple-negative breast cancer
TPC	Treatment of physician's choice
Trop-2	Tumor-associated calcium signal transducer 2

3. Tables and Figures

3.1 Table of tables

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4. Summary

This single technology assessment investigates the clinical and health economic value of sacituzumab govitecan (Trodelvy®) compared to the relevant current treatment used in Denmark for adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease.

Compared with other forms of breast cancer (BC), triple-negative breast cancer (TNBC) has often faster growing tumors and is associated with a poorer prognosis and an earlier risk of relapse. Along with a worse prognosis and earlier rate of relapse [1, 2], patients with TNBC are more likely to develop distant metastases than patients with other subtypes of BC [3, 4]. Hence, there exists a particularly high unmet need for effective and tolerable therapies for unresectable or mTNBC that can improve outcomes without compromising the health-related quality of life (HRQoL) for patients who have progressed on chemotherapy and have received two or more prior systemic therapies, including at least one of them for advanced disease.

In Denmark, approximately 90-100 patients (see section 5.1.6) with unresectable or mTNBC are potentially eligible for treatment with sacituzumab govitecan every year. We estimate that out of those eligible patients around 25 patients would be treated annually in year 4 and 5.

Intervention
Sacituzumab govitecan consists of two active components: a monoclonal antibody that has been linked to a small molecule, SN-38. The monoclonal antibody has been designed to recognize and bind to Trop-2, a transmembrane glycoprotein that is overexpressed in many cancers.
Upon binding sacituzumab govitecan is internalized with the subsequent release of SN-38 from a hydrolysable linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death. The recommended dose of sacituzumab govitecan is 10 mg/kg body weight administered as an IV infusion once weekly on Day 1 and Day 8 of 21-day treatment cycles. Treatment should be continued until disease progression or unacceptable toxicity.

Comparator
Currently, recommendation for treatment of second-line or later unresectable or mTNBC in Denmark is to treat with sequential single-drug chemotherapy[5]. Eligible chemotherapy drugs include capecitabine, vinorelbine, eribulin, and gemcitabine. Treatment choice depends on multiple factors, including the patient's age, general condition, previous treatment, toxicity, comorbidities, and patient preference. Therefore, all these single-drug chemotherapy drugs are considered as appropriate comparators for this assessment.
Single-drug chemotherapy is chosen as the relevant comparator in this analysis according to the comparator arm in the ASCENT phase III study. The comparator arm of the ASCENT study, treatment of physician's choice (TPC), consists of either capecitabine (12.6%), vinorelbine (19.8%), eribulin (53.1%), and gemcitabine (14.5%). Consequently, this treatment basket aligns with the current treatments used in Danish clinical practice for unresectable or mTNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease. This has been validated by several Danish clinical experts (See also section 11)[6].

Clinical evidence
Sacituzumab govitecan has been studied in patients with mTNBC in a phase 1/2 study (IMMU-132-01) and a phase 3 study (ASCENT), both of which have been completed [7-10]. IMMU-132-01 was a multicentre, open-label, single-group, phase I/II basket-design trial that evaluated the safety and efficacy of sacituzumab govitecan in 495 previously treated

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patients with advanced epithelial cancers, including 108 mTNBC patients [8]. The primary endpoints were safety and overall response rate [7].
ASCENT was an international, multicentre, open-label, randomized, phase 3 study in 529 patients with unresectable, locally advanced, or metastatic TNBC who were refractory or had relapsed after receiving two or more prior chemo-therapies, including one or more prior therapy for locally advanced or metastatic disease [10, 11]. The primary endpoint was progression-free survival (PFS) by blinded independent central review in patients without brain metastases, and select secondary endpoints were investigator-assessed PFS and OS for the intention-to-treat (ITT) population (i.e., all randomized patients) [10].

Clinical comparison
The ASCENT phase III study forms the basis of the comparative analysis and provides efficacy and safety data for sacituzumab govitecan in patients with relapsed or refractory mTNBC who have progressed on chemotherapy and have received two or more prior systemic therapies, including at least one of them for advanced disease. Evidence from ASCENT indicates that sacituzumab govitecan is highly effective when used in its full licensed indication. For patients in the ITT population, the median progression-free survival (PFS) was 4.8 months according to both IRC assessment and investigator assessment. For patients in the ITT population, the median overall survival (OS) was 11.8 months.

The clinical value of sacituzumab govitecan compared to TPC is best demonstrated by the critical outcome measures PFS and OS. The results from the direct comparison for PFS, demonstrate that sacituzumab govitecan provides a statistically significant 3.1-month gain in median PFS compared with TPC in the ITT population (median 4.8 months vs. 1.7 months; HR 0.43 [95%CI: 0.347-0.541]) and 0.38 [95%CI: 0.31-0.48]) according to IRC- and investigator assessment, respectively. This exceeds the minimal clinically important difference of 3 months in median PFS, according to the previous guidelines by DMC [12]. For OS in the ITT population, the direct comparison indicates that sacituzumab govitecan provides a statistically significant 4.9-month gain in median OS compared with TPC (median 11.8 months vs. 6.9 months; HR 0.51 [95% CI: 0.41-0.62]). This exceeds the minimal clinically important difference of 3 months in median OS, according to the previous guidelines by DMC [12].

Safety outcomes were compared directly and by narrative in ASCENT between sacituzumab govitecan and TPC, for patients in the ITT population. Sacituzumab govitecan had a consistent and generally manageable safety profile and was well tolerated in the treated population. The most common (>10%) treatment-related AEs was neutropenia all grades (reported in 63% of patients given sacituzumab govitecan), diarrhea (59%), and nausea (57%). No cases of severe cardiovascular toxicity or grade >2 neuropathy was reported; one patient had grade 3 interstitial lung disease (pneumonitis), which resolved following treatment discontinuation. No treatment-related deaths were seen in the sacituzumab govitecan group, while one treatment-related death was noted in the TPC group. For patients receiving sacituzumab govitecan a total of 188 (72.9%) treatment-related AEs grade 3 or higher were reported. Fewer patients receiving sacituzumab govitecan discontinued treatment due to AEs (4.7%) compared to patients receiving TPC (5.4%).

EORTC QLQ-C30 was used in ASCENT to measure HRQoL, and over the course of the study, significant improvements from baseline in HRQoL were seen with sacituzumab govitecan compared with TPC for the functional and symptom domains of global health status/quality of life, physical functioning, emotional functioning, fatigue, pain, dyspnea, and insomnia. Diarrhea scores were significantly worse for sacituzumab govitecan vs TPC; however, this did not appear to adversely impact global HRQoL or physical functioning.

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In the analysis, the most relevant comparator for sacituzumab govitecan is composed by treatment of physician's choice (TPC) basket composed by capecitabine (12.6%), vinorelbine (19.8%), eribulin (53.1%) and gemcitabine (14.5%), as presented in the ASCENT trial [10] and validated by a Danish clinician [6] to be relevant to Danish clinical practice.

A partitioned survival model was used to model mean estimated costs, and QALYs and associated incremental cost-effectiveness ratio (ICER). The base case analysis of the health economics evaluation compares sacituzumab govitecan with TPC in a Danish setting from a restricted societal perspective. The analysis was performed using a 20-year time horizon, and costs and benefits were discounted with 3.5%, in line with Danish clinical practice.
The cost-utility analysis predicted that sacituzumab govitecan was more effective and more costly compared to TPC, with an ICER of [redacted]

The expected budget impact of introducing sacituzumab govitecan in Denmark is estimated to be [redacted]

In conclusion, sacituzumab govitecan address the unmet need for a more effective, tolerable, and convenient treatment that improves clinical outcomes for mTNBC patients who have received two or more prior systemic therapies, including at least one of them for advanced disease.

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

5.1 The medical condition and patient population

5.1.1 The pathophysiology of the disease

BC is a heterogeneous disease [13]. TNBC is a basal-like BC subtype defined as a tumor lacking hormone receptor expression (i.e., estrogen receptor [ER]- and progesterone receptor [PR]-negative) and without overexpression of human epidermal growth factor 2 (i.e., HER2-negative)[14]. TNBC comprises approximately 10% to 15% of all BC cases worldwide [3, 15-20]. In Denmark, the proportion of TNBCs is reported to be 9,1 % [21]. The pathophysiologic characteristics of TNBC include a larger mean tumor size and a higher histologic grade than what is seen in non–basal-like BC subtypes [14].

Tumor-associated calcium signal transducer 2 (Trop-2), expressed by the TACSTD2 gene, is a transmembrane protein thought to play a role in the growth of cancer cells and their invasion throughout the body [22, 23]. Trop-2 signaling is thought to affect several intracellular pathways, including calcium signaling pathways that impact cell cycle progression [22]. Relative to normal tissue, Trop-2 expression is increased in numerous solid tumor types, particularly TNBC, where it has been found to be overexpressed in most patients (80%) [23-26]. An Italian study of 702 consecutive patients with Stage I to III BC who underwent BC surgery found that the presence of membrane-associated Trop-2 was linked to worse overall survival (OS), while intracellular Trop-2 was linked to a better prognosis [27].

5.1.2 The clinical presentation/symptoms

The clinical presentation of TNBC is the same as for other molecular subtypes of BC, with the most common presentation being a new lump or mass [2, 28]. Other signs and symptoms of BC include swelling in the surrounding

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lymph nodes, nipple changes (e.g., discharges), skin changes (e.g., erythema, skin ulcers, eczema), breast pain or heaviness, and other persistent changes in the breast [28, 29].

5.1.3 Prognosis with current treatment options

Compared with other forms of BC, TNBC has faster-growing tumors and is associated with a poorer prognosis and an earlier risk of relapse[30]. Along with a worse prognosis and earlier rate of relapse [2], patients with TNBC are more likely to develop distant metastases than patients with other subtypes of BC [3, 4]. A feature of mTNBC that distinguishes it from other metastatic breast cancer (mBC) subtypes is the location of metastases, which tend to occur more frequently in the visceral organs (lungs, liver, and central nervous system (CNS)), and less frequently in bone [14]. Treatment of TNBC is guided by stage, molecular subtype, prognostic biomarkers, tumor grade, and patient age, among other factors [31, 32]. For Stage IV TNBC (metastatic disease), the principal systemic treatment option is cytotoxic chemotherapy [5, 29, 31, 33-35]. As shown in several real-world treatment pattern studies, patients with mTNBC often progress rapidly through multiple lines of chemotherapy, particularly after reaching second line (2L) and beyond [36-38], and survival and response outcomes are often poor. Median OS in studies of patients with mTNBC treated with first line (1L) chemotherapy ranges from approximately 10 to 13 months [39-41]. In a meta-analysis of mTNBC subgroups treated in 2L or later with single-agent chemotherapy from 7 cohorts in 6 trials (Phase II and III), the pooled objective response rate (ORR) for the chemotherapy treatment arms was 11% (95% CI: 9%, 14%) [42]. Furthermore, 7 Phase III studies of second- or later-line chemotherapy in patients with mTNBC reported a range of ORRs between 9% and 18%, a range in median OS from 8.1 to 15.2 months, and a median duration of response (DOR) of 4.2 or 5.9 months (reported in 2 subgroup analyses from 1 study) [42].

5.1.4 Prognosis in patients with CNS metastasis

A German-based retrospective analysis reviewed the records of 2,441 patients with invasive BC (11.6% with TNBC) treated at a single center between 1998 and 2006 [4]. When assessing different multivariate risk factors, TNBC was found to be the strongest predictor of developing brain (cerebral) metastases (HR 4.2; 95% CI: 2.3, 7.6; P<0.0001), followed by HR-/HER2+- (HR 3.4; 95% CI: 3.1, 10.9; P=0.005). In the subgroup of patients with TNBC (4.9% of whom had Stage IV disease), the median time to development of BMs was 22 months, and the risk of development was higher in those with large primary tumors and in younger patients (diagnosis before age <50 years) [4]. A cohort study of 2,448 patients with Stage I to III TNBC treated at a single US cancer center (diagnosis between 1990 and 2010) found that, of the 805 patients who had developed distant metastases, 115 (14.3%) developed their first metastases in the brain [43]. At 2 and 5 years, the general cumulative incidence of BMs as first site of distant recurrence was 3.7% and 5.4%, respectively; these incidence rates increased with each stage of disease.

A Swedish study from 2020, compared younger and older patients with TNBC and found the proportions of patients with BMs to be about 53% in older patients and 17% in younger patients [44].

Patients with BMs are generally recognized to have a poor prognosis. In a retrospective analysis of 116 patients with mTNBC treated at a cancer center in the US, patients whose first metastatic presentation included CNS metastasis (14% of total) were shown to have a 3.4-fold greater rate of death compared with those without an initial CNS metastasis (95% CI: 1.9, 6.1) [39]. The median survival time of patients with a CNS metastasis at any point (46% of total) was 4.9 months from the time of first CNS metastasis.

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5.1.5 Incidence and prevalence in Denmark

Table 1: Incidence and prevalence in the past 5 years – metastatic TNBC

Year	2016	2017	2018	2019	2020
Incidence in Denmark	130-152	128-150	135-157	137-160	128-150
Prevalence in Denmark	1.792-2.090	1.843-2.150	1.895-2.210	1.949-2.274	-

Incidence of metastatic TNBC

In Denmark the annual incidence of breast cancer in 2016-2020 has ranged between 4.810-5.105 with minor annual variances [45]. The annual incidence of TNBC in Denmark was estimated by multiplying 9% [21] with the annual general breast cancer incidence for each given year in the period 2016-2020. Of the TNBC patients, approximately 30-35%, will be diagnosed with unresectable or metastatic TNBC based on clinical expert interview [6] and advisory board [46] (see also section 11). The estimated annual incidence numbers are illustrated in Table 1.

Prevalence of metastatic TNBC in Denmark

Estimates for the prevalence of TNBC patients in Denmark are not available. Consequently, to estimate the prevalence of TNBC, the prevalence of all breast cancer for 2016-2019, derived from Danish Cancer registry, have been multiplied with 9%, corresponding to the proportion of patients expected to be TNBC. Based on data from the DBCG database, approximately 9% [21] of all diagnosed breast cancers are TNBC. Data for 2020 has not been published from the Danish Cancer registry at the time of conducting this application. Therefore, no prevalence estimate has been included for 2020. Of the TNBC patients approximately 30-35%, will be diagnosed with unresectable or metastatic TNBC based on clinical expert interview [6] and advisory board [46]. This methodology will, however, most likely greatly overestimate the prevalence of mTNBC patients in Denmark as mTNBC median survival time is estimated to be three times lower than other types of breast cancers with a median survival of 14.8 months versus 50.1 months in HER2+ patients [30]. Hence, the prevalence is expected to be significantly lower than the estimates indicated in Table 1.

Table 2: Estimated number of patients eligible for treatment

Year	2022	2023	2024	2025	2026
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	90-100	90-100	90-100	90-100	90-100

Estimated number of patients eligible for sacituzumab govitecan

The number of eligible patients with mTNBC in Denmark are estimated by using the estimated incidence numbers for mTNBC patients in Denmark above (Table 1). The incidence estimates reported in table 1 reflects the patients diagnosed with mTNBC eligible for first line treatment. Sacituzumab govitecan have been approved for patients that have received two or more prior systemic therapies, including at least one of them for advanced disease. It assumed that approximately 70% of patients in 1L will received subsequent therapy, based on feedback and validation from clinical experts [11] (see also section 11). Consequently, the number of patients eligible for treatment with sacituzumab govitecan that have received two or more prior systemic therapies are 90-100 annually.

We anticipate that on year five following the introduction 25% of the eligible patients will be treated with sacituzumab govitecan annually, based on dialogue with Danish Breast Cancer oncologists (see section 9 for further details).

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5.1.6 Patient population relevant for this application

The eligible population will be adult patients with unresectable or mTNBC, who have received two or more prior systemic therapies, including at least one of them for advanced disease, reflecting the ITT population of the ASCENT trial [10, 47].

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The treatment patterns in Denmark are described by the guidelines issued by Danish Breast Cancer Group (DBCG) for patients with palliative and systemic treatment of metastatic breast cancer (mBC) [5] and one single technology assessment within mTNBC issued by Danish Medicines Council (DMC) [48]. The principal systemic treatment option for patients with mTNBC is chemotherapy. Several studies have demonstrated efficacy of chemotherapy in second and third line mTNBC, however, based on the available evidence, as stated in the DBCG guideline, it is not possible to determine one specific chemotherapeutic agent or treatment sequence in first or subsequent lines.
The chemotherapy treatments described in the DBCG guideline are eribulin, capecitabine, vinorelbine and gemcitabine combined with carboplatin.[5]

The DBCG guideline recommend chemotherapy based on the patient's response and benefits and risks of former therapy including, patients' performance status, and patient preferences for treatment. If patients with mTNBC progress or have unacceptable adverse events (AEs) on a given chemotherapy regimen, DBCG guidelines recommend subsequent lines of single-drug chemotherapy. At each subsequent line of therapy, clinicians should assess the effect of ongoing treatment, the benefits and risks of additional therapies, patients' performance status, and patient preferences for treatment, including palliative care.[5]

Based on the DBCG guidelines, single agent chemotherapies are generally recommended for mTNBC patients who have received two or more prior systemic therapies. The recommended drugs are capecitabine, eribulin, vinorelbine and gemcitabine or any unused agents from previous lines.

For patients with newly diagnosed mTNBC who have PD-L1–positive disease, atezolizumab plus nab-paclitaxel may be given in 1L if the patients either have not received (neo) adjuvant chemotherapy or have received it more than 12 months prior [48]. [redacted]

Gemcitabine combined with carboplatin is also used in clinical practice in second and subsequent lines in patients previously treated with capecitabine and or vinorelbine, although to a limited extent. Single-drug chemotherapy is generally recommended above chemotherapy combination due to the increased toxicity outweighing the benefits[5].

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5.2.2 Choice of comparator(s)

Sacituzumab govitecan is indicated for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease [47]. Consequently, possible comparators include second and further line treatments for mTNBC.

As described throughout section 5.2.1, for second- and further lines, the only available treatments for mTNBC in Denmark are single-drug or combination chemotherapy. Eligible chemotherapy drugs include capecitabine, vinorelbine, eribulin, and gemcitabine combined with carboplatin. There is not one preferred choice of chemotherapy. The choice of chemotherapy treatment depends on multiple factors, including patient's age, general condition, previous treatment, toxicity, comorbidities, and patient preference. Therefore, all the mentioned chemotherapy drugs could be considered as potential comparators.

The DBCG guideline also indicate that chemotherapy (capecitabine) and immunotherapy (atezolizumab plus nab-paclitaxel) are typically the choice for 1L treatment, if appropriate. Consequently, the comparator used in ASCENT (treatment of physician's choice (TPC), consisting of either capecitabine (12.6%), vinorelbine (19.8%), eribulin (53.1%), and gemcitabine (14.5%)) align with the expected treatment used for these patients in a Danish setting (see Figure 1). In the ASCENT trial 63-68% of patients had previously received capecitabine, which aligns with what would be expected in Danish clinical practice. The proportion of patients in the ASCENT study that had previously received atezolizumab were 28-30% which also aligns with what would be expected in Danish clinical practice. As capecitabine often has been used in 1L or as adjuvant treatment, the most common 2L choice is eribulin, as illustrated in Figure 1, which also aligns with the majority (53.1%) of patients in the ASCENT received treatment with eribulin.
Hence, the TPC arm in the ASCENT trial is considered representative of Danish clinical practice, which has also been validated by five Danish oncologists representing the majority of the treating centers in Denmark (see section 11).

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5.2.3 Description of the comparator(s)

The drug name, generic drug name and ATC-code for each comparator is presented in Table 3. Detailed information about the mode of action, posology, method of administration, dosing, treatment duration, necessary monitoring, need for diagnostics or other tests, packaging and whether the drug should be administrated as monotherapy or as combination therapy is presented below.

Table 3: Comparator's name, active substance and ATC-code

Drug name	Generic drug name (active substance)	ATC-code	Reference
Halaven	Eribulin	L01XX41	European Medicines Agency, 2021 [49]
Xeloda	Capecitabine	L01BC06	European Medicines Agency, 2021 [50]
Navelbine	Vinorelbine	L01CA04	European Medicines Agency, 2014 [51]
Gemzar	Gemcitabine	L01BC05	European Medicines Agency, NA [52]

5.2.3.1 Eribulin

Eribulin is a monotherapy used to treat LA or mBC which has continued to spread after at least one previous treatment for advanced cancer. Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged and irreversible mitotic blockage [49].

The recommended dose of eribulin is based on the patient's body surface area (m^2). Calculation of the individual dose to be administered to a patient must be based on the strength of the ready-to-use solution that contains 0.44 mg/ml eribulin and the dose recommendation of 1.23 mg/m2. The dose should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle. A doctor should determine how many cycles of treatment the patient should receive[49]. Doctors should consider giving patients an antiemetic as eribulin may cause nausea or vomiting. Doses may be delayed or reduced if patients have very low levels of neutrophils (a type of white blood cell) and platelets (components that help the blood to clot) in their blood or if liver or kidney function is impaired [49].

Monitoring of complete blood counts should be performed on all patients prior to each dose of eribulin. Treatment with eribulin should only be initiated in patients with ANC values ≥ 1.5 x 109 /l and platelets > 100 x 109 /l. Moreover, patients should be closely monitored for signs of peripheral motor and sensory neuropathy. The development of severe peripheral neurotoxicity requires a delay or reduction of the dose. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmia, or concomitant treatment with medicinal

products known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Hypokalemia, hypocalcemia, or hypomagnesaemia should be corrected prior to initiating eribulin and these electrolytes should be monitored periodically during therapy [49].

5.2.3.2 Capecitabine

Capecitabine is used for LA or mBC. Capecitabine can be used in combination with docetaxel or as monotherapy. Capecitabine is a cytotoxic medicine that belongs to the group 'anti-metabolites'. The mode of action is that Capecitabine is converted to the medicine fluorouracil in the body, but more is converted in tumor cells than in normal tissues. In the body, fluorouracil takes the place of pyrimidine (which is part of the DNA and RNA) and interferes with the enzymes involved in making new DNA. As a result, it prevents the growth of tumor cells and eventually kills them [50].

Before starting treatment, it is recommended that patients are tested to check that they have a working dihydropyrimidine dehydrogenase (DPD) enzyme. Capecitabine is available as tablets (150 and 500 mg) and should be taken orally within 30 minutes after a meal [50]. The recommended dose of Capecitabine is based on the patient's height and weight. Given as monotherapy, the recommended starting dose for capecitabine is 1250 mg/m2 administered twice daily (morning and evening; equivalent to 2500 mg/m2 total daily dose) for 14 days followed by a 7-day rest period.[50]

Doses need to be adjusted for patients with liver or kidney disease and for patients who develop certain side effects. For patients with partial DPD deficiency, a lower starting dose may be considered. Once the dose has been reduced, it should not be increased later. Treatment should be discontinued if progressive disease or intolerable toxicity is observed. Careful monitoring during the first cycle of treatment is recommended for all patients [50].

5.2.3.3 Vinorelbine

Vinorelbine is a therapy used for LA or mBC and should be given as monotherapy. Vinorelbine belongs to the group of cytostatic medicines. The mode of action is that Vinorelbine inhibit tubulin polymerization and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentration. The induction of tubulin spiralization is less than that produced by vincristine. Vinorelbine blocks mitosis at G2-M, causing cell death in interphase or at the following mitosis [53].

Vinorelbine should be administrated 25 mg/m2 orally once weekly for 21-day treatment cycles [10]. The patient must be monitored during treatment for thrombocyte and leucocyte counts.

5.2.3.4 Gemcitabine

Gemcitabine is a therapy used for LA or mBC and should be used in combination with paclitaxel. Gemcitabine belongs to the groups of cytotoxic medicines. These medicines kill dividing cells, including cancer cells [52]. The mode of action is that Gemcitabine exhibits antitumor activity. The drug exhibits cell phase specificity by primarily inhibiting cell proliferation in DNA synthesis (S-phase) and on the G1/S-phase boundary [54].

Gemcitabine is available as 200 and 100 mg powder for solution for infusion. Gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m2) administered on Day 1 over approximately 3-hours as an IV

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infusion, followed by gemcitabine (1250 mg/m2) as a 30-minute IV infusion on Days 1 and 8 of each 21-day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient [52].
The patient must be monitored before each dose for platelet, leucocyte, and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10^6/l) prior to initiation of gemcitabine + paclitaxel combination.

5.3 The intervention

Sacituzumab govitecan (Trodelvy®) is a Trop-2–directed antibody-drug conjugate, composed of the following components[55, 56]:

- Sacituzumab (hRS7 IgG1κ), a humanized monoclonal anti–Trop-2 antibody
- SN-38, a topoisomerase inhibitor and the small molecule moiety of sacituzumab
- The hydrolysable linker CL2A, which links sacituzumab to SN-38

Sacituzumab govitecan binds to Trop-2–expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker.[55, 56] SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I–induced single-strand breaks.[55, 56] The resulting DNA damage leads to apoptosis and cell death.[55, 56]
SN-38, the metabolite of irinotecan, is metabolized via the UGT enzyme encoded by the UGT1A1 gene.[55-58] Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity and increased risk of drug toxicity due to the reduced ability of the body to metabolize the drug.[55, 56, 58]
Individuals who are homozygous for the UGT1A1*28 allele are potentially at increased risk for neutropenia, febrile neutropenia, anemia, and diarrhea from sacituzumab govitecan.[55, 56] Approximately 20%, 10%, and 2% of the Black, White, and East Asian populations, respectively, are homozygous for the UGT1A1*28 allele.[55, 56]

The recommended dose of sacituzumab govitecan is 10 mg/kg administered as an intravenous (IV) infusion once weekly on Days 1 and 8 of 21-day treatment cycles.[55, 56] Treatment is continued until patients experience disease progression or unacceptable toxicity.[55, 56]
Prior to each dose of sacituzumab govitecan, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting is recommended.[55, 56] Premedication with antipyretics, H1 and H2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions.[55] Use a 2- or 3-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or a neurokinin 1–receptor antagonist, as well as other drugs as indicated).[55]
No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild hepatic impairment (bilirubin ≤1.5 upper limit of normal [ULN] and aspartate aminotransferase/alanine aminotransferase [AST/ALT] <3 ULN).[55, 56] The safety of sacituzumab govitecan in patients with moderate or severe hepatic impairment has not been established[55, 56]. Sacituzumab govitecan has not been studied in patients with serum bilirubin >1.5 ULN, AST and ALT >3 ULN, or AST and ALT >5 ULN, and associated with liver metastases.[55, 56]
No recommendations can be made for the starting dose in patients with moderate or severe hepatic impairment.[55]
No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild renal impairment.[56] The safety of sacituzumab govitecan in patients with moderate renal impairment or end-stage renal disease (creatinine clearance ≤30 mL/min) has not been established.[56] The use of sacituzumab govitecan should be avoided in these patients.[56]
Sacituzumab govitecan should only be administered as an IV infusion, not as an IV push or bolus.[55, 56] The first infusion should be administered over a period of 3 hours.[55, 56] Patients have to be observed during the infusion and for at least 30 minutes following the initial dose for signs or symptoms of infusion-related reactions.[55, 56] For subsequent infusions, the infusion should be administered over a period of 1 to 2 hours if prior infusions were

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tolerated.[55, 56] Withhold or discontinue sacituzumab govitecan to manage adverse reactions, as described in EMA EPAR [47]

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

Based on the DMC methods guideline, the DMC can accept that systematic literature review is not carried out if one or several studies have already directly compared the new pharmaceutical with the relevant comparator.

The pivotal RCT phase-3 ASCENT trial provides head-to-head data with the relevant comparator TPC, consisting of either capecitabine (12.6%), vinorelbine (19.8%), eribulin (53.1%), and gemcitabine (14.5%), aligning with the current standard treatment in Denmark. As no further comparative studies with sacituzumab govitecan have been conducted, a literature search will not contribute any additional relevant information. The study matches the clinical practice in Denmark, and the phase 3 RCT provides the highest level of evidence possible.

6.2 List of relevant studies

Illustrated below in Table 4 is the full list of the references used as evidence included for this submission, with publication type, study and relevance to the dossier given for each citation.

Table 4: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. Bardia A et al. N Engl J Med.2019;380(8):741-751.	A Phase I/II Study of IMMU-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients With Epithelial Cancer	NCT01631552	Study start December 17 2012; Study completed August 13, 2020
Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. Bardia A et al and ASCENT Clinical Trial Investigators. N Engl J Med. 2021 Apr 22;384(16):1529-1541.	An International, Multi-Center, Open-Label, Randomized, Phase III Trial of sacituzumab govitecan versus Treatment of Physician Choice in Patients with Metastatic Triple-Negative Breast Cancer Who Received at least Two Prior Treatments	NCT02574455	Study start November 7, 2017; Study Completed March 11, 2020

For detailed information about included studies, refer to appendix B.

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7. Efficacy and safety

7.1 Efficacy and safety of sacituzumab govitecan compared to TPC for adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease

7.1.1 Relevant studies

Sacituzumab govitecan has been studied in patients with mTNBC in a Phase I/II study and a Phase III study, both of which have been completed [7, 8, 10, 59]. Table 5 illustrates the study design, population, treatments and endpoints included in the two trials.
IMMU-132-01 was a multicenter, open-label, single-group, basket-design trial that evaluated the safety and efficacy of sacituzumab govitecan in previously treated patients with advanced epithelial cancers (n=108 with mTNBC) [8].

ASCENT was an international, multi-center, open-label, randomized study in patients with unresectable, LA, or metastatic TNBC who were refractory or had relapsed after receiving ≥2 prior chemotherapies, including ≥1 prior therapy for LA or metastatic disease [10].

Table 5: Clinical trials conducted for sacituzumab govitecan in mTNBC

Trial NCT number	Study design	Population	Treatments	Primary and key secondary endpoints
Phase I/II study				
IMMU-132-01 NCT01631552 (Bardia 2017, Bardia 2019)	• Phase I/II, multicenter, open-label, single-group, basket-design trial • Primary/study completion date: August 2020	• Adult patients (aged ≥18 years) with mTNBC who were refractory or relapsing after receiving ≥2 prior standard therapies for metastatic disease • ECOG PS 0 or 1	• Sacituzumab govitecan 10 mg/kg IV on Days 1 and 8 of every 21-day cycle	Primary • Safety • ORR (complete response or partial response at any time) per RECIST v1.1 Secondary • DOR • TTR • Clinical benefit (complete response, partial response, or stable disease ≥6 months) • PFS • OS

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Phase III study

ASCENT (IMMU-132-05) NCT02574455 (Bardia 2021, Immunomedics 2020, ClinicalTrials.gov 2021)	• Phase III, international, multicenter, open-label, randomized study • Primary completion date: March 2020 • Study completion date: December 2020 (planned); study was ended early*	• Adult patients (aged ≥18 years) with unresectable, LA, or metastatic TNBC who were refractory or had relapsed after receiving ≥2 prior chemo-therapies, including ≥1 prior therapy for LA or metastatic disease • Previous taxane treatment in either the adjuvant, neoadjuvant, or advanced stage • ECOG PS 0 or 1	• Sacituzumab govitecan 10 mg/kg IV on Days 1 and 8 of every 21-day cycle • TPC	Primary • PFS (BM-ve population, as assessed by BICR) Secondary • PFS (all randomized patients; investigator assessment) • OS • ORR • DOR • TTR • QoL • Safety

*The efficacy demonstrated by sacituzumab govitecan over TPC led to early halting of the study by unanimous recommendation of the Data Safety Monitoring Committee.

BICR=blinded independent central review; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; IV=intravenous; mTNBC=metastatic triple-negative breast cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QoL=quality of life;

RECIST v1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; TPC=treatment of physician's choice; TTR=time to response.

7.1.1.1 IMMU-132-01

IMMU-132-01 was a multicenter, open-label, single-group, Phase I/II basket-design trial that evaluated the safety and efficacy of sacituzumab govitecan in previously treated patients with advanced epithelial cancers, including mTNBC [8]. The Phase I portion was conducted to determine the maximum tolerated dose of sacituzumab govitecan; it was determined that 8 to 10 mg/kg (per infusion) should be the doses to be evaluated in Phase II clinical studies, as they showed minimal toxicity over repeated cycles [60].
This section will focus on the Phase II portion of the trial, where sacituzumab govitecan 10 mg/kg was administered IV as a single agent on Days 1 and 8 of every 21-day treatment cycle until patients experienced disease progression or unacceptable AEs.

Inclusion and exclusion criteria

Table 6 presents the key inclusion and exclusion criteria.

Table 6: IMMU-132-01: key inclusion and exclusion criteria

Inclusion	Exclusion
• Age ≥18 years • ECOG PS 0 or 1 • Confirmed mTNBC (per ASCO/ACP guidelines), based on most recent biopsy • Treatment history of ≥2 prior therapies* in a metastatic setting, including prior taxane (any setting) • Adequate bone marrow, renal, and hepatic function • Expected survival ≥6 months • Measurable disease by CT or MRI	• Pregnancy or lactation • BM unless treated and without progression, and no high-dose corticosteroids for at least 4 weeks • Presence of bulky disease (any single mass >7 cm in greatest dimension) unless approved by medical monitor • Active Grade ≥2 anorexia, nausea, or vomiting, and/or signs of intestinal obstruction

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- Prior malignancies within 3 years, except nonmelanoma skin cancer or carcinoma in situ of the cervix
- Positivity for HIV, HBV, or HCV
- Known history of unstable angina, MI, or CHF within 6 months
- Clinically significant cardiac arrhythmia (other than stable AF) requiring anti-arrhythmia therapy

*Qualifying agents include chemotherapy and biologic, targeted, or immunotherapy agents, but do not include anti-HER2 or hormonal agents (for any reason).

ACP=American College of Pathologists; AF=atrial fibrillation; ASCO=American Society of Clinical Oncology; CHF=congestive heart failure; CT=computed tomography; COPD=chronic obstructive pulmonary disease; ECOG PS=Eastern Cooperative Oncology Group performance status; HBV=hepatitis B virus; HCV=hepatitis C virus; HER2=human epidermal growth factor receptor 2; HIV=human immunodeficiency virus; MI=myocardial infarction; MRI=magnetic resonance imaging; mTNBC=metastatic triple-negative breast cancer; TNBC=triple-negative breast cancer.

Primary and secondary endpoints

The Phase II portion of the IMMU-132-01 trial had safety and ORR as primary endpoints

Secondary endpoints included:

- DOR
- Time to response (TTR)
- Clinical benefit rate (CBR); complete response, partial response, or stable disease ≥6 months.
- PFS
- OS

Baseline characteristics

The baseline demographics and characteristics of patients with mTNBC in the IMMU-132-01 trial are presented in Table 7.

Table 7: IMMU-132-01: baseline characteristics in patients with mTNBC

Characteristic	Patients (n=108)
Female sex	107 (99.1)
Median age, years (range)	55 (31, 80)
Race or ethnicity	
White	82 (75.9)
Black	8 (7.4)
Asian	3 (2.8)
Other/not specified	15 (13.9)
ECOG PS	
0	31 (28.7)
1	77 (71.3)

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Median number of prior anticancer therapies (range)	3 (2, 10)
Prior taxanes or anthracyclines for metastatic or nonmetastatic disease	
Taxanes	106 (98.1)
Anthracyclines	93 (86.1)
Prior chemotherapy drugs for metastatic disease	
Cyclophosphamide	20 (18.5)
Platinum agents	74 (68.5)
Gemcitabine	59 (54.6)
Fluoropyrimidine agents	56 (51.9)
Eribulin	49 (45.4)
Vinorelbine	17 (15.7)
Prior use of checkpoint inhibitors	18 (16.7)
Most common sites of metastases	
Visceral organs (solid organs, except brain)	83 (76.9)
Lung or pleura	61 (56.5)
Liver	45 (41.7)
Other visceral organs (adrenal glands, pancreas, kidney)	7 (6.5)
Nonvisceral sites	25 (23.1)

Note: Data are reported as n (%) unless otherwise stated.
ECOG PS=Eastern Cooperative Oncology Group performance status; mTNBC=metastatic triple-negative breast cancer.

7.1.1.2 ASCENT

ASCENT was an international, multicenter, open-label, randomized, Phase III study in patients with unresectable, LA, or metastatic TNBC who were refractory or had relapsed after receiving ≥2 prior chemotherapies, including ≥1 prior therapy for LA or metastatic disease [10]. Sacituzumab govitecan 10 mg/kg was administered IV as a single agent on Days 1 and 8 of every 21-day treatment cycle until patients experienced disease progression or unacceptable toxicity. The comparator defined as treatment of physician's choice (TPC), consisted of either capecitabine (12.6%), vinorelbine (19.8%), eribulin (53.1%), and gemcitabine (14.5%).

Inclusion and exclusion criteria

Table 8 presents selected inclusion and exclusion criteria in ASCENT.

Table 8: ASCENT: selected inclusion and exclusion criteria

Inclusion	Exclusion
• Age ≥18 years • ECOG PS 0 or 1 • Cytologically or histologically confirmed mTNBC	• Pregnancy or lactation • Gilbert's Syndrome

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- Unresectable, LA, or metastatic TNBC who were refractory or had relapsed after receiving ≥2 prior chemotherapies, including ≥1 prior therapy for LA or metastatic disease
    - No cap on the number of prior chemotherapies for LA or metastatic disease
    - Earlier adjuvant or neoadjuvant therapy for more limited disease qualified as 1 of the required prior regimens if the development of unresectable, LA, or metastatic disease occurred within 12 months after completion of chemotherapy
- Eligible for one of the TPC chemotherapy options (eribulin, vinorelbine, gemcitabine, or capecitabine)
- Adequate hematologic, hepatic, and renal function
- Measurable disease* by CT or MRI (per RECIST v1.1)
- At least 2 weeks beyond prior anticancer treatments and recovered from all acute toxicities to Grade ≤1 (alopecia and peripheral neuropathy to Grade ≤2)
- At least 2 weeks beyond high-dose systemic corticosteroids
- Patients with treated, nonprogressive BMs who had not received high-dose corticosteroids for ≥4 weeks

- Prior malignancies within 3 years, except nonmelanoma skin cancer or carcinoma in situ of the cervix
- Positivity for HIV, HBV, or HCV
- Known history of unstable angina, MI, or CHF within 6 months
- Infection requiring antibiotic use within 1 week of randomization
- Known history of clinically significant active COPD, or other moderate-to-severe chronic respiratory illness present within 6 months

*Bone-only disease was not permitted.

CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; CT=computed tomography; ECOG PS=Eastern Cooperative Oncology Group performance status; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; MRI=magnetic resonance imaging; RECIST v.1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; TNBC=triple-negative breast cancer; TPC=treatment of physician's choice.

Primary and secondary endpoints

The primary endpoint in ASCENT was PFS by blinded independent central review (BICR) in the BM-ve population [10]. Secondary endpoints, which were assessed in the ITT population (i.e., all randomized patients) included:

- Investigator-assessed PFS
- OS
- ORR
- DOR
- TTR
- QoL
- Safety

Baseline characteristics

The baseline demographics and characteristics of patients in the ASCENT trial are presented in Table 9 (ITT population) and Table 10 (BM-ve population, used for the primary endpoint analysis).

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Table 9: ASCENT patient baseline characteristics (ITT population)

Characteristic	Sacituzumab govitecan (n=267)	TPC (n=262)
Female sex	265 (99)	262 (100)
Median age, years (range)	54 (27, 82)	53 (27, 81)
Race		
White	215 (81)	203 (78)
Black	28 (11)	34 (13)
Asian	13 (5)	9 (3)
Other	11 (4)	16 (6)
ECOG PS		
0	121 (45)	108 (41)
1	146 (55)	154 (59)
BRCA1/2 mutation status		
Positive	20 (8)	23 (9)
Negative	150 (56)	146 (56)
TNBC at initial diagnosis		
Yes	192 (72)	180 (69)
No	75 (28)	82 (31)
Number of prior systemic therapies		
Median (range)	4 (2, 17)	4 (2, 14)
Mean (SD)	5 (2)	5 (2)
2 therapies	33 (12)	32 (12)
3 therapies	66 (25)	60 (23)
≥4 therapies	168 (63)	170 (65)
Setting of prior systemic therapies		
Adjuvant	161 (60)	148 (57)
Neoadjuvant	124 (46)	125 (48)
Metastatic	258 (97)	260 (99)
Locally advanced disease	10 (4)	5 (2)
Types of prior treatments		
Systemic chemotherapy or immunotherapy	267 (100)	262 (100)
Surgery	252 (94)	250 (95)
Radiotherapy (non-brain)	223 (84)	206 (79)
Most common prior chemotherapy		
Cyclophosphamide	221 (83)	216 (82)
Paclitaxel	204 (76)	210 (80)
Capecitabine	171 (64)	183 (70)
Carboplatin	164 (61)	179 (68)
Doxorubicin	142 (53)	141 (54)

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Docetaxel	101 (38)	83 (32)
Prior use of PD-1/PD-L1 inhibitors	79 (30)	74 (28)
Most common sites of disease*		
Lung only	131 (49)	115 (44)
Liver	107 (40)	114 (44)
Bone	62 (23)	63 (24)
Mediastinal lymph nodes	61 (23)	68 (26)
Axillary lymph nodes	59 (22)	78 (30)

Note: Data are presented as n (%) unless otherwise stated.

*Based on independent central review of target and nontarget lesions.

BRCA1/2=breast cancer gene 1 or 2; ECOG PS=Eastern Cooperative Oncology Group performance status; ITT=intention-to-treat; PD-1=programmed cell-death protein 1; PD-L1=programmed death-ligand 1; SD=standard deviation; TNBC=triple-negative breast cancer; TPC=treatment of physician's choice.

Table 10 ASCENT: patient baseline characteristics (BM-ve population*)

Characteristic	Sacituzumab govitecan (n=235)	TPC (n=233)
Female sex	233 (99)	233 (100)
Median age, years (range)	54 (29, 82)	53 (27, 81)
Race		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other	10 (4)	15 (6)
ECOG PS		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
***BRCA1/2* mutation status**		
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
TNBC at initial diagnosis		
Yes	165 (70)	157 (67)
No	70 (30)	76 (33)
Number of prior systemic therapies		
Median (range)	4 (2, 17)	4 (2, 14)
Mean (SD)	4 (2)	5 (2)
2 therapies	31 (13)	31 (13)
3 therapies	61 (26)	55 (24)
≥4 therapies	142 (60)	147 (63)

Setting of prior systemic therapies		
Adjuvant	140 (60)	129 (55)
Neoadjuvant	113 (48)	111 (48)
Metastatic	226 (96)	231 (99)
Locally advanced disease	8 (3)	4 (2)
Types of prior treatments		
Systemic chemotherapy or immunotherapy	235 (100)	233 (100)
Surgery	222 (95)	222 (95)
Radiotherapy (non-brain)	196 (83)	185 (79)
Most common prior chemotherapy		
Taxane**	235 (100)	233 (100)
Anthracycline†	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	159 (68)
Capecitabine	147 (63)	159 (68)
Prior PARP inhibitors	17 (7)	18 (8)
Prior use of PD-1/PD-L1 inhibitors	67 (29)	60 (26)
Most common sites of disease‡		
Lung only	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Axillary lymph nodes	57 (24)	73 (31)
Bone	48 (20)	55 (24)

Note: Data are presented as n (%) unless otherwise stated.

*Primary analysis population in ASCENT.

**Includes paclitaxel, paclitaxel albumin, and docetaxel.

†Includes, doxorubicin, daunorubicin, epirubicin, and variations of those treatment names.

‡Based on independent central review of target and nontarget lesions.

BRCA1/2=breast cancer gene 1 or 2; ECOG PS=Eastern Cooperative Oncology Group performance status; PARP=poly(ADP-ribose) polymerase; PD-1=programmed cell-death protein 1; PD-L1=programmed death-ligand 1; SD=standard deviation; TNBC=triple-negative breast cancer; TPC=treatment of physician's choice.

7.1.2 Efficacy and safety – results per study

7.1.2.1 Phase I/II (IMMU-132-01) study

In IMMU-132-01 the primary efficacy endpoint was ORR, and secondary endpoints included PFS and OS. Safety endpoints included AEs grade 3 or higher and discontinuations due to AEs. HRQoL was not investigated in the study.

7.1.2.1.1 Primary efficacy endpoint

There were 108 patients with mTNBC in the IMMU-132-01 study; of these, 2.8% reported a complete response (CR) and 30.6% a PR. The BICR assessment noted a similar ORR of 33.3% (95% CI: 25.4, 44.0).

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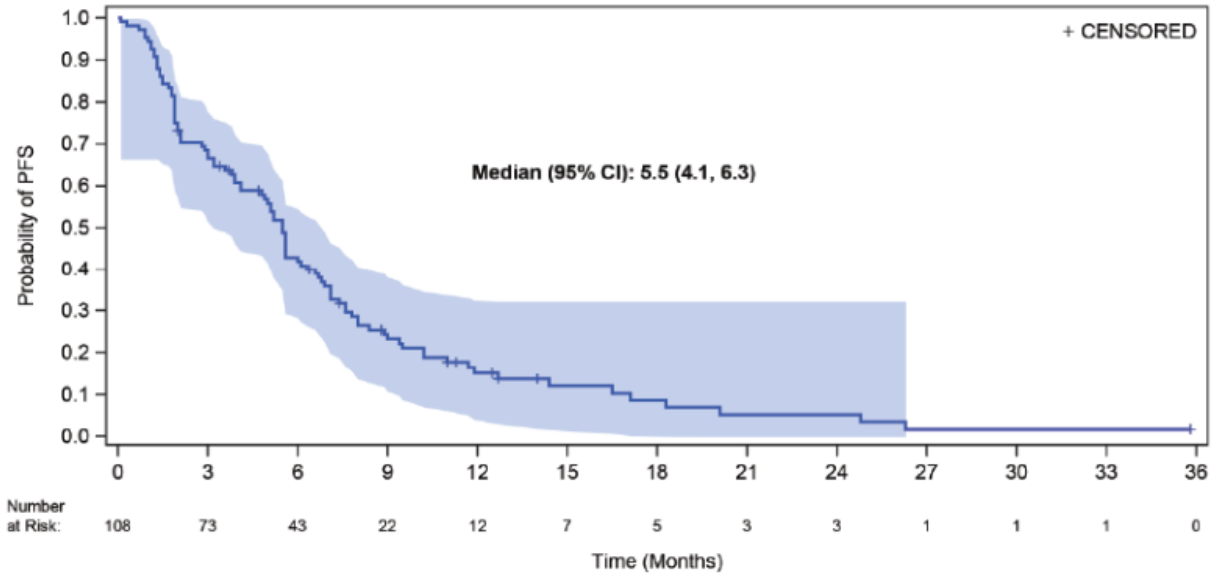
7.1.2.1.2 Secondary endpoints

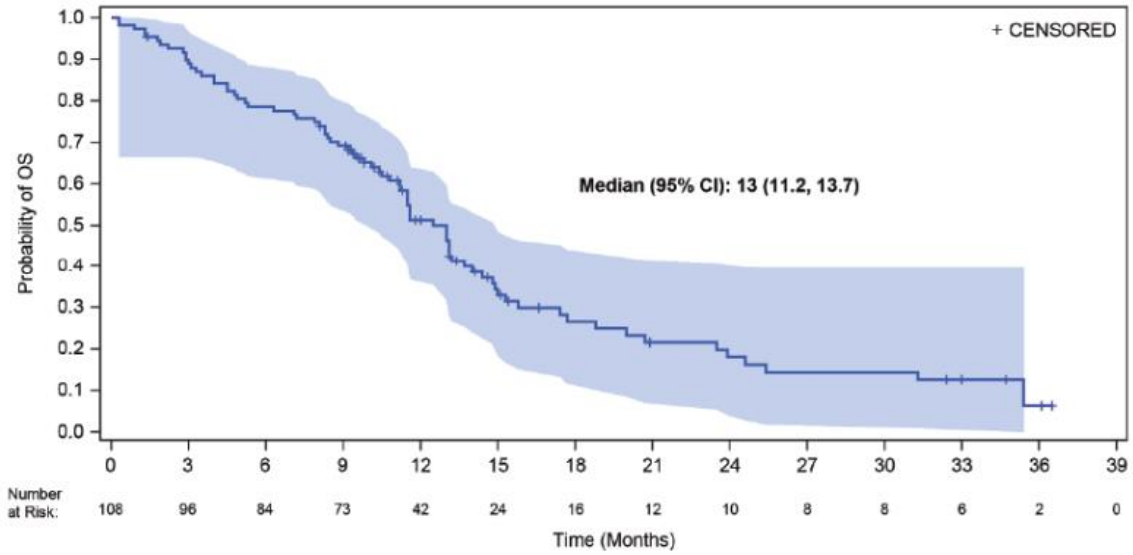
The median PFS was 5.5 months (95% CI: 4.1, 6.3); the probability of PFS at 6 and 12 months was 41.9% and 15.1%, respectively. The median OS was 13.0 months (95% CI: 11.2, 13.7), with an estimated probability of survival at 6 and 12 months of 78.5% and 51.3%, respectively. Kaplan-Meier (KM) analyses of PFS and OS are presented in Figure 1 and Figure 3, respectively. Summary survival statistics are shown in Table 11.

Figure 2: IMMU-132-01: PFS in patients with mTNBC (n=108)



CI=confidence interval; mTNBC=metastatic triple-negative breast cancer; PFS=progression-free survival.
SOURCE: Bardia et al 2019 [8].

Figure 3: IMMU-132-01: OS in patients with mTNBC (n=108)



CI=confidence interval; mTNBC=metastatic triple-negative breast cancer; OS=overall survival

Table 11: Summary survival statistics from IMMU-132-01 (n=108)

Efficacy measure	Patients (n=108)
Patients with disease progression event*, n (%)	94 (87.0)
Death*, n (%)	77 (71.3)
Median PFS, months (95% CI)	5.5 (4.1, 6.3)
Median OS months (95% CI)	13.0 (11.2, 13.7)

Note: PFS, OS, and time-to-event end points were analyzed with the use of Kaplan-Meier methods, with medians and corresponding 95% CIs determined according to the Brookmeyer and Crowley method with log-log transformation.

*At the time of data cutoff (December 1, 2017).

CI=confidence interval; mTNBC=metastatic triple-negative breast cancer; OS=overall survival; PFS=progression-free survival.

7.1.2.1.3 Safety

A total of 78 (72.2%) AEs grade 3 or higher was reported in the study population according to CTCAE version 4.0 that (occurred in at least 10% of the patients). Moreover, 4 (3.7%) patients discontinued/withdrawal treatment due to AEs[47]. The most common treatment-related AEs (occurring in ≥15% of patients) were nausea (67%), neutropenia (64%), and diarrhea (62%) (Table 12) [8].[47] The safety database cut-off date of the initial submission was 11 March 2020. At EMA request Gilead provided treatment and follow-up durations and safety data using the final database lock for IMMU-132-01 (final database lock 02 April 2021). As of the prior data DCO date of 11 March 2020, there were no participants continuing sacituzumab govitecan treatment in Study IMMU-132-01, the updated safety and treatment and follow-up duration data are similar to the 11 March 2020 DCO data, therefore, the tables included refer to the DCO Date of 11 March 2020.

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7.1.2.2 Phase III (ASCENT) study results

The relevant populations in the ASCENT study concerned the ITT-population and the Brain Metastasis negative (BM-ve) population. In the ITT-population, efficacy endpoints included PFS (by IRC assessment and investigator assessment), OS and ORR (by IRC assessment and investigator assessment). HRQoL was measured using ECORTC QLQ-C30, and safety endpoints included treatment discontinuation/withdrawal due to AEs and AEs grade 3 or higher. In the BM-ve population, efficacy endpoints included PFS (by IRC assessment and investigator assessment), OS and ORR (by IRC assessment and investigator assessment). HRQoL. Safety endpoints were not reported separately for the BM-ve population.

The high efficacy demonstrated by sacituzumab govitecan over TPC, in both the ITT-population and the BM-ve population, led to early halting of the study in March 2020 by unanimous recommendation of the Data and Safety Monitoring Committee.[47]

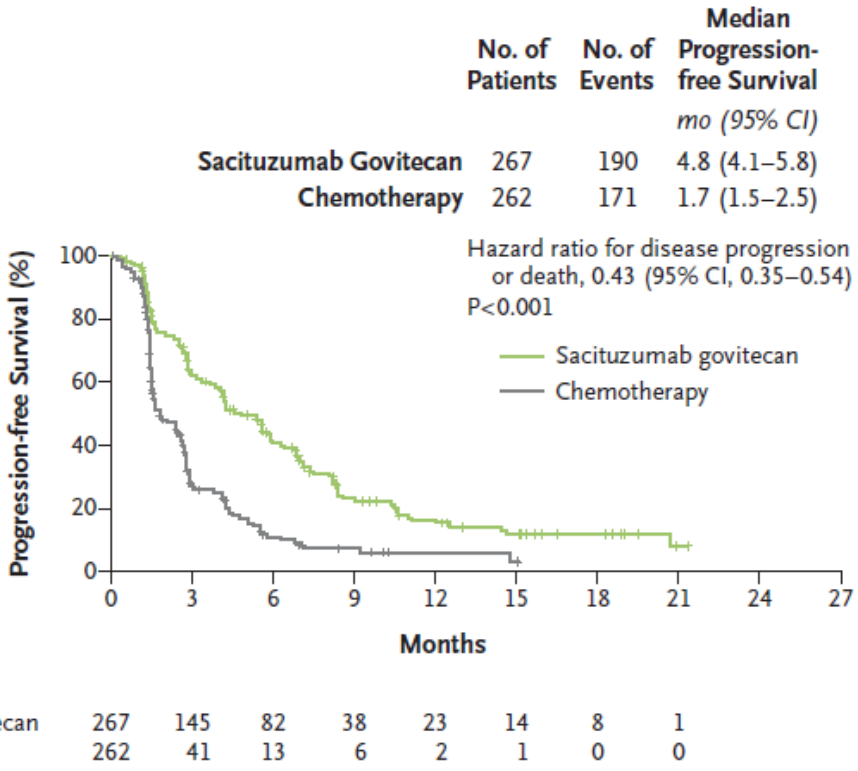
The final data cutoff 11 March 2020 was in accordance with the number of events in the prespecified final analysis planned for the study and included any updates to the data after the Data and Safety Monitoring Committee review. The final database lock (25 February 2021) included further efficacy data collected from the remaining 17 participants after the final data cut for the CSR (study participants pending transition to another clinical study) and confirmed the findings of the final analysis. The data available from the 25 February 2021 data cutoff is presented in addition to the final data cutoff 11 March 2020 reported for the ITT population.

7.1.2.2.1 ITT population

For the ITT population in the Phase III ASCENT study in pre-treated patients with mTNBC (all patients, with or without BMs), sacituzumab govitecan demonstrated a significant benefit over standard single-agent chemotherapy (treatment

of physician's choice; TPC) for the endpoint of PFS by IRC assessment, with a median PFS of 4.8 months for patients treated with sacituzumab govitecan compared with 1.7 months for those treated with TPC (HR 0.43; 95% CI: 0.35, 0.54; *P*<0.001) (Figure 4) [47]. PFS results by investigator assessment in the ITT population demonstrated a HR of 0.38 (95% CI: 0.31, 0.48) (Appendix D). The 25 February 2021 data cutoff confirmed the results with a hazard ratio of 0.41 (95% CI: 0.33, 0.52) and 0.38 (95% CI: 0.31, 0.47) for PFS by IRC assessment and investigator assessment, respectively [47].

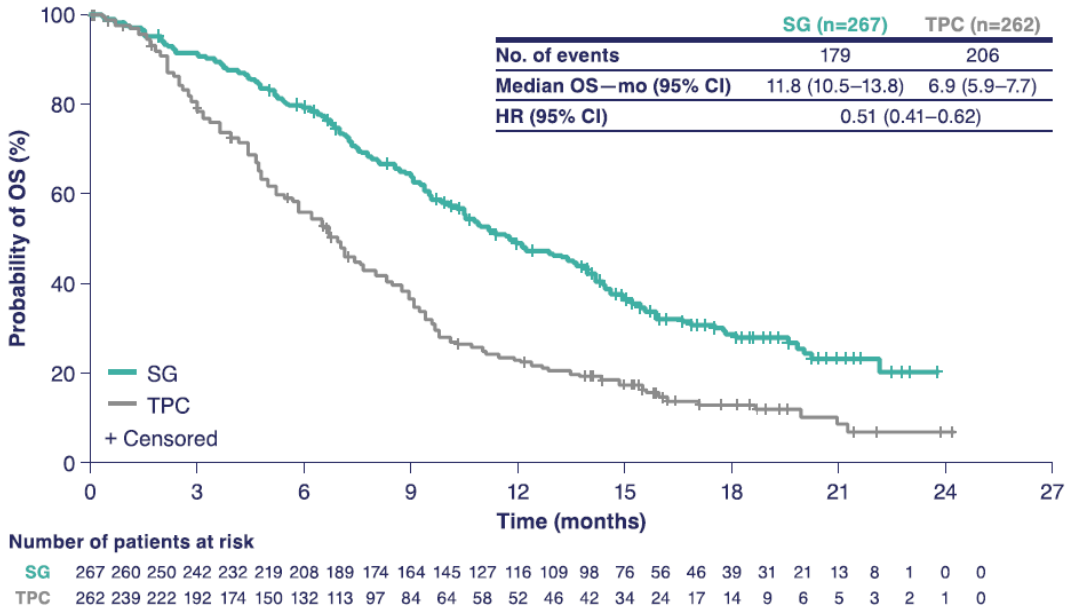
Figure 4: ASCENT: PFS in the ITT population



CI=confidence interval; ITT=intention-to-treat; PFS=progression-free survival.

With respect to OS, sacituzumab govitecan demonstrated a significant benefit over TPC in the ITT population (median OS 11.8 months vs 6.9 months; HR 0.51; 95% CI: 0.41, 0.62) at the final 11 March 2020 data cutoff (Figure 5). The 25 February 2021 data cutoff confirmed the results with a hazard ratio of 0.51 (95% CI: 0.42, 0.62) [47].

Figure 5: ASCENT: OS in the ITT population



CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; OS=overall survival; SG=sacituzumab govitecan; TPC=treatment of physician's choice.34

Significant benefit in the secondary endpoint of ORR was noted for patients treated with sacituzumab govitecan compared with patients treated with TPC both according to IRC and investigator assessment, as illustrated in Table 13[47].

Table 13: ASCENT: ORR of treatment efficacy in the ITT population

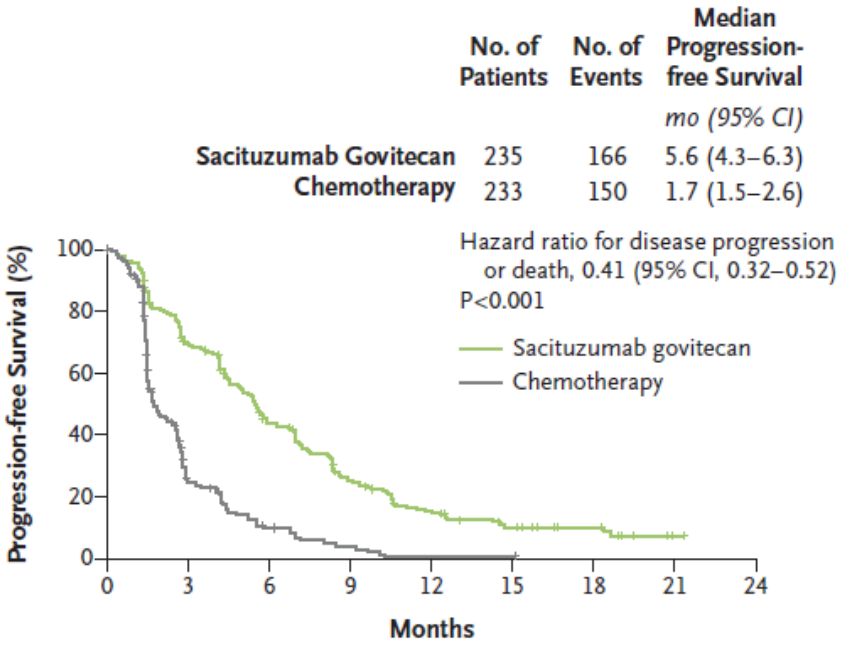
Efficacy measure	Sacituzumab govitecan (n=267)	TPC (n=262)	Odds ratio (95% CI)	*P*-value
ORR according to IRC assessment, n (%)	83 (31.1%)	11 (4.2%)	10.994 (5.659, 21.358)	<0.0001
ORR according to investigator assessment, n (%)	83 (31.1%)	16 (6.1%)	7.156 (4.037, 12.685)	<0.0001

*Includes complete response and partial response.
CI=confidence interval; ITT=intention-to-treat; ORR=objective response rate; TPC=treatment of physician's choice

7.1.2.2.2 BM-ve population

In the ASCENT BM-ve population (the primary analysis population), sacituzumab govitecan also demonstrated a significant benefit over TPC, with a median PFS of 5.6 months for patients treated with sacituzumab govitecan compared with 1.7 months for those treated with TPC (HR 0.41; 95% CI: 0.32, 0.52; *P*<0.0001) by IRC assessment (Figure 6) [47]. The PFS was similar for investigator assessment with a median PFS of 5.5 months for patients treated with sacituzumab govitecan compared with 1.7 months for those treated with TPC (HR 0.35; 95% CI: 0.28-0.44) [47].

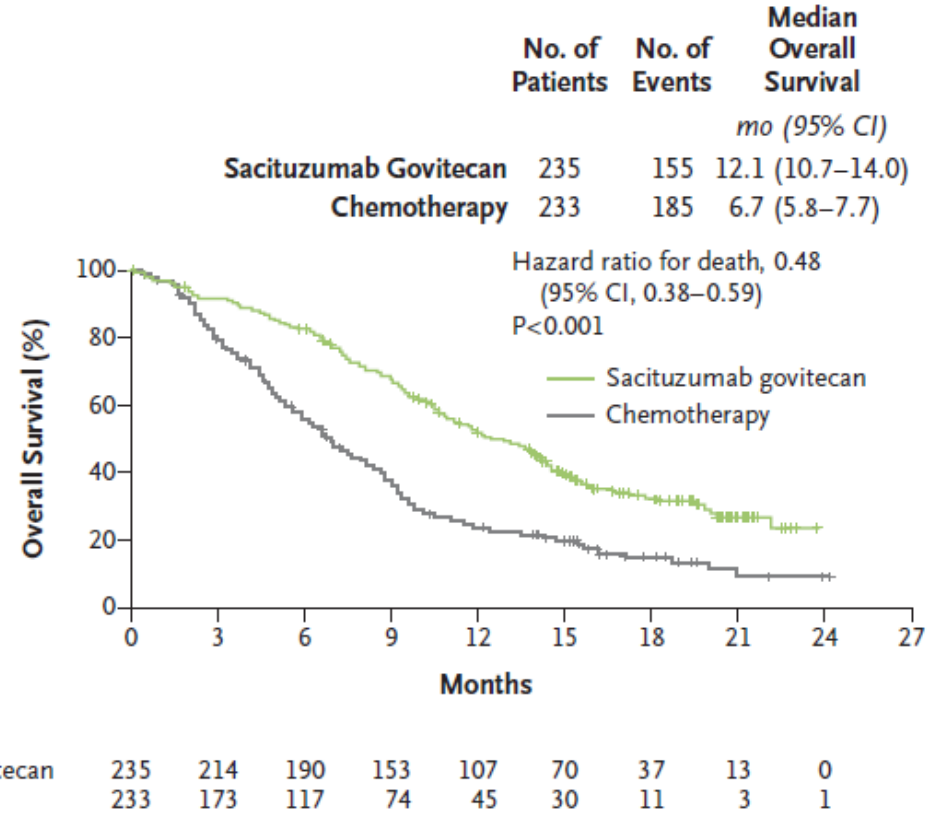
Figure 6: ASCENT: PFS in the BM-ve population



CI=confidence interval; PFS=progression-free survival.

With respect to OS, sacituzumab govitecan demonstrated a significant benefit over TPC in the BM-ve (median OS: 12.1 months vs 6.7 months; HR 0.48; 95% CI: 0.38, 0.59; *P*<0.001) (Figure 7)[47].

Figure 7: ASCENT: OS in the BM-ve population



CI=confidence interval; OS=overall survival.

Finally, a significant benefit in the endpoint of ORR was noted for patients treated with sacituzumab govitecan compared with patients treated with TPC both according to IRC and investigator assessment, as illustrated in Table 14 [47].

Table 14: ASCENT: ORR of treatment efficacy in the BM-ve population

Efficacy measure	Sacituzumab govitecan (n=235)	TPC (n=233)	Odds ratio (95% CI)	*P*-value
ORR according to IRC assessment, n (%)	82 (34.9)	11 (4.7)	10.859 (5.590, 21.095)	<0.0001
ORR according to investigator assessment, n (%)	80 (34.0%)	15 (6.4%)	10.859 (5.590, 21.095)	<0.0001

*Includes complete response and partial response.

CI=confidence interval; ORR=objective response rate; TPC=treatment of physician's choice; BM-ve=brain metastasis-negative

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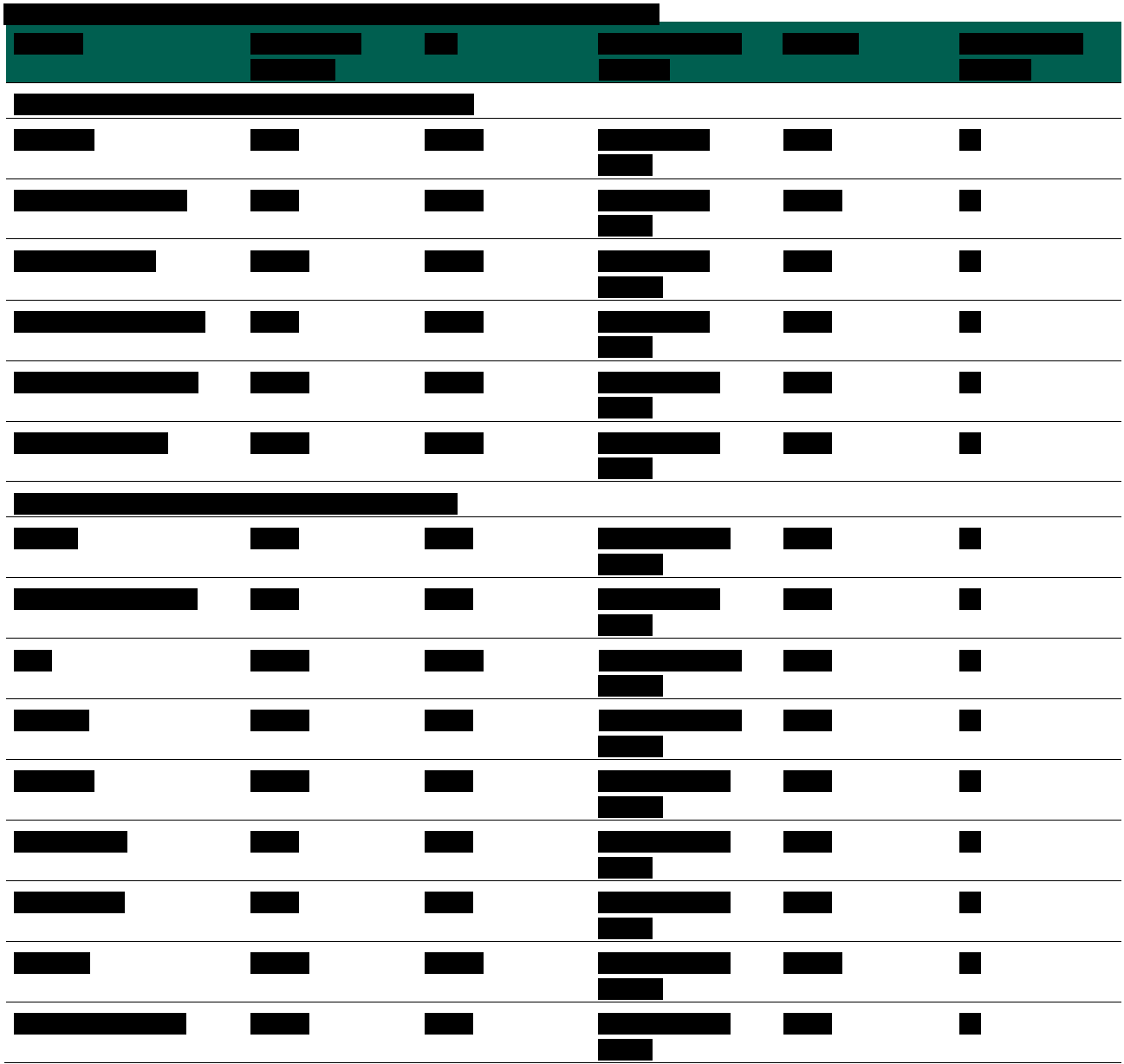

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7.1.2.2.4 Safety

The safety data cut-off date for the pivotal trial (ASCENT) was 11 March 2020. Updated safety data were presented for 25 February 2021 data cut-off [10].
With the updated data, the median duration of treatment in ASCENT for the sacituzumab govitecan group compared with the TPC group was 4.4 months versus 1.3 months. A higher percentage of the sacituzumab govitecan group compared with the TPC group received study treatment ≥6 months (36.8% vs 5.8%) and ≥12 months (11.2% vs 0.4%).[47]

In ASCENT, sacituzumab govitecan had a consistent and generally manageable safety profile and was well tolerated in the treated population. Few patients receiving sacituzumab govitecan in ASCENT discontinued treatment (the rate of AEs leading to discontinuation was approximately 5%). No treatment-related deaths were seen in the sacituzumab govitecan group, while 1 treatment-related death was noted in the TPC group. For patients receiving sacituzumab govitecan a total of 188 (72.9%) treatment-related AEs grade 3 or higher were reported (Table 16).[47]

The proportions of patients with any treatment related AE and Grade ≥ 3 AEs were higher in the sacituzumab govitecan treated group compared to the TPC group (TEAEs: 97.7% vs. 85.7% and Grade ≥ 3 TEAEs 72.1% vs. 64.7%). In ASCENT, the more frequently reported treatment-related AEs in the sacituzumab govitecan arm in comparison to the TPC group were diarrhea (65.1% vs 17.0%), neutropenia (64.0% vs 43.8%), nausea (62.4% vs 30.4%), fatigue (51.6% vs 39.7%), alopecia (46.9% vs 16.1%), anemia (39.5% vs 27.7%), constipation (37.2 % vs 23.2%) and vomiting (33.3 % vs 16.1%). Neutropenia was the most common Grade ≥ 3 AE; other Grade ≥ 3 AEs occurring in at least 5% of patients were: neutrophil count decreased, diarrhea, anemia, white blood cell count decreased, febrile neutropenia, fatigue, and dyspnea.[47]
A similar frequency of SAEs was observed in the sacituzumab govitecan arm (26.7%) compared to the TPC arm (28.1%) in the pivotal trial. The most common (>2%) SAEs in the sacituzumab govitecan arm were febrile neutropenia (5%), diarrhea (3.5%), neutropenia (2.7%) and pneumonia (2.7%). In the total sacituzumab govitecan-exposed safety population 34.7 % of patients had reported SAEs which is in line with the frequency observed in the pivotal trial.[47]

Regarding dose reduction, a slightly lower number of AEs leading to dose reduction has been observed in the SG arm compared with the TPC arm. The AEs that most frequently led to a reduction of sacituzumab govitecan included neutropenia and diarrhea. In contrast, AEs leading to a treatment interruption occurred in a higher percentage of patients in the sacituzumab govitecan group compared with the TPC group (62.8% vs 38.8%) in ASCENT. Neutropenia was the most frequent AE leading to a treatment interruption in the sacituzumab govitecan and TPC groups (46.1% vs 21.0%).[47]

Neutropenia is an identified risk of sacituzumab govitecan, and hematologic parameters, including platelets count, must be monitored before starting and at regular intervals during sacituzumab govitecan treatment. Neutropenia is the AE that most frequently led to a dose reduction or dose delay of sacituzumab govitecan. Grade ≥3 neutropenia occurred in 48.4% of all the neutropenia cases.[47]

Anemia occurred in a higher percentage of patients in the sacituzumab govitecan group compared with the TPC group (39.5% vs 27.7%) in ASCENT. Infections were more frequent in the sacituzumab govitecan group than the TPC group (53.1% vs 35.7%) in ASCENT. Infections that were more frequent (approximately ≥5%) with sacituzumab govitecan than TPC included the following: Urinary tract infection (12.8% vs 8.0%), upper respiratory tract infection (12.0% vs 3.1%), and nasopharyngitis (7.0% vs 2.2%). The most common gastrointestinal AESI was diarrhea with 65.1% of the patients with an event of any grade, 11.3% with grade 3 events and 3.5% with SAE.

In pivotal study ASCENT, hypersensitivity occurred in a higher percentage of patients in the sacituzumab govitecan group compared with the TPC group (34.1% vs 20.5%). The most frequent hypersensitivity events in both the sacituzumab govitecan and TPC groups were cough (7.4% vs 6.7%, respectively) and dyspnea (7.0% vs 6.7%, respectively).[47]

Table 16: Overall Summary of AEs in ASCENT (updated safety data 25/02/2021)[47]

Event	Sacituzumab govitecan (n=258)	TPC (n=224)
Number of participants with any TEAEs	257 (99.6)	219 (97.8)
Number of participants with any treatment-related TEAEs	252 (97.7)	192 (85.7)
Any serious TEAE	69 (26.7)	63 (28.1)
Number of participants with any TEAEs with CTCAE Grade 3, 4, or 5	188 (72.9)	145 (64.7)
TEAEs leading to study drug withdrawal/discontinuation	12 (4.7)	12 (5.4)
Treatment-related deaths	0	1 (0.4)
TEAEs leading to study drug interruption	162 (62.8)	87 (38.8)

CTCAE = Common Terminology Criteria for Adverse events; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TPC = treatment of physician's choice

Percentages are based on big N. For each row category, a participant with 2 or more adverse events in that category is counted only once. Participants may be counted in multiple categories.

Treatment-related TEAEs include TEAEs that were considered by the Investigator to be related or probably related to study drug or TEAEs with a missing causality. Adverse events were graded using CTCAE version 5.0.

The most common (>10%) treatment-related AEs was neutropenia (reported in 63% of patients given sacituzumab govitecan diarrhea (59%), and nausea (57%). No cases of severe cardiovascular toxicity or Grade >2 neuropathy was reported; one patient had Grade 3 interstitial lung disease (pneumonitis) (Table 17).[47]

Table 17: ASCENT: most common treatment-related AEs of special interest

TEAEs	Sacituzumab govitecan (n=258)			TPC (n=224)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Neutropenia*	63	34	17	43	20	13
Diarrhea	59	10	0	12	<1	0
Nausea	57	2	<1	26	<1	0
Alopecia	46	0	0	16	0	0
Fatigue	45	3	0	30	5	0
Anemia**	34	8	0	24	5	0
Vomiting	29	1	<1	10	<1	0
Leukopenia†	16	9	1	11	4	1
Febrile neutropenia	6	5	1	2	2	<1

Note: All data reported as % of patients.
*Includes neutropenia and decreased neutrophil count.
**Includes anemia, decreased red blood cell count, and decreased hemoglobin.
†Includes leukopenia and decreased white blood cell count.

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TEAE= Treatment-emergent adverse event, AE=adverse event; GI=gastrointestinal; mTNBC=metastatic triple-negative breast cancer; TPC=treatment of physician's choice.

7.1.3 Comparative analyses of efficacy and safety

Method of synthesis
ASCENT, the phase III study, forms the basis of the comparative analysis, and therefore only data from the ASCENT trial is presented. The data from the ASCENT trial is reported in section 7.1.2.2. The relevant outcomes for the comparative analysis concern OS, PFS, ORR, HRQoL (EORTC QLQ-C30), AEs grade 3 or higher and discontinuations due to AEs.

Results from the comparative analysis
The clinical value of sacituzumab govitecan compared to TPC is best demonstrated by the critical outcome measures PFS and OS. The results from the direct comparison for PFS, demonstrate that sacituzumab govitecan provides a 3.1-month gain in median PFS compared with TPC in the ITT population (median 4.8 months vs. 1.7 months; HR 0.43 [95%CI: 0.347-0.541]) and 0.38 [95%CI: 0.31-0.48]) according to IRC- and investigator assessment, respectively. This demonstrates that sacituzumab govitecan provides clinical relevant difference in median PFS[63].
For OS in the ITT population, the direct comparison indicates that sacituzumab govitecan provides a 4.9-month gain in median OS compared with TPC (median 11.8 months vs. 6.9 months; HR 0.51 [95% CI: 0.41-0.62]). This demonstrates that sacituzumab govitecan provides clinical relevant difference in median OS[63].

In the BM-ve population the results from the direct comparison for PFS demonstrate that sacituzumab govitecan provides a 3.9-month gain in median PFS compared with TPC (median 5.6 months vs. 1.7 months; HR 0.409 [95% CI: 0.332-0.519]) according to IRC assessment, and a 3.8-month gain (median 5.5 months vs. 1.7 months; HR: 0.35 [95% CI: 0.28-0.44] according to investigator assessment. This demonstrates that sacituzumab govitecan provides clinical relevant difference in median PFS[63]. For OS in the BM-ve population, the direct comparison indicates that sacituzumab govitecan provides a 5.4-month gain in median OS compared with TPC (median 12.1 months vs. 6.7 months; HR 0.476 [95% CI: 0.383-0.592]). This demonstrates that sacituzumab govitecan provides clinical relevant difference in median OS[63].

Safety outcomes were compared directly in ASCENT between sacituzumab govitecan and TPC, for patients in the ITT population. Sacituzumab govitecan had a consistent and generally manageable safety profile and was well tolerated in the treated population. The most common (>10%) treatment-related AEs was neutropenia (reported in 63% of patients given sacituzumab govitecan), diarrhea (59%), and nausea (57%). No cases of severe cardiovascular toxicity or grade >2 neuropathy was reported; one patient had grade 3 interstitial lung disease (pneumonitis), which resolved following treatment discontinuation. No treatment-related deaths were seen in the sacituzumab govitecan group, while one treatment-related death was noted in the TPC group. For patients receiving sacituzumab govitecan a total of 188 (72.9%) treatment-related AEs grade 3 or higher were reported. Fewer patients receiving sacituzumab govitecan discontinued treatment due to AEs (4.7%) compared to patients receiving TPC (5.4%).

EORTC QLQ-C30 was investigated in ASCENT, and over the course of the study, significant improvements from baseline in HRQoL were seen with sacituzumab govitecan compared with TPC for the functional and symptom domains of global health status/quality of life, physical functioning, emotional functioning, fatigue, pain, dyspnea, and insomnia. Diarrhea scores were significantly worse for sacituzumab govitecan vs TPC; however, this did not appear to adversely impact global HRQoL or physical functioning.

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8. Health economic analysis

For the health economic analysis of sacituzumab govitecan, a cost-utility analysis was performed, comparing sacituzumab govitecan with TPC of eribulin, vinorelbine, gemcitabine or capecitabine, confirmed by Danish clinicians to be representative of Danish clinical practice, as described in 5.2.2 [6]. The outcomes of analysis were incremental cost per QALYs and LYs gained.

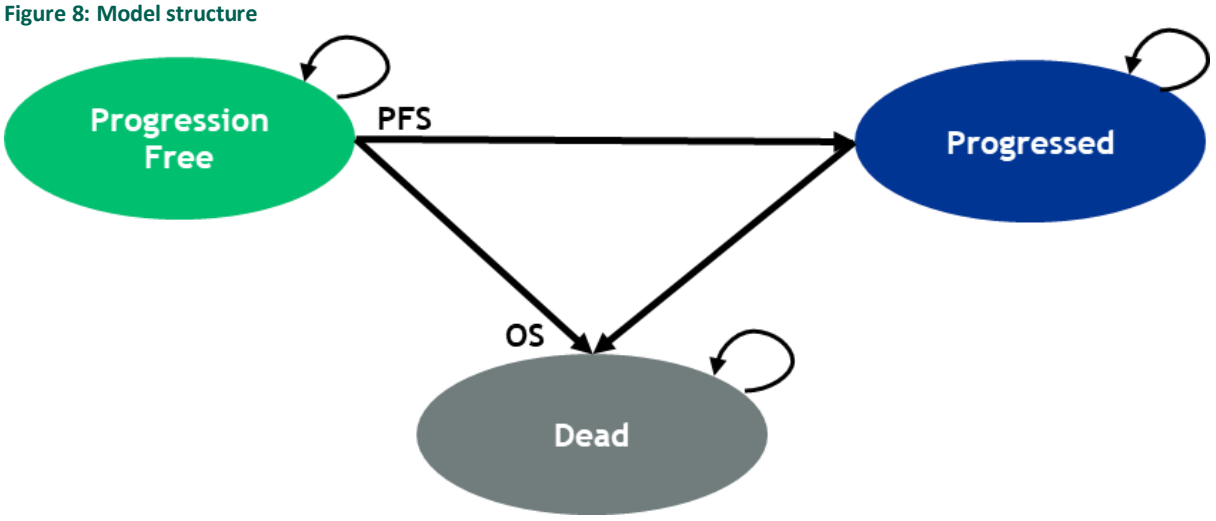
Both the quality of life and life span are of interest, as triple negative breast cancer in the metastatic setting (mTNBC) is associated with relatively short survival. Hence, additional lifetime spent with the best possible health-related quality of life was considered as relevant outcomes of the analysis.

The base-case analysis includes both treatment, subsequent treatment and healthcare utilization costs. Direct non-medical and indirect costs include travel costs and productivity loss which are included in the sensitivity analysis.

8.1 Model

The analysis used a partitioned three health-states model which follows individuals over time. Figure 8 illustrates the three health states used to model individual survival outcomes over the time horizon: progression free (PF), progressed disease (PD), and death. Individuals who are eligible for treatment enter the model, initiate treatment, and experience an interval of PFS. Individuals who are alive but whose disease has progressed continue to the PD health state and may receive subsequent treatments. It is assumed that individuals could die at any time point in the model.

Figure 8: Model structure



OS = overall survival; PFS = progression-free survival

Progression and death were tracked using treatment specific and independent PFS and OS curves. The model is constrained in the following way:

- The risk of death in the model´s population cannot be lower than the all-cause mortality of the general population at each model cycle, determined by published life tables.
- PFS is constrained by OS, such that the number of individuals who are PF cannot exceed the total number of individuals alive.

The model structure captures the expected patient pathway from treatment initiation to death and reflects differences in costs and outcomes among patients receiving alternative systemic therapies for pretreated TNBC or mTNBC. Costs

and health-related utilities are allocated to each health state and multiplied by the number of patients in each state to calculate weighted costs and QALYs per cycle.
Treatment costs included costs of drug acquisition, administration, subsequent treatment and monitoring. Costs associated with adverse events (AEs) were estimated per episode and were applied once at the beginning of the simulation, based on the proportion of patients in each treatment arm who experience each AE.
As the model progresses cycle by cycle for the duration of the time horizon, cost and utility data were summed per treatment arm, allowing for the calculation of differences in accumulated costs and effectiveness between model arms at model completion. The model cycle length of one week was chosen to provide precision in the tracking of the number of patients in each health state over time in the model. Half-cycle correction was applied in the analysis.

Advanced metastatic breast cancer is a disease with high mortality rates and treatments may impact overall survival by modifying disease specific survival, which motivates a lifetime horizon. However, although a disease associated with high mortality, some patient may have a rather long survival and studies have for example indicated that more than 10% of patients diagnosed with primary metastatic breast cancer in general (i.e. not TNBC specifically) survive beyond 10 years [64].

At 20 years the ICER of the analysis was relative stable, an increase to 25 years changes the ICER with less than 1%. A 20-year time horizon was chosen for the base case analysis in Denmark. Alternative time horizons are also tested in sensitivity analyses. The cycle length of the model was one week (7 days). Half-cycle correction was considered in the model allowing for a better approximation of the area under the curve. For each cycle, instead of using the output calculated for a specific cycle, the average of the output at the current and previous cycles was taken.

A discount rate of 3.5% was applied based on the socio-economic discount rate from the Ministry of Finance [65].

The global model was validated internally, externally and a cross validation was conducted. To ensure it reflects Danish clinical practice, a clinical expert was consulted [6]. Furthermore, the model directly uses trial-based time-to-event endpoints from the ASCENT study [10].

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

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

The input data used in the base case was taken from the pivotal trial ASCENT [10]. The ITT population of the ASCENT trial formed the basis of the health economic analysis. This was considered appropriate in order to maintain randomization and because the BM-ve subgroup is not clinically relevant in Denmark due to the lack of routine screening of BM in breast cancer. Moreover, where needed, data was extrapolated based on goodness-of-fit statistics and clinical plausibility, supported with the aid of a Danish clinical expert. A summary of included inputs is presented in Table 18.

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

8.2.2.1 Patient population

The pivotal trial assessing sacituzumab govitecan (ASCENT) included patients with mTNBC with or without brain metastases aged 18 years or older. The mean age at baseline of the overall ITT population was 54 years (range 27 to 82, SD = 11.5) with median weight of 71.1 kg (SD = 16.9) and 99.6% were female. The patient population in the health economic analysis submitted reflects the overall patient population in ASCENT.

Baseline characteristics of participants in ASCENT are assumed to be representative for Denmark. The assumption was validated by a Danish clinical expert [6]. Table 19 shows the characteristics of the patient population used in the model compared to Danish clinical practice.

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8.2.2.2 Intervention

Metastatic mTNBC is an aggressive disease that, despite diagnosis and treatment in earlier stages, can frequently recur and progress rapidly to more advanced stages [18, 39, 66, 67]. Along with a worse prognosis and earlier rate of relapse [1, 2] patients with TNBC are more likely to develop distant metastases than patients with other subtypes of BC [3, 4]. The principal systemic treatment option for patients with mTNBC is chemotherapy [31, 33-35, 68, 69]; there have not been any specific agents approved for locally advanced or mTNBC.

Sacituzumab govitecan is indicated for the treatment of unresectable advanced or metastatic triple negative breast cancer patients who have received two prior regimens. Sacituzumab govitecan had the marketing authorization as per EU decision by November 23rd and it is currently not introduced in Denmark.

The key clinical documentation in this health economic assessment is the pivotal trial ASCENT [10].
Inputs used in the cost-effectiveness analysis are primarily informed by the clinical trial ASCENT and clinical literature in combination with clinical expertise [6]. In the model, treatments were administered according to treatment cycles of 21 days. Sacituzumab govitecan is 10 mg/kg and was administered as an intravenous (IV) infusion once weekly on days 1 and 8 of 21-day treatment cycles. Posology of the intervention are based on ASCENT and are showed in Table 20.
To estimate the treatment duration of sacituzumab govitecan as well as associated drug acquisition and administration costs, the extended mean of the treatment exposure from ASCENT was used.

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8.2.2.3 Comparators

For TNBC patients without expression of programmed cell death ligand-1 (PD-L1–negative) there is no preferred 1st line of chemotherapy. Therefore, the choice of treatment depends on multiple factors, including patient's age, general condition, previous treatment, toxicity, comorbidities, and patient preference. For PD-L1-positive patients who have completed their neo- or adjuvant chemotherapy more than 12 months before and who have not previously received chemotherapy for disseminated disease the recommendation is atezolizumab in combination with nab-paclitaxel as 1st line treatment [5].
Taxanes and anthracyclines are typically the choice as 1st line treatment for patients who have not received adjuvant anthracycline-taxane-based chemotherapy; in case of progression or recurrence after receiving both, treatment options include capecitabine, vinorelbine, eribulin and gemcitabine, as well as combinations of these. Carboplatin is also considered as a treatment that may be effective in patients with TNBC [5].

The most relevant comparator for the sacituzumab govitecan in Denmark is a monotherapy of either capecitabine, vinorelbine, eribulin and gemcitabine. According to Danish treatment guidelines, these options are relevant for patients with unresectable or mTNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease [5].

In the model the comparators are represented by a TPC basket composed by capecitabine (12.6%), vinorelbine (19.8%), eribulin (53.1%) and gemcitabine (14.5%), as presented in the ASCENT trial [10] and validated by a clinician [6] to ensure that it reflects Danish clinical practice. Table 21 shows the posology of the TPC basket.

Table 21: Comparator

Comparator – TPC	Clinical documentation [10]	Used in the model [10]	Expected Danish clinical practice [5].
Posology	Drug: eribulin 1 mg/m2 administered as IV infusion on the 1st and 8th day of 21-day treatment cycles.	Drug: eribulin 1 mg/m2 administered as IV infusion on the 1st and 8th day of 21-day treatment cycles.	Drug: eribulin 1 mg/m2 administered as IV infusion on the 1st and 8th day of 21-day treatment cycles.
	Drug: vinorelbine 25 mg/m2 orally once weekly for 21-day treatment cycles	Drug: vinorelbine 25 mg/m2 orally once weekly for 21-day treatment cycles	Drug: vinorelbine 25 mg/m2 orally once weekly for 21-day treatment cycles
	Drug: gemcitabine 1,000 mg/m2 administred as IV infusion on days 1, 8 and 15 of a 28-day cycle	Drug: gemcitabine 1,000 mg/m2 administred as IV infusion on days 1, 8 and 15 of a 28-day cycle	Drug: gemcitabine 1,000 mg/m2 administred as IV infusion on days 1, 8 and 15 of a 28-day cycle

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Comparator – TPC	Clinical documentation [10]	Used in the model [10]	Expected Danish clinical practice [5].
	Drug: capecitabine 1,125mg/m2 orally twice daily for 2 weeks followed by 1-week rest period in a 21-day cycle	Drug: capecitabine 1,125mg/m2 orally twice daily for 2 weeks followed by 1-week rest period in a 21-day cycle	Drug: capecitabine 1,125mg/m2 orally twice daily for 2 weeks followed by 1-week rest period in a 21-day cycle
Length of treatment	Treatment was continued until disease progression, unacceptable toxic effects, withdrawal from the trial, or death.	TTD	TTD
The comparator's position in the Danish clinical practice	Patients with unresectable, locally advanced, or metastatic TNBC who were refractory or had relapsed after receiving two or more prior chemotherapies.	Patients with unresectable, locally advanced, or metastatic TNBC who were refractory or had relapsed after receiving two or more prior chemotherapies.	Patients with unresectable, locally advanced, or metastatic TNBC who were refractory or had relapsed after receiving two or more prior chemotherapies.

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes used to assess sacituzumab govitecan were PFS and OS curves, sourced from the ASCENT trial [10].

The Danish treatment guidelines for metastatic/advanced breast cancer aim to ensure optimal treatment. Survival is used as indicator for efficacy [5]. Together with safety and tolerability, efficacy represents a relevant factor regarding treatment decisions in Denmark. Both PFS and OS as well as safety and quality of life were main endpoints in the ASCENT trial [10], and are applied in the health economic analysis for sacituzumab govitecan. Hence, we consider that the clinical data derived from the pivotal trial is relevant for Danish clinical practice.

A partitioned survival model was used to analyze the cost-effectiveness of sacituzumab govitecan in Denmark. The model was directly based on key outcomes of the ASCENT pivotal trial, which directly represents treatment goals for Denmark: Progression free survival, quality of life, and overall survival.

Table 22 shows the summary of described value, while Table 23 shows the summary of value regarding relevance.
The values in the model represent the extrapolated survival and consequently differ from the observed survival in the clinical trial. However, extrapolations were based on the observed survival in ASCENT and are assumed to be representative for Danish clinical practice [70]. For more information regarding the survival extrapolation see section 8.3.

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Table 23: Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study: **Progression free survival**	Defined as the time from randomization to documented disease progression or death from any cause, whichever occurs first. Determined by independent review committee (IRC).	PFS represents a relevant outcome measure with regards to treatments for mTNBC. Based on PFS, treatments may be prioritized over others.	Relevant.
Secondary endpoint: **Overall survival**	Defined as time from randomization to death from any cause.	OS represents a relevant outcome measure with regards to treatments for mTNBC. Based on OS, treatments may be prioritized over others.	Relevant.

8.2.2.5 Adverse reaction outcomes

Safety was one of the secondary outcomes in the ASCENT trial. Adverse events included amongst others neutropenia, diarrhea, leukopenia and fatigue. The frequency differed across patients and between the treatment options [10]. Only grade 3/4 Adverse events occurring in ≥3% of study subjects, in either sacituzumab govitecan or TPC arm from ASCENT trial, were included in the model (Table 24).

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8.3 Extrapolation of relative efficacy

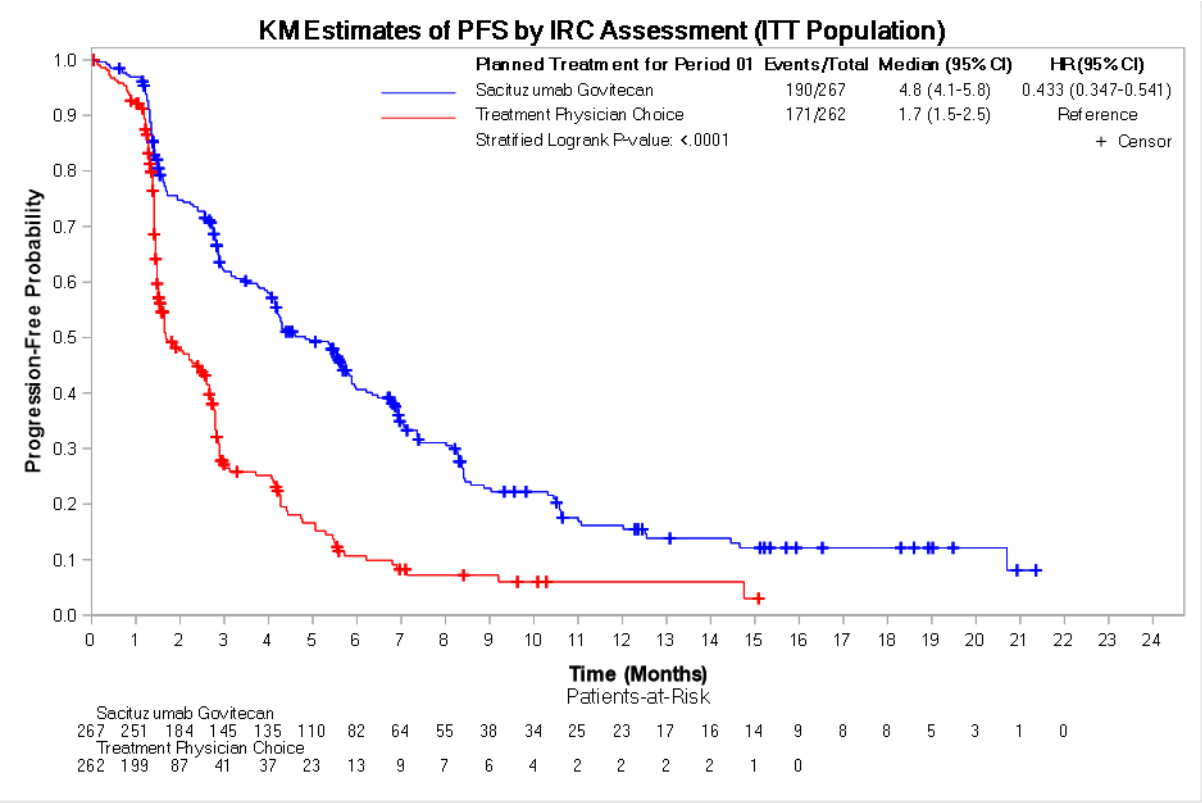
8.3.1 Time to event data

The inputs regarding effectiveness for sacituzumab govitecan and TPC were sourced from the pivotal trial ASCENT. The two main inputs regarding effectiveness used in the model and economic analysis were PFS and OS. The intention to treat (ITT) or overall population from the ASCENT trial was used to conduct the survival analyses for OS and PFS [10].

8.3.1.1 Progression free survival

Figure 9).

Figure 9: Kaplan – Meier estimates for progression free survival for ASCENT



CI: confidence interval; HR: hazard ratio; IRC: independent review committee; ITT: intention to treat; KM: Kaplan-Meier; PFS: progression-free survival

Although the PFS data from the ASCENT trial was reasonably mature (71% and 65% for sacituzumab govitecan and TPC, respectively [71]), it still required extrapolation to estimate the unrestricted mean difference in PFS between the two arms needed for the economic analysis. Considering that the treatment effect of sacituzumab govitecan is unlikely to be constant over the entire time horizon of the analysis, the base case analysis does not assume a constant acceleration factor or hazard ratio and only independent model fits were considered in the sensitivity analyses. However, the proportionality of the two arms were explored, see Appendix G – Extrapolation

The seven standard survival models were fitted to the individual subject data in ASCENT. The survival times are assumed to have one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma and 51eneralized gamma. The distributions fitted to PFS with the corresponding fit statistics, Akaike information criterion (AIC) and Bayesian information criterion (BIC), are presented in Table 25.

[redacted]

The curves for the seven survival distributions fitted to the PFS data, including the long-term extrapolations, for sacituzumab govitecan and TPC are shown in Table 25 and Figure 27: PFS in ITT population: Long-term extrapolation by separately fitted distributions for TPC
in the Appendix G – Extrapolation. Smoothed and unsmoothed hazards are also show in Appendix G – Extrapolation
The best fit in total AIC and BIC was found to be the log-logistic distribution. The development of the risk of progression is shown in Figure 10Figure 10.

[redacted]

The log-logistic appears to be clinically plausible with converging hazards with time and was thus selected for the base case (Figure 11).

Figure 11: Survival model overlayed with Kaplan-Meier estimate from ASCENT for progression free survival

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The remaining distributions were explored in scenario analyses and the ICER was found to be stable to the choice of survival model (Table 49). The clinical plausibility, validated with expert clinicians [6] to reflect the Danish clinical practice, together with visual assessment and statistical fit of the PFS curves was deemed acceptable to determine the distribution for PFS, given the maturity of the subject-level data from ASCENT and reasonably similar extrapolations across distributions.

8.3.1.2 Overall survival

The OS KM curves for the sacituzumab govitecan and TPC treatment arms in the ITT population from ASCENT are presented in Figure 12. Sacituzumab govitecan extended median OS by 4.9 months over TPC; in the population receiving sacituzumab govitecan the median OS was 11.8 months (95% CI: 10.5 – 13.8) compared to 6.9 months (95% CI: 5.9 – 7.7) for TPC. A total of 20.8% and 6.8% of the subjects were alive at the end of the trial follow-up in the sacituzumab govitecan and TPC treatment arms, respectively.

Figure 12: Kaplan-Meier estimates for overall survival from ASCENT

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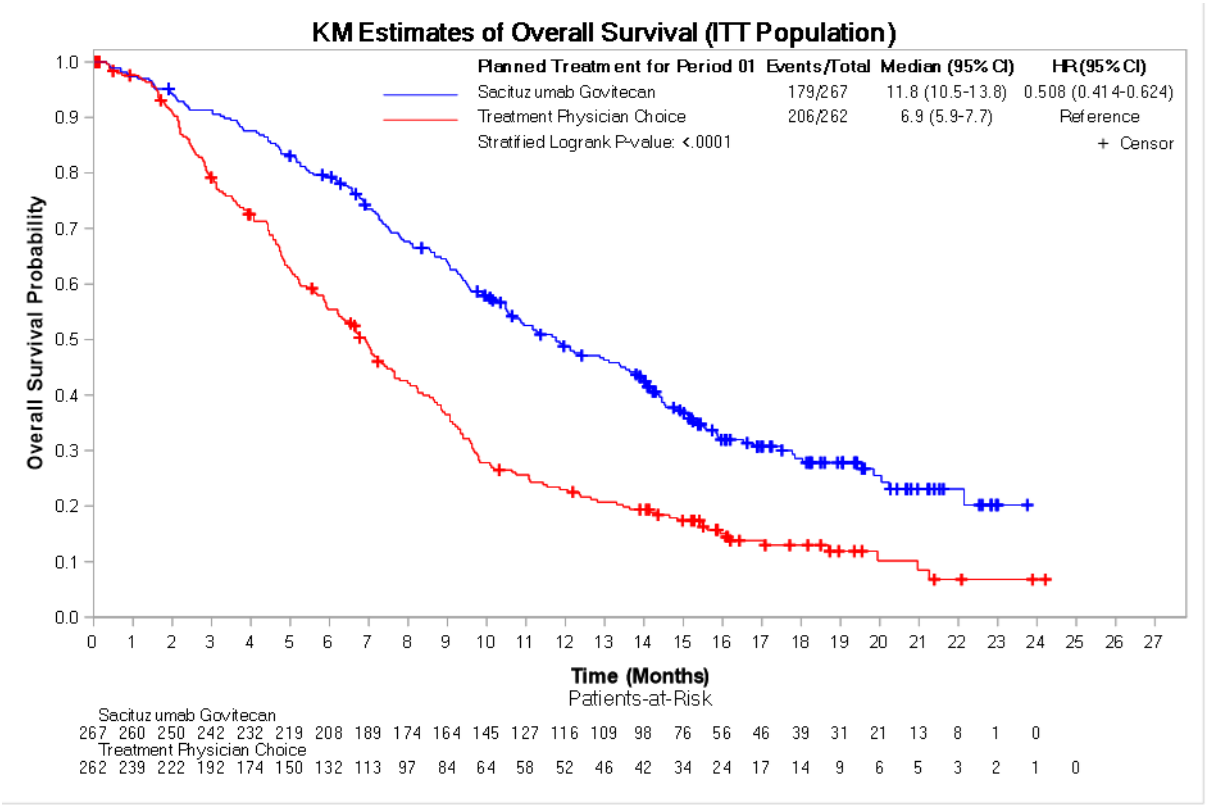

CI: confidence interval; HR: hazard ratio; IRC: independent review committee; ITT: intention to treat; KM: Kaplan-Meier; OS: Overall survival.

Although the OS data from the ASCENT trial was reasonably mature, it still required extrapolation to estimate the unrestricted mean difference in OS needed for the economic analysis. As for PFS, only separate fits were considered. The seven standard survival distributions were fitted to the subject level data in ASCENT. The distributions fitted to OS with corresponding AIC and BIC are presented in Table 26.

[redacted]

The development of the risk of death or hazard of the best fitting log-logistic distribution is presented in Figure 13. The risk of death increased after randomisation to then decrease after reaching a peak. The difference between the two arms of the model was seen to be the largest during active treatment with sacituzumab govitecan and TPC, i.e., during the trial. With time the two hazards converge (hazard ratio → 1).

The resulting log-logistic OS curve overlayed with the KM-estimate from ASCENT is presented in

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Figure 14.

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The clinical plausibility of the log-logistic distribution was validated with a clinical expert [6].

As the ICER shows variation over the choice of survival model (see Table 49), the hazards for the survival models with worse statistical fit are presented in Appendix G – Extrapolation. Smoothed and unsmoothed hazards are also shown in Appendix G – Extrapolation. The proportional hazard models, the exponential and Weibull as well as the gamma display a constant treatment effect that lacks clinical validity. The generalised gamma and Gompertz predict an increasing and worse hazard for sacituzumab govitecan compared to TPC which is in direct contrast to the data from ASCENT. The lognormal shows a similar development of the hazard to the log-logistic but with a slower convergence of the hazards. Given the low clinical plausibility of the survival models with worse statistical fit, the log-logistic distribution was selected for the base case analysis, the best combination of both statistical fit and clinical plausibility.

The curves for the seven survival distributions fitted to the OS data, including the long-term extrapolations, for sacituzumab govitecan and TPC are shown in Figure 36 and Figure 35. As for PFS, the best fit was found to be the log-logistic distribution.

8.3.1.3 Treatment duration

Treatment duration for sacituzumab govitecan and TPC was taken from ASCENT to best capture resource use of drug. The goodness-of-fit statistics (AIC and BIC) of the separately fitted distributions in the safety population are presented in Table 27.

[redacted]

Based on the goodness-of-fit statistics and visual inspection of the predicted vs. observed TTD curves, Weibull, exponential, gamma, and generalized gamma distributions provided good and almost identical fit. From these four distributions, the exponential was selected for parsimony. The remaining distributions were explored in scenario analyses. Treatment duration as used in the base case analysis is presented in Figure 15.

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

8.4.1 Overview of health state utility values (HSUV)

Health related quality of life (HRQoL) was assessed in the ASCENT trial using data from the EORTC QLQ-C30, a validated 30-item questionnaire containing both single- and multi-item measures. These include a Global Health Status/QoL scale, five functional scales (i.e., physical, role, emotional, cognitive, and social functioning), and nine symptom scales (i.e., fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties).

In the ASCENT clinical trial, EORTC QLQ-C30 questionnaires were completed by subjects at baseline, on day 1 of each cycle (until disease progression warranting discontinuation or unacceptable toxicity), and at final study visit (four weeks after the last dose of study drug or in event of premature study termination).
The HRQoL-evaluable population was defined as those in the ITT population who had completed ≥1 of the EORTC QLQ-C30 scales at baseline and had ≥1 evaluable assessment at post-baseline visits. In the sacituzumab govitecan group 88.4% were HRQoL evaluable and 69.8% of the TPC group.

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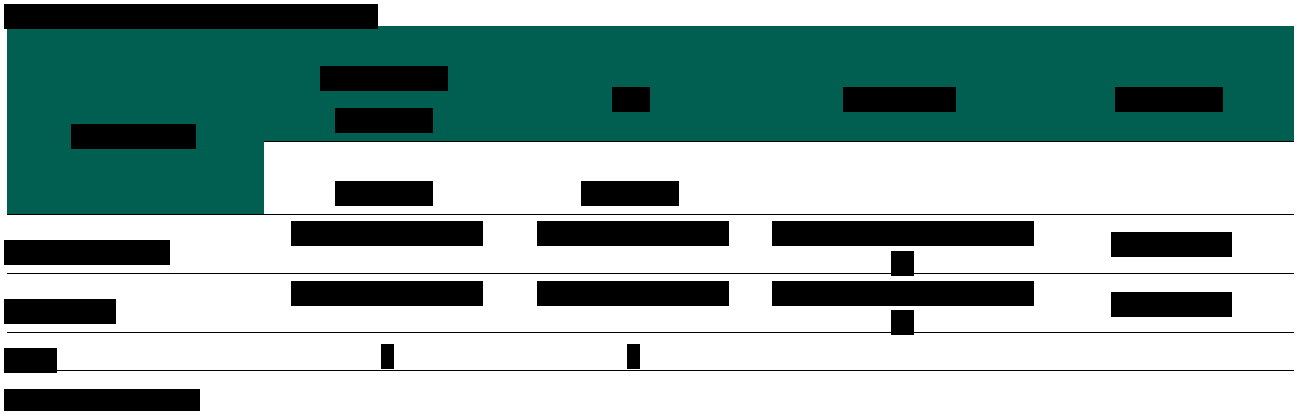
Mapping from the EORTC QLQ-C30 to EQ-5D was required to estimate utilities for subjects enrolled in ASCENT clinical trial. Therefore, the measurements collected in the ASCENT trial were mapped onto the EQ-5D-3L using Longworth mapping algorithm [72]. Details on the mapping method are found in Appendix I Mapping of HRQoL data

Utility values were applied to each health state in the model to capture patient QoL associated with treatment and disease outcomes. Specifically, the model assigns utility values to PFS by treatment, and a single utility value to PD applicable for all treatments, assuming the QoL of the patients post progression does not differ based on initial treatment received.
Mean health states utility values used in the economic model are shown in Table 28.

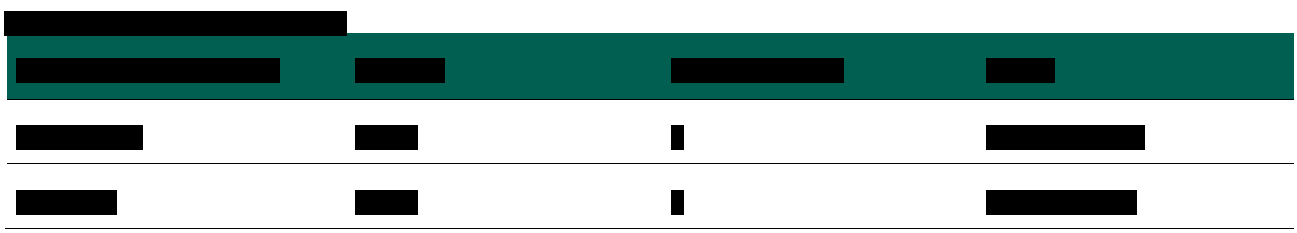


8.4.2 Disutility due to adverse events

The disutility associated with AEs was not included in the base case as treatment specific HRQoL as measured in ASCENT was used. This measurement will include the effect of any AE – thus including additional disutility would lead to double counting the utility decrement associated with an AE.

Utility decrements associated with adverse events (AEs) were not explicitly collected in the ASCENT study and these values were sourced from previous NICE appraisals in BC (TA423 [73]) and the published literature. Where there were no data for certain AEs, utility decrements were assumed to be equivalent to the greatest decrement identified in the literature across the other AEs.

The model has the ability to estimate the average utility loss due to AEs for each treatment by considering the treatment-specific AE rates, the mean utility decrements associated with these AEs and the mean duration of each AE episode. The total utility loss due to AEs (-0.002 for sacituzumab govitecan and -0.001 for TPC) was applied once at the start of the model, assuming that AEs occurred within the early period of treatment. Table 29 reports the disutility associated to each AE.



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8.4.3 Age-adjustment of the quality of life

The QALY-weights in the analysis were age-adjusted. The methodology for the age-adjustment consisted in using the Danish general population utilities stratified by age groups to calculate the age-dependent multipliers. The age-dependent multipliers were then used to adjust the individual's undiscounted utility levels each cycle according to their age. Table 30 shows the Danish general population utility values stratified by age groups and Table 31 and Table 31 shows the matrix with the age-dependent multipliers used in the model.

Table 30: Danish general population utility values stratified by age groups

Age group	Utility values
0-17	1
18-29	0.871
30-39	0.848
40-49	0.834
50-69	0.818
70-79	0.813
80+	0.721

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Source: DMC [75].

Table 31: Matrix containing the age-dependent multipliers used in the Danish setting

Age group and age-dependent multipliers	0	18	30	40	50	70	80
0	1	0,871	0,848	0,834	0,818	0,813	0,721
18		1	0,97359	0,95752	0,93915	0,93341	0,82778
30			1	0,98349	0,96462	0,95873	0,85024
40				1	0,98082	0,97482	0,86451
50					1	0,99389	0,88142
70						1	0,88684
80							1

8.4.4 Health state utility values used in the health economic model

Health state utility values (HSUVs) in the cost-effectiveness analysis were based on HRQoL measured in ASCENT [71]. HSUVs were based on mapped EQ-5D-3L values (from EORTC QLQ-C30, see section above and Appendix I Mapping of HRQoL data). EQ-5D utility scores from all visits were analyzed using mixed-effects linear regression with a random intercept for each patient to account for the clustering of multiple observations. The utility models investigated the potential effect on EQ-5D utilities of treatment arm and progression status (PD vs. PF), one at a time (univariate models) and in combinations (multivariate models). In addition, all models were adjusted for baseline utility.

For the progression free health state, according to the multivariate model, utility increased significantly by 0.084 ($p<0.001$) in the sacituzumab govitecan treatment arm vs. TPC treatment arm. The predicted HSUV for sacituzumab govitecan progression free was 0.710 versus 0.626 for TPC. The use of these estimates for the HSUV for the progression free health state is that they are derived directly from ASCENT, from the relevant patient population with the relevant treatment. The different HSUV between the two arms is justified as treatment is considered to be a significant factor of utility when patients are progression free and therefore utilities by treatment arms were used in the base case.

For the progressed health state, there was no reason to believe that the treatment effect to HRQoL will be preserved over time, and therefore the model uses the same utility value for both treatment arms. The HSUV was estimated to 0.619.
The 'Dead' health state was set to 0, while HSUVs for adverse events were not used in the analysis as the HRQoL data from ASCENT are assumed to capture effects of adverse reactions. However, the use of HSUVs for adverse reactions were included in a sensitivity analysis and values are given in Table 29.

To conclude, in the base case analysis, the EQ-5D-3L values from the pivotal clinical trial ASCENT was used. These values represent the best QoL estimates for the relevant patient group. The QoL values from ASCENT also captures the QoL estimates for the most relevant comparator in Denmark, represented by the TPC basket validated with the help of a

clinical expert [6] to reflect the Danish clinical practice. Further, QoL estimates directly from the trial also capture any disutility associated with adverse events, removing uncertainty associated with sourcing this disutility from other sources. The utilities for the two arms of ASCENT were found to be significantly different which motivates the use of different utility values in the analysis.

8.5 Resource use and costs

Healthcare utilization and resource use were estimated, and linked costs were included in the health economic model. Table 32-Table 34 present drug acquisition costs of the intervention, the comparator and post-progression treatments, respectively. For the analysis, the pharmacy purchasing price (wholesale price) was used. Table 37 presents administration costs for intravenous chemotherapy used in the model. Healthcare utilization frequencies for routine care as well as monitoring and associated costs are presented in Table 38-Table 40. Table 41 shows the costs linked to the management of adverse events. Additionally, end-of-life costs were included to reflect increased resource use towards the end of life (Table 42).

According to the restricted societal perspective of the health economic analysis indirect and non-healthcare direct costs were included. These include travel costs and time spent due to treatment for patients and are presented in Table 32.

Table 32: Unit cost for Intervention (sacituzumab govitecan)

Drug	Strength (mg)	Pack size	Unit cost (DKK) - AIP	Source
Sacituzumab govitecan	10mg/ml	20 ml	6 976.00	GILEAD

Table 33: Unit cost for Comparators (TPC)

Drug – code	Strength (mg)	Pack size	Unit cost (DKK) – AIP*	Source
Eribulin – 176930	0.44 mg/ml	2 ml	2 401.11	Medicinpriser.dk
Vinorelbine – 003164	20 mg	1	412.50	Medicinpriser.dk
Gemcitabine - 420717	100 mg/ml	2 ml	1 000.00	Medicinpriser.dk
Capecitabine - 161150	150 mg	60	163.00	Medicinpriser.dk

*Accessed in December 2021

Table 34: Unit costs for subsequent treatments

Drug – code	Strength (mg)	Pack size	Unit cost (DKK) – AIP*	Source
Docetaxel (Infusion) – 170823	80 mg	4 ml	150.00	Medicinpriser.dk
Carboplatin (IV) – 439635	450 mg	1	203.00	Medicinpriser.dk
Epirubicin – 045066	2 mg	25 ml	180.00	Medicinpriser.dk

*Accessed in December 2021

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The subsequent treatment composition, usage and duration, which were assumed to be the same regardless of prior treatment, were derived from the ASCENT trial follow-up analysis and are presented in Table 36. Post progression treatments were validated by a Danish clinical expert with experience of treating the relevant patient population in Denmark [6].

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Table 37: Cost of administration

Resource	Unit cost (DKK)	Comment	Source
Simple Parenteral Chemotherapy at First Attendance	1,735	Assumed for Sacituzumab govitecan-same cost as complex chemotherapy	DRG Kode, 09MA98 – MDC09 1-dagsgruppe, pat. mindst 7 år; Diagnosekode, DC509 Brystkræft UNS; Behandlingskode, BWAA62 Medicingivning ved intravenøs infusion [76].
Complex Parenteral Chemotherapy at First Attendance	1,735	Administration cost for gemcitabine and vinorelbine.	DRG Kode, 09MA98 – MDC09 1-dagsgruppe, pat. mindst 7 år; Diagnosekode, DC509 Brystkræft UNS; Behandlingskode, BWAA62 Medicingivning ved intravenøs infusion [76].

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Complex Chemotherapy, including Prolonged Infusional Treatment, First Attendance	17,556	Administration cost for Eribulin on the first attendance.	DRG kode, 27MP21 – Kemoterapi, kompleks; Diagnosekode, DC509 Brystkræft UNS; Behandlingskode, BWHA262 Behandling med eribulin [76].
Subsequent Elements of a Chemotherapy Cycle	1,735	Administration cost for further chemotherapy cycle	DRG Kode, 09MA98 – MDC09 1-dagsgruppe, pat. mindst 7 år; Diagnosekode, DC509 Brystkræft UNS; Behandlingskode, BWAA62 Medicingivning ved intravenøs infusion [76].

Simple Parenteral (IV) Chemotherapy at First Attendance:
The cost of a complex intravenous administration was assumed to be DKK 1,735 per administration. The unit cost was sourced from the 2021 DRG tariffs [76].

Complex Parenteral (IV) Chemotherapy at First Attendance:
The cost of a complex intravenous administration was assumed to be DKK 1,735 per administration. The unit cost was sourced from the 2021 DRG tariffs [76].

Complex Chemotherapy, including Prolonged Infusional Treatment, First Attendance:
The cost of a complex intravenous administration with prolonged infusional treatment on the first attendance was assumed to be DKK 17,556 per administration. The unit cost was sourced from the 2021 DRG tariffs [76], and it was applied to eribulin on the first attendance.

Subsequent Elements of a Chemotherapy Cycle:
The cost of subsequent elements of chemotherapy cycle was assumed to be DKK 1,735 per administration. The unit cost was sourced from the 2021 DRG tariffs [76].

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Table 40: Healthcare utilization cost

Item	Unit cost (DKK)	Comment	Reference*
Health care visits			
Oncologist visit	1,735	Konsultation hos speciallæge i gynækologi og obstetrik - DRG Kode, 09MA98 – MDC09 1-dagsgruppe, pat. mindst 7 år; Diagnosekode, DC509 Brystkræft UNS	[76]
Specialist nurse	0	Assumed to be covered within cost of oncologist visit	Assumption
Item	**Unit cost (DKK)**	**Comment**	**Reference***
Monitoring resources			
CT scan	1,835	30PR07 CT-scanning, ukompliceret, el. Osteodensitometri	[76]
Full blood count	20.75	7110 Blod	[77]
Liver function	230	ALAT, ALB, ASAT, BASP, GGT	[78]
Renal function	230	Assumed to be equal to liver function	[78]

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Item	Unit cost (DKK)	Comment	Reference*
ECG	179.85	7117 Elektrokardiogram (EKG) - 12 afledninger	[77]
Metabolic panel	3,406	EPC00116 - Metabolisk screening;U	[78]

*Accessed in December 2021

Oncologist visit

For all the health states, oncologist visits were included based on the assumption that the relevant patient population attends follow-up visits within specialized care both in a progression-free and progressed health state, the assumption was validated by a clinical expert [6]. The cost applied in the model represents the cost per one oncologist visit, estimate to be DKK 1,735 and was derived from the DRG 2021 tariffs.

Specialist nurse visit

For all the health states, specialist nurse visits were included based on the assumption that the relevant patient population attends follow-up visits within specialized care both in a progression-free and progressed health state, the assumption was validated by a clinical expert [6]. The unit cost was estimated to be covered by the cost of an oncologist visit.

CT Scan

Based on clinical expert feedback, patients are monitored by CT every third month in both the progression free and progressed health state. The cost per scan was based on the 2021 DRG tariffs and the unit cost was estimated to be DKK 1,835.

Full blood count

For all the health states in both treatment arms, full blood count tests were included based on the assumption that the relevant patient population is monitored frequently in connection with treatment both in a progression-free and progressed health state, with different frequencies for sacituzumab govitecan and TPC. The cost per test was estimated to be DKK 20.75.

Liver function

For all the health states in the TPC arm and in case of progressed disease in sacituzumab govitecan, liver function tests were included based on the assumption that the relevant patient population is monitored frequently in connection with treatment both in a progression-free and progressed health state. The cost per test reflects the cost of one sample and respective analyses. The unit cost was estimated to be DKK 230.

Renal function

For all the health states in the TPC arm and in case of progressed disease in sacituzumab govitecan, renal function tests were included based on the assumption that the relevant patient population is monitored frequently in connection with treatment both in a progression-free and progressed health state. The cost per test reflects the cost of one sample and respective analyses. The unit cost was estimated to be DKK 230.

ECG

For all the health states in the TPC arm and in case of progressed disease in sacituzumab govitecan, ECG (Echocardiogram) scan were included based on the requirement for cardiac monitoring linked to the treatment of mTNBC. The cost per scan was estimated to be DKK 179.85.

Metabolic Panel

For all the health states in the TPC arm and in case of progressed disease in sacituzumab govitecan, metabolic panel tests were included based on the assumption that the relevant patient population is monitored frequently in connection with treatment both in a progression-free and progressed health state. The cost per test reflects the cost of one sample and respective analyses. The unit cost was estimated to be DKK 3,406.

The management of adverse events was included in the model for grade 3/4 treatment-emergent adverse events occurring in at least 3% of patients for both sacituzumab govitecan and the comparator. Table 41 shows the included adverse events as well as the assumed unit costs for each event. In the model, each adverse event is assumed to last one week.

Table 41: Healthcare utilization inputs for the management of adverse events

Input	Cost (DKK)	Comment/assumption	Reference
Neutropenia	9,225 DKK	48PR02 Immunmodulerende behandling, 1-dags	[76]
Diarrhoea	5,130 DKK	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.	[76]
Leukopenia	9,225 DKK	48PR02 Immunmodulerende behandling, 1-dags	[76]
Anemia	5,246 DKK	16MA04 Hæmoglobinopati	[76]
Febrile neutropenia	13,853 DKK	48PR02 Immunmodulerende behandling, 1-dags + 16PR02 Transfusion af blod, øvrig	[76]
Fatigue	3,987 DKK	23MA03 Symptomer og fund, u. kompl. bidiag.	[76]
Dyspnoea	3,987 DKK	23MA03 Symptomer og fund, u. kompl. bidiag.	[76]
Hypophosphataemia	3,987 DKK	23MA03 Symptomer og fund, u. kompl. bidiag.	[76]
Pneumonia	31,104.5 DKK	Average 04MA14/04MA13 (Lungebetændelse og pleurit, pat. 18-59 år/Lungebetændelse og pleurit, pat. mindst 60 år)	[76]
Nausea	5,130 DKK	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.	[76]
Pulmonary embolism	31,012 DKK	04MA04 Lungeemboli	[76]
Pleural effusion	10,300 DKK	04MP12 Andre sygdomme i luftveje, udredning	[76]

Neutropenia

The cost of management of neutropenia was applied for every occurrence. The management of neutropenia was derived from the Danish DRG list [76]. A cost of DKK 9,225 was applied.

Diarrhoea

The cost of management of diarrhea was applied for every occurrence. The management was assumed to be the same as the management of inflammation of the esophagus, stomach and intestines (complicated). The cost of DKK 5,130 was derived from the Danish DRG list [76].

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Leukopenia
The cost of management of leukopenia was applied for every occurrence. The management of leukopenia was derived from the Danish DRG list [76]. A cost of DKK 9,225 was applied.

Anemia
The cost of management of anemia was applied for every occurrence. The management of anemia was derived from the Danish DRG list [76]. A cost of DKK 5,246 was applied.

Febrile neutropenia
The cost of management of febrile neutropenia was applied for every occurrence. The management of febrile neutropenia, including the handling of the fever symptoms, was derived from the Danish DRG list [76]. A cost of DKK 13,853 was applied.

Fatigue
The cost of management of fatigue was applied for every occurrence. The cost of DKK 3,987 was derived from the Danish DRG list [76].

Dyspnoea
The cost of management of dyspnoea was applied for every occurrence. The cost of DKK 3,987 was derived from the Danish DRG list [76].

Hypophosphataemia
The cost of management of hypophosphataemia was applied for every occurrence. The cost of DKK 3,987 was derived from the Danish DRG list [76].

Pneumonia
The cost of management of pneumonia was applied for every occurrence. The cost of DKK 31,104.50 was derived from the Danish DRG list [76].

Nausea
The cost of management of nausea was applied for every occurrence. The cost of DKK 5,130 was derived from the Danish DRG list [76].

Pulmonary embolism
The cost of management of pulmonary embolism was applied for every occurrence. The cost of DKK 31,012 was derived from the Danish DRG list [76].

Pleural effusion
The cost of management of pleural effusion was applied for every occurrence. The cost of management of pleural effusion was derived from the Danish DRG list [76]. A cost of DKK 10,300 was applied.

A one-off cost is applied at the transition to the death health state to represent the cost of palliative care. No other costs are associated with the death health state. The end of life cost or 'Terminal care cost' is presented in Table 42. The cost was derived from the DRG tariffs.

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Table 42: End of life cost

Unit cost (DKK)	Source
88,471	Palliative specialized care, large effort, DRG code 26MP45 [76]

For the analysis, a restricted societal perspective was applied including time spent due to treatment and transportation cost. For one hour of time a value of DKK 180 was assumed. Table 43 shows the estimated use of time and linked indirect cost for routine care. Table 44 shows the proportion of productivity losses applied for patients. It was assumed that the productivity loss applies to 100% of the patients regardless of health state. The indirect costs are applied for each cycle and are presented as part of the health state costs.

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8.6 Results

8.6.1 Base case overview

An overview of the base case is presented in Table 45.

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8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

The impact of individual parameters on the ICER was tested in one-way deterministic sensitivity analyses (OWSA). Key model settings, cost inputs and utility inputs were systematically and independently varied over a plausible range. The ICER was recorded at the upper and lower values to produce a tornado diagram.

The results of the deterministic sensitivity analyses are presented in Figure 16 and Table 48. This figure and table present the ten parameters that have the greatest impact on the ICER for sacituzumab govitecan compared to TPC. The parameters that had the greatest impacts on the ICER were sacituzumab govitecan drug acquisition costs, the time horizon, and the sacituzumab govitecan TTD curve parameter, which determines the treatment duration of sacituzumab govitecan.

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In Table 49 below the results of the scenario analyses are presented.

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8.7.2 Probabilistic sensitivity analyses

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9. Budget impact analysis

The budget impact of sacituzumab govitecan is presented below in
Table 50-Table 54. Prices are pharmacy purchasing price (PPP/AIP). All costs relevant to the regions have been included: drug costs (Table 32-Table 36), the administration of drugs (Table 37), adverse events (Table 41), death (Table 42), disease management and monitoring (Table 39-Table 40). Per patient costs from the first five years of the cost-effectiveness analysis was used to inform the budget impact analysis. The calculation employs an open cohort with patients entering each year.

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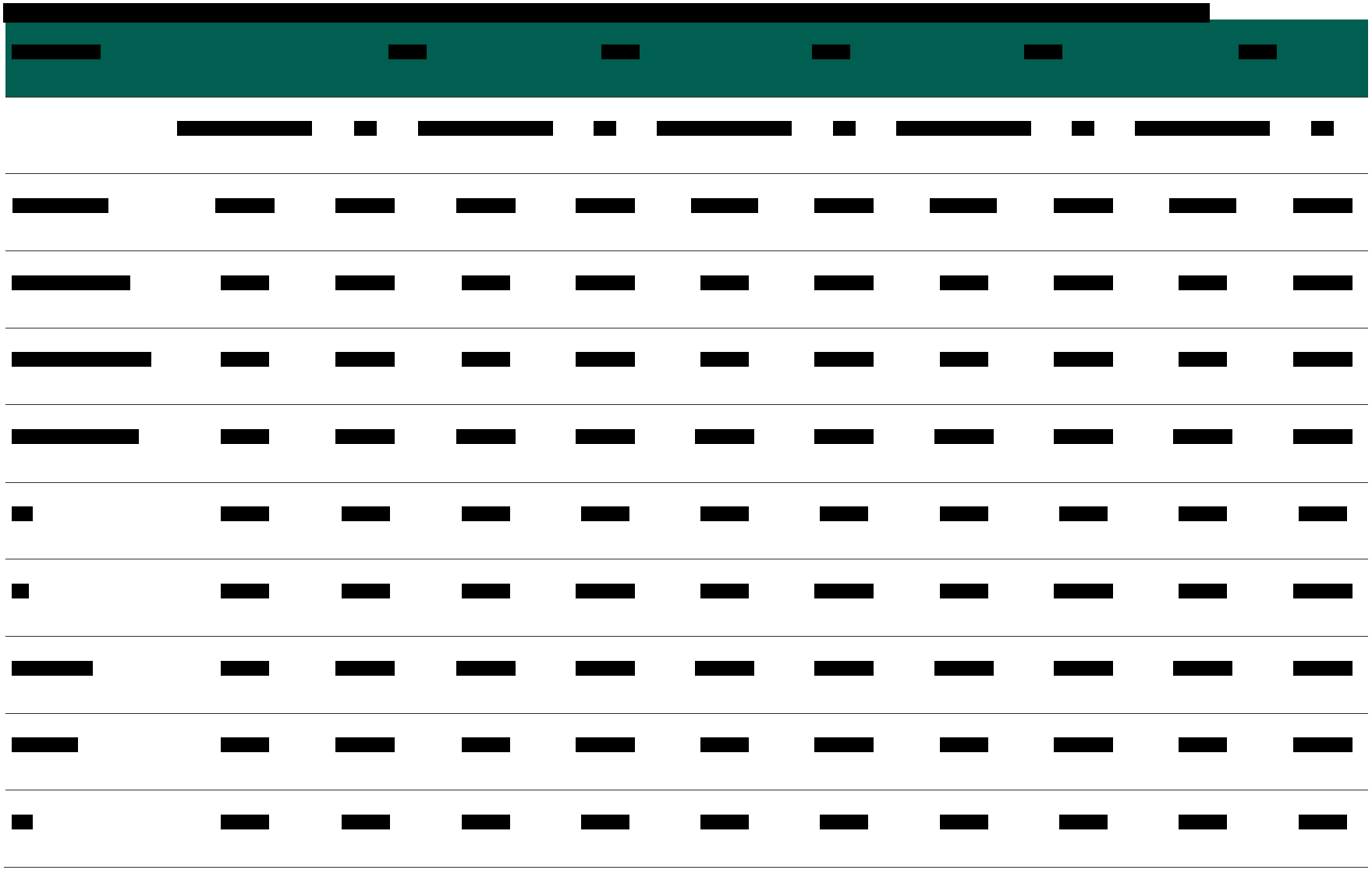

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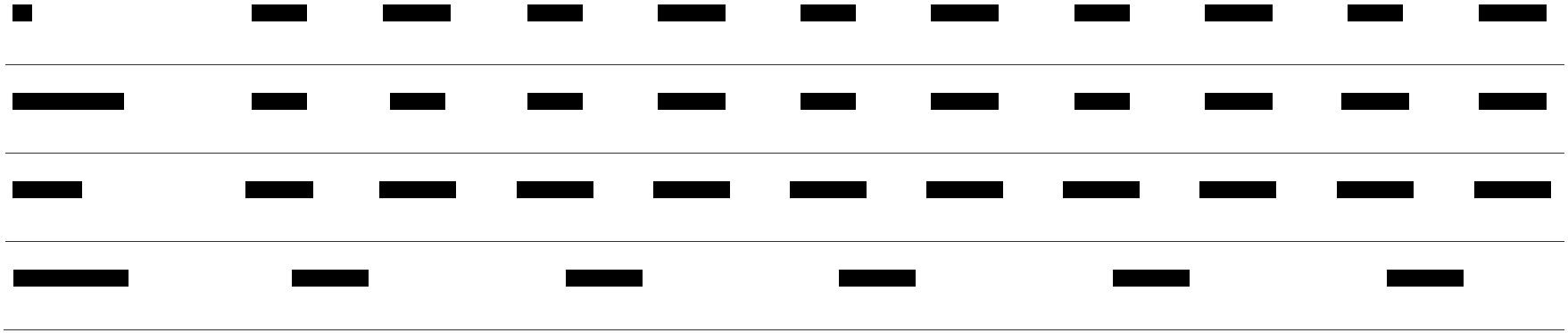

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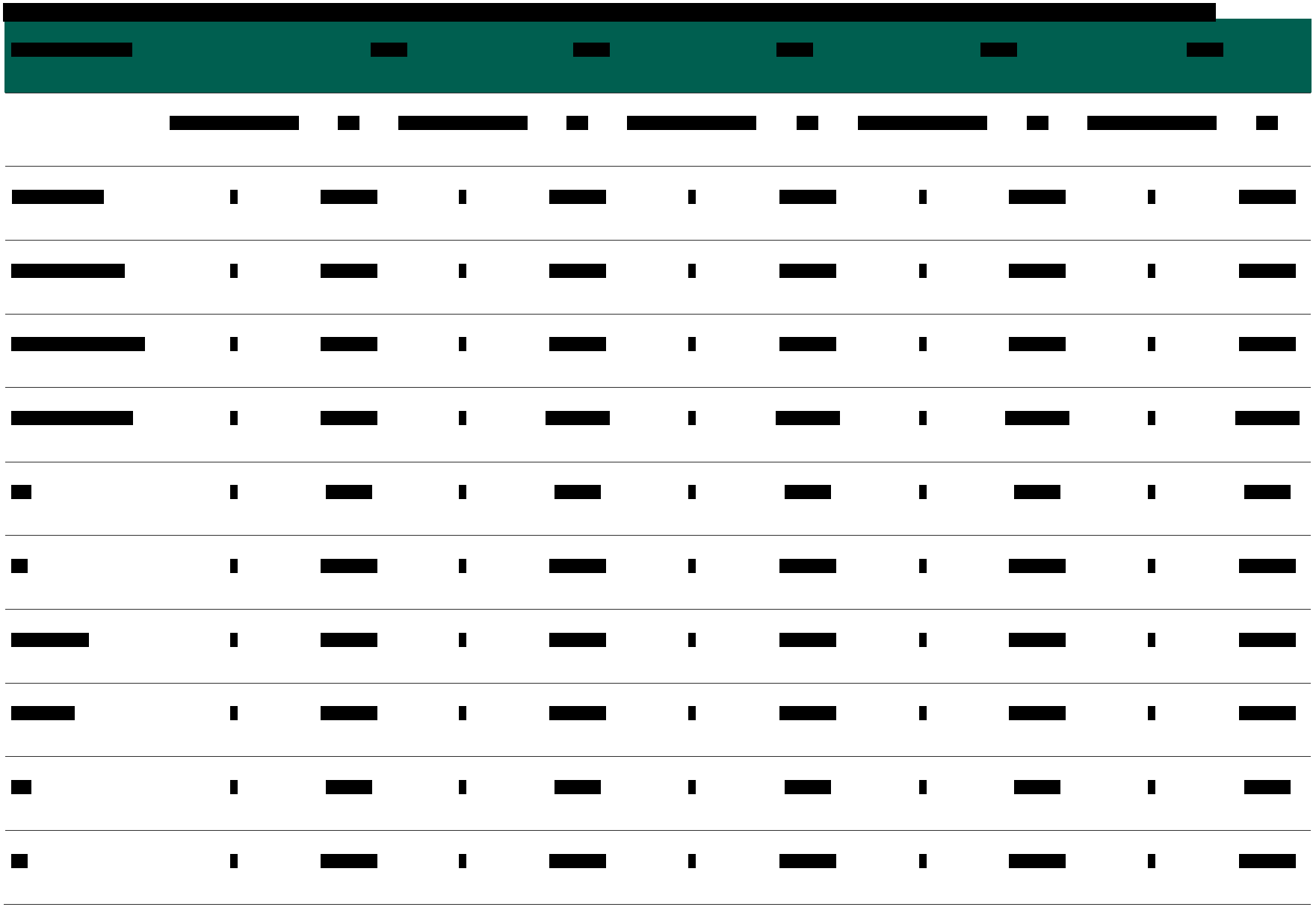

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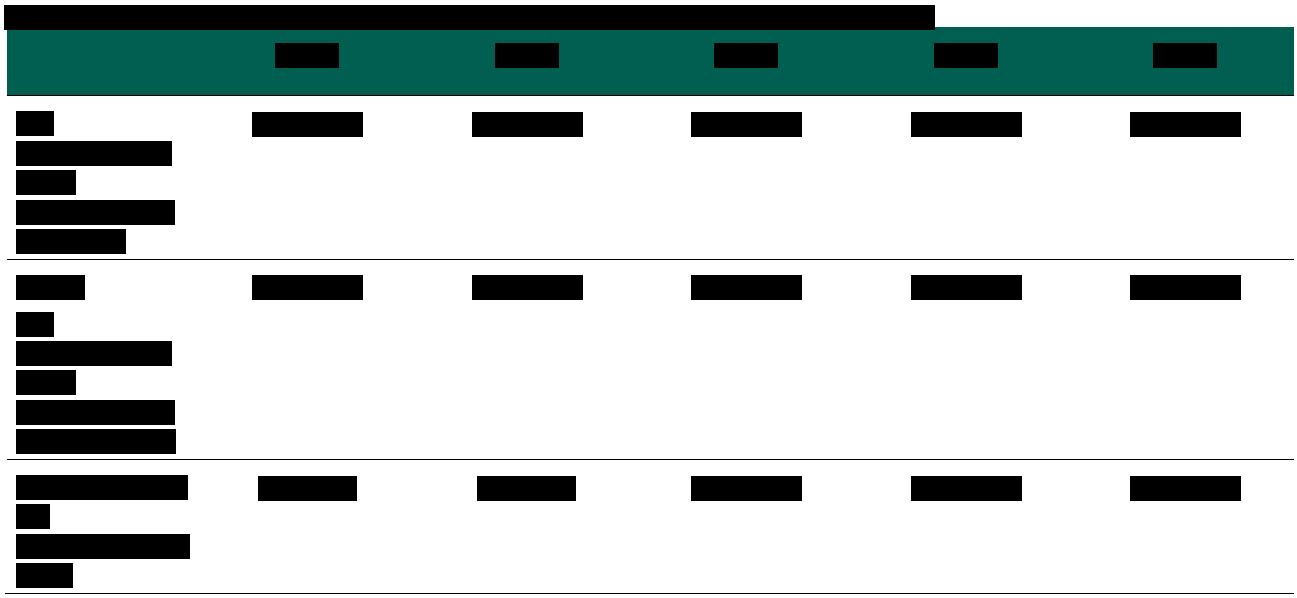

10. Discussion on the submitted documentation

10.1 Summary of submitted evidence

Sacituzumab govitecan is a Trop-2–directed antibody and topoisomerase inhibitor conjugate and is indicated for the treatment of adults with unresectable or metastatic TNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease [55, 56]. For the health economic assessment of sacituzumab govitecan a direct comparison was conducted using data from the pivotal trial ASCENT. The comparator in the clinical trial, a combination of monotherapy composed by eribulin, vinorelbine, gemcitabine and capecitabine (Treatment of physician's choice, TPC), was considered to be the most relevant comparator in Danish clinical practice.

ASCENT was an international, multicenter, open-label, randomized, phase 3 study in 529 patients with unresectable, locally advanced, or mTNBC who were refractory or had relapsed after receiving two or more prior chemotherapies, including one or more prior therapy for locally advanced or metastatic disease [10, 11].

The strength of the ASCENT results is reflected in the consistency of benefit observed in the total population and across the prespecified subgroup. The PFS benefit seen with sacituzumab govitecan was consistent across all study populations including all patients enrolled.

Sacituzumab govitecan provides a statistically significant and clinical important 4.9-month gain in median OS compared with the treatment currently provided in Denmark to patients with unresectable or metastatic triple-negative breast cancer (mTNBC).
Within a diseade area with a high unmet need, Sacituzumab govitecan is an effective, tolerable and convenient treatment which improve outcomes without compromising the health-related quality of life (HRQoL).

10.2 Cost-effectiveness analysis

Sacituzumab govitecan compared to TPC was associated with higher costs and gains in QALYs with a cost per additional QALY gained of [redacted] per life-year gained over a lifetime time horizon (20 years) in the base case. The results of the analysis were sensitive to the time horizon, the choice of OS distribution and the choice of TTD distribution.

The QALY benefit of sacituzumab govitecan compared to TPC manifests from time spent in the progression-free health state and longer overall survival. The incremental cost was due to additional drug acquisition costs associated with sacituzumab govitecan, which was impacted by drug pack prices, drug doses (including parameters for patient body weight or body surface area used in dose calculations), and treatment duration.

The probabilistic sensitivity analysis results were very similar to the deterministic results which demonstrates the robustness of the analysis. [redacted]

Over a lifetime time horizon, mTNBC patients treated with sacituzumab govitecan were estimated to incur mean total costs of [redacted] in the base-case with a [redacted].

10.2.1 Strength of the analysis

A transparent, cost-effectiveness model was developed in Microsoft Excel and Microsoft Visual Basic for Applications. The model was adapted to a Danish setting according to the DMC's guidelines. The three-health state partitioned survival model structure aligns with the approach used in previous technology appraisals in breast cancer. The model captures the lifetime of patients and uses a 7-day cycle length, which provides sufficient granularity to capture any important differences in costs and outcomes between comparator treatments.

Where possible, data were used from the pivotal ASCENT trial in the base-case analysis, which represents the target population. Extensive survival analyses were performed for PFS and OS, including various parametric models fitted to the trial data. Additionally, the model includes health state utility weights derived from HRQoL data collected in the ASCENT trial. Unit costs were taken from recognized national sources (where available). Extensive sensitivity analysis was performed, including univariate and probabilistic sensitivity analyses incorporating all model parameters.

10.2.2 Limitations

Some inputs to the analysis were based on assumptions and clinical expert opinion, such as the composition of the TPC basket and the proportion of patients receiving different post-progression treatments.
Long-term extrapolation of OS curves from short-term clinical trials is always subject to uncertainty and hence should be validated against long-term data from other sources. However, long-term validation specifically for this patient population is difficult due to a lack of real-world evidence.

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

Not applicable

Appendix B Main characteristics of included studies

Table 55: Main characteristics of IMMU-132-01

Trial name: IMMU-132-01	NCT number: NCT01631552
Objective	To evaluate the safety and efficacy of sacituzumab govitecan-hziy administered in 21-day treatment cycles at a dose selected in Phase I.
Publications – title, author, journal, year	Efficacy and Safety of Anti-Trop-2 Antibody Drug Conjugate Sacituzumab Govitecan (IMMU-132) in Heavily Pretreated Patients With Metastatic Triple-Negative Breast Cancer, Bardia et al., Journal of Clinical Oncology, 2017. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer, Bardia et al., The New England Journal of Medicine, 2019.
Study type and design	Phase I/II, multicenter, open-label, single-group, basket-design trial. This study is completed. No crossover was allowed.
Sample size (n)	Sacituzumab Govitecan 10 mg/kg, N=108

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Main inclusion and exclusion criteria

Inclusion Criteria:

- Individuals able to understand and give written informed consent.
- Age ≥18 years
- Histologically or cytologically confirmed epithelial cancer of one of the following types:
    - Gastric adenocarcinoma (GC)
    - Esophageal cancer (EC)
    - Hepatocellular carcinoma (HCC)
    - Non-small-cell lung cancer (NSCLC)
    - Small-cell lung cancer (SCLC)
    - Epithelial ovarian cancer (EOC)
    - Cervical Cancer
    - Endometrial Cancer
    - TNBC
    - Non-triple-negative breast cancer
    - Papillary thyroid cancer (excludes follicular, medullary, Hurthle cell, and anaplastic thyroid cancer)
    - Glioblastoma multiforme (GBM)
    - Hormone-refractory prostate cancer (HRPC)
    - Head and neck cancers- squamous cell (SCCHN)
    - Renal cell cancer (clear cell) (RCC)
    - Urothelial cancer
    - Stage IV (metastatic) disease (except for individuals with GBM).
    - Refractory to or relapsed after at least one prior standard therapeutic regimen
    - Adequate performance status (ECOG 0 or 1)
    - Expected survival ≥ 6 months.
    - Measurable disease by CT or MRI.
- At least 2 weeks beyond treatment (chemotherapy, investigational drugs including small molecular inhibitors, immunotherapy and/or radiation therapy) or major surgery and recovered from all acute toxicities to Grade 1 or less (except alopecia).
- At least 2 weeks beyond high dose systemic corticosteroids (however, low dose corticosteroids < 20 mg prednisone or equivalent daily are permitted).
- Adequate hematology without ongoing transfusional support (hemoglobin > 9 g/dL, absolute neutrophil count (ANC) > 1,500 per mm^3, platelets > 100,000 per mm^3).
- Adequate renal and hepatic function (creatinine ≤ 2.0 x institutional upper limit of normal (IULN), bilirubin ≤ 1.5 IULN, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 x IULN or 5 x IULN if know liver metastases).
- Otherwise, all toxicity at study entry ≤ Grade 1.

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Trial name: IMMU-132-01	NCT number: NCT01631552

Exclusion Criteria:

- Women who are pregnant or lactating.
- Women of childbearing potential and fertile men unwilling to use effective contraception during study until conclusion of 12-week post-treatment evaluation period.
- Individuals with Gilbert's disease.
- Individuals with BMs can be enrolled only if treated, non-progressive BMs and off high-dose steroids (> 20 mg prednisone or equivalent) for at least 4 weeks.
- Presence of bulky disease (defined as any single mass > 7 cm in its greatest dimension). Individuals with a mass over 7 cm, but otherwise eligible, may be considered for enrollment after discussion and approval with the medical monitor.
- Individuals with active ≥ grade 2 anorexia, nausea or vomiting, and/or signs of intestinal obstruction.
- Individuals with non-melanoma skin cancer or carcinoma in situ of the cervix are eligible, while individuals with other prior malignancies must have had at least a 3-year disease-free interval.
- Individuals known to be HIV positive, hepatitis B positive, or hepatitis C positive.
- Known history of unstable angina, MI, or CHF present within 6 months or clinically significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy.
- Known history of clinically significant active COPD, or other moderate-to-severe chronic respiratory illness present within 6 months.
- Prior history of clinically significant bleeding, intestinal obstruction, or GI perforation within 6 months of initiation of study treatment.
- Infection requiring IV antibiotic use within 1 week.
- History of an anaphylactic reaction to irinotecan or ≥ Grade 3 GI toxicity to prior irinotecan,
- Other concurrent medical or psychiatric conditions that, in the Investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.

Intervention	Participants (n=108) received Sacituzumab govitecan 10 mg/kg of body weight via IV infusion on Days 1 and 8 of a 21-day treatment cycle until disease progression or unacceptable toxicity.
Comparator(s)	Not relevant.
Follow-up time	Median follow-up of 9.7 months (range 0.3-36.5)
Is the study used in the health economic model?	No

Trial name: IMMU-132-01	NCT number: NCT01631552
Primary, secondary and exploratory endpoints	Primary endpoints: • Safety (AEs and SAEs, laboratory safety evaluations, vital signs, physical examination, and 12-lead ECG) • ORR, defined as complete response + partial response per Response Evaluation Criteria in Solid Tumors, version 1.1 Secondary endpoints: • DOR • TTR • CBR; complete response, partial response, or stable disease ≥6 months • PFS defined as the time from randomization until objective tumor progression by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death, whichever came first. • OS defined as the time from the start of study treatment to death from any cause Other endpoints: • Blinded independent central review of staging scans was also obtained for the 56 patients (of the 108 with mTNBC) who had complete or partial remission, or at least a 20% reduction in the baseline sum of the diameters of the target lesions, according to local site evaluation, but results are not included in this application.
Method of analysis	All efficacy analyses were ITT. The response rate and the exact 95% CIs were calculated with the use of the Clopper–Pearson method. PFS and OS and time-to-event end points were analyzed with the use of Kaplan–Meier methods, with medians and corresponding 95% CIs determined according to the Brookmeyer and Crowley method with log–log transformation.
Subgroup analyses	Not applicable
Other relevant information	No

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Table 56: Main characteristics of ASCENT

Trial name: ASCENT	NCT number: NCT02574455
Objective	To compare the efficacy of sacituzumab govitecan to the treatment of physician's choice as measured by independently-reviewed Independent Review Committee PFS in participants with LA or TNBC previously treated with at least two systemic chemotherapy regimens for unresectable, LA or metastatic disease, and BM-ve at baseline.
Publications – title, author, journal, year	Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. Bardia A et al., and ASCENT Clinical Trial Investigators. The New England Journal of Medicine. 2021
Study type and design	An International, Multi-Center, Open-Label, Randomized, Phase III Trial. Enrolled patients were randomly assigned in a 1:1 ratio to receive sacituzumab govitecan or single-agent chemotherapy. No crossover was allowed. This study is completed.
Sample size (n)	ITT population (n=529) assigned to receive: • sacituzumab govitecan, n=267, or • treatment of physician's choice., n=262

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Main inclusion and exclusion criteria

Inclusion Criteria:

- Age ≥18 years
- Histologically or cytologically confirmed TNBC based on the most recent analyzed biopsy or other pathology specimen. Triple negative is defined as <1% expression for ER and PR and negative for HER2 by in-situ hybridization.
- Refractory to or relapsed after at least two prior standard therapeutic regimens for advanced/metastatic TNBC.
- Prior exposure to a taxane in localized or advanced/metastatic setting.
- Eligible for one of the chemotherapy options listed as TPC (eribulin, capecitabine, gemcitabine, or vinorelbine) as per investigator assessment.
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 .
- Measurable disease by CT or magnetic resonance imaging (MRI) as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Bone-only disease is not permitted.
- At least 2 weeks beyond prior anti-cancer treatment (chemotherapy, endocrine therapy, radiotherapy, and/or major surgery), and recovered from all acute toxicities to Grade 1 or less (except alopecia and peripheral neuropathy).
- At least 2 weeks beyond high dose systemic corticosteroids (however, low dose corticosteroids < 20 mg prednisone or equivalent daily are permitted provided the dose is stable for 4 weeks).
- Adequate hematology without ongoing transfusional support (hemoglobin > 9 g/dL, absolute neutrophil count (ANC) > 1,500 per mm^3, platelets > 100,000 per mm^3).
- Adequate renal and hepatic function (creatinine clearance [CrCL] > 60 mL/min, bilirubin ≤ 1.5 institutional upper limit of normal [IULN], aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤ 2.5 x IULN or ≤ 5 x IULN if known liver metastases and serum albumin ≥3 g/dL).
- Recovered from all toxicities to Grade 1 or less by National Cancer Institute common terminology criteria for AEs (NCI CTCAE) v4.03 (except alopecia or peripheral neuropathy that may be Grade 2 or less) at the time of randomization. Participants with Grade 2 neuropathy are eligible but may not receive vinorelbine as TPC.
- Participants with treated, non-progressive BMs, off high-dose steroids (>20 mg prednisone or equivalent) for at least 4 weeks can be enrolled in the trial.

Exclusion Criteria:

- Women who are pregnant or lactating.
- Women of childbearing potential or fertile men unwilling to use effective contraception during study and up to three months after treatment discontinuation in women of child-bearing potential and six months in males post last study drug.
- Participants with Gilbert's disease.
- Participants with non-melanoma skin cancer or carcinoma in situ of the cervix are eligible, while participants with other prior malignancies must have had at least a 3-year disease-free interval.
- Participants known to be human immunodeficiency (HIV) positive, hepatitis B positive, or hepatitis C positive.

Trial name: ASCENT	NCT number: NCT02574455
	• Infection requiring antibiotic use within one week of randomization. • Other concurrent medical or psychiatric conditions that, in the Investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.
Intervention*	Sacituzumab Govitecan 10 mg/kg was administered IV as a single agent on Days 1 and 8 of every 21-day treatment cycle until patients experienced disease progression or unacceptable toxicity. 267 patients received the intervention.
Comparator(s)*	A total of 262 participants received Treatment of Physician's Choice TPC (ie, eribulin, capecitabine, gemcitabine, or vinorelbine), administered as a single-agent regimen that was selected by the investigator before participant randomization. Participants continued treatment until progression of disease requiring treatment discontinuation or occurrence of unacceptable AEs. Interventions: • Eribulin: administered IV over 2 to 5 minutes at a dose 1.4 mg/m^2 at North American sites and 1.23 mg/m^2 at European sites on Days 1 and 8 of a 21-day cycle. Lower doses were administered on the same schedule to participants with moderate hepatic impairment (ie, Child-Pugh B; 0.7 mg/m^2 and 0.67 mg/m^2 for North American and European sites, respectively). A total of 122 patients received eribulin. • Capecitabine: 1000 to 1250 mg/m^2 were administered in a 21-day cycle, with capecitabine administered orally twice daily for 2 weeks followed by 1-week rest period. A total of 22 patients received capecitabine. • Gemcitabine: 800 to 1200 mg/m^2 were administered IV over 30 minutes on Days 1, 8, and 15 of a 28-day cycle. A total of 31 patients received gemcitabine. • Vinorelbine: 25 mg/m^2 will be administered as a weekly IV injection over 6-10 minutes. Vinorelbine will not be allowed as TPC for any participant with Grade 2 neuropathy. A total of 43 patients received vinorelbine.
Follow-up time	17.7 (range: 5.8, 28.1)
Is the study used in the health economic model?	Yes

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Trial name: ASCENT	NCT number: NCT02574455
Primary, secondary, and exploratory endpoints	Primary endpoint: • PFS by Independent Review Committee (IRC) assessment per RECIST v1.1 in patients without BMs at baseline Secondary endpoints: Secondary endpoints were analyzed in the BM-ve and ITT Populations by IRC assessment (assessment by investigator as supportive sensitivity analyses) • PFS, time from randomization until objective tumor progression or death, whichever came first • OS time from randomization until death • ORR, percentage of patients who had either a confirmed CR or PR • TTR (time to response), time from randomization or the start of study treatment to the first recorded objective response (ie, CR or PR) • DOR number of days between the first date showing a documented response of CR or PR and the date of progression or death • CBR; percentage of patients with either CR, PR, or stable disease with a duration of ≥6 months • Quality of life, assessed using the EORTC Quality of Life Questionnaire of Cancer Patients, version 3.0 (QLQ-C-30). • Safety (AEs, TEAEs, SAE, Treatment discontinuations due to TEAEs (%))
Method of analysis	All efficacy analyses were ITT analyses. PFS, OS, and ORR were analyzed with the use of the Kaplan–Meier method, with medians and corresponding 95% CIs determined according to the Brookmeyer and Crowley method with log–log transformation. Treatment effect was compared with the use of a stratified log-rank test. HRs and their 95% CIs were estimated with the use of a stratified Cox proportional-hazards model. The percentage of patients with an objective response was compared between the treatment groups with the use of the stratified Cochran–Mantel– Haenszel method. The same stratification factors that were used for the randomization were used in the stratified efficacy analyses.
Subgroup analyses	All subgroup analyses were prespecified in the statistical analysis plan. The subgroups were defined based on the BM-ve population. BM-ve population (n=468) assigned to received sacituzumab govitecan (n=235), or TPC (n=262).
Other relevant information	None

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

Table 57: Baseline characteristics of patients in studies included for the analysis

Baseline characteristics of patients in studies included for the analysis of efficacy and safety				
		IMMU-132-01	ASCENT*	
Intervention		Sacituzumab Govitecan, 10 mg/kg	Sacituzumab Govitecan, 10 mg/kg	Treatment of physician's choice.
Baseline population, n		108	267	262
Women (%)		99.1	99.3	100
Geographic region for randomization stratification	North America	-	175 (65.5)	172 (65.6)
	Rest of world	-	92 (34.5)	90 (34.4)
Race	White, n (%)	82 (75.9)	215 (80.5)	203 (77.5)
	Black, n (%)	8 (7.4)	28 (10.5)	34 (13.0)
	Asian, n (%)	3 (2.8)	13 (4.9)	9 (3.4)
	Other or not specified, n (%)	15 (13.9)	11 (4.1)	13 (6.1)
Age (years) mean (SD)		-	54 (11.34)	54 (11.69)
Age (years) median		55 (31-80)	54 (27-82)	53 (27-81)
ECOG performance- status-score, n (%)	0	31 (28.7)	121 (45.3)	108 (41.2)
	1	77 (71.3)	146 (54.7)	154 (58.8)
Previous chemotherapy regimens, n (%)	2-3	-	184 (68.9)	181 (69.1)
	>3	-	83 (31.1)	81 (30.9)
Previous anticancer regimens, median (range)		3 (2-10)	-	-
BRCA1 or BRCA2 mutation status, n (%)	Negative	-	150 (56.2)	146 (55.7)
	Positive	-	20 (7.5)	23 (8.8)
Number of prior Systemic Therapies, mean (SD)		-	4.5 (2.05)	4.6 (2.14)
Setting of systemic therapies, n (%)	Adjuvant	-	161 (60.3)	148 (56.5)
	Neo-adjuvant	-	124 (46.4)	125 (47.7)
	Metastatic	-	258 (96.6)	260 (99.2)
	Locally advanced disease	-	10 (3.7)	5 (1.9)
Treatment of Physician Choice, n (%)	Eribulin	17 (15.7)	115 (43.1)	139 (53.1)
	Capecitabine	56 (51.9)	48 (18.0)	33 (12.6)
	Gemcitabine	59 (54.65)	46 (17.2)	38 (14.5)
	Vinorelbine	17 (15.7)	58 (21.7)	52 (19.8)

*ITT population.

12.1.1 Comparability of patients across studies

Not applicable.

12.1.2 Comparability of the study populations with Danish patients eligible for treatment

The study population in ASCENT have been assessed by Danish clinical experts to reflect the characteristics of the relevant Danish patient population. As described in section 5.1 and 5.2 are the current choice of treatment very patient dependent and varies dependent of previous treatment, toxicity on previous treatments and performance status.

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Appendix D Efficacy and safety results per study

Table 58: Outcomes measure, definition, validity and clinical relevance

Outcome measure	Definition	Validity	Clinical relevance
PFS by IRC Assessment	PFS was defined as the time from randomization until objective tumor progression or death or was censored at the last radiographic assessment for patients without progression or death, according to RECIST v.1.1.	Used in prior DMC submission for TNBC and treatment guideline protocol [12].	The minimal clinically important difference for PFS is a median of 3 months [12].
PFS by investigator assessment	PFS was defined as the time from randomization until objective tumor progression or death or was censored at the last radiographic assessment for patients without progression or death, according to RECIST v.1.1.	Used in prior DMC submission for TNBC and treatment guideline protocol [12].	The minimal clinically important difference for PFS is a median of 3 months [12].
OS	OS was defined as the time from the start of study treatment to death from any cause. Patients without documentation of death are censored on the date that they were last known to be alive.	Used in prior DMC submission for TNBC and treatment guideline protocol [12].	The minimal clinically important difference for OS is a median of 3 months [12].
ORR by IRC assessment	ORR was defined as the percentage of participants who had either a confirmed complete response (CR) or partial response (PR) using RECIST v1.1 criteria.. CR: Disappearance of all target and non-target lesions; and normalization of tumor marker levels	E.A. Eisenhauera, et al (2009), *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).* EUROPEAN JOURNAL OF CANCER [80].	The ORR is measured to assess the patient's response of treatment with Sacituzumab Govitecan vs. TPC in patients with TNBC.

Outcome measure	Definition	Validity	Clinical relevance
	initially above upper limits of normal. PR: >30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD; and appearance of one or more new lesions and/or unequivocal progression of existing non-target lesion.		
ORR by investigator assessment	ORR is defined as the best confirmed overall response of either CR or PR. The best overall response is derived based on independent or investigator assessed tumor response at each tumor assessment according to RECIST 1.1. Responses of CR and PR are confirmed no less than 4 weeks later.	E.A. Eisenhauera, et al (2009), *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).* EUROPEAN JOURNAL OF CANCER [80].	The ORR is measured to assess the patient's response of treatment with Sacituzumab Govitecan vs. TPC in patients with TNBC.
HRQoL	QoL assessed using the EORTC QLQ-C-30	Used in prior DMC submission for TNBC and treatment guideline protocol [12].	The minimal clinically important difference in QoL described as a meaningful difference using a validated scheme [12].
Treatment discontinuations due to TEAEs (%)	TEAEs were graded using CTCAE version 5.0 [8]. adverse and version 4.03 [10].	Used in prior DMC submission for TNBC and treatment guideline protocol [12].	The minimal clinically important difference for treatment discontinuations due to AEs is 5%-point [12].
AEs grade 3 or higher	AEs were graded using CTCAE version 5.0 [8]. adverse and version 4.03 [10].	Used in prior DMC submission for TNBC and treatment guideline protocol [12].	The minimal clinically important difference for patients experiencing one or more grade 3-4 AEs is 5%-point or narrative assessment [12].

12.1.3 Results per study

Table 59: Results of IMMU-132-01

Results of IMMU-132-01 (NCT number: NCT01631552)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS by investigator assessment	Sacituzumab govitecan	108	5.5 months (4.1-6.3)	NA	NA	NA	NA	NA	NA	Data cut-off was 01.12.2017. PFS were analyzed with the use of Kaplan–Meier methods, with medians and corresponding 95% CIs determined according to the Brookmeyer and Crowley method with log–log transformation.	Bardia et al., 2019 [8].
	NA	NA	NA								
Median OS	Sacituzumab govitecan	108	13 months (11.2-13.7)	NA	NA	NA	NA	NA	NA	Data cut-off was 01.12.2017. OS were analyzed with the use of Kaplan–Meier methods, with medians and corresponding 95% Cis determined according to the Brookmeyer and Crowley method with log–log transformation.	Bardia et al., 2019 [8].
	NA	NA	NA								

Results of IMMU-132-01 (NCT number: NCT01631552)											
ORR (complete response or partial response at any time) per RECIST v1.1	Sacituzumab govitecan	108	36 (33.3%) (24.6-43.1)	NA	NA	NA	NA	NA	NA	Data cut-off was 01.12.2017. Assessment of response was performed according to Response Evaluation Criteria in Solid Tumors, version 1.1.	Bardia et al, 2019 [8].
	NA	NA	NA								
EORTC QLQ-C30	Sacituzumab govitecan	NA	NA	NA	NA	NA	NA	NA	NA	Not reported in IMMU-132-01	
	NA										

Results of ASCENT: ITT population											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS by IRC assessment	Sacituzumab govitecan	267	4.8 (4.1-5.8) months	3.1	NA	NA	HR: 0.433	0.347-0.541	<0.0001	Data cut-off was 11 March 2020 The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model	EMA's CHMP assessment report [47].
	Chemotherapy	262	1.7 (1.5-2.5) months								

Results of ASCENT: ITT population											
										with adjustment for stratification, and study arm. Assessed using RECIST v.1.1.	
Median PFS by investigator assessment	Sacituzumab govitecan	267	4.8 (4.1-5.8) months	3.1	NA	NA	HR: 0.382	0.309-0.473	<0.0001	Data cut-off was 11 March 2020 The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm. Assessed using RECIST v.1.1.	EMA's CHMP assessment report [47].
	Chemotherapy	262	1.7 (1.5-2.5) months								
Median OS	Sacituzumab govitecan	267	11.8 (10.5-13.8) months	4.9	NA	NA	HR: 0.508	0.414-0.624	<0.001	Data cut-off was 11 March 2020 The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model adjusted for stratification factors: numbers of prior chemotherapies and region.	EMA's CHMP assessment report [47].
	Chemotherapy	262	6.9 (5.9-7.7) months								
	Sacituzumab govitecan	267	83 (31.1%), 25.6-37.0	26%	20.8, 32.9	<0.0001	OR: 10.994	5.659-21.358	<0.0001	Data cut-off was 11 March 2020	

Results of ASCENT: ITT population											
ORR by IRC assessment	Chemotherapy	262	11 (4.2%), 2.1-7.4							ORR, percentage of patients who had either a confirmed CR or PR. Using stratified log-rank test and stratified Cox regression adjusted for stratification factors: numbers of prior chemotherapy, presence of know BMs at study entry, and region.	EMA's CHMP assessment report [47].
ORR by investigator assessment	Sacituzumab govitecan	267	83 (31.1%), 25.6-37.0	24.9%	18.7, 31.2	<0.0001	OR: 7.165	4.037-12.685	<0.0001	Data cut-off was 11 March 2020 ORR, percentage of patients who had either a confirmed CR or PR. Using stratified log-rank test and stratified Cox regression adjusted for stratification factors: numbers of prior chemotherapy, presence of know BMs at study entry, and region.	EMA's CHMP assessment report [47].
	Chemotherapy	262	16 (6.1%), 3.5-9.7								
EORTC QLQ-30 GHS/QoL	Sacituzumab govitecan	267	0.66 (-2.21-3.53)	4.08	0.82-7.35	NA	NA	NA	NA	Data cut-off was 11 March 2020 The analysis of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) using a	EMA's CHMP assessment report [47].
	Chemotherapy	262	-3.42 (-6.77--0.08)								

Results of ASCENT: ITT population					
			linear mixed effects model for repeated measures (MMRM) analysis was performed to assess the extent of missing quality of life (QoL) data over time and estimate the treatment differences on the change from baseline scores in all functions and symptom domains (data cutoff 11 March 2020).		

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Table 62: Results of ASCENT: Subgroup analysis in BM-ve population

Results of ASCENT: Subgroup analysis in BM-ve population (NCT02574455)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS by IRC assessment	Sacituzumab govitecan	235	5.6 (4.3-6.3) months	3.9	NA	NA	HR: 0.409	0.332-0.519	<0.0001	Data cut-off 11 March 2020. The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.	EMA's CHMP assessment report [47].
	Chemotherapy	233	1.7 (1.5-2.6)								

Results of ASCENT: Subgroup analysis in BM-ve population (NCT02574455)											
										Assessed using RECIST v.1.1.	
Median PFS by investigator assessment	Sacituzumab govitecan	235	5.5 months	3.8	NA	NA	HR: 0.35	0.28-0.44	NA	Data cut-off 11 March 2020. NA	EMA's CHMP assessment report [47].
	Chemotherapy	233	1.7 months								
Median OS	Sacituzumab govitecan	235	12.1 (10.7-14.0) months	5.4	NA	NA	HR: 0.476	0.383-0.592	<0.0001	Data cut-off 11 March 2020. The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model adjusted for stratification factors: numbers of prior chemotherapies and region.	EMA's CHMP assessment report [47].
	Chemotherapy	233	6.7 (5.8-7.7)								
ORR by IRC assessment	Sacituzumab govitecan	235	82 (34.9 %), 28.8-41.4	30.2	23.5, 36.8	<0.0001	OR: 10.859	5.590-21.095	<0.0001	Data cut-off 11 March 2020. ORR, percentage of patients who had either a confirmed CR or PR. Using stratified log-rank test and stratified Cox regression adjusted for stratification factors: numbers of prior chemotherapy, presence of know BMs at study entry, and region.	EMA's CHMP assessment report [47].
	Chemotherapy	233	11 (4.7%), 2.4-8.3								

Results of ASCENT: Subgroup analysis in BM-ve population (NCT02574455)											
ORR by investigator assessment	Sacituzumab govitecan	235	80 (34.0%), 28.0-40.5	27.6	20.7, 34.4	<0.0001	OR: 10.859	5.590-21.095	<0.0001	Data cut-off 11 March 2020. ORR, percentage of patients who had either a confirmed CR or PR. Using stratified log-rank test and stratified Cox regression adjusted for stratification factors: numbers of prior chemotherapy, presence of know BMs at study entry, and region.	EMA's CHMP assessment report [47].
	Chemotherapy	233	15 (6.4%), 3.6-10.4								
QoL-30	Sacituzumab govitecan	NA	NA	NA	NA	NA	NA	NA	NA		
	Chemotherapy	NA	NA								

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Appendix E Safety data for intervention and comparator(s)

Table 63: Safety results of IMMU-132-01

Safety results of IMMU-132-01 **(NCT number: NCT01631552)***											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Treatment discontinuations due to TEAEs (%)	Sacituzumab govitecan	108	4 (3.7%)	NA	NA	NA	NA	NA	NA	NA	EMA's CHMP assessment report [47].
	NA	NA	NA								
AEs grade 3 or higher	Sacituzumab govitecan	108	78 (72.2%)	NA	NA	NA	NA	NA	NA	AEs grade 3-5 that occurred in at least 5% of the patients in either treatment group. According to Common Terminology Criteria for AEs [CTCAE], version 4.0) that occurred in at least 10% of the patients .	EMA's CHMP assessment report [47].
	NA	NA	NA								

*Updated data based on final data (2nd April 2021)

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Table 65: Safety results of ASCENT in ITT population

Safety results of ASCENT in ITT population (NCT02574455)*											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Treatment discontinuations/withdrawal due to TEAEs (%)	Sacituzumab govitecan	258	12 (4.7%)	-0.7%	-4.6, 3.2	0.72	OR: 0.86	0.37, 1.95	0.72	Data cut-off was 25 February 2021 NA	EMA's CHMP assessment report [47].
	Chemotherapy	224	12 (5.4%)								

Safety results of ASCENT in ITT population (NCT02574455)*											
AEs grade 3 or higher	Sacituzumab govitecan	258	188 (72.9%)	8.14%	-0.15, 16.42	0.054	OR: 1.46	0.99, 2.16	0.054	Data cut-off was 25 February 2021 AEs grade 3-5 that occurred in at least 5% of the patients in either treatment group. According to Common Terminology Criteria for AE [CTCAE], version 4.03) that occurred in at least 10% of the patients.	EMA's CHMP assessment report [47].
	Chemotherapy	224	145 (64.7%)								

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Appendix F Comparative analysis of efficacy and safety

Table 67: Comparative analysis of ASCENT: ITT population

Comparative analysis of ASCENT: ITT population (NCT02574455)									
Outcome	**Studies included in the analysis**	**Absolute difference in effect**			**Relative difference in effect**			**Method used for quantitative synthesis**	**Result used in the health economic analysis?**
		Difference	**CI**	***P* value**	**Difference**	**CI**	***P* value**		
Median PFS by IRC assessment	1	3.1	NA	NA	HR: 0.433	0.347-0.541	<0.0001	Data cut-off 11 March 2020. The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm. Assessed using RECIST v.1.1.	*Yes*
Median PFS by investigator assessment	1	3.1	NA	NA	HR: 0.382	0.309-0.473	<0.0001	Data cut-off 11 March 2020. The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm. Assessed using RECIST v.1.1.	

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Comparative analysis of ASCENT: ITT population (NCT02574455)								
Median OS	1	4.9	NA	NA	HR: 0.508	0.414-0.624	<0.001	Data cut-off 11 March 2020. The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model adjusted for stratification factors: numbers of prior chemotherapies and region.
ORR by IRC assessment	1	27%	0.21, 0.33	<0.0001	OR: 10.994	5.659-21.358	<0.0001	Data cut-off 11 March 2020. ORR, percentage of patients who had either a confirmed CR or PR. Using stratified log-rank test and stratified Cox regression adjusted for stratification factors: numbers of prior chemotherapy, presence of know BMs at study entry, and region.
ORR by investigator assessment	1	24.9%	18.7, 31.2	<0.0001	OR: 7.156	4.037-12.658	<0.0001	Data cut-off 11 March 2020. ORR, percentage of patients who had either a confirmed CR or PR. Using stratified log-rank test and stratified Cox regression adjusted for stratification factors: numbers of prior chemotherapy, presence of know B;s at study entry, and region.

Comparative analysis of ASCENT: ITT population (NCT02574455)								
HRQoL (ECORTC QLQ-C30)	1	4.08	0.82-7.35	NA	NA	NA	NA	Data cut-off 11 March 2020. The analysis of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) using a linear mixed effects model for repeated measures (MMRM) analysis was performed to assess the extent of missing quality of life (QoL) data over time and estimate the treatment differences on the change from baseline scores in all functions and symptom domains.
AEs grade 3 or higher	1	8.14%	-0.15, 16.42	0.054	OR: 1.46	0.99, 2.16	8.14%	Data cut-off was 25 February 2021 AEs grade 3-5 that occurred in at least 5% of the patients in either treatment group. According to Common Terminology Criteria for AE [CTCAE], version 4.03) that occurred in at least 10% of the patients.
Discontinuations due to AEs	1	-0.7%	-4.6, 0.3	0.72	OR: 0.86	0.38-1.95	0.72	Data cut-off was 25 February 2021 NA

Table 68: Comparative analysis of ASCENT: Subgroup analysis in BM-ve population

Comparative analysis of ASCENT: Subgroup analysis in BM-ve population (NCT02574455)				
Outcome		**Absolute difference in effect**	**Relative difference in effect**	**Method used for quantitative synthesis**

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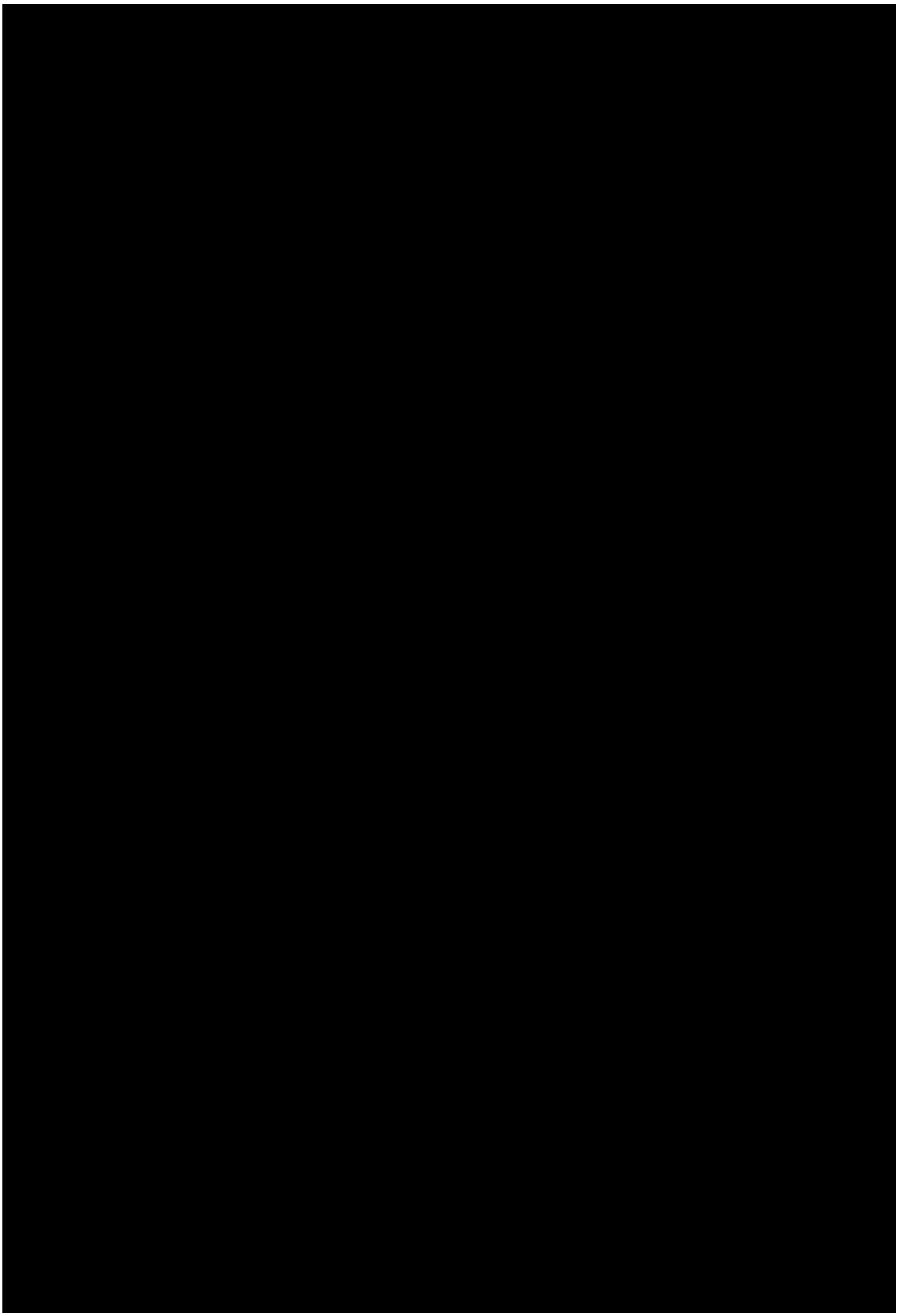
Comparative analysis of ASCENT: Subgroup analysis in BM-ve population (NCT02574455)								
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	**Result used in the health economic analysis?**
Median PFS by IRC assessment**	Sacituzumab Govitecan Chemotherapy	3.9	NA	NA	HR: 0.409	0.332-0.519	<0.0001	Data cut-off 11 March 2020. The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm. Assessed using RECIST v.1.1.	*Yes/No*
Median PFS by investigator assessment**	Sacituzumab Govitecan Chemotherapy	3.8	NA	NA	HR: 0.35	0.28-0.44	NA	Data cut-off 11 March 2020. NA	
Median OS**	Sacituzumab Govitecan Chemotherapy	5.4	NA	NA	HR: 0.476	0.383-0.592	<0.0001	Data cut-off 11 March 2020. The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model adjusted for stratification factors: numbers of prior chemotherapies and region.	
ORR by IRC assessment **	Sacituzumab Govitecan	30.2%	23.5, 36.9	<0.0001	OR: 10.859	5.590-21.095	<0.0001	Data cut-off 11 March 2020.	

Comparative analysis of ASCENT: Subgroup analysis in BM-ve population (NCT02574455)									
	Chemotherapy							ORR, percentage of patients who had either a confirmed CR or PR. Using stratified log-rank test and stratified Cox regression adjusted for stratification factors: numbers of prior chemotherapy, presence of know BMs at study entry, and region.	
ORR by investigator assessment**	Sacituzumab Govitecan	27.6%	20.8, 34.4	<0.0001	OR: 10.859	5.590-21.095	<0.0001	Data cut-off 11 March 2020. ORR, percentage of patients who had either a confirmed CR or PR. Using stratified log-rank test and stratified Cox regression adjusted for stratification factors: numbers of prior chemotherapy, presence of know BMs at study entry, and region.	
	Chemotherapy								



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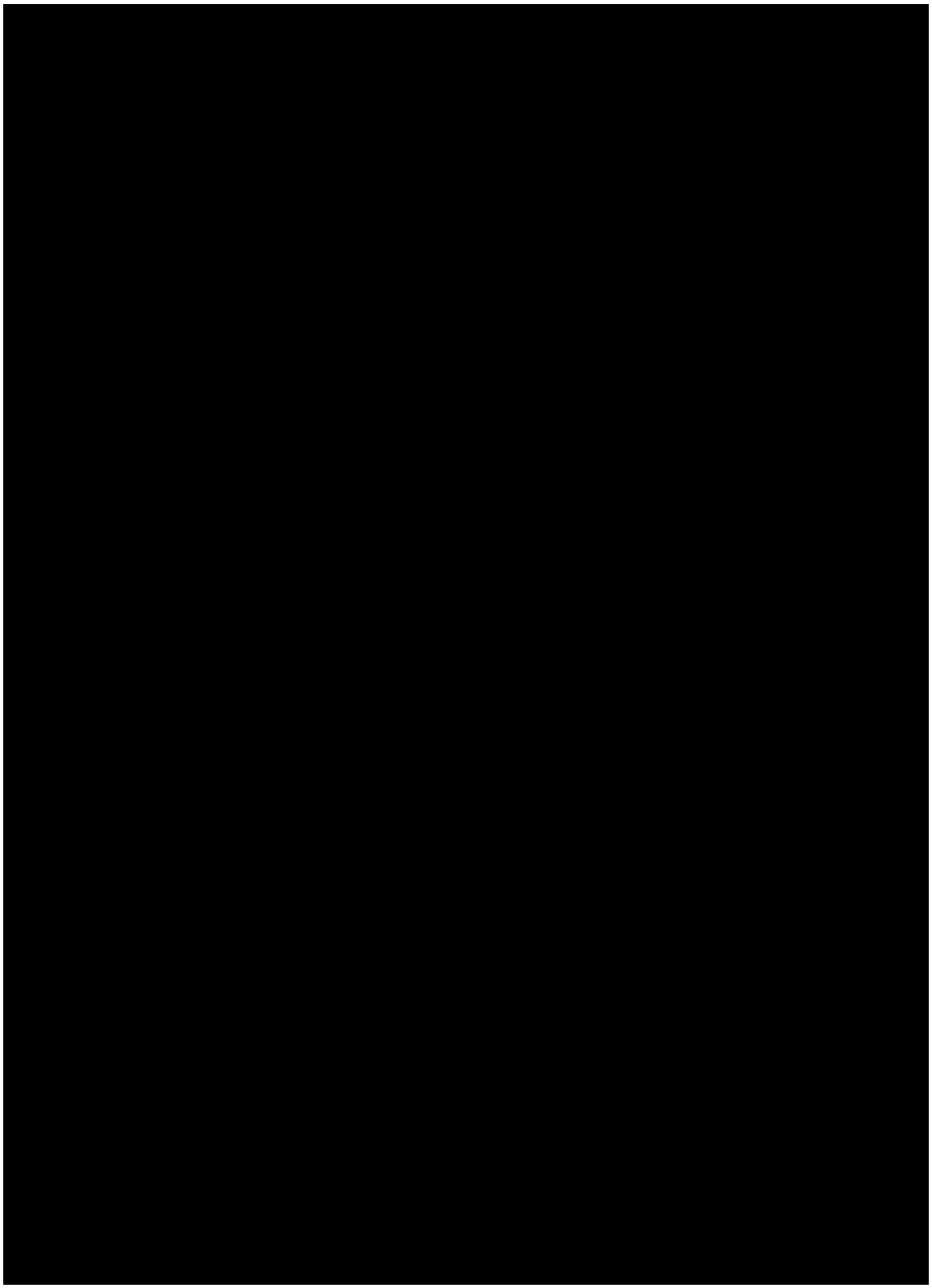

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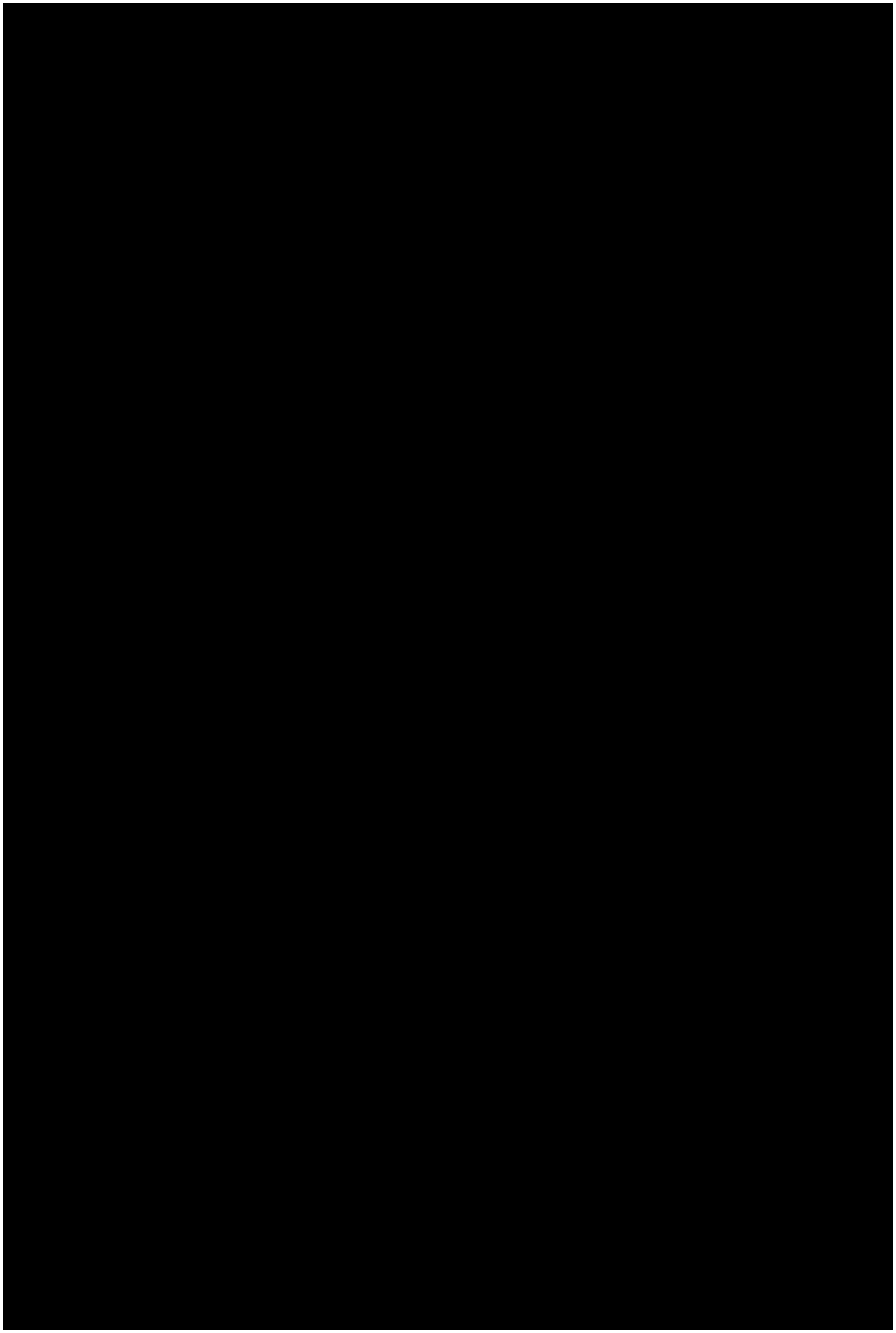

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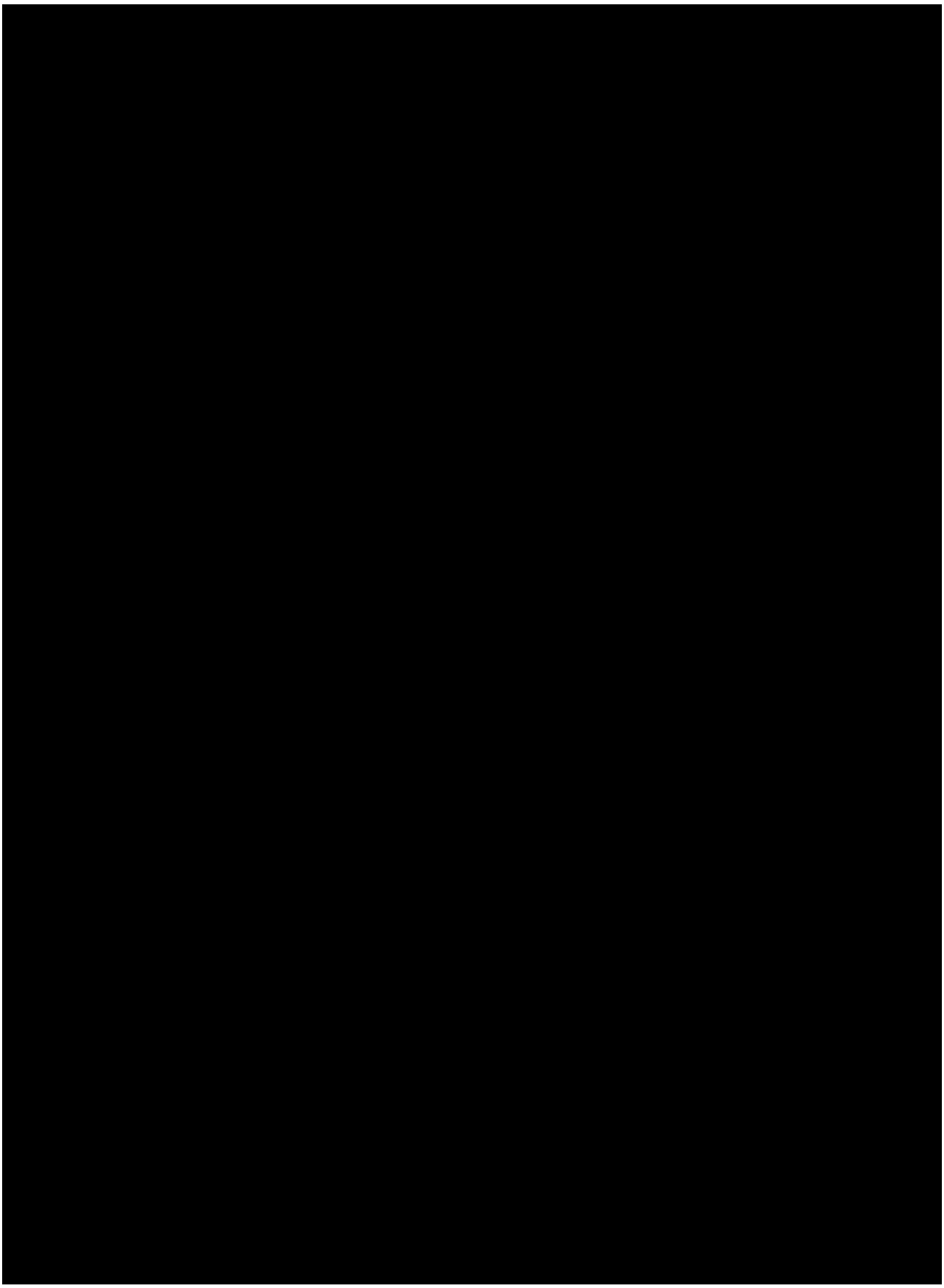

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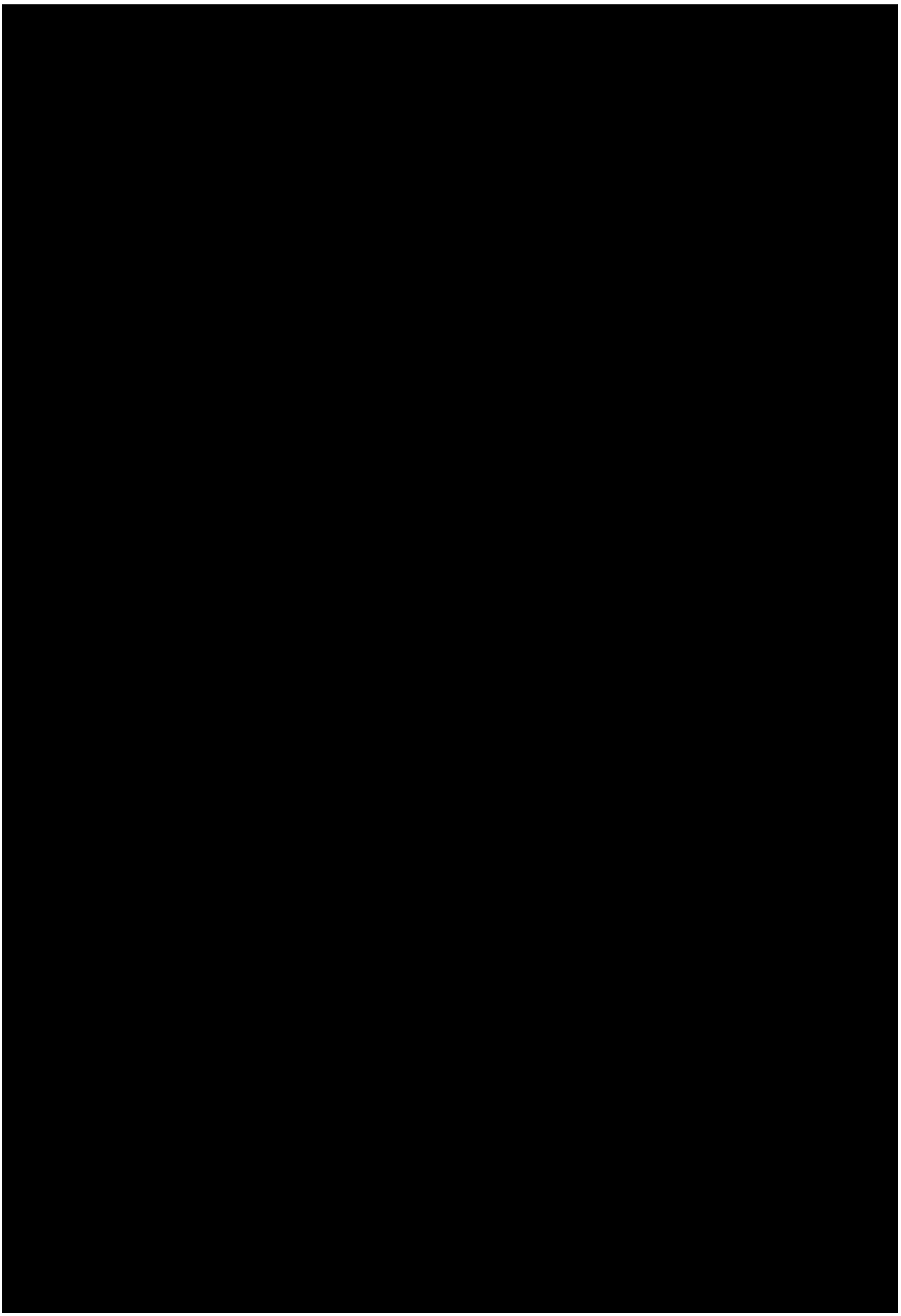

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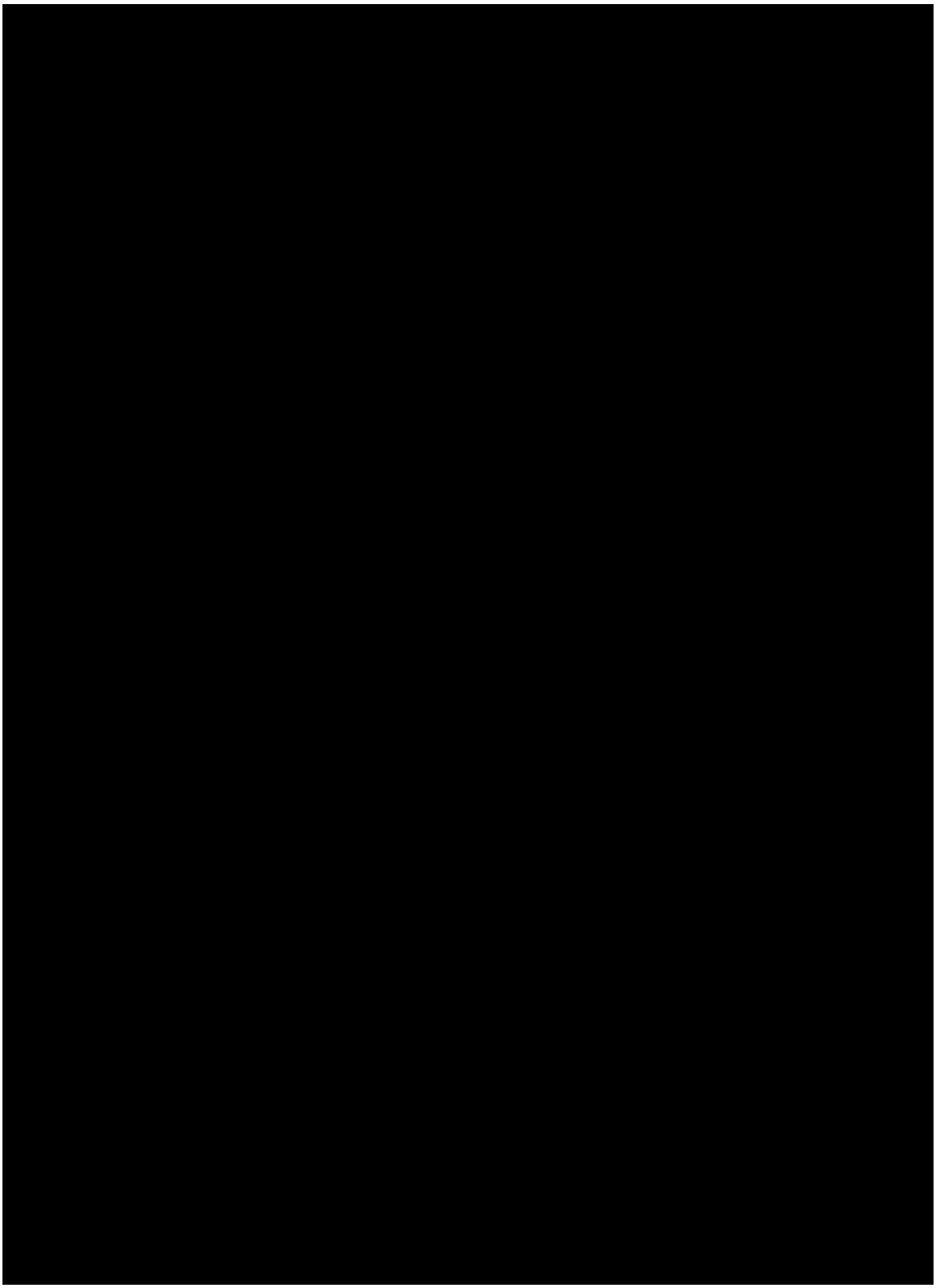

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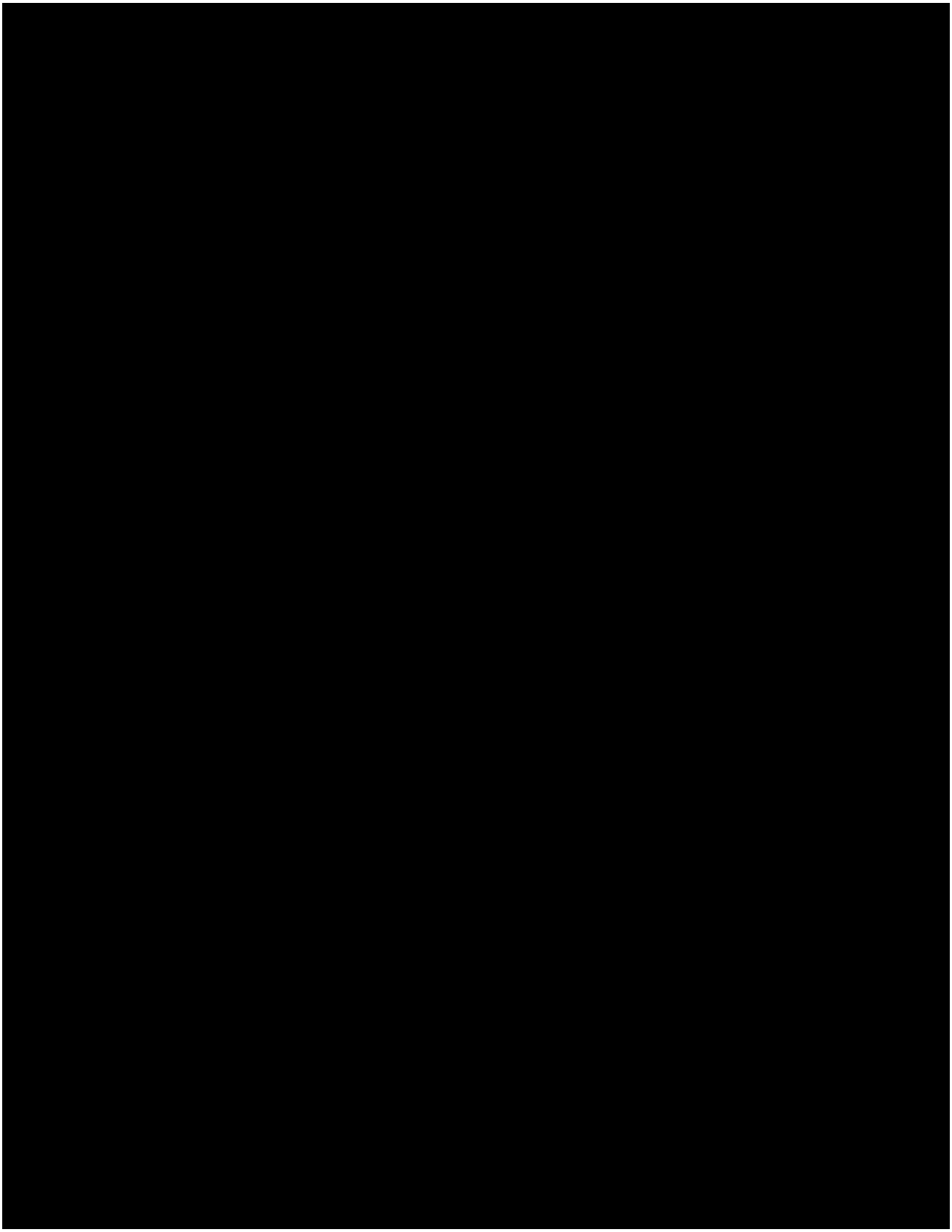

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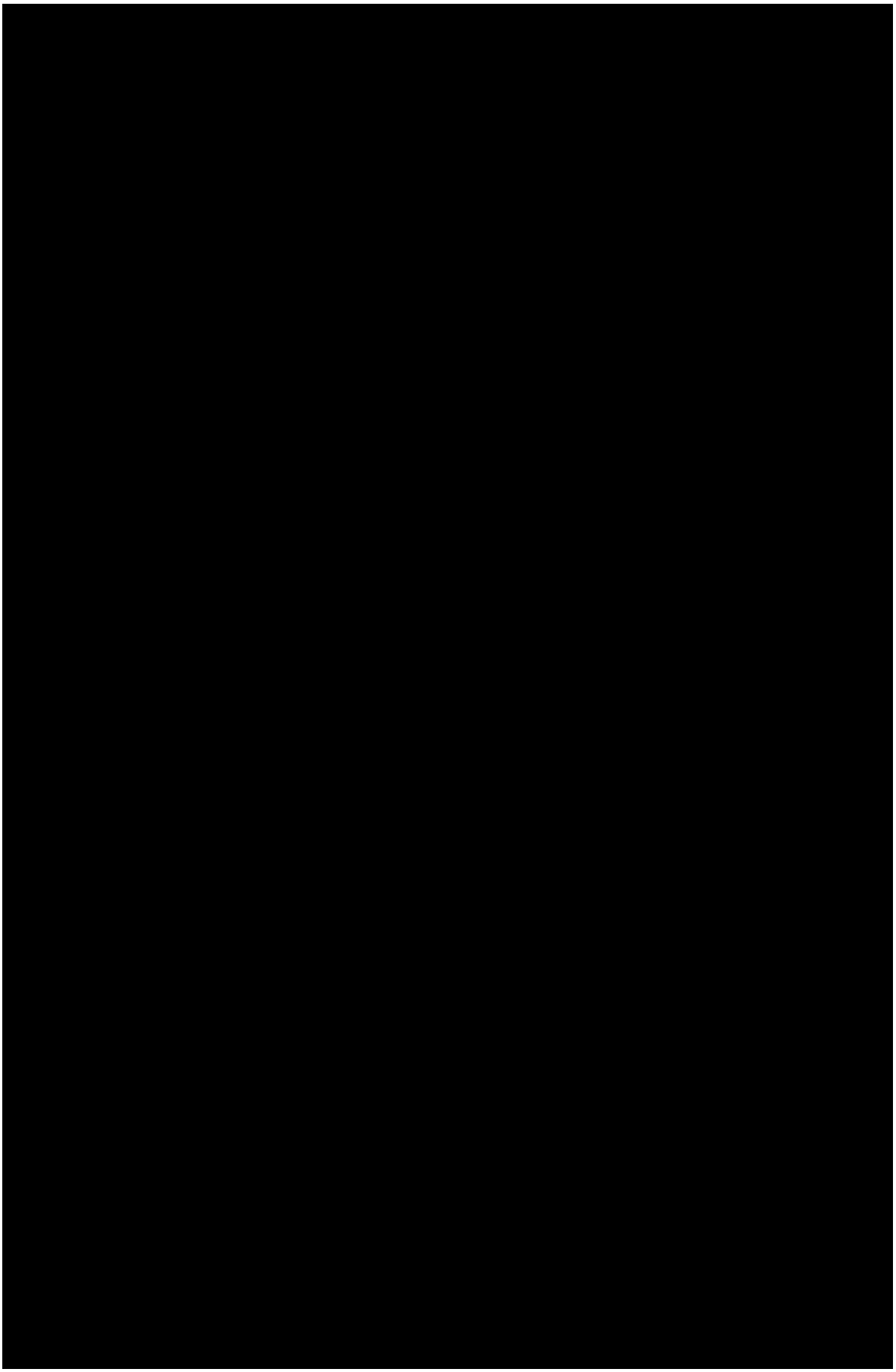

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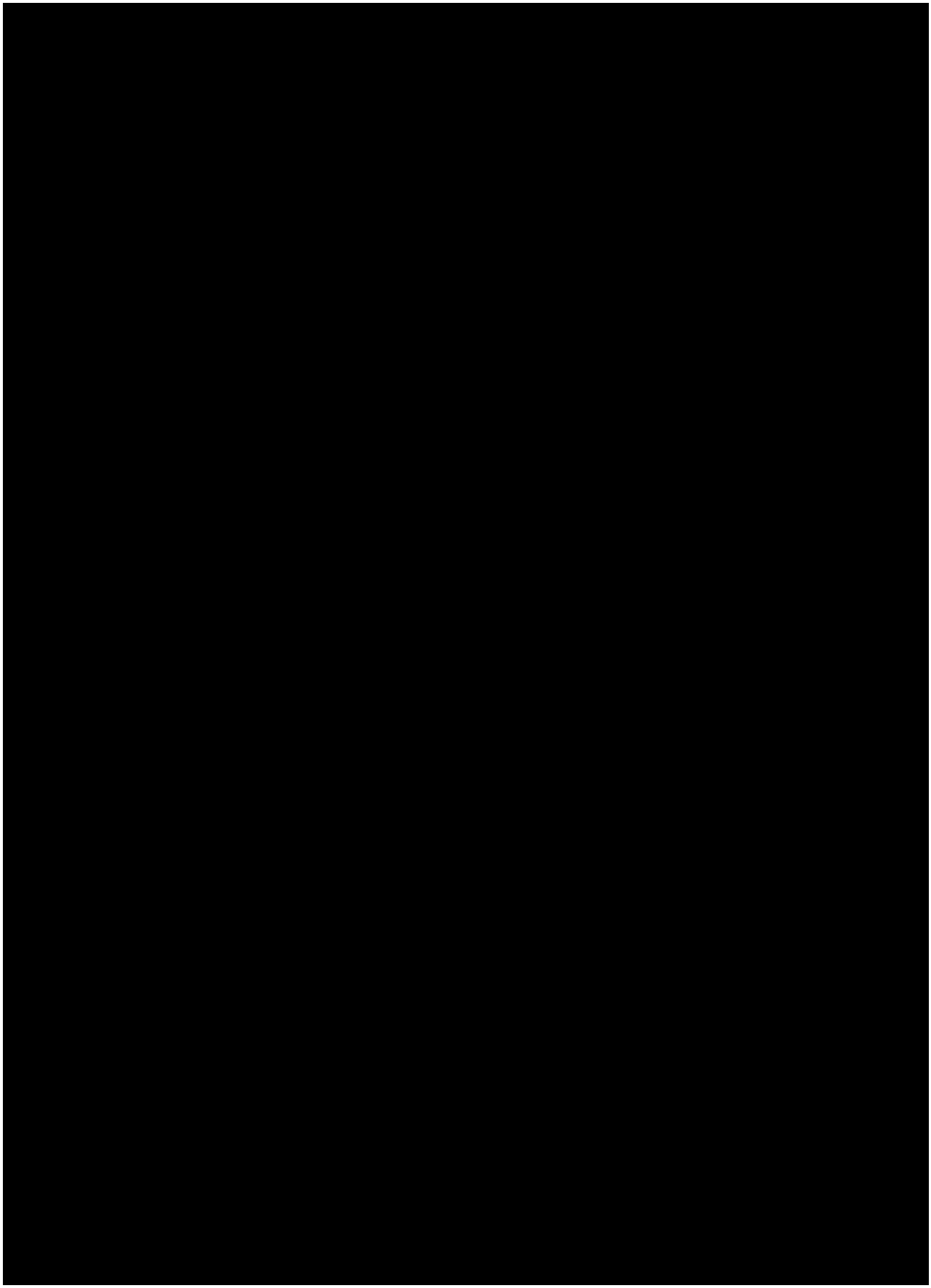

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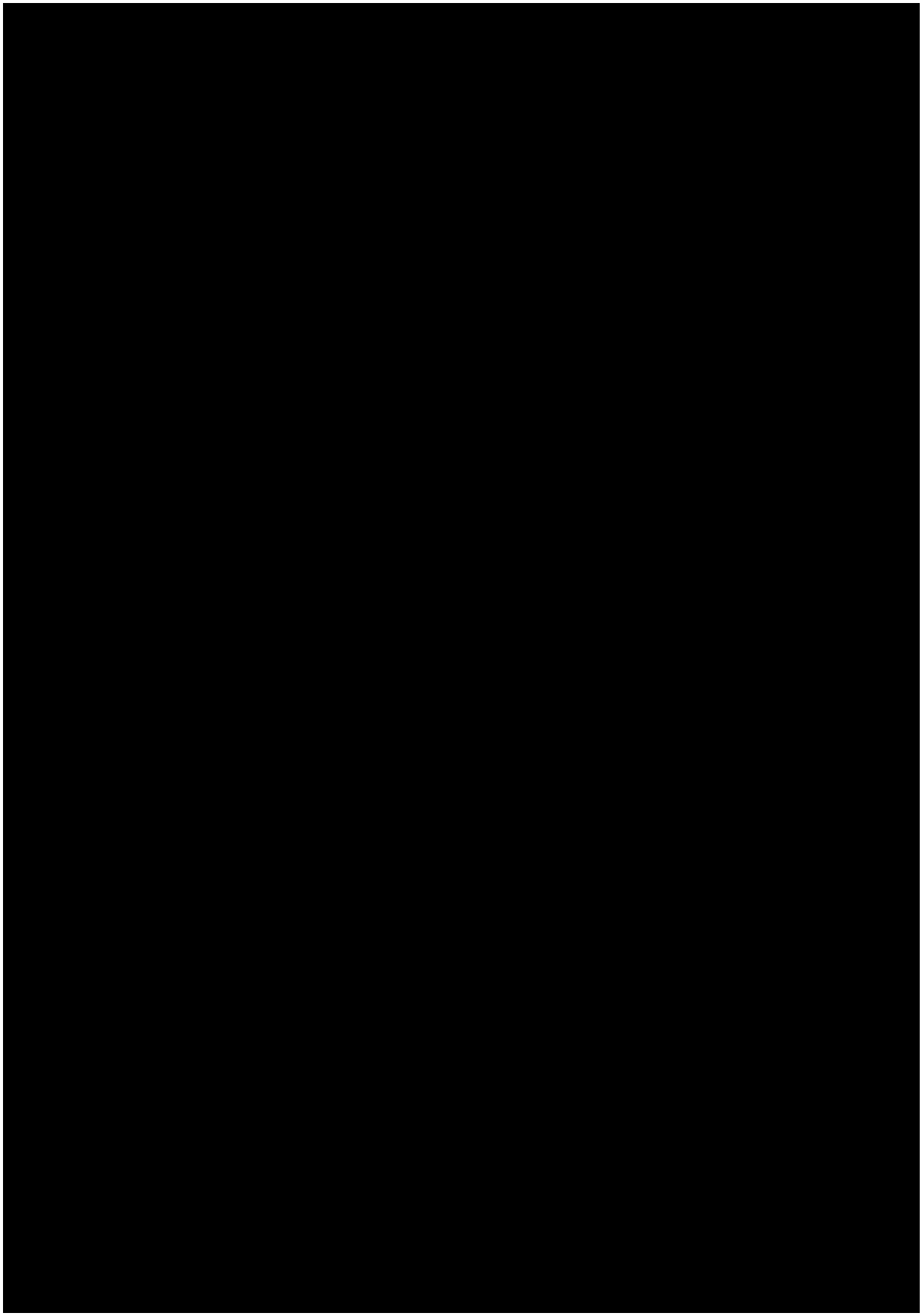

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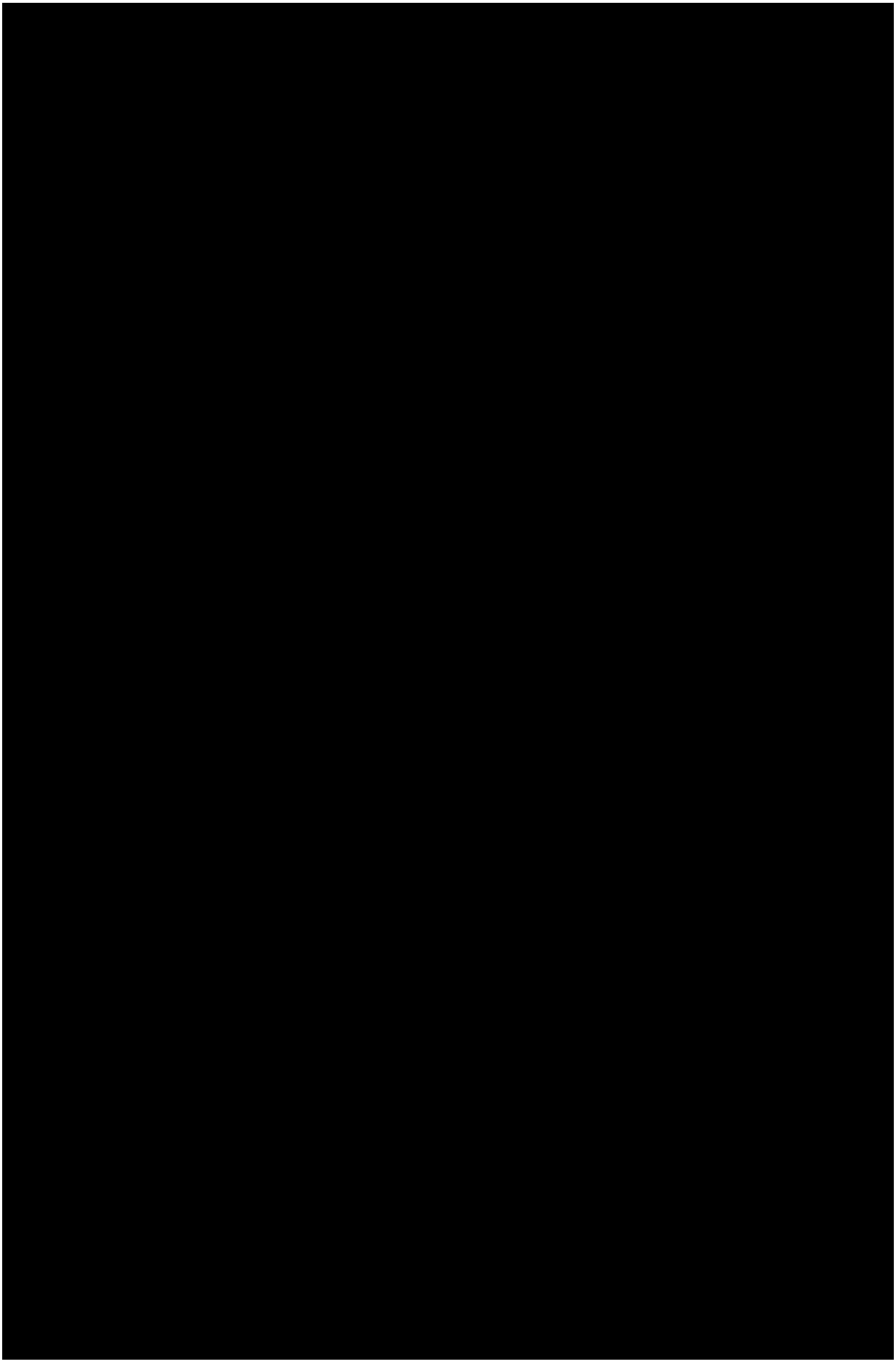

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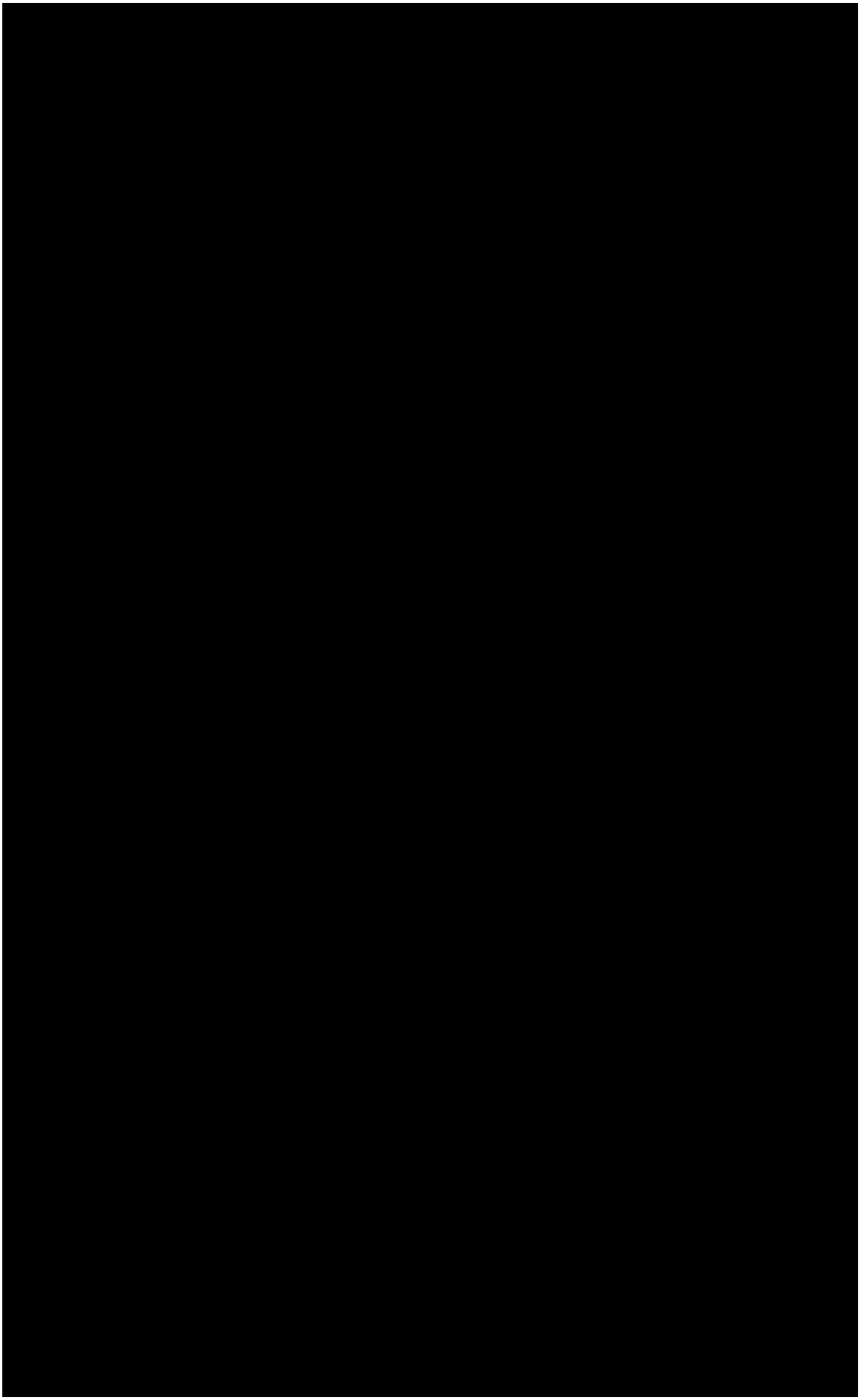

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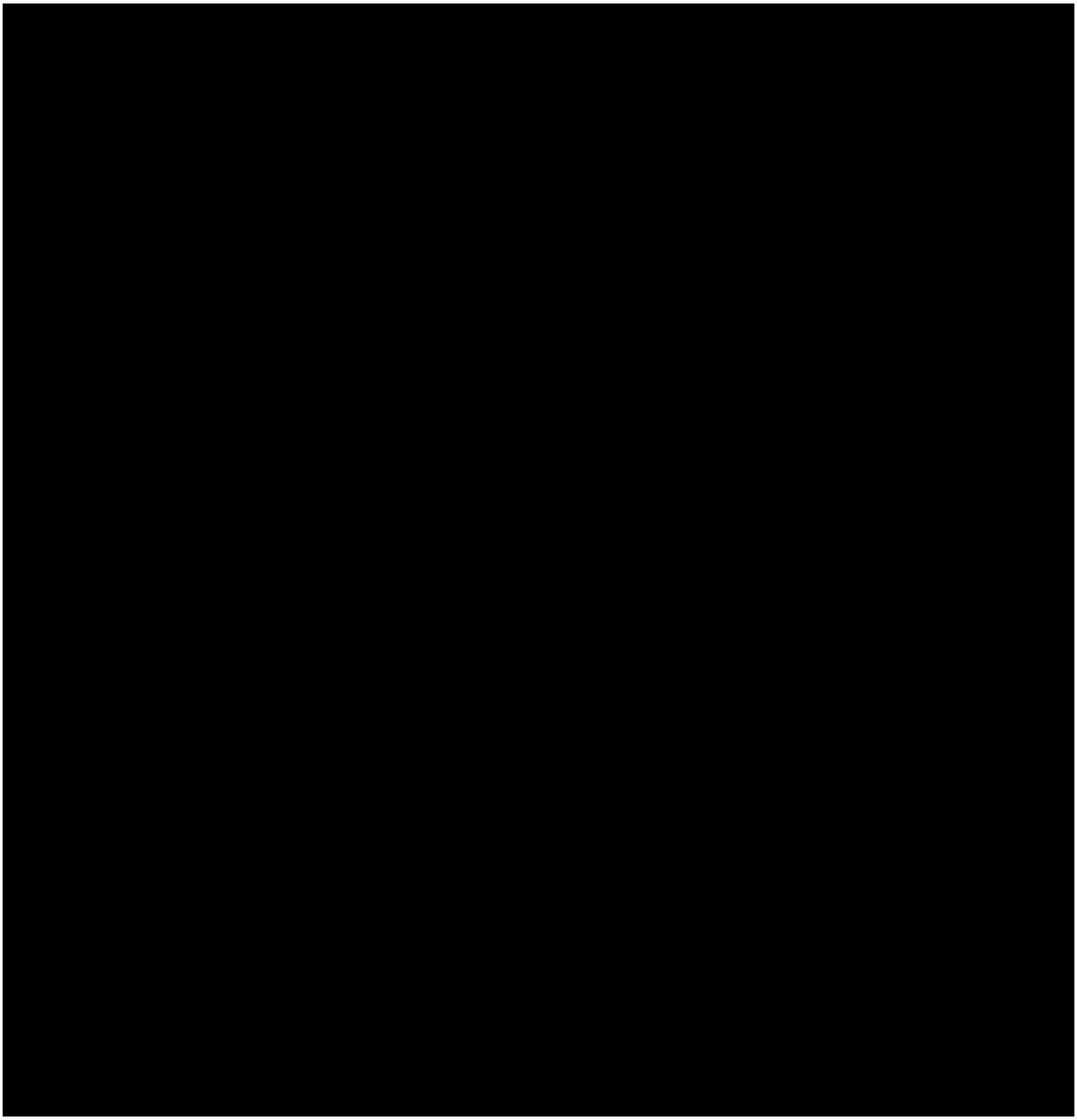

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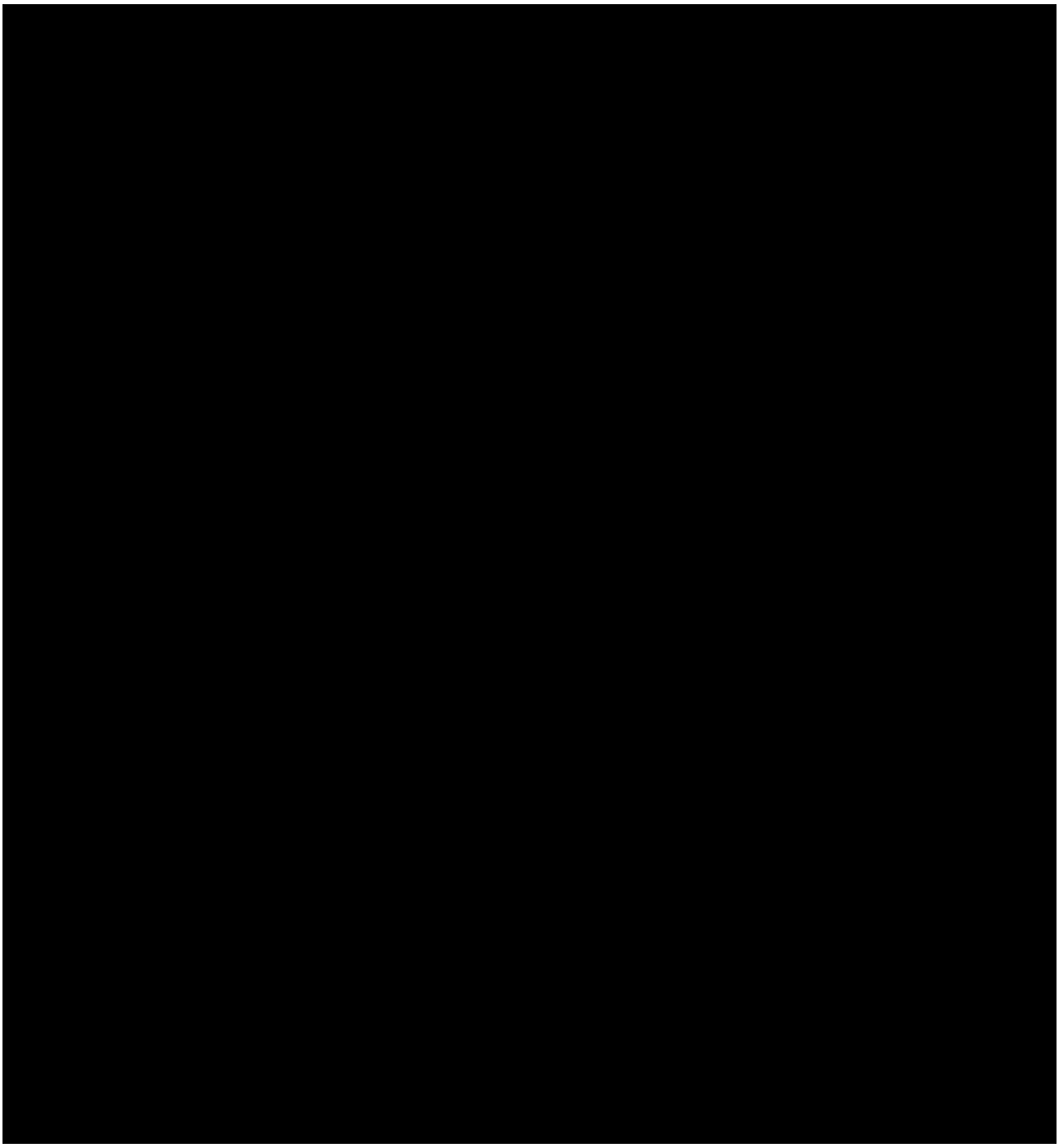

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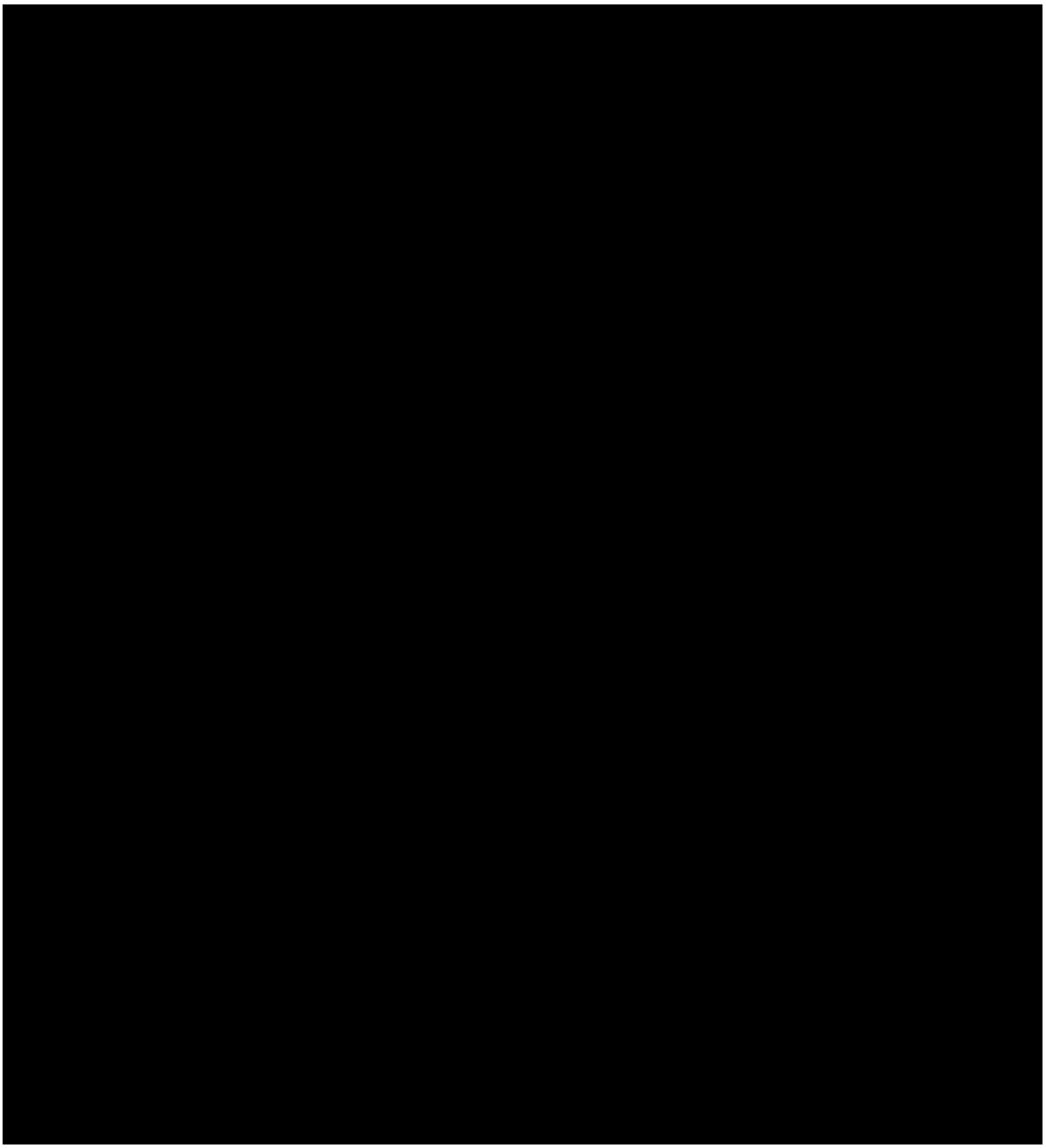

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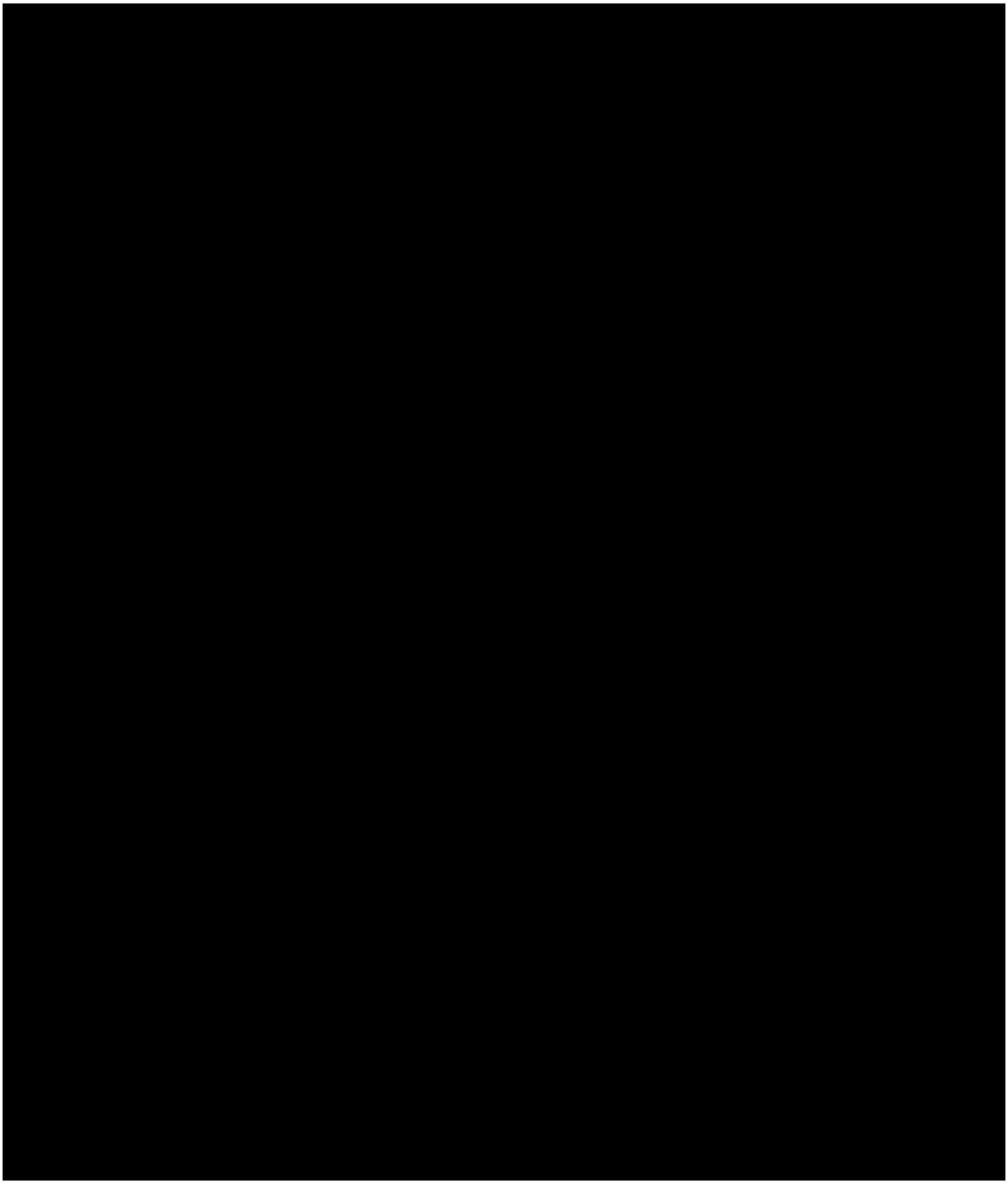

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Appendix H – Literature search for HRQoL data

Not applicable

Appendix I Mapping of HRQoL data

Below the mapping method used to estimate the HSUVs is explained.
The objective of the analysis was to use data mapped from the EORTC QLQ-C30 to EQ-5D-3L for use in the cost-effectiveness analysis of Sacituzumab govitecan. Specifically, these inputs aimed to quantify the decrement in QoL experienced by patients due to progression to compute QALYs.

12.6 Methods

The number and proportion of available and missing observations, mean, and SD were reported at scheduled visits for each randomized treatment arm and for the overall population to understand the sample size available for inclusion in the regression models of utilities. For illustration purposes, the mean EQ-5D utility scores were plotted along with their 95% CIs at scheduled cycle visits and at end-of-treatment (EOT) visits for each randomized treatment arm and for the overall population. Visit flags in the ASCENT clinical trial were used only for plotting and were not used explicitly in the regression analysis, since the time-dependent covariates were derived based on the date of the assessment.
All patients in the ITT population were considered as eligible for the utility analysis who had EQ-5D-3L utility score observation available at baseline and at least one other observation on a later date. An analytical dataset was created including one record per patient per visit. Each record included a time-dependent variable indicating the patients' health status at the time of the utility measurement (Table 69).

Table 69: Derivation of Time-dependent Health State Variable

Time-dependent Covariate	Derivation Definition
Progression status based on IRC: **PF** **PD**	Time-varying covariate taking values: **PF**: from baseline until date of progression **PD**: from date of progression onward For those individuals who did not experience progression, the progression status was defined as "unknown" from the date of censoring. EQ-5D measurements with "unknown" progression status were not used in the analyses.

IRC: independent review committee, PD: progressed disease, PF: progression free.

EQ-5D utility scores from all visits were analyzed using mixed-effects linear regression with a random intercept for each patient to account for the clustering of multiple observations. The utility models investigated the potential effect on EQ-5D utilities of treatment arm and progression status (PD vs. PF), one at a time (univariate models) and in combinations (multivariate models).

In addition, all models were adjusted for baseline utility (centered at the mean value of the eligible population) to consider between-patient differences in utilities at baseline. Centering makes the interpretation of all other model coefficients easier. A value of zero represents a patient with

average baseline utility. Therefore, the intercept term in the model refers to an “average” patient in the ASCENT clinical trial in terms of baseline utility.

Regression coefficients and adjusted mean utility values associated with each health state included in the final model (e.g., progressed, not progressed) were provided with 95% Cis.

12.7 Results

12.7.1 Descriptive analysis

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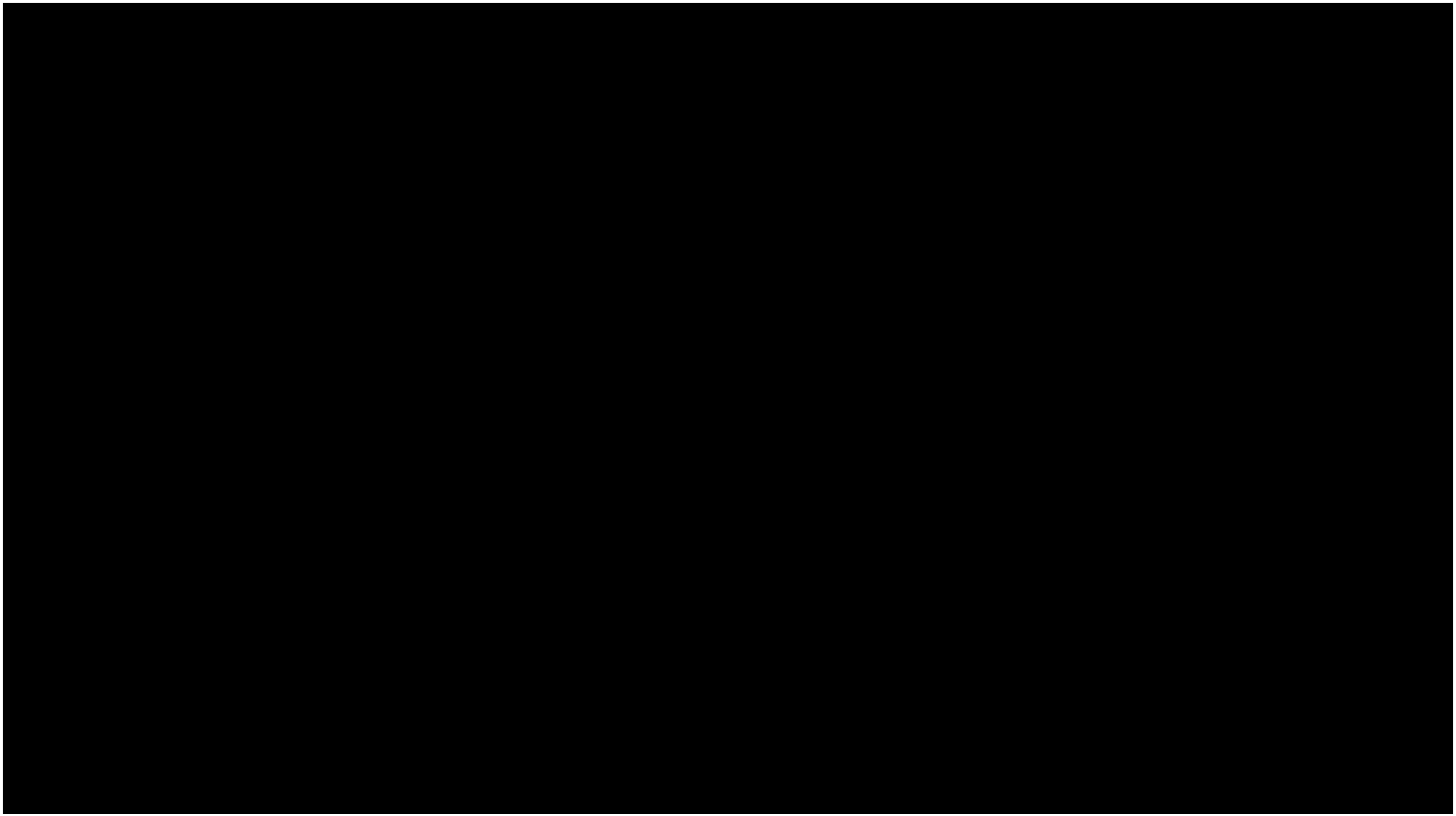

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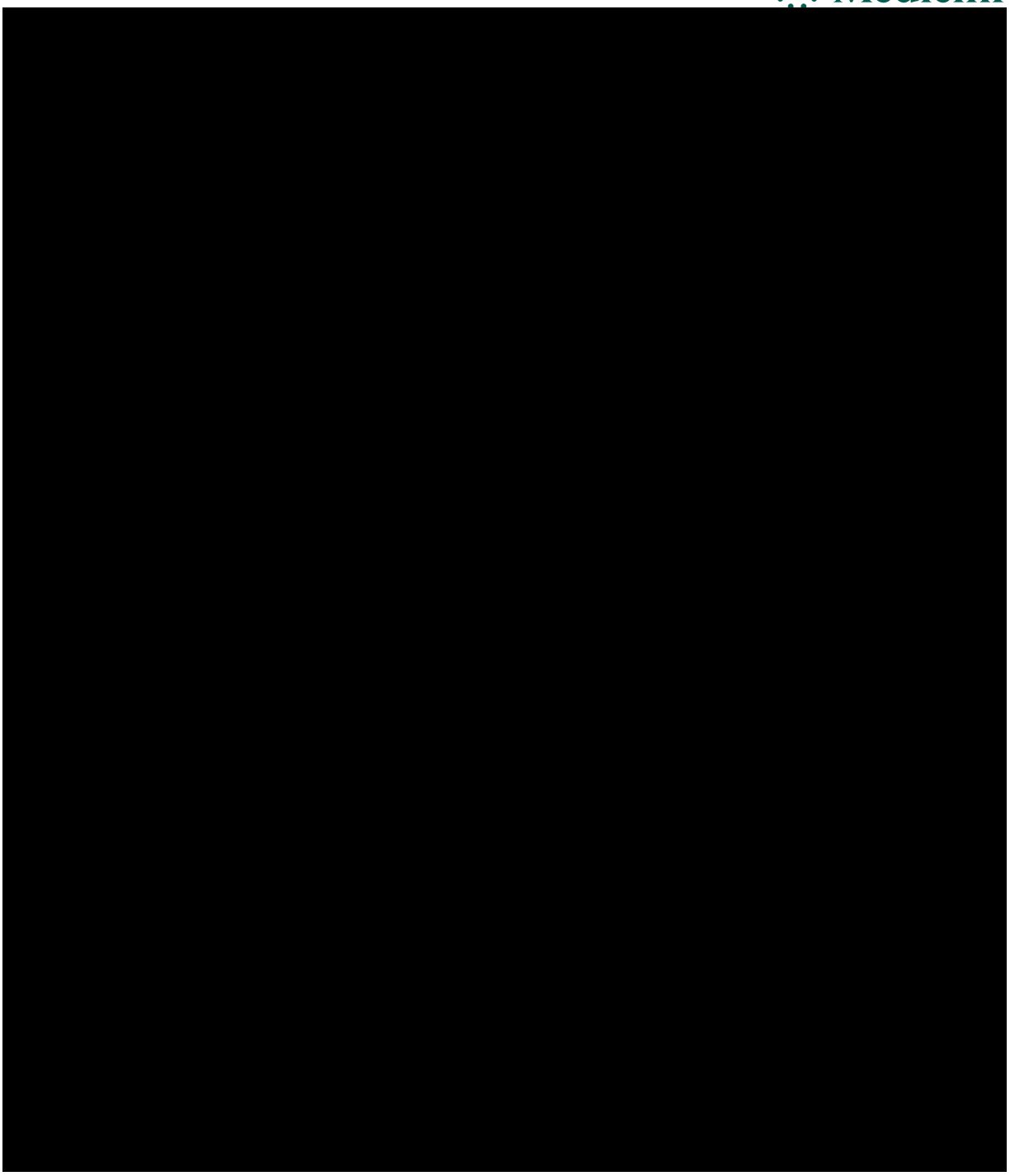

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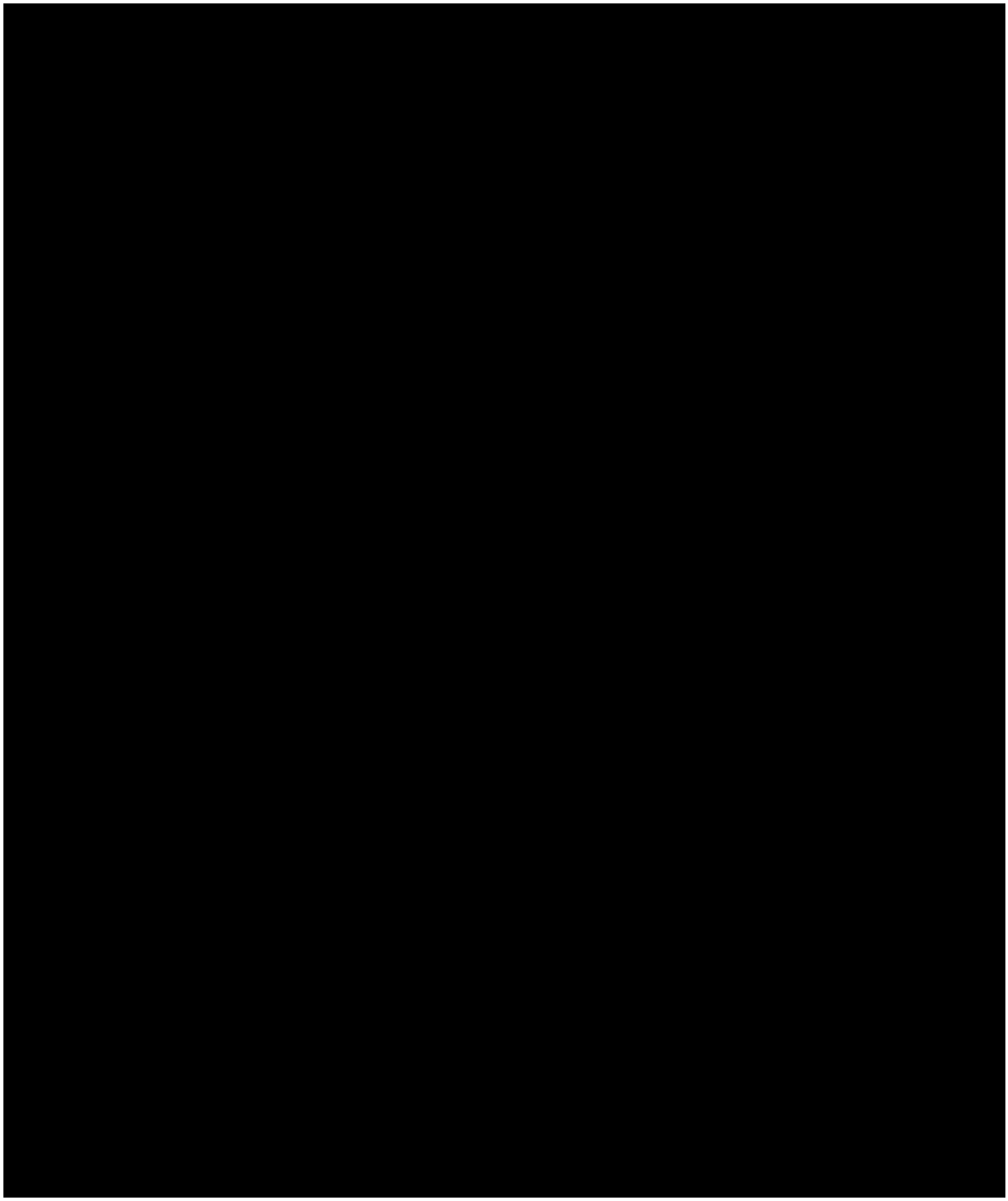

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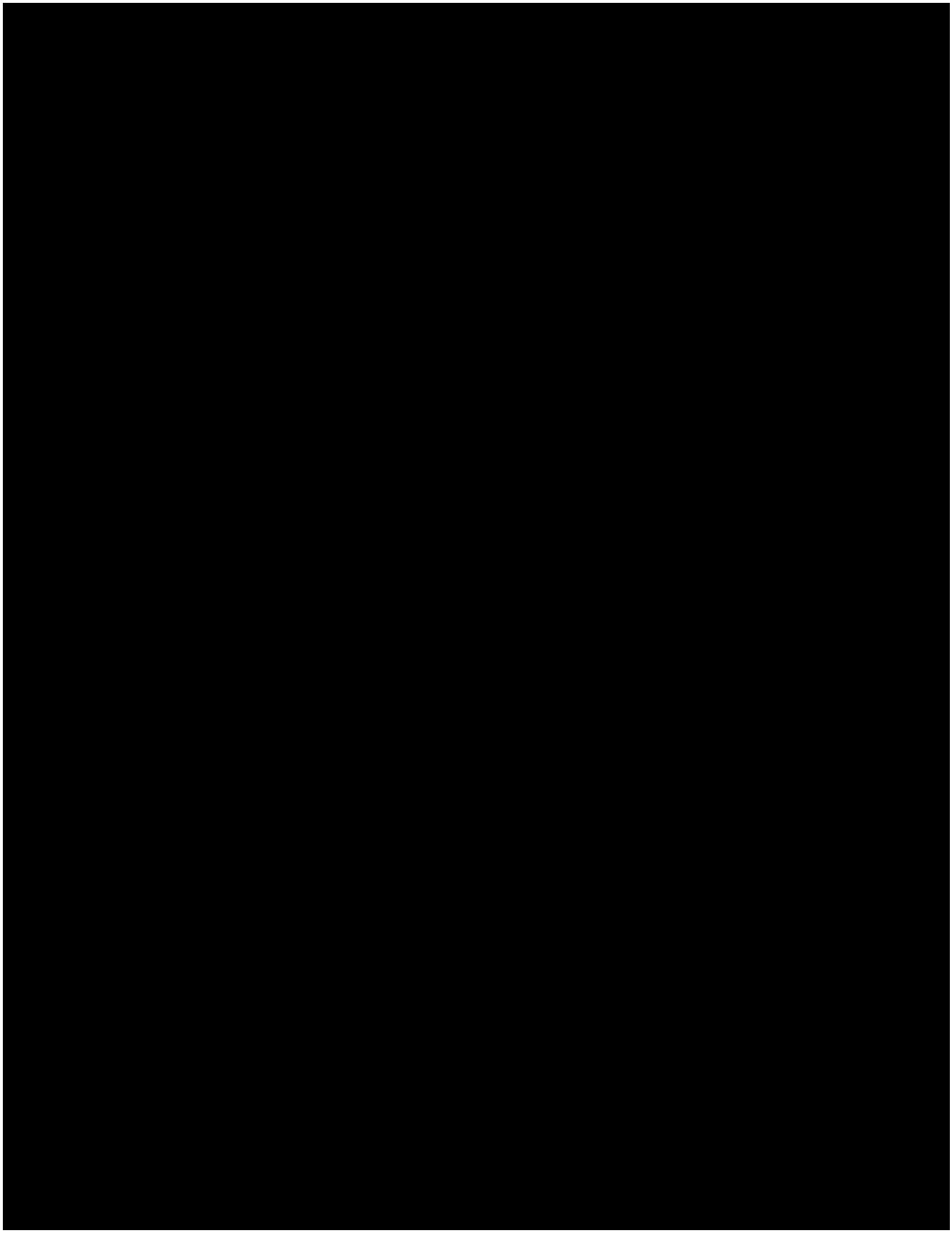

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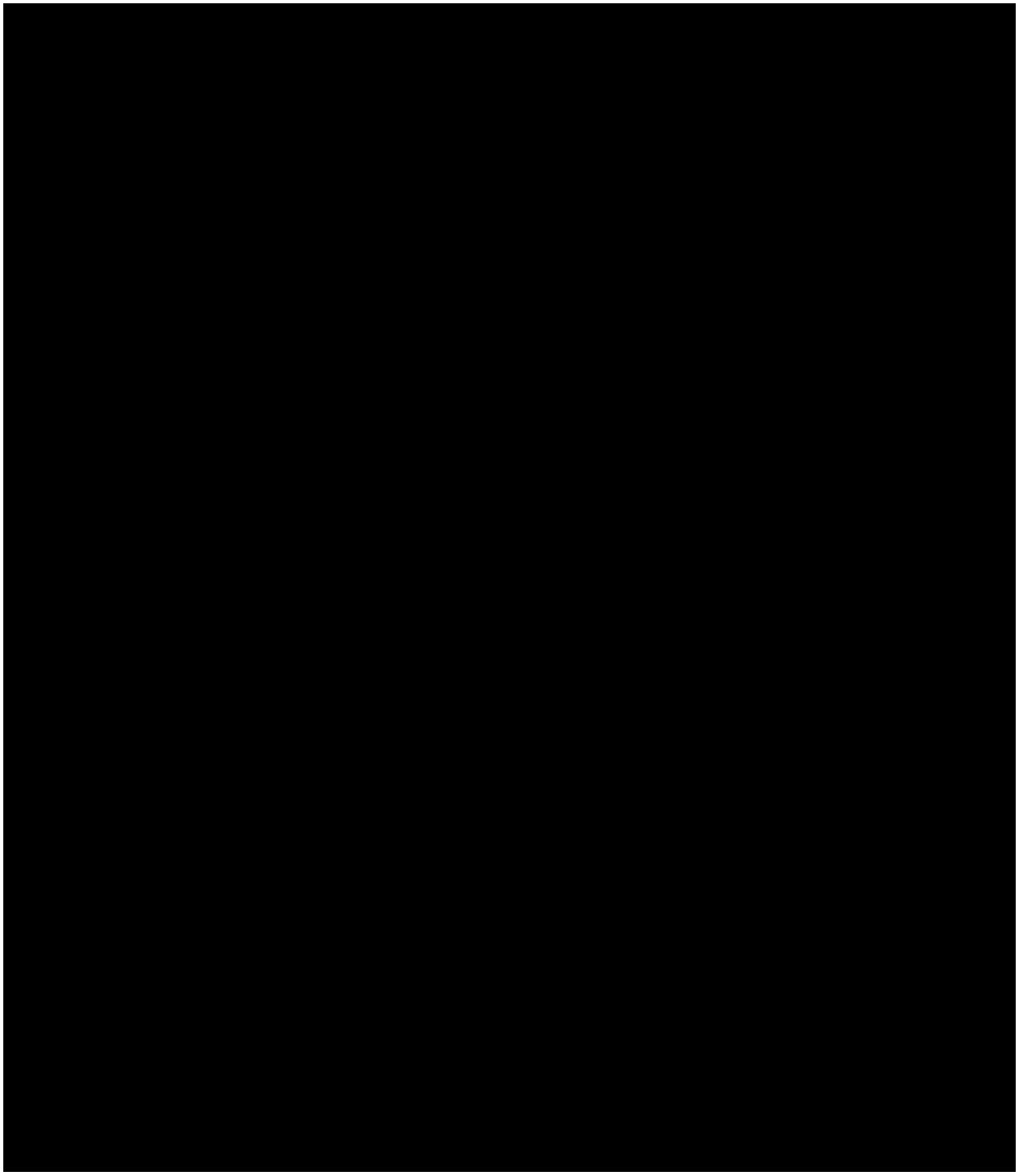

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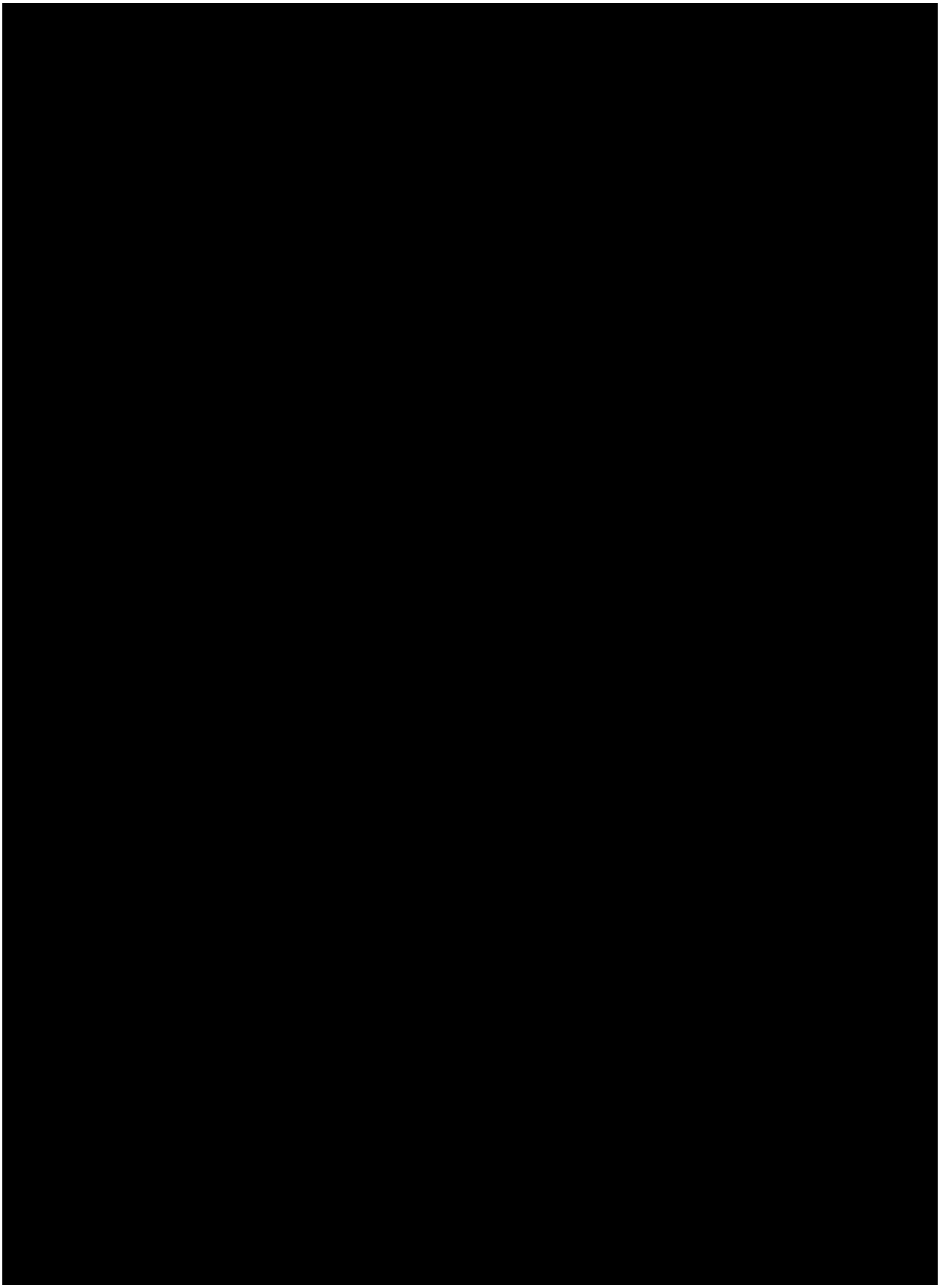

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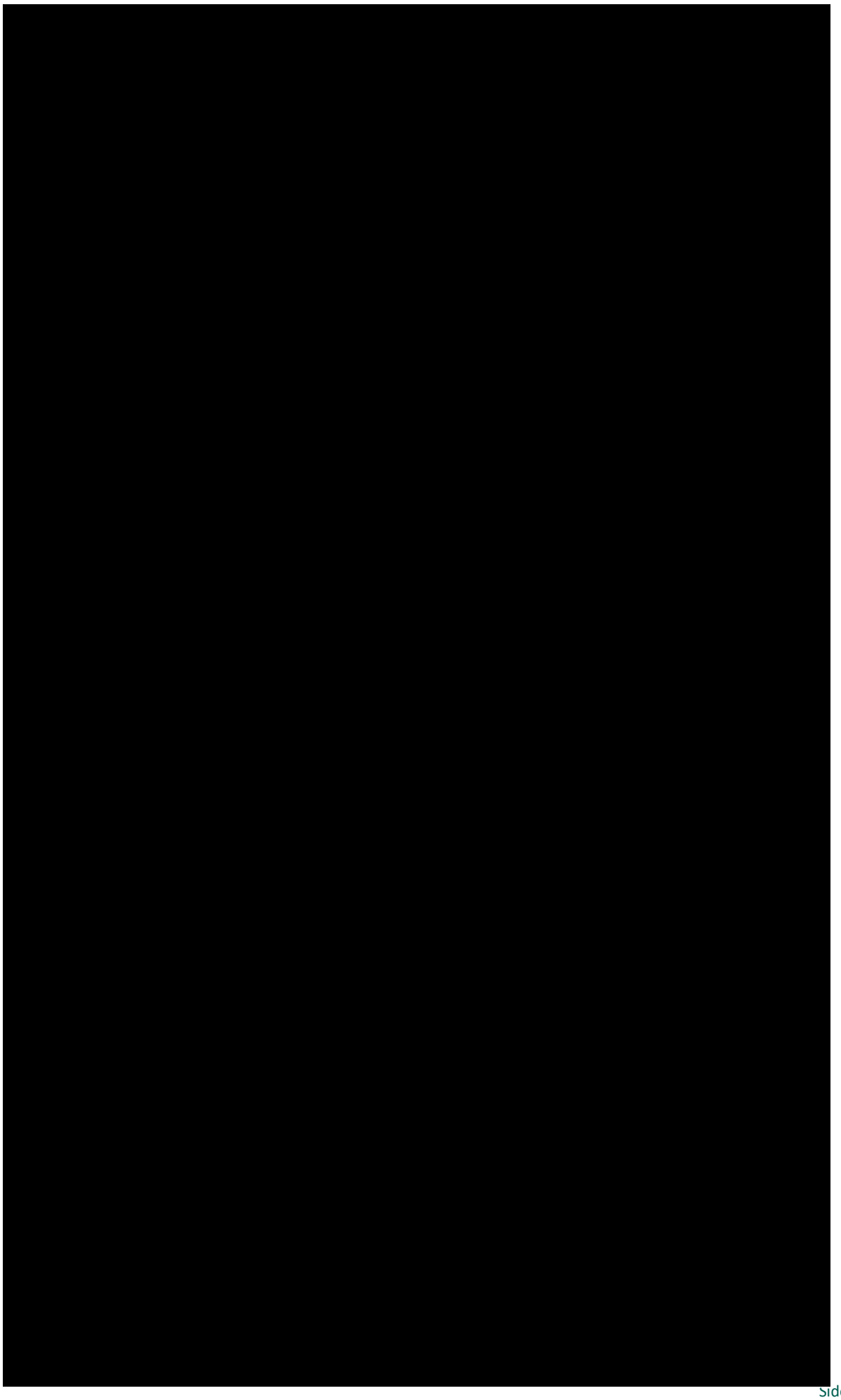

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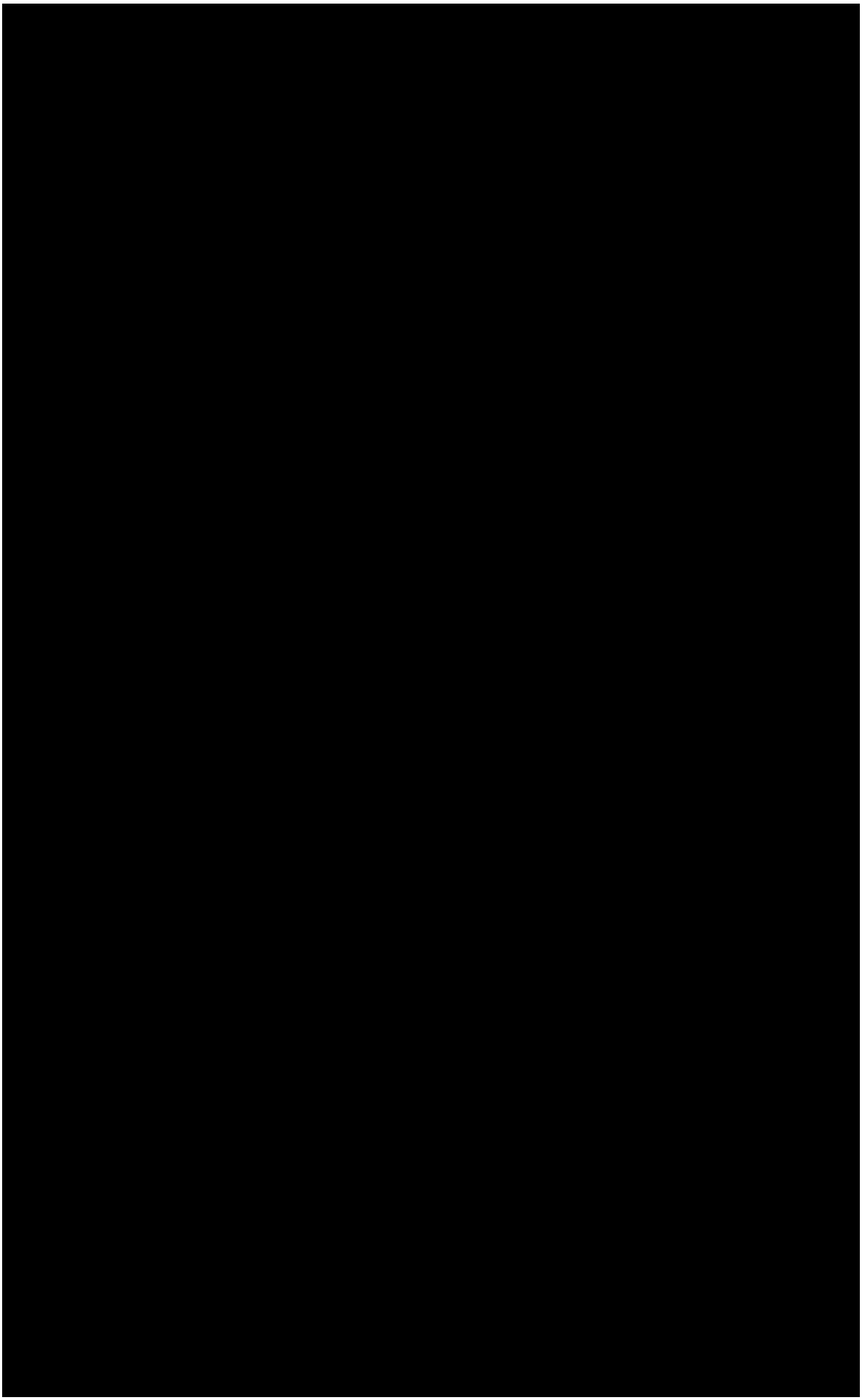

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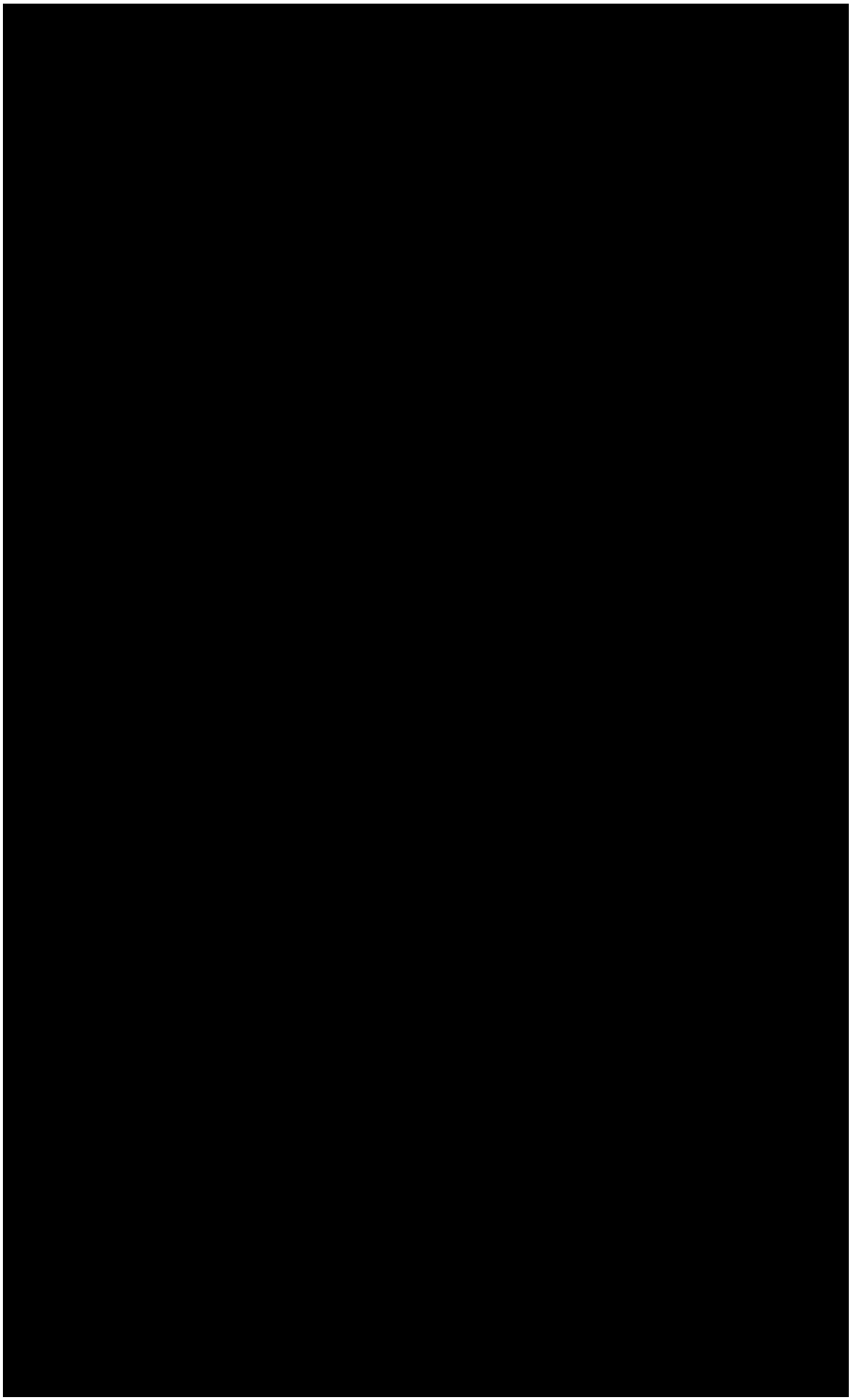

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