Appendices to Abbott response 28 July 2008

Appendix 1: Systematic Literature Review and Meta-Analysis of SC-treated Placebo Arms in Randomized Controlled Trials

Remission in Biologic-Eligible Patients with Crohn's Disease Treated with Placebo

UEGW ABSTRACT NUMBER 1168, Accepted for poster presentation at UEGW 2008.
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***Introduction*:** When considering the effectiveness of biologic therapies (e.g. tumour necrosis factor antagonists) in treating patients with moderate to severe Crohn's disease (CD), a systematic review of the rates of remission achieved with placebo in biologic-eligible patients may be of interest to treating physicians.

***Aims & Methods*:** We sought to examine the impact of placebo on remission in biologic-eligible patients with moderately to severely active CD using data from placebo arms of the trials of biologics. A systematic literature review of [redacted] was used to identify randomized controlled trials that included placebo arms comprising patients who exclusively received nonbiologic treatments for CD. Remission status was extracted from the trials. Time in remission was summarized across placebo arms of biologic trials that included patients with similar severities of disease. In addition, [redacted] The remission rate for the placebo arm of the biologic trials was predicted using the [redacted]

***Results*:** In total, [redacted] biologic and non-biologic study arms with relevant remission data were included in this analysis. Of the [redacted] arms, [redacted] distinct treatment arms were identified as placebo arms of the biologic trials, which included a total of [redacted] patients with similar severities of disease. These patients had CD duration for an average of [redacted] years and a CDAI of [redacted] at baseline. Weighted by sample size and duration of the trial, results demonstrated that patients receiving placebo spent [redacted] of the time in remission. [redacted]

***Conclusion*:** The placebo remission rate for patients with moderately to severely active CD eligible for biologic treatment was generally low. Physicians should be aware of the low placebo remission rate for patients with moderate to severe CD despite conventional treatments.

The following gives more details of this research:

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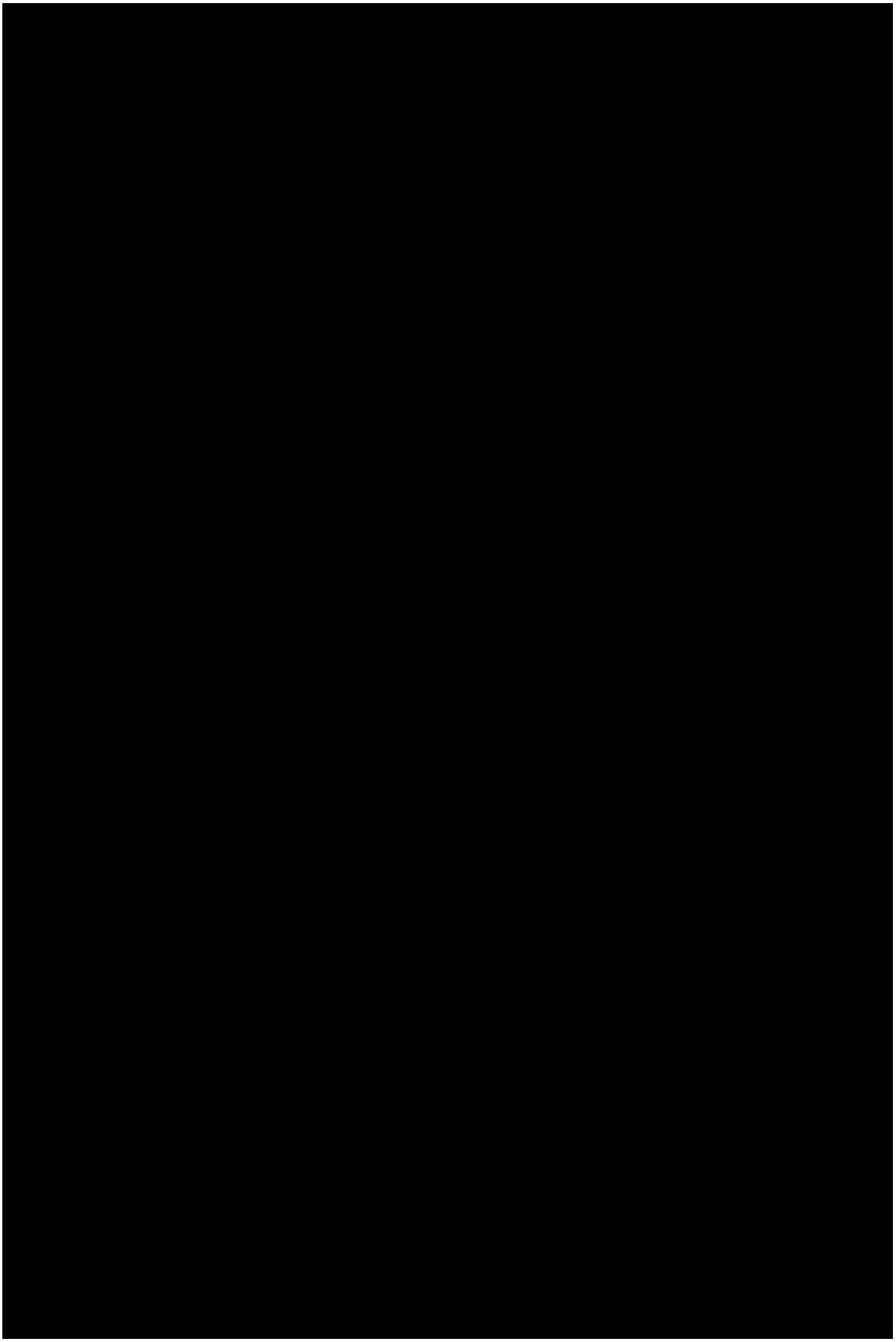

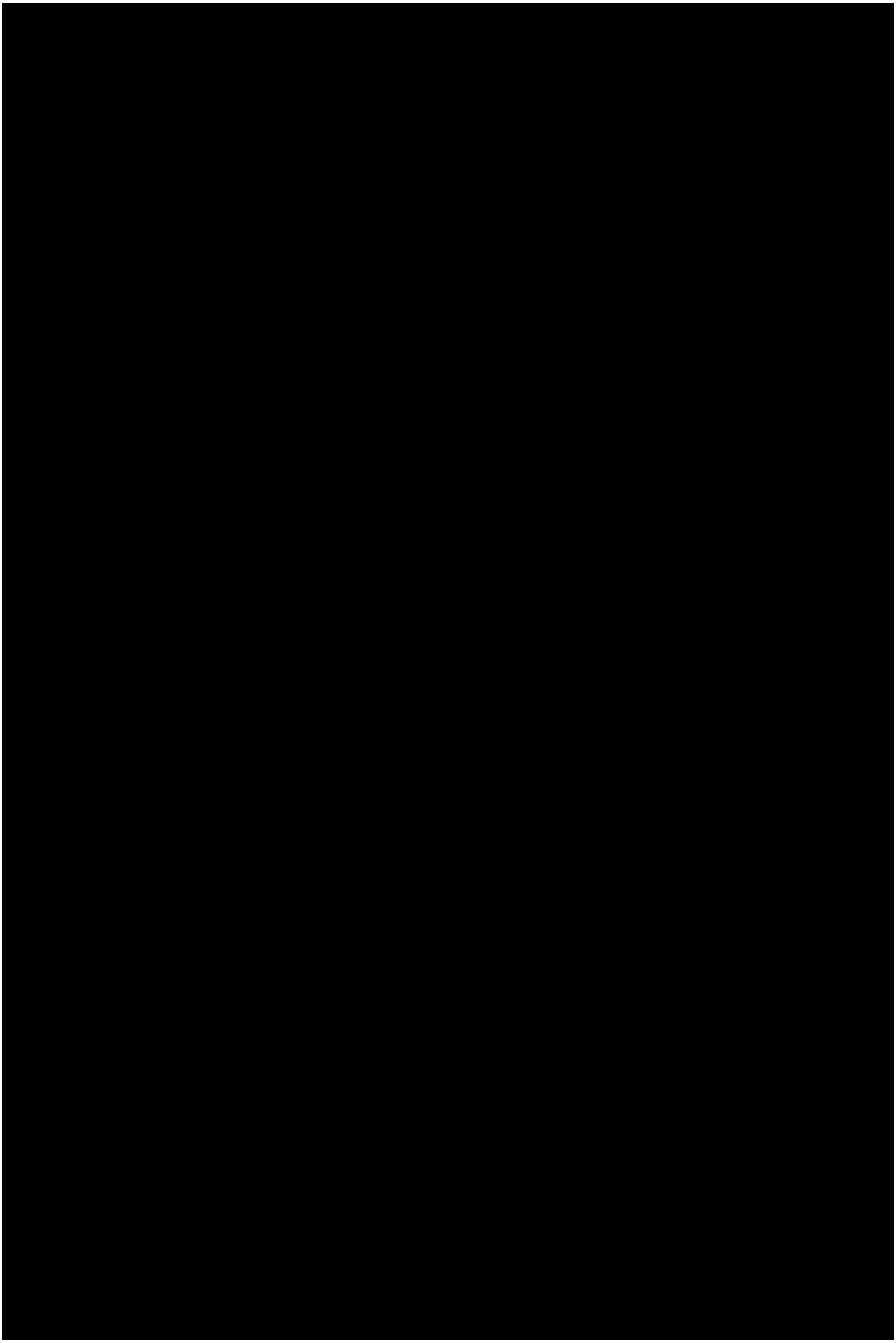

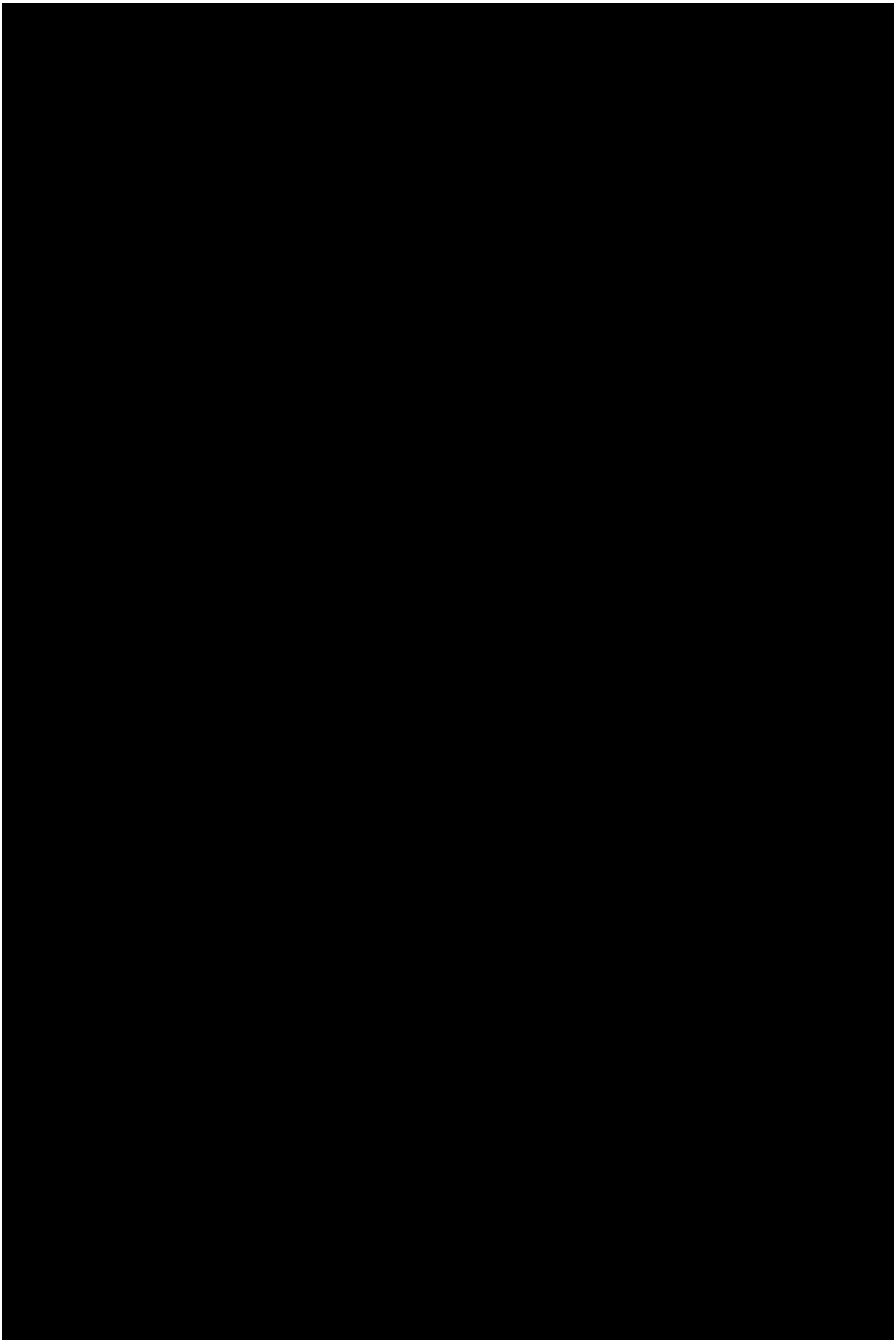

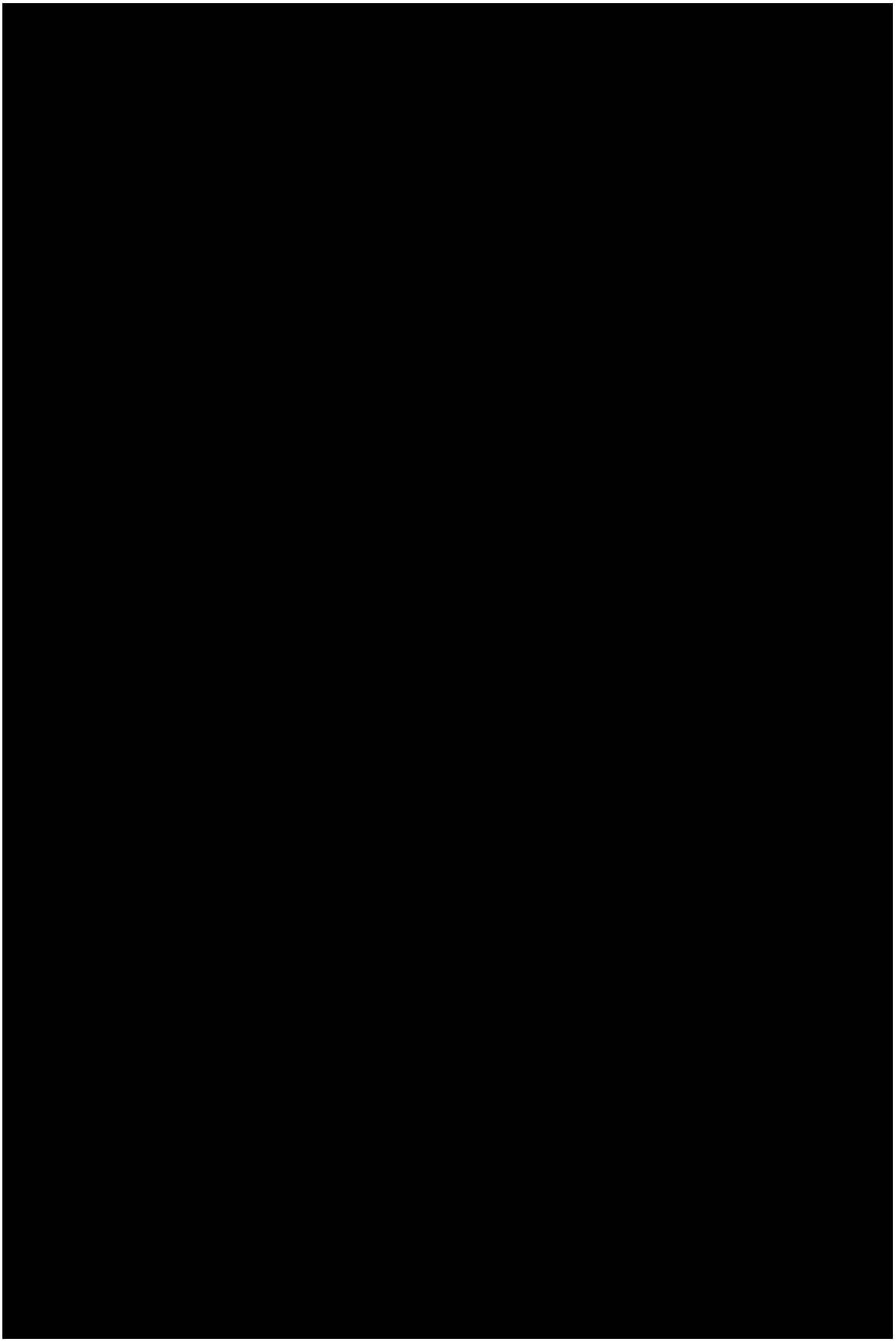

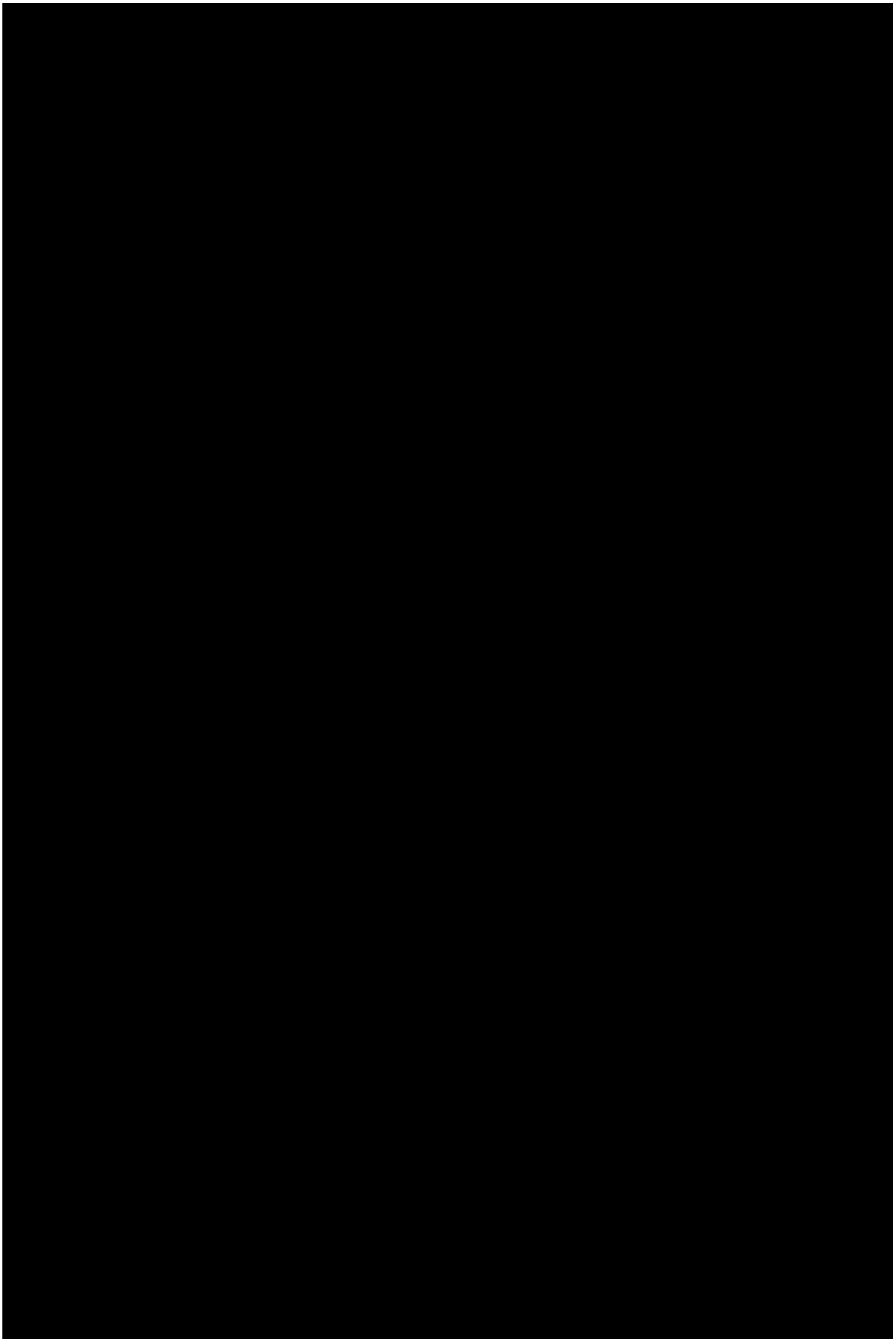

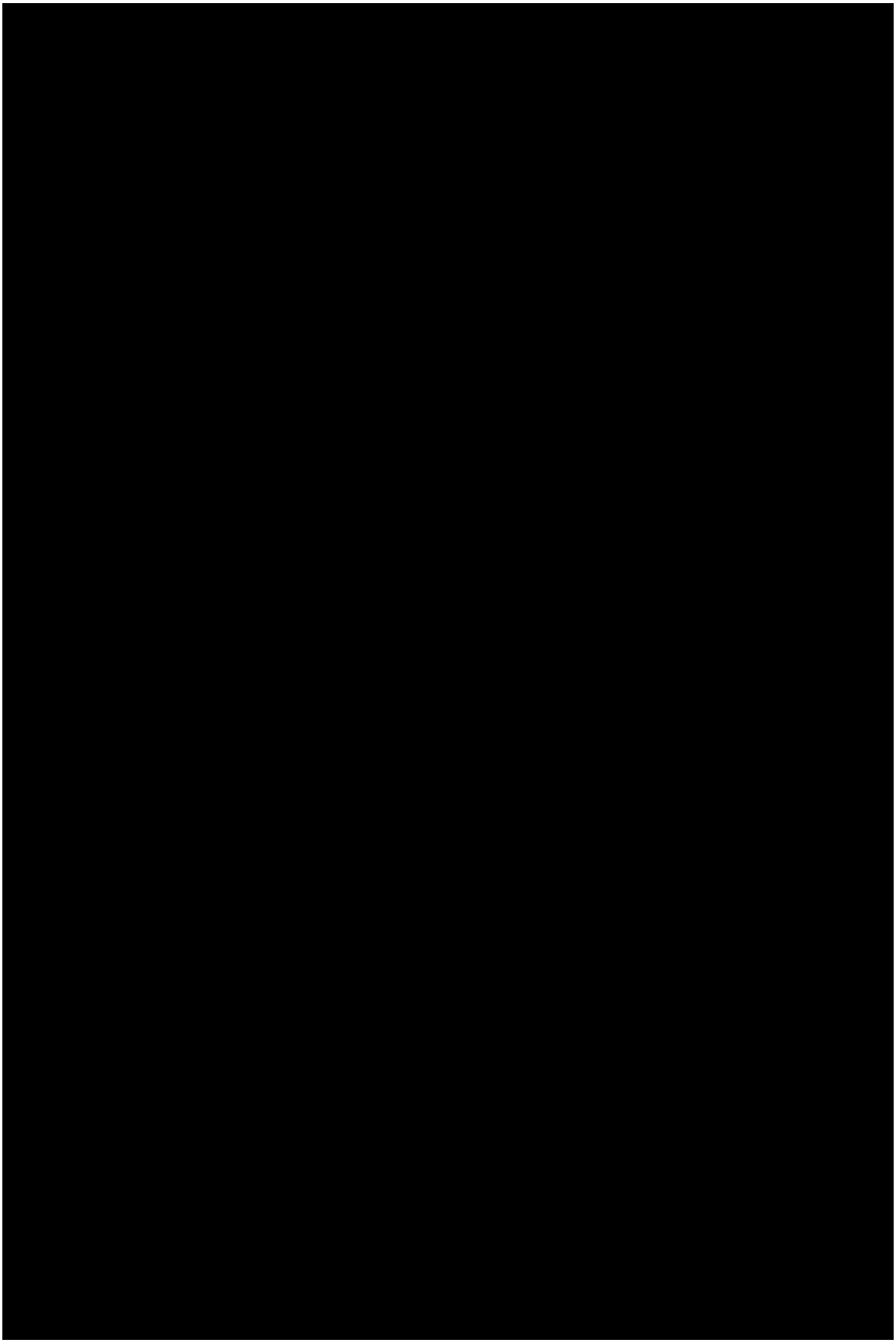

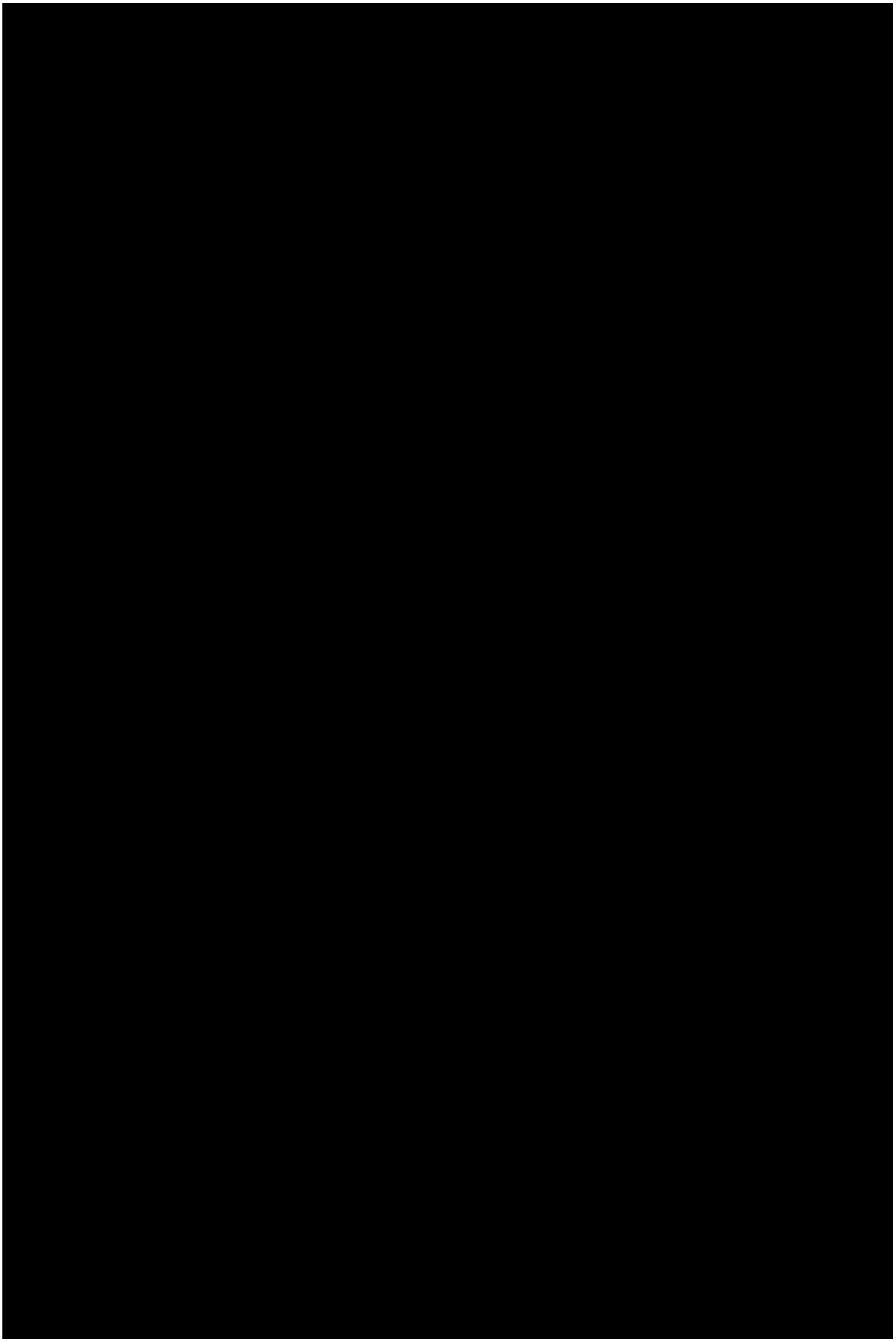

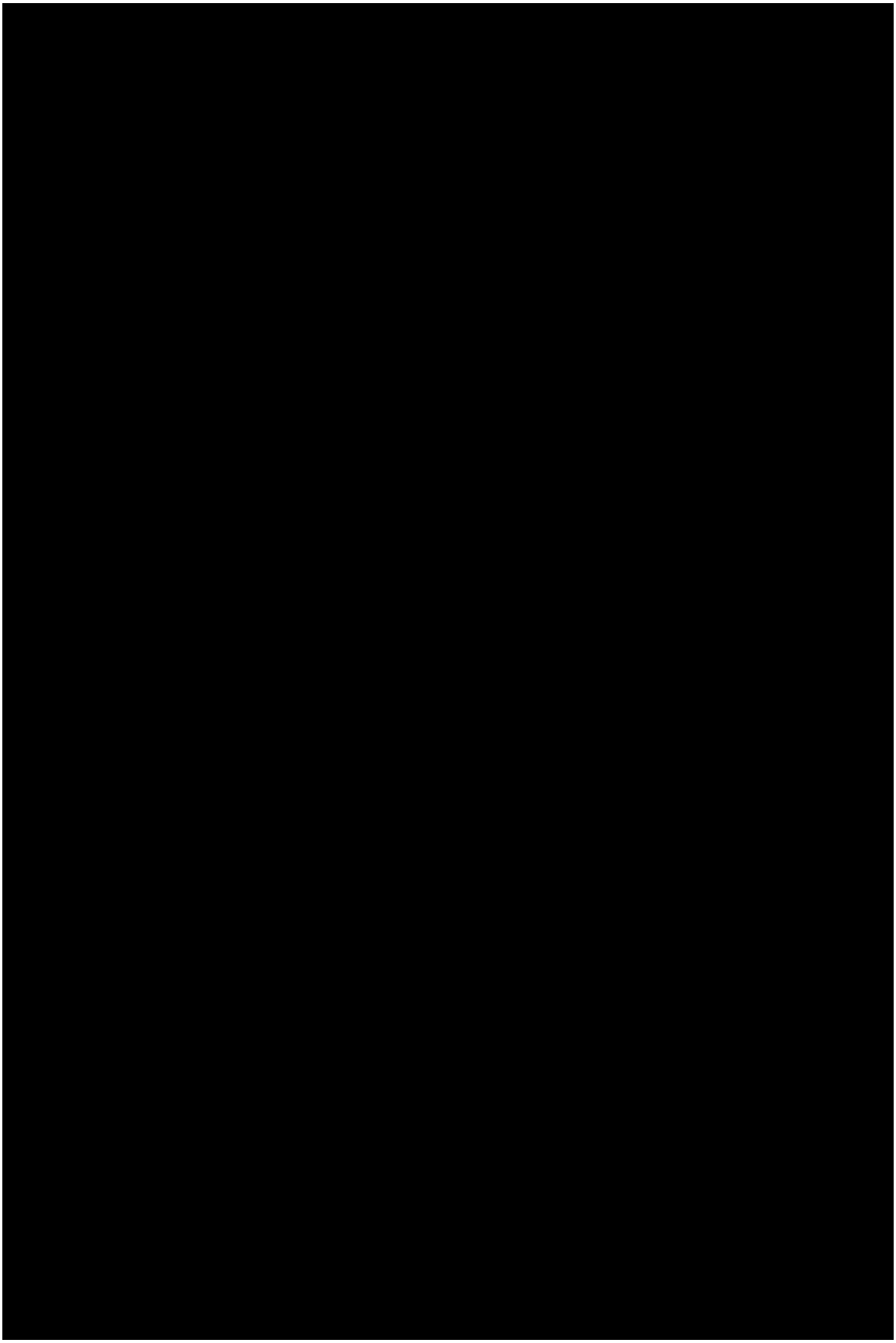

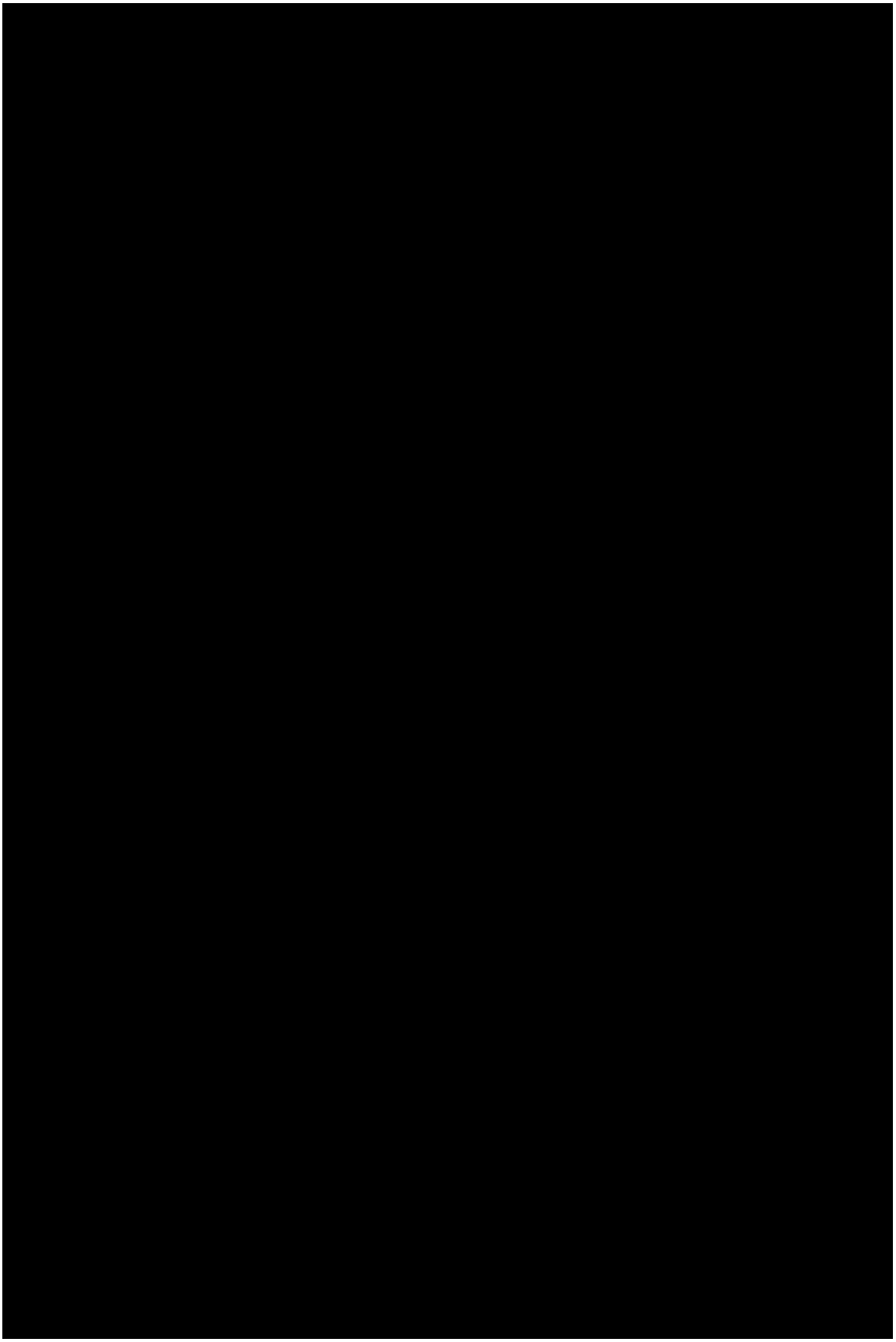

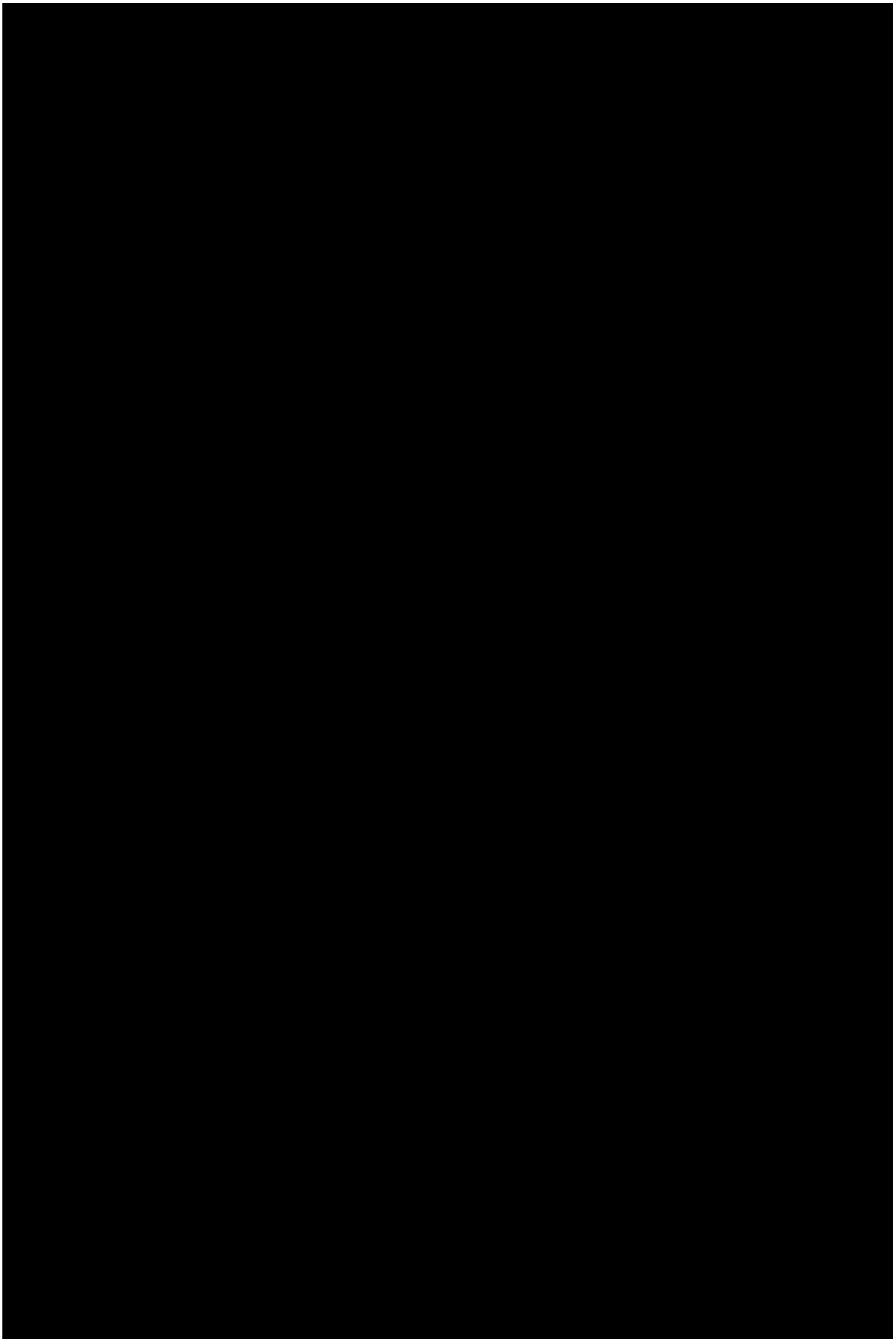

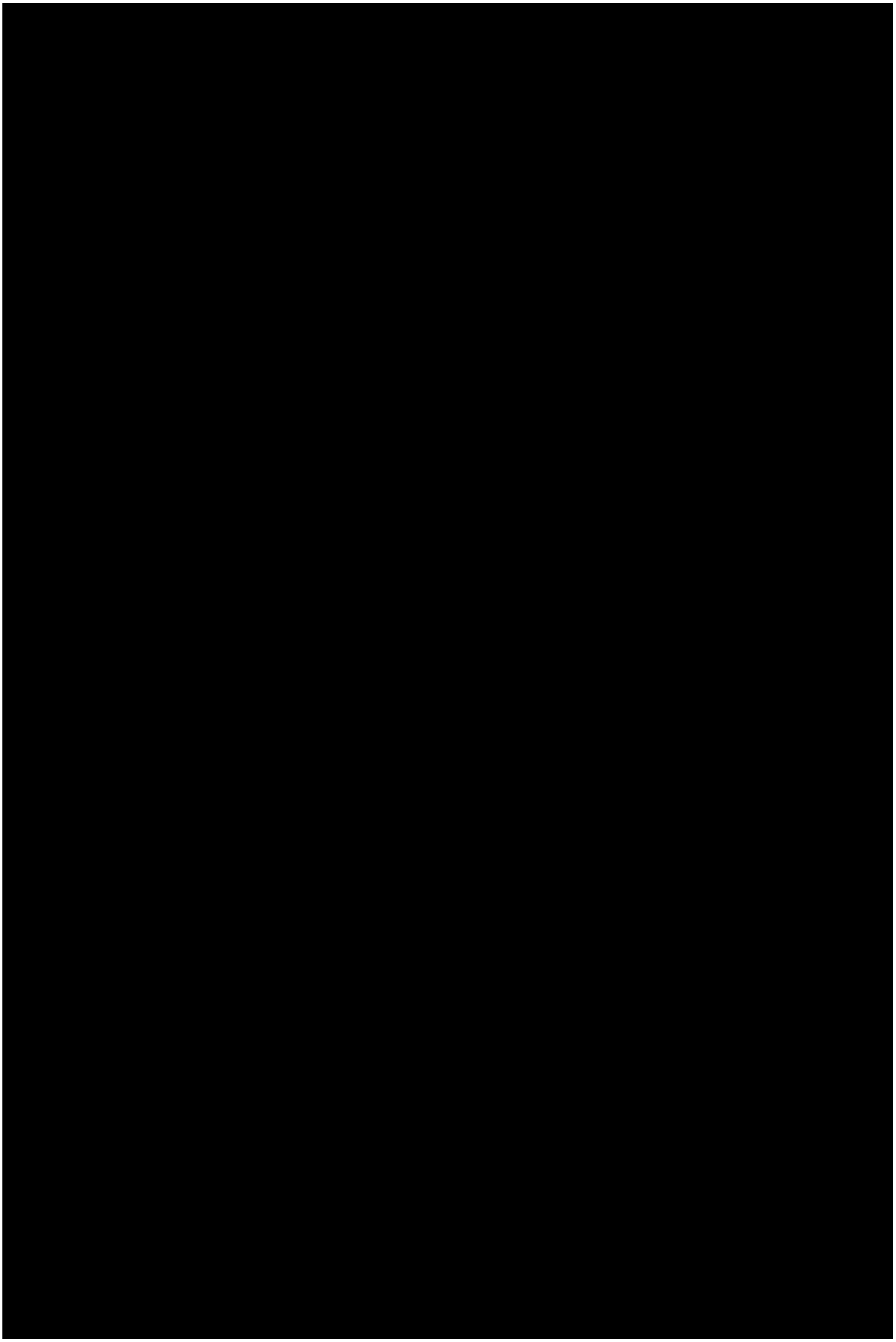

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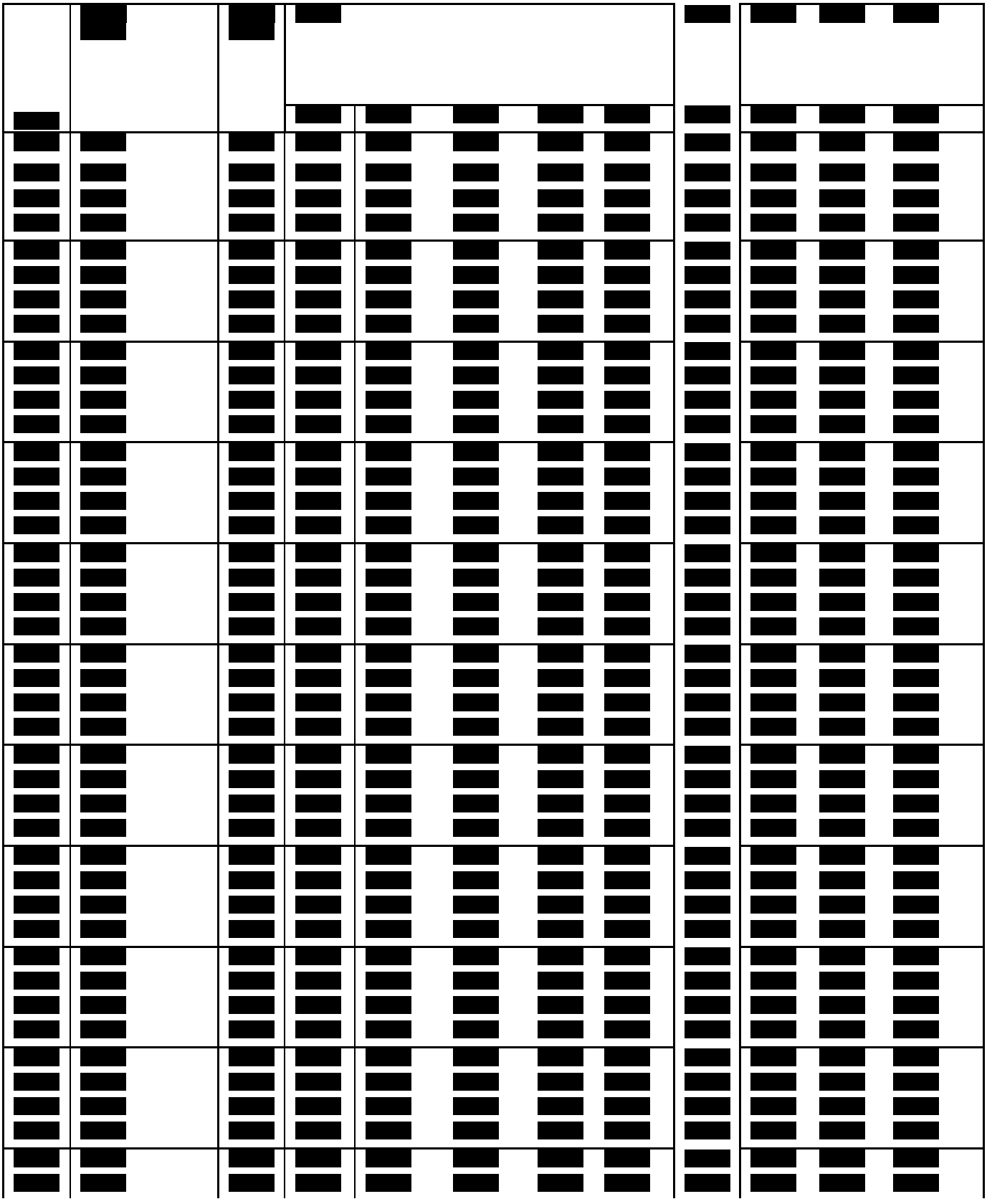
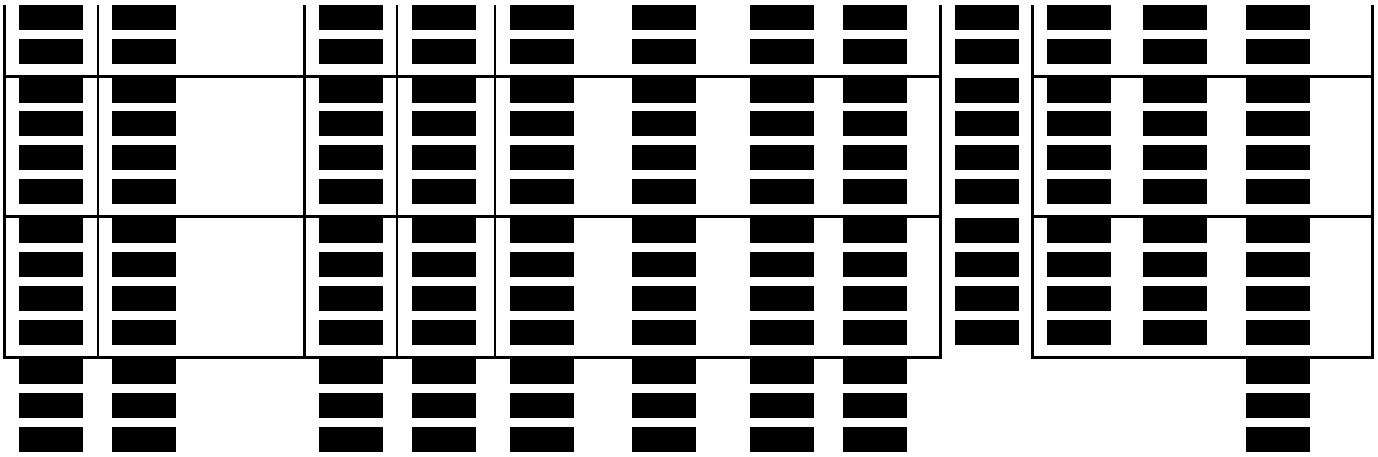
Appendix 2: Average Drug Dose (in mg) Across CDAI-based Disease States of Adalimumab over Time for Moderate to Severe Patients in CHARM EOW Arm





Appendix 3: Adalimumab sustains quality of life improvements over 2 years

Adalimumab Sustains Quality-of-Life Improvements in Patients With Crohn's Disease: 2-Year Data From CHARM

P078

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Abstract

AIMS: Adalimumab, a fully human monoclonal antibody targeting tumor necrosis factor, has demonstrated efficacy in inducing and maintaining remission, providing rapid and sustained improvements in quality of life (QOL) for patients with Crohn's disease participating in the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM).[1,2] We assessed long-term effects of adalimumab on QOL through 2 years from CHARM baseline.

METHODS: In CHARM, patients were randomized to placebo, 40 mg adalimumab every other week (EOW), or 40 mg adalimumab weekly (EW). Patients with flare/nonresponse could receive open-label adalimumab at/after Week 12. At the end of CHARM (56 weeks), patients could enroll in an open-label extension (OLE) in which those on blinded therapy received adalimumab EOW and those already on open-label adalimumab maintained their therapies. In CHARM and the OLE, patients could change from EOW to EW for flares/nonresponse. In this analysis, patients initially randomized to adalimumab in CHARM were followed through 2 years of exposure. The percentages of patients from each originally randomized adalimumab group with Inflammatory Bowel Disease Questionnaire (IBDQ)≥170 (which correlates with clinical remission) were calculated using both last-observation-carried-forward (LOCF) and nonresponder imputation. LOCF analyses were performed for total IBDQ values and Short Form 36 Health Survey (SF-36) Mental Component Summary (MCS) and Physical Component Summary (PCS) scores over time for EOW, EW, and combined adalimumab groups. Paired Student *t* tests compared values at each visit with baseline values.

RESULTS: Of 328 patients who entered the OLE, 144 had been randomized to adalimumab EOW and 184 had been randomized to adalimumab EW in CHARM. The percentages of patients achieving IBDQ≥170 at Weeks 56 and 116, respectively, were 63.2% and 54.9% in EOW, 59.8% and 59.2% in EW, and 61.3% and 57.3% in the combined EOW+EW groups (LOCF). Nonresponder imputation yielded similar results. Mean total IBDQ, SF-36 PCS, and SF-36 MCS scores (Figure 2–4) overall demonstrated sustained QOL improvements with adalimumab maintenance.

CONCLUSIONS: Clinically important improvements in QOL achieved with adalimumab in the CHARM trial were sustained through 2 years of adalimumab maintenance therapy.

Introduction

- Adalimumab (HUMIRA®) is a fully human monoclonal antibody antagonist specific to tumor necrosis factor (TNF)
- Adalimumab is approved in the United States and Europe for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis
- The Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) was a 56-week, randomized, double-blinded, placebo-controlled, Phase III trial that confirmed the sustained efficacy and safety of adalimumab in maintaining clinical remission in patients with moderately to severely active Crohn's disease[1]
- Following CHARM, patients were allowed to enroll in an open-label extension (OLE) in which all patients received open-label adalimumab therapy

Purpose

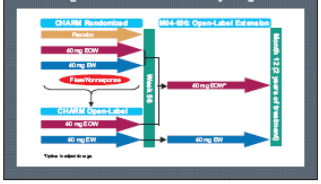
- The purpose of this analysis was to assess the long-term effects of adalimumab on quality of life in patients with Crohn's disease participating in CHARM and its OLE through 2 years

Patients and Methods

CHARM and OLE Study Design

- All patients received open-label induction with adalimumab 80 mg at baseline and 40 mg at Week 2 (Figure 1)
- At Week 4, all patients were randomized to adalimumab 40 mg every other week (EOW), adalimumab 40 mg weekly (EW), or placebo
- At/after Week 12, patients could switch to open-label adalimumab EOW and then to open-label adalimumab EW for protocol-defined flares or nonresponse
- Per protocol, patients who switched to open-label adalimumab EW therapy could not decrease their dosage back to EOW
- Following CHARM (56 weeks), patients could enroll in an OLE in which those who completed CHARM on blinded therapy received open-label adalimumab 40 mg EOW and those already receiving open-label adalimumab therapy continued
- In the OLE, patients were allowed to increase the adalimumab dosage from EOW to EW for disease flare or nonresponse

Figure 1. CHARM and OLE Study Design



Patient Inclusion Criteria for CHARM

- Moderately to severely active Crohn's disease (220≤Crohn's Disease Activity Index [CDAI]≤450)
- Concomitant treatment with 5-aminosalicylates, corticosteroids, and immunosuppressants (azathioprine, 6-mercaptopurine, methotrexate) was permitted provided the patient was on stable doses
- Previously anti-TNF–exposed patients were allowed, provided anti-TNF had been discontinued at least 12 weeks prior to screening and the patient met any of the following criteria:
  - a) Responded and then stopped the agent
  - b) Responded and lost their response
  - c) Responded and became intolerant
  - d) Did not tolerate the anti-TNF agent

  (primary nonresponders were not eligible)
- This analysis included patients initially randomized to the adalimumab EOW and EW dosage groups in CHARM who entered the OLE (intention-to-treat population)
- Quality-of-life measures included the following:
  - Inflammatory Bowel Disease Questionnaire (IBDQ)
  - Short Form 36 Health Survey (SF-36) Physical (PCS) and Mental (MCS) Component Summaries
- Paired Student *t* tests were used to compare results for adalimumab EOW, EW, and the combined EOW and EW dosage groups with baseline. Last-observation-carried-forward (LOCF) analyses were used.
- Percentages of patients with IBDQ≥170, which correlates with clinical remission, were calculated using both nonresponder imputation and LOCF

Results

- Of 328 patients who entered the OLE, 144 had been randomized to adalimumab EOW and 184 had been randomized to EW in CHARM (Table 1)

Table 1. Baseline Demographics of Patients Randomized to Adalimumab EOW or EW in CHARM and Entered the OLE*

Characteristic	EOW (N=144)	EW (N=184)
Male, %	36	42
Age (yrs), mean	37	38
Body weight (kg), mean	70	73
C-reactive protein (mg/dL), mean	1.9	2.1
Baseline CDAI score, mean	311	306
Previous corticosteroid exposure, %	84	86
Previous TNF-antagonist exposure, %	46	46

*Patients randomized to EOW or EW who exited CHARM to OLE

- Patients receiving adalimumab demonstrated significant and sustained improvement in IBDQ, SF-36 PCS, and SF-36 MCS over time (Figures 2–4)

Figure 2. Improvement in IBDQ With Adalimumab Over Time

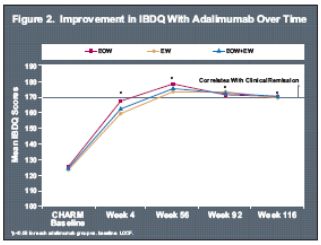


Figure 3. Improvement in SF-36 PCS With Adalimumab Over Time

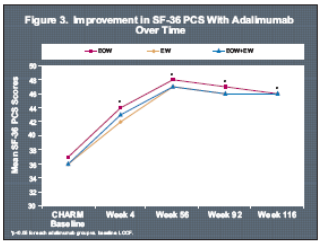
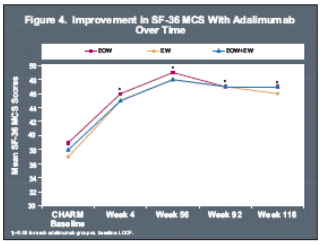


Figure 4. Improvement in SF-36 MCS With Adalimumab Over Time



- The percentages of patients achieving IBDQ≥170 at Weeks 56 and 116 using LOCF were 63% and 55% in the EOW group, 60% and 59% in the EW group, and 61% and 57% in the EOW+EW group. Nonresponder imputation yielded similar results (Figures 5 and 6).

Figure 5. Patients Receiving Adalimumab in CHARM and OLE Who Achieved IBDQ≥170 (LOCF)

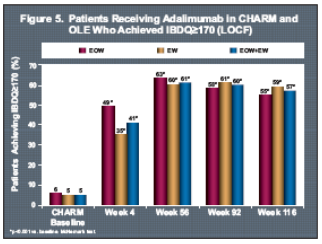
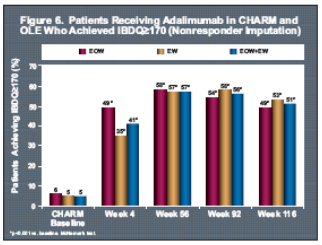


Figure 6. Patients Receiving Adalimumab in CHARM and OLE Who Achieved IBDQ≥170 (Nonresponder Imputation)



CONCLUSIONS

- Patients randomized to either adalimumab 40 mg EOW or EW in CHARM achieved clinically important improvements in quality-of-life measures
- Quality-of-life improvements were maintained over 2 years of adalimumab maintenance therapy

References

1. Colombel JF, et al. *Gastroenterology.* 2007;132(1):52–65.
2. Loftus EV, et al. *Am J Gastroenterol.* 2007;102(Suppl 2):S457.

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Appendix 4: Addendum of Results

The incremental costs, QALYs, and cost/QALY ratio are presented in disaggregated form in the following tables.

Incremental Costs

Table 1: Incremental Direct Medical Costs of Adalimumab versus Standard Care in the First Year of Therapy

Moderate and Severe CD patients (CDAI≥150)			
	Adalimumab	**Standard care**	**Difference**
Drug	£6,533	£0[a]	£6,533
Health state related costs	£1,249	£2,049	-£800
Hospitalisation	£2,028	£5,265	-£3,237
Total costs	£9,810	£7,315	£2,496
Severe CD patients (CDAI≥300)			
	Adalimumab	**Standard care**	**Difference**
Drug	£7,119	£0 [a]	£7,119
Health state related costs	£1,429	£2,407	-£979
Hospitalisation	£2,598	£7,485	-£4,886
Total costs	£11,146	£9,892	£1,254

a. Drug costs for standard care set to zero as a conservative approach

Incremental QALYs

Table 2: QALYs and Incremental QALYs by Treatment over One Year

	Moderate and Severe Patients (CDAI ≥ 150)	**Severe Patients (CDAI ≥ 300)**
Standard care	0.7743	0.7339
Adalimumab	0.8566	0.8384
Incremental QALYs of Adalimumab therapy	0.0823	0.1045

ICER (£/QALY) for One Year of Therapy

Table 3: Cost-per-QALY of Adalimumab versus Standard Care for One Year of Therapy

	Moderate and Severe Patients (CDAI≥150)	**Severe Patients (CDAI≥300)**
Adalimumab vs. Standard care	£30,319	£11,998

Probabilistic Sensitivity Analysis Results

Figure 1: Cost-Effectiveness Acceptability Curve for One Year of Adalimumab Therapy versus Standard Care for Moderate to Severe Patients (Includes Stochastic Variation on the Probability of Being in the Remission, Moderate, Severe and Very Severe States for the adalimumab and SC Arms via a Dirichlet Distribution)

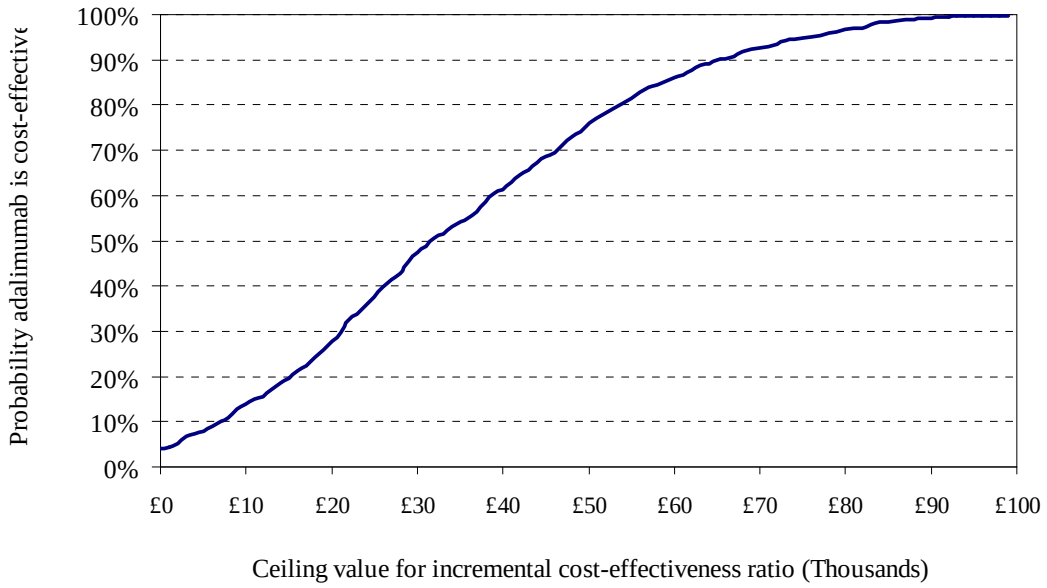
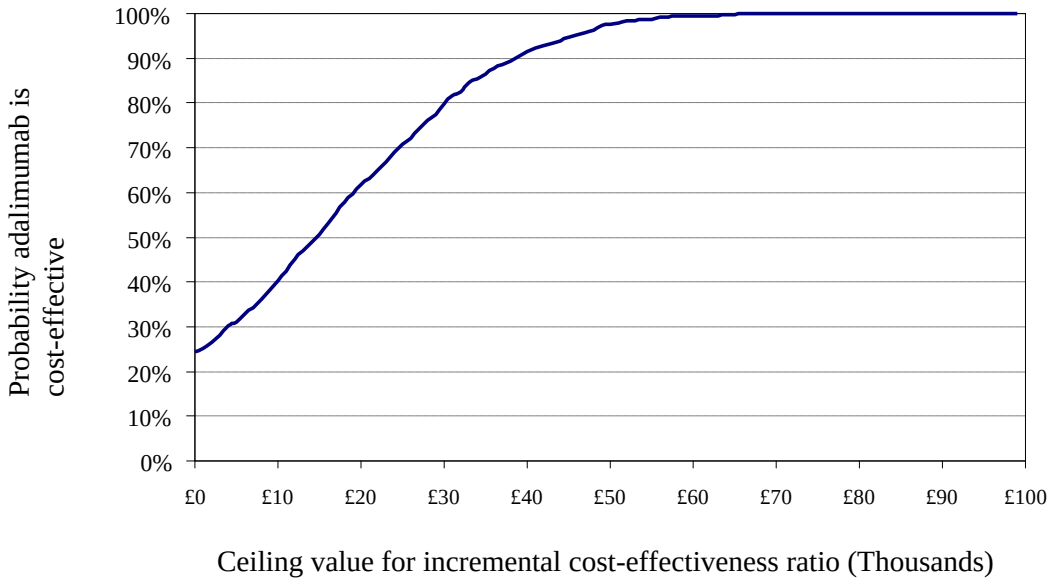


Figure 2: Cost-Effectiveness Acceptability Curve for One Year of Adalimumab Therapy versus Standard Care for Severe Patients (Includes Stochastic Variation on the Probability of Being in the Remission, Moderate, Severe and Very Severe States for the adalimumab and SC Arms via a Dirichlet Distribution)



Univariate Sensitivity Analysis

A number of sensitivity analyses using changes to the base case were explored, and the results are summarised in Table 4.

Table 4: Univariate Sensitivity Analysis

	Base Case (BC) Assumption	Change in BC Assumption	ICER	
			All Patients	Patients with CDAI ≥300
Base Case	-	-	£30,319	£11,998
Treatment Efficacy				
Missing Health State	LVCF	Simulated Placebo	£54,921	£30,964
Utility				
All values	Regression Source: Gregor *et al.* (1997)	- 10%	£33,687	£13,331
		+ 10%	£27,562	£10,907
Unit Costs				
Hospitalisation	£7,441 Source: Bassi *et al.* (2004)	- 20%	£38,185	£21,347
		+ 20%	£22,453	£2,648
		- 40%	£46,051	£30,697
		+ 40%	£14,587	Dominant
CDAI State Costs				
Non-drug, Non-Hospital CDAI State Cost	Remission, moderate, severe and very severe weekly costs of £8.45, £23.66, £43.11, £78.55 Source: Bassi *et al.* (2004)	£0 per week; no difference in cost associated with different disease states	£40,042	£21,361
Drug Costs				
Induction Cost	80 mg / 40 mg	160 mg / 80 mg	£42,192	£21,111
Indirect Costs	Not included	Included	£21,857	£1,679

Model Extension: Lifetime Cost and Utility Estimates

Table 5: Lifetime Model Extension Cost/QALY for Moderate to Severe Patients

Cost-per-QALY for Lifetime Therapy			
	Adalimumab	**Standard Care**	**Difference**
Costs (£)	£147,262	£127,838	£19,424
QALY	15.088	13.474	1.614
Cost per QALY	£12,035/QALY		

Table 6: Lifetime Model Extension Cost/QALY for Severe Patients

Cost-per-QALY for Lifetime Therapy			
	Adalimumab	**Standard Care**	**Difference**
Costs (£)	£174,328	£172,481	£1,847
QALY	14.905	12.776	2.129
Cost per QALY	£868/QALY		

References