1.8.2 Risk Management Plan

Pioglitazone

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DATE: 13 May 2011 Version 12.0

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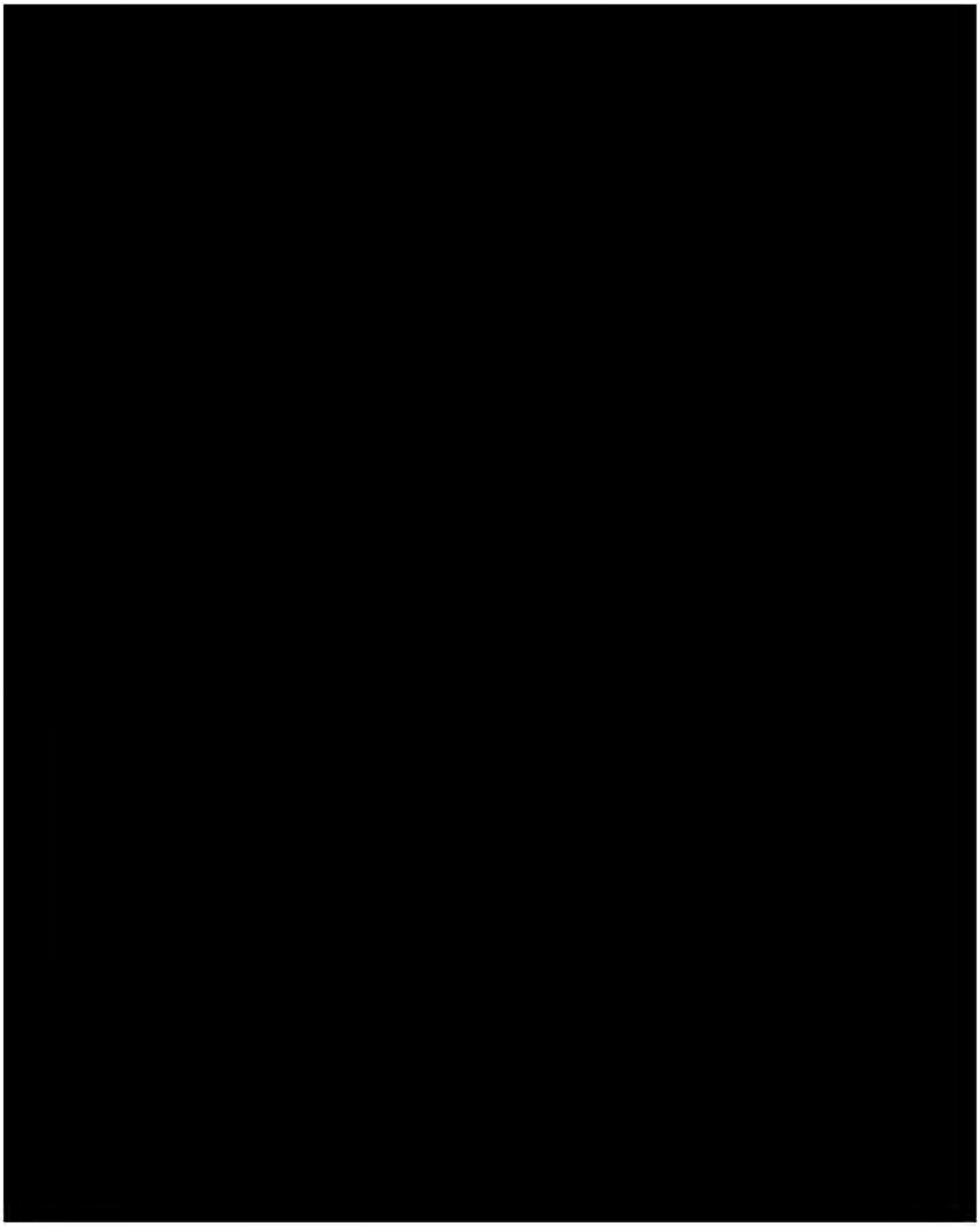

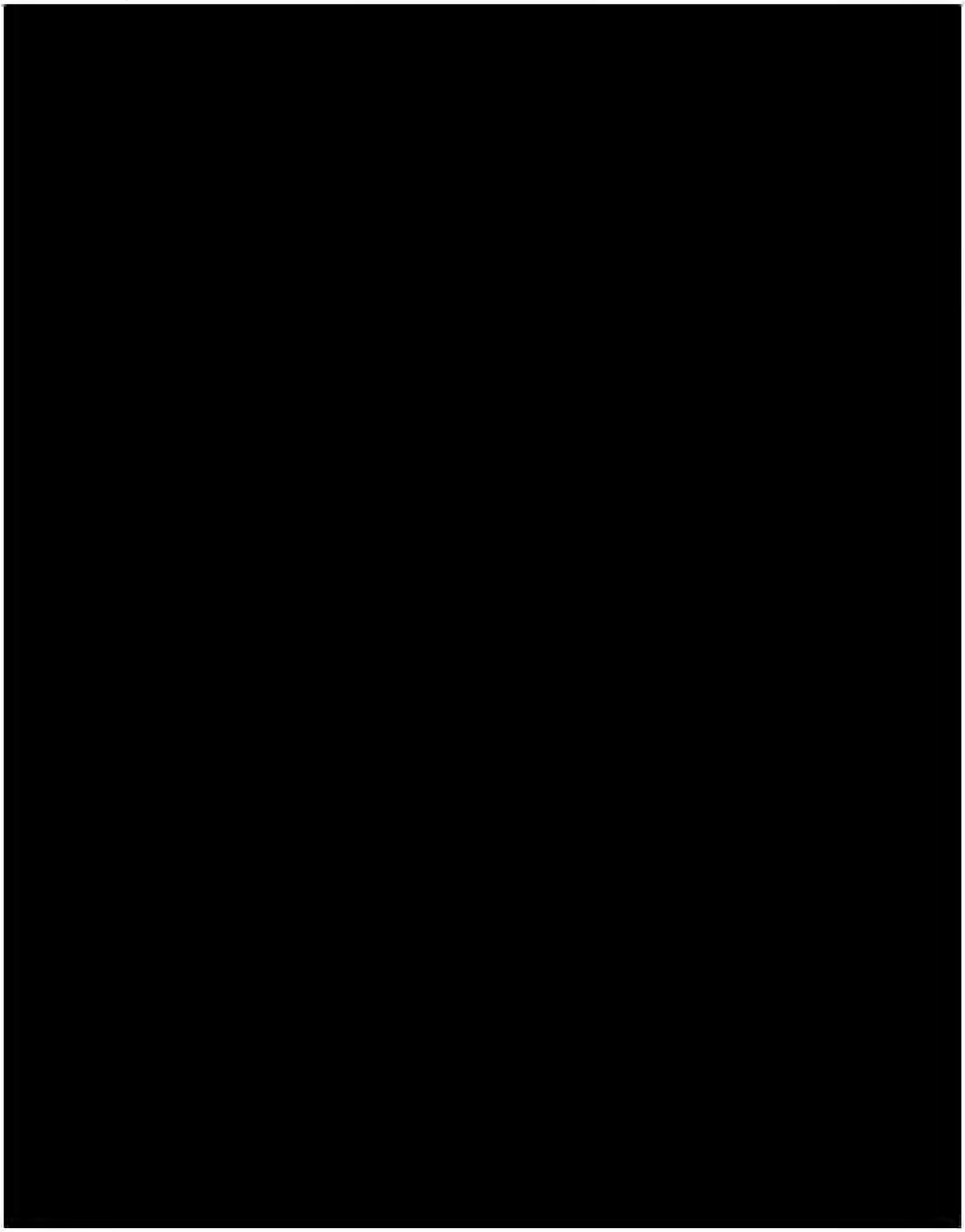

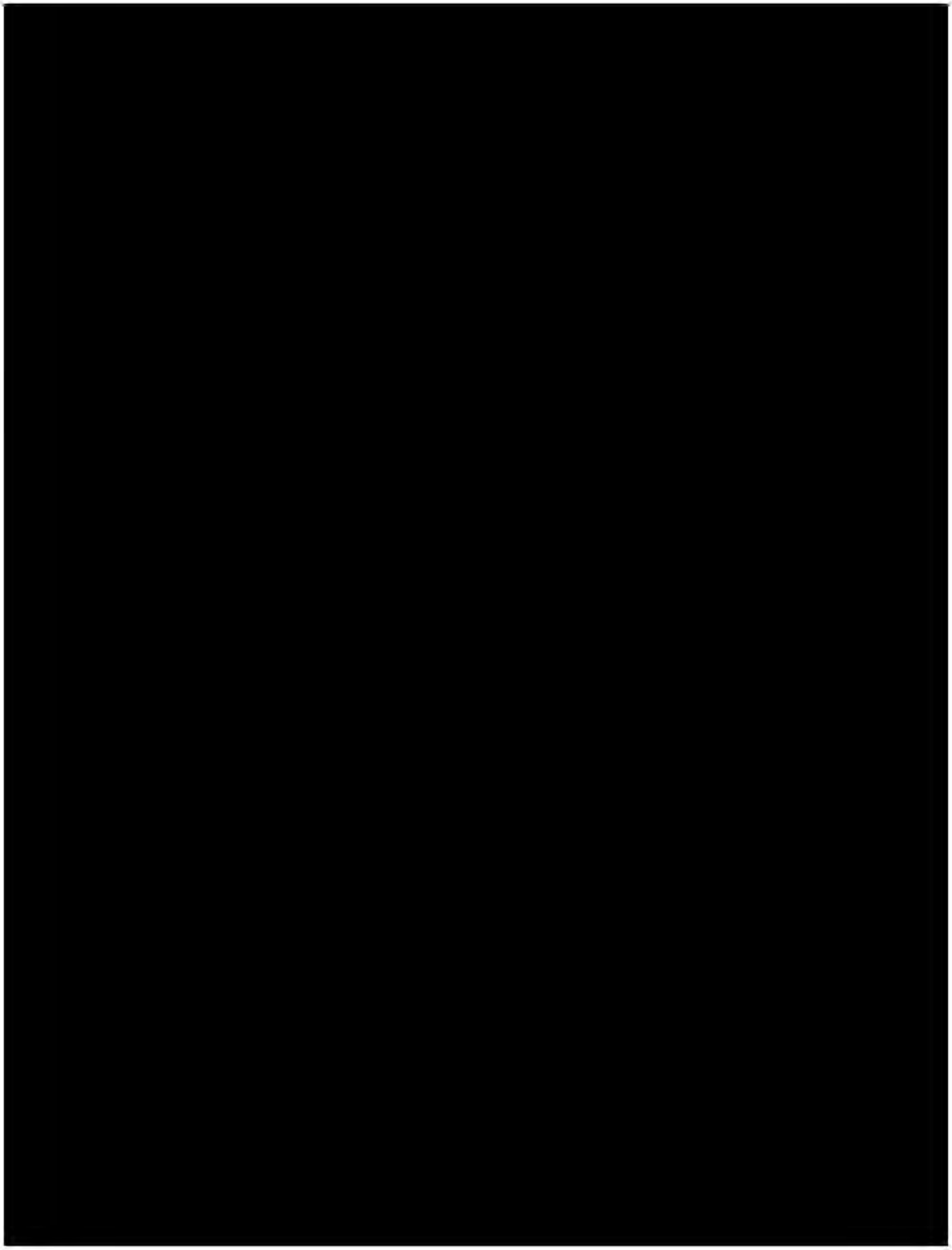

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LIST OF ABBREVIATIONS

A1c	glycosylated haemoglobin
ADR	adverse drug reaction
ALT	alanine aminotransferase
AMI	acute myocardial infarction
AUC	area under the plasma concentration-time curve
BMI	body mass index
BCBS	Blue Cross Blue Shield
CHD	coronary heart disease
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	maximum observed plasma concentration
CPMP	Committee for Proprietary Medicinal Products
CrCl	creatinine clearance
CYP	cytochrome P-450
DHPC	Direct Healthcare Professional Communication
DSRU	Drug Safety Research Unit
ECF	extracellular fluid
EEA	European Economic Area
EMA	European Medicines Agency
FDC	fixed-dose combination
FUM	Follow-Up Measure
GPRD	General Practice Research Database
HCl	hydrochloride
HF	heart failure
HR	hazard ratio
IBD	International Birth Date
IIT	investigator-initiated trial
ISAC	Independent Scientific Advisory Committee
IVUS	intravascular ultrasound
KPNC	Kaiser Permanente Northern California
LFT	liver function test
MAH	Marketing Authorisation Holder
MI	myocardial infarction
NALFD	nonalcoholic liver fatty disease
NYHA	New York Heart Association
OCT	ocular coherence tomography
PEM	Prescription Event Monitoring
PIL	Patient Information Leaflet

[redacted]

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PPAR	peroxisome proliferator-activated receptor
PPARγ	peroxisome proliferator-activated receptor gamma
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RR	relative risk
SOP	standard operating procedure
SPC	Summary of Product Characteristics
T1/2	terminal elimination half-life
TBW	total body water
TGRD (EU)	Takeda Global Research & Development Centre (Europe) Ltd.
TZD	thiazolidinedione
ULN	upper limit of normal
WHO	World Health Organization

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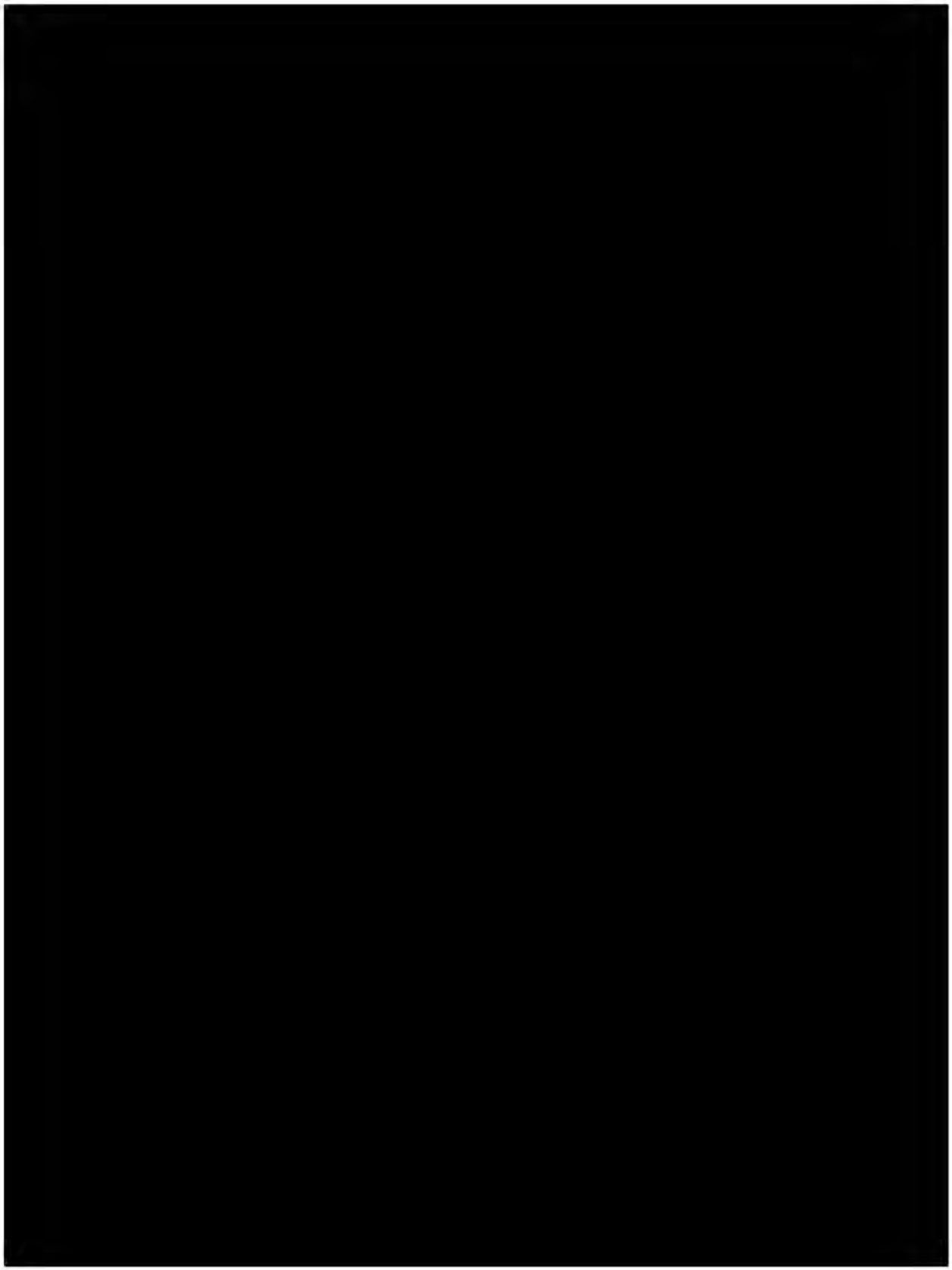
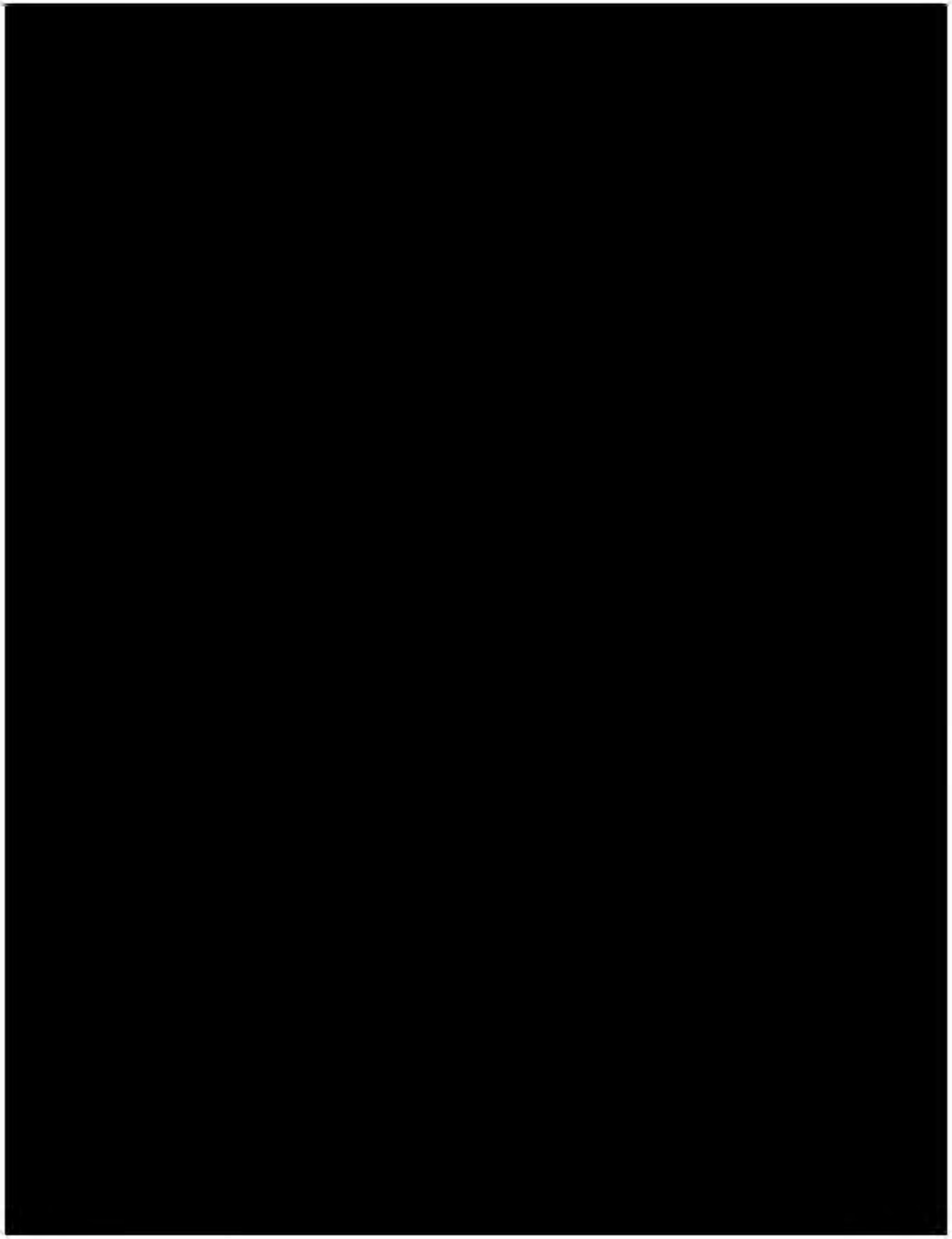
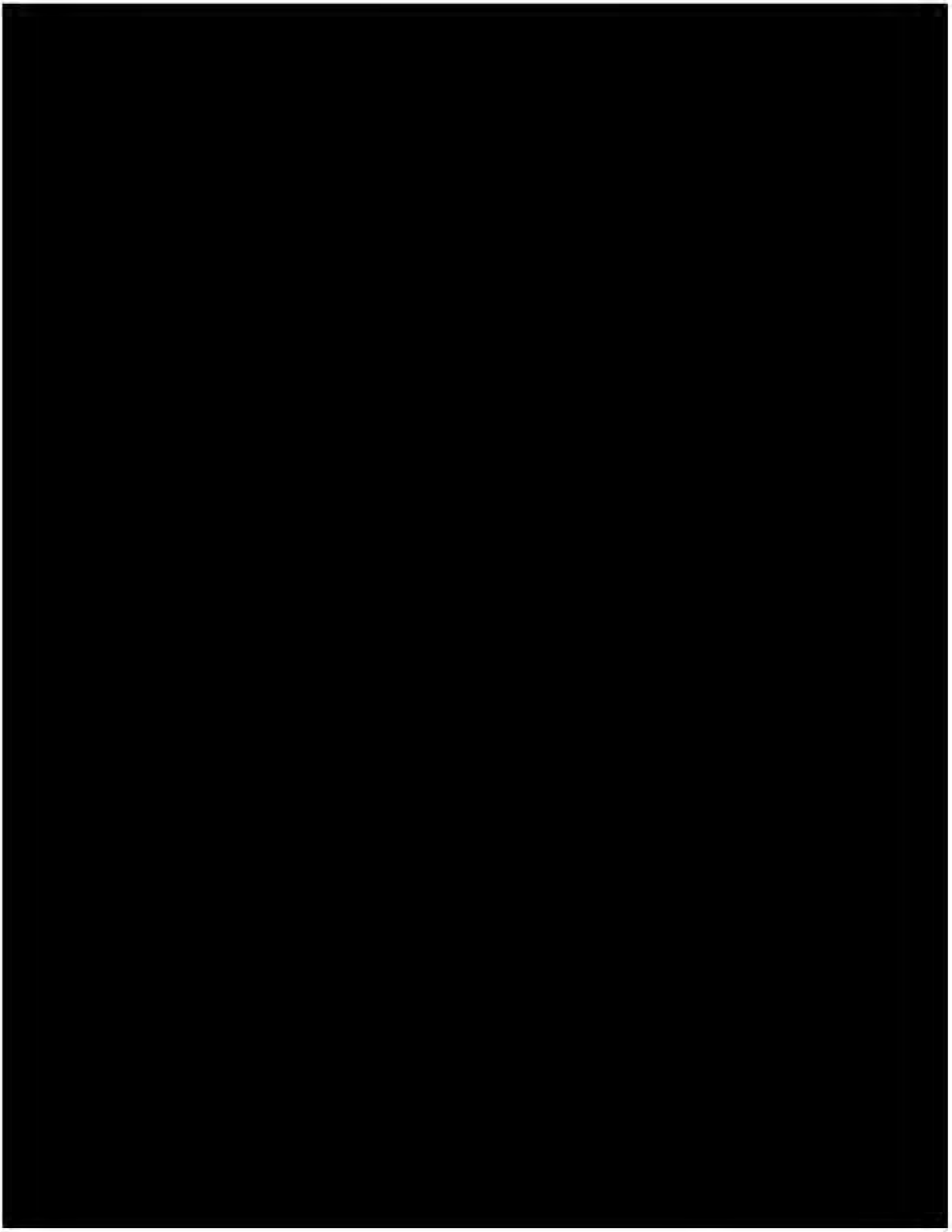
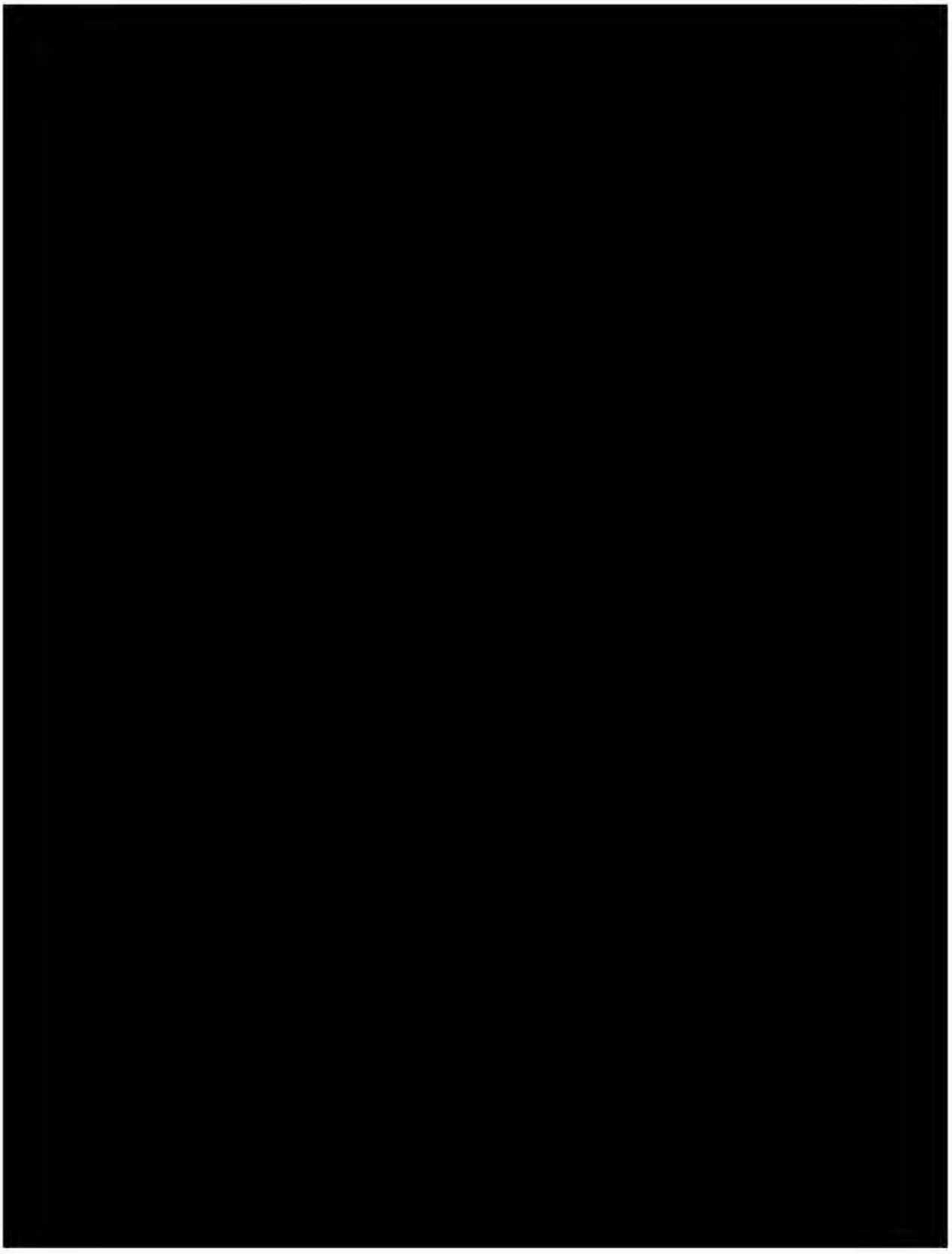


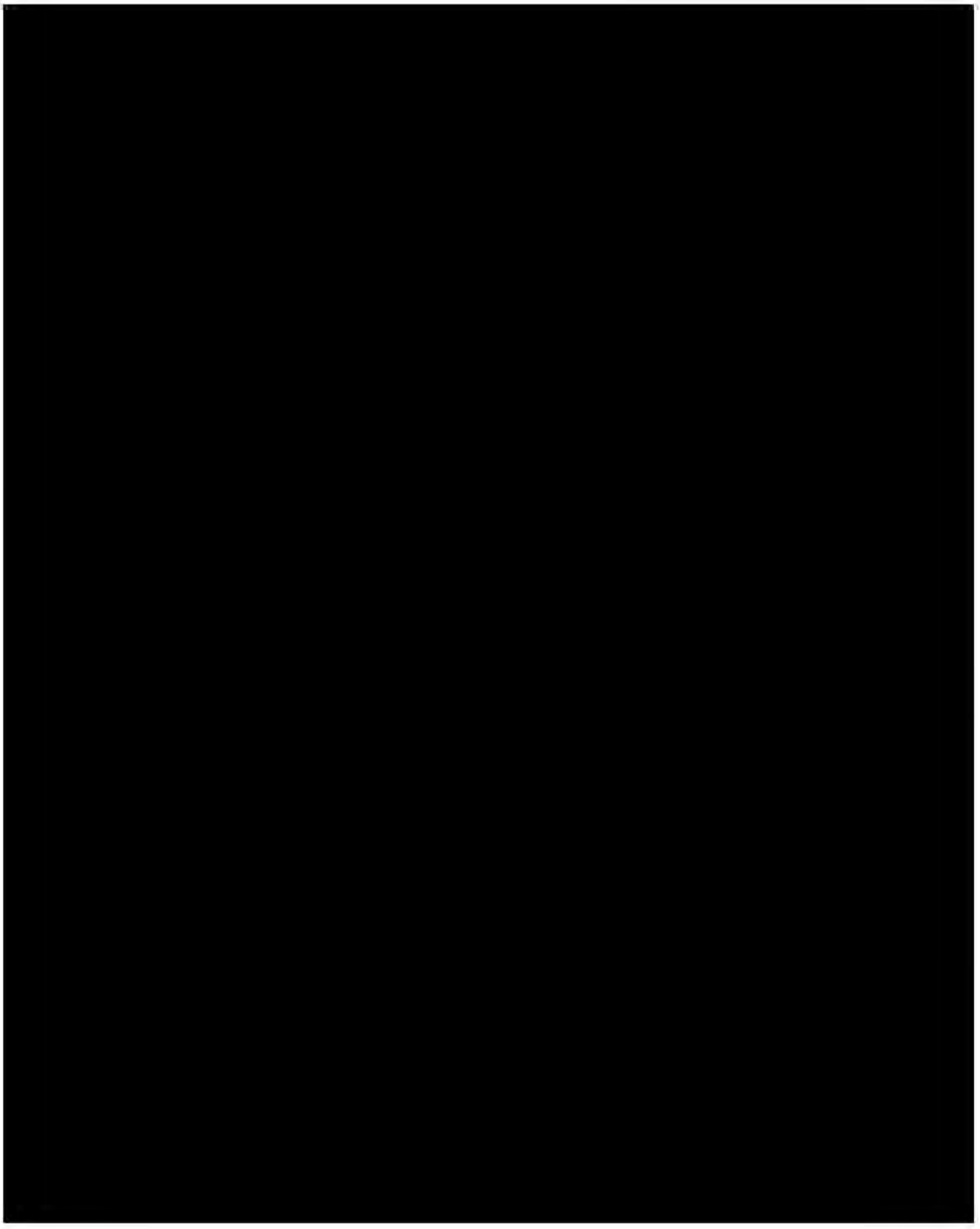


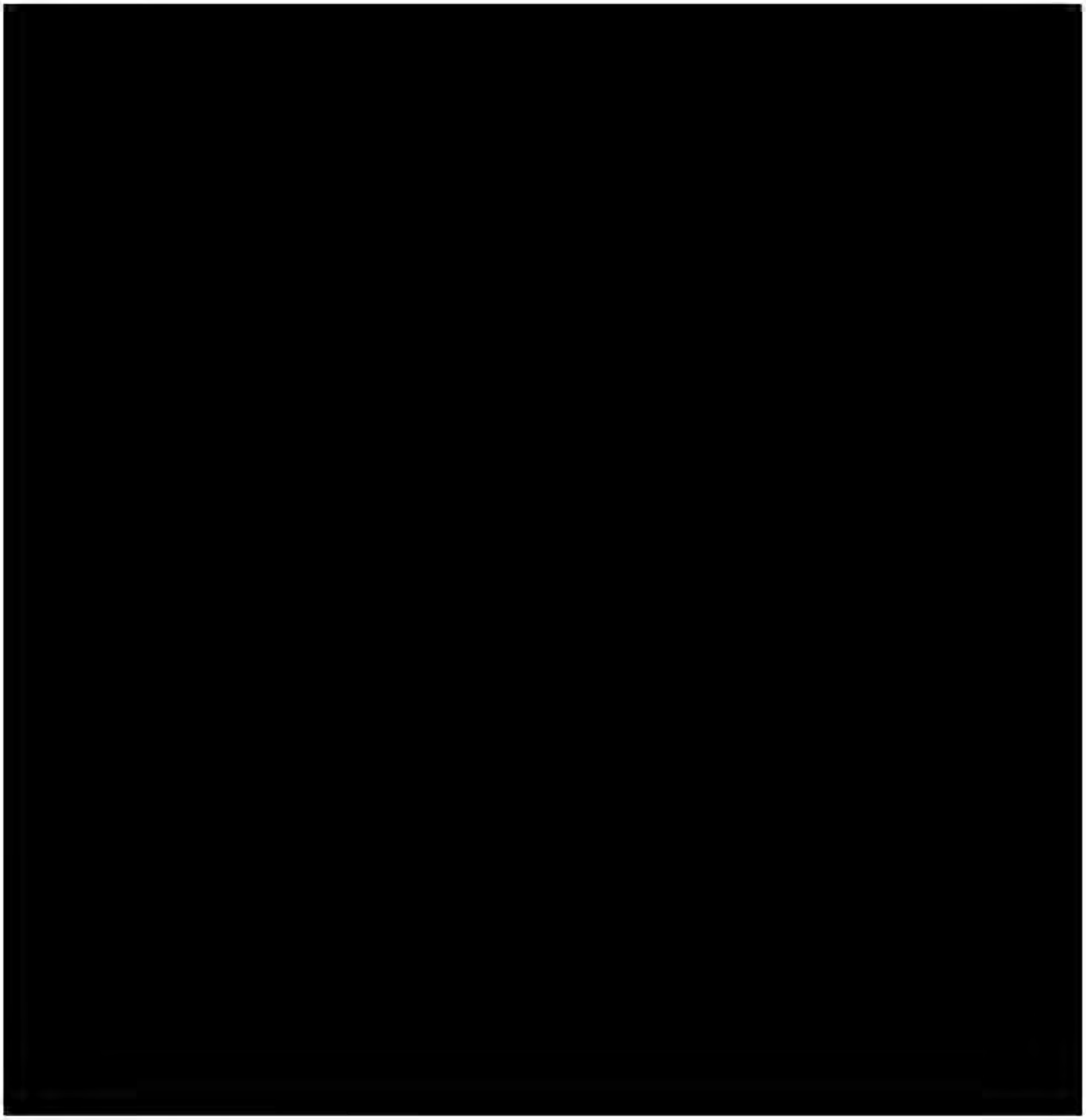
2) As part of the Article 20 procedure a meta-analysis of bladder cancer across clinical trials (both placebo-controlled and active-controlled) has been conducted as requested. Controlled clinical trials from the TGRD database were examined in the form of a meta-analysis using bladder cancer as an endpoint. The protocol (Study Number AD-4833_406) and study report for this meta-analysis study is submitted in Annex 5 and Annex 6; additionally, a synopsis is provided in Annex 3. A summary is also provided in Sections 2.2, 2.4, and 2.6.

3) As part of the Article 20 procedure, the MAH was also requested to provide proposals and justification with supportive evidence for any measures, including changes to the summary of product characteristics (SPC) and package leaflet, which could be taken in order to minimize the risk of bladder cancer. The MAH has provided proposed wording for the SPC and package leaflet and in addition a proposed Direct Healthcare Professional Communication (DHPC). The proposed SPC and package leaflet are submitted in Annex 2 and DHPC in Annex 8. A summary is also provided in Sections 3.0 and 4.0 of the RMP









1.2.1.2 Epidemiological study exposure

Epidemiological studies have included a Prescription Event Monitoring (PEM) study (CHMP commitment for events of malignancies) performed by the Drug Safety Research Unit (DSRU), United Kingdom. Results of this study indicated no significant findings (made available to the CHMP in February 2005). In addition, interim findings from an ongoing KPNC cohort study (1st interim analysis submitted August 2005; 2nd interim analysis submitted August 2007; 3rd interim analysis submitted November 2009), and a nested case-control study from the cohort (1st interim analysis submitted July 2006; 2nd interim analysis submitted November 2009)

[redacted]

Table 6 Epidemiological Exposure

Study	Study type (eg, cohort or case/ control)	Population studied	Duration (study period)	Number of persons (in each group or of cases and controls)	Person time (if appropriate)
[redacted]					
KPNC bladder cancer cohort study (protocol provided in Annex 5)	Prospective cohort study	Type 2 diabetics	Cohort established between 01 January 1997 and 31 December 2002. This cohort will be followed forward over an approximately 10-year period.	193,127 persons with type 2 diabetes mellitus; the numbers ever exposed to pioglitazone vs never exposed to pioglitazone vary with each analysis. 1st interim analysis (submitted August 2005), 17,084 exposed to pioglitazone vs 176,043 never exposed 2nd interim analysis (submitted August 2007), 23,122 exposed to pioglitazone vs 169,988 never exposed. 3rd interim analysis (submitted December 2009), 30,173 exposed to pioglitazone vs 162,926 never exposed.	Multiple analyses over a 10-year period. 1st interim analysis, median exposure 1.4 years (range 0.1-4.1) 2nd interim analysis, median exposure 1.7 years (range 0.2-6.2). 3rd interim analysis, median exposure 2.0 years (range 0.2-8.5).
KPNC bladder cancer nested case-control (protocol provided in Annex 5)	Nested case-control within the above cohort	Type 2 diabetics	Subset of above cohort.	[redacted]	
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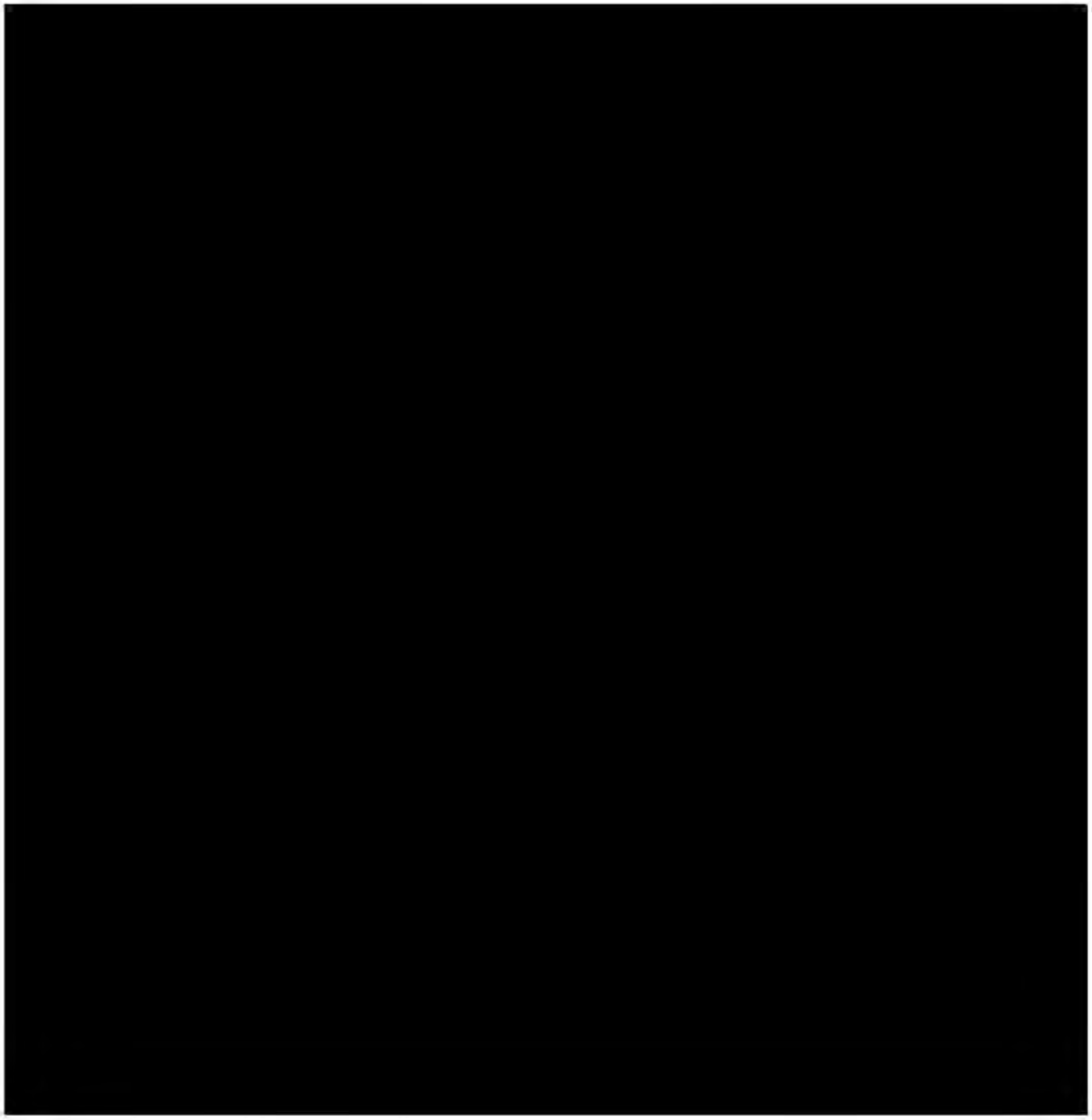

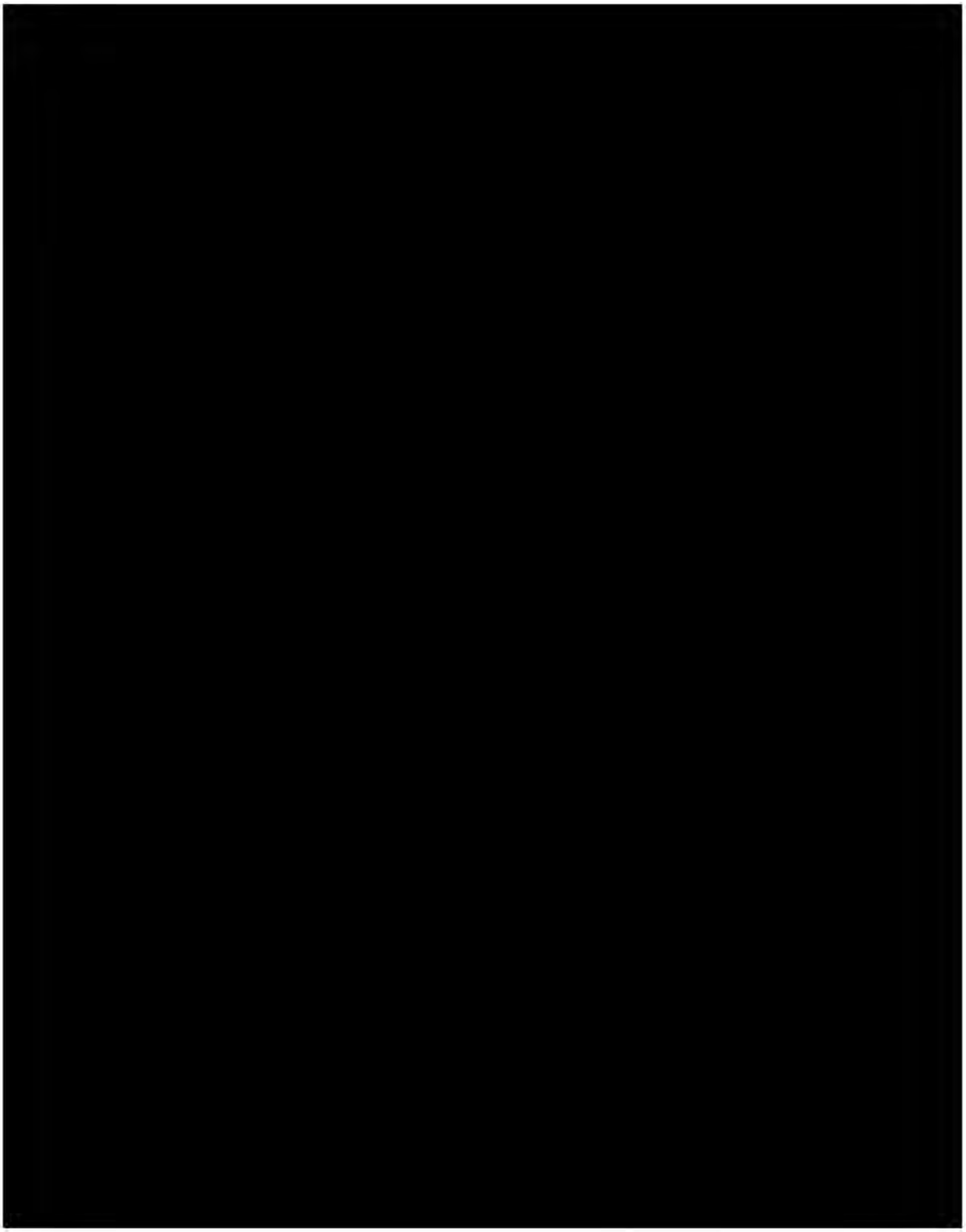

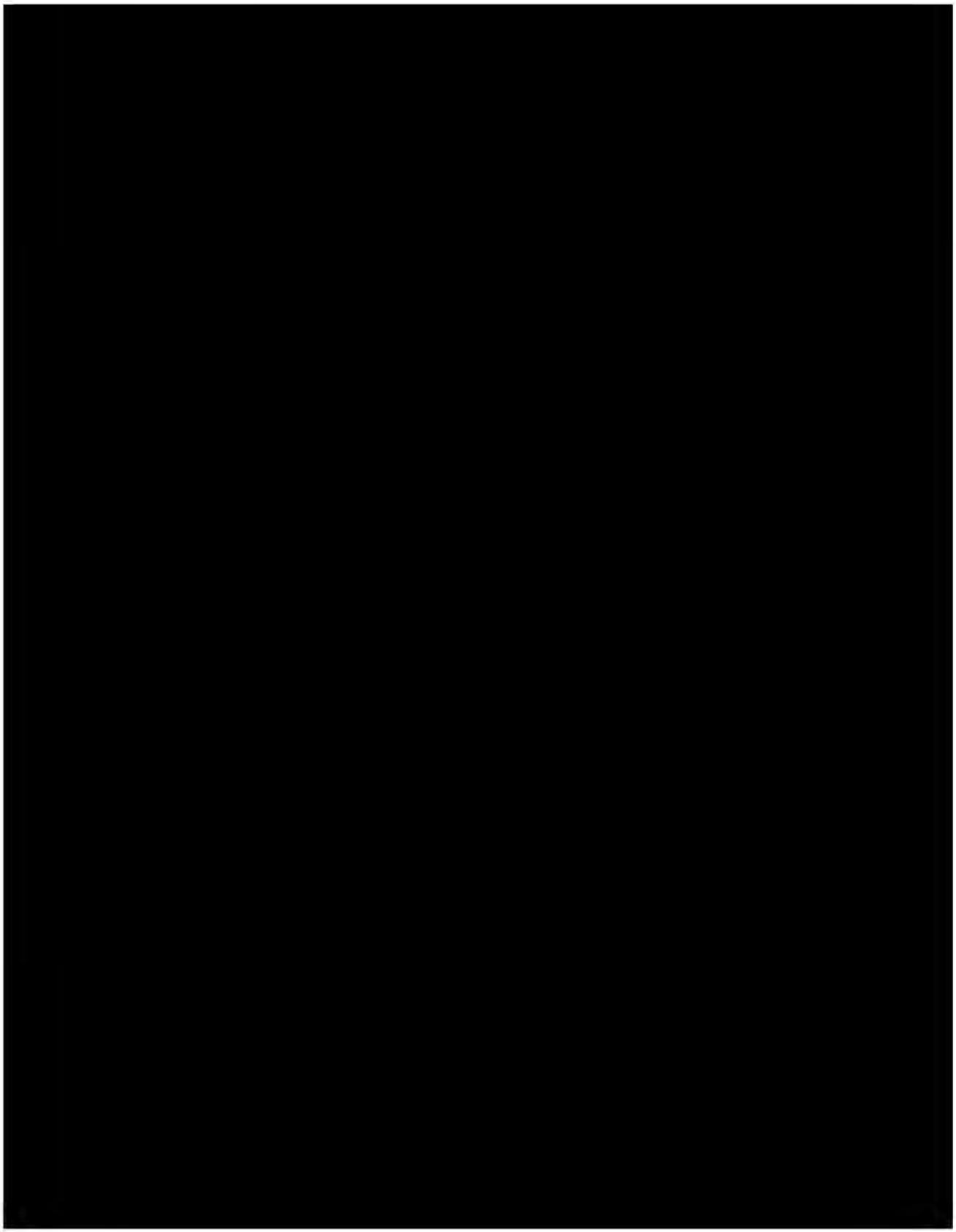

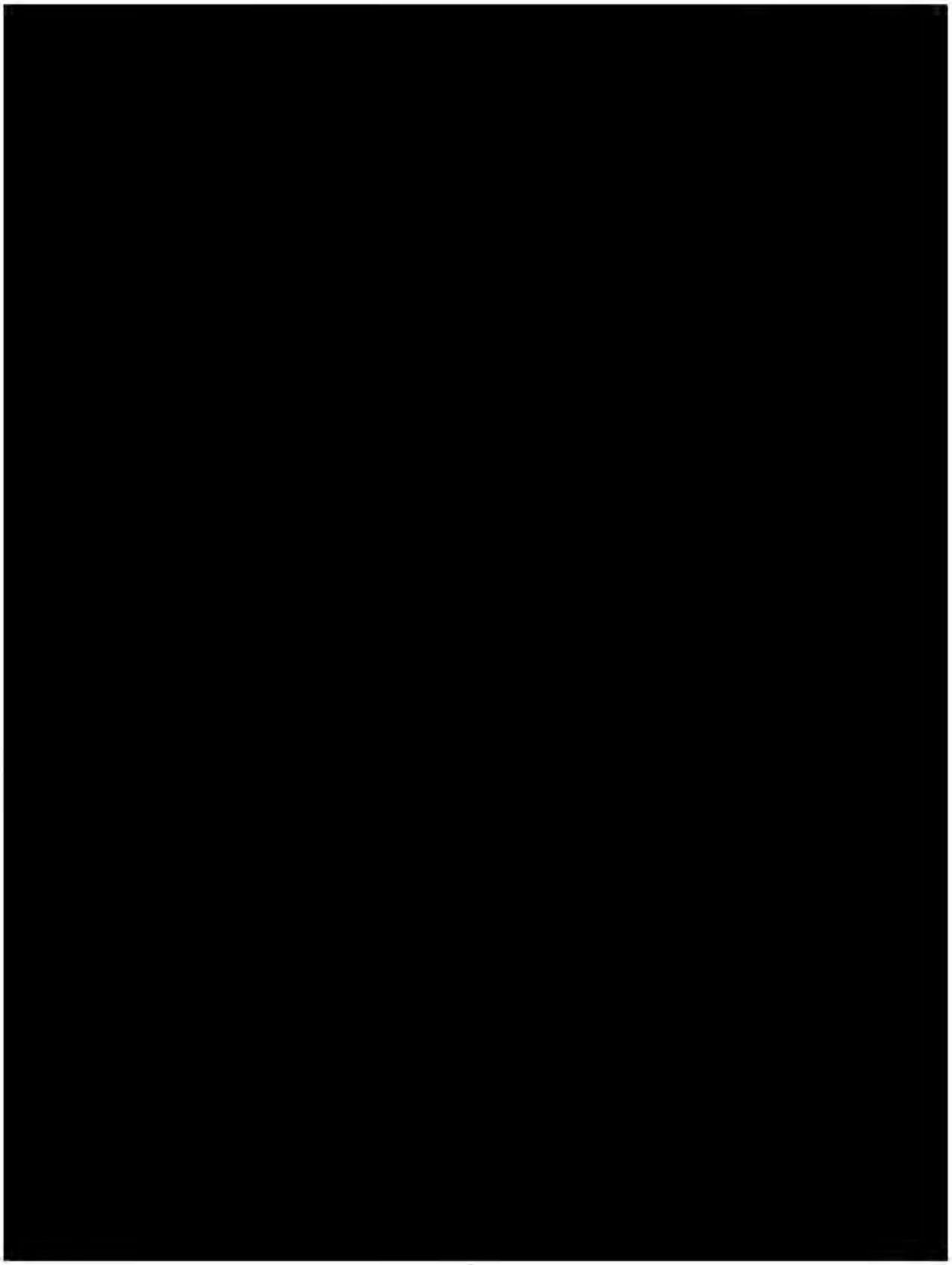

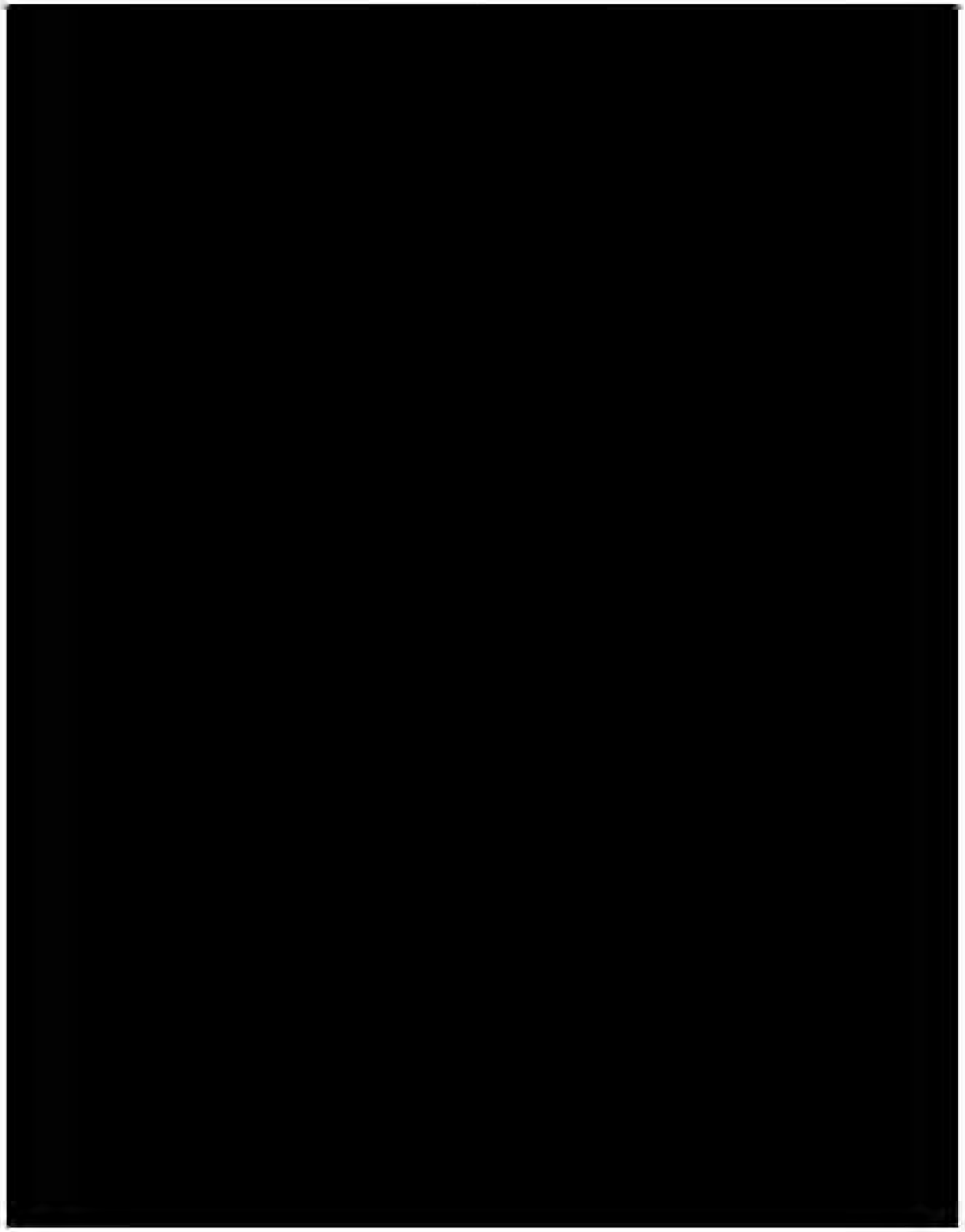

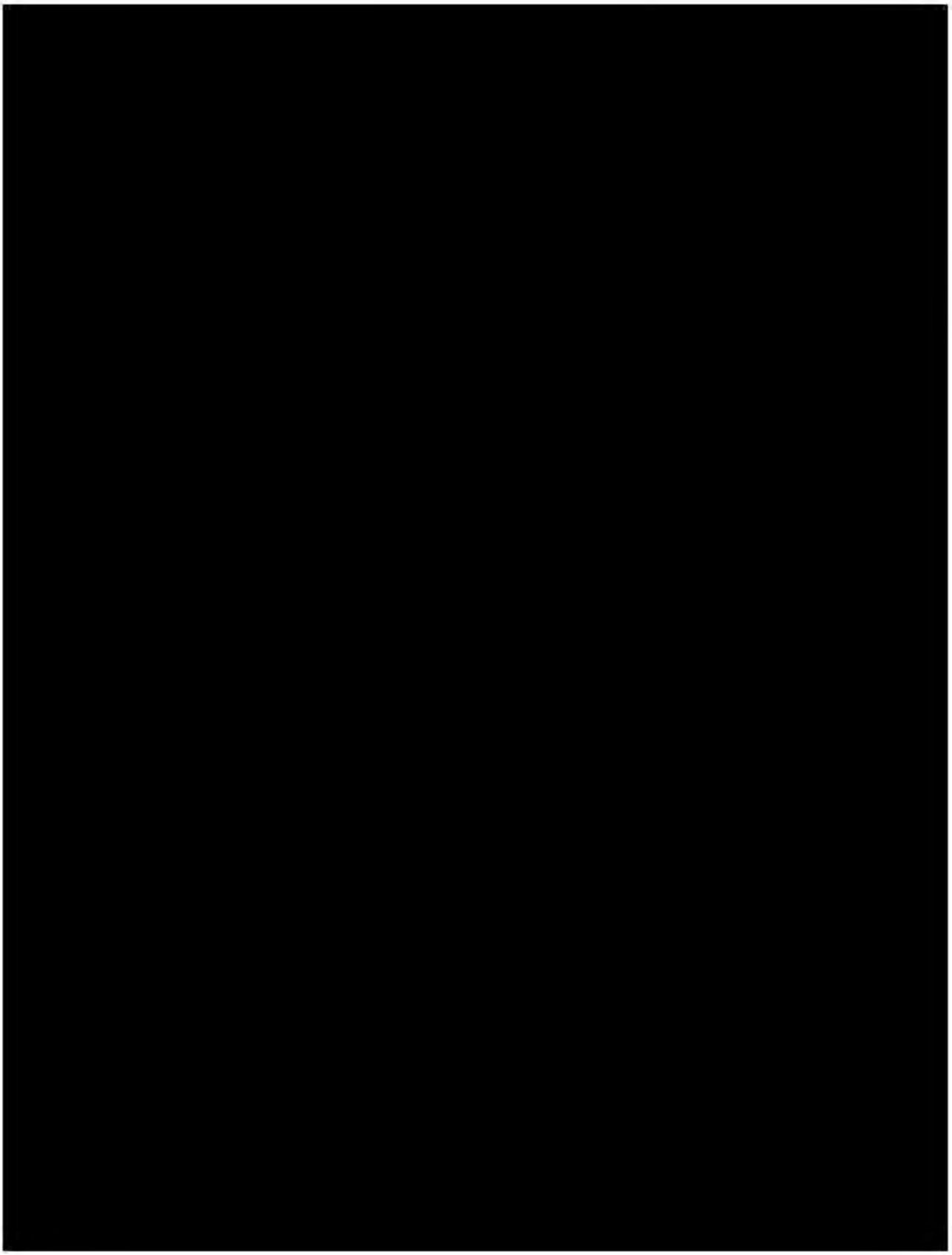

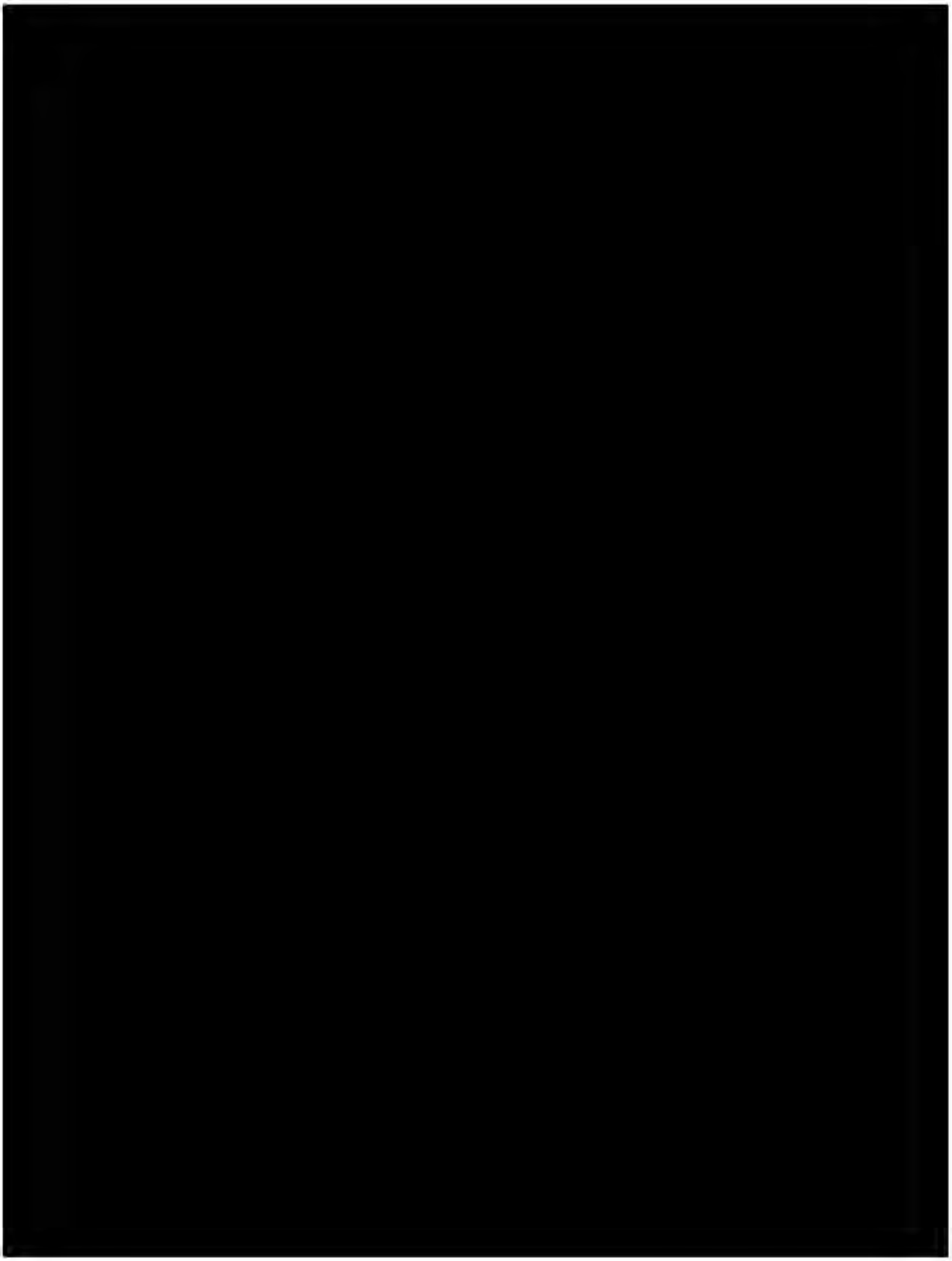

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1.4.3 Regulatory action taken

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Since 2004, discussions and an ongoing research program have been implemented to investigate the potential risk of bladder cancer including the ongoing KPNC study [redacted]

In March 2011, an Article 20 procedure was initiated by the European Medicines Agency (EMA), in the context of results from the KPNC study suggesting a weak association of bladder

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cancer for patients on long-term (>2 years) treatment with pioglitazone and recently increased spontaneous reporting

Table 9 Regulatory Action Taken

Issue	Country	Action taken	Date
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Benefit/risk re-evaluation in the context of potential association with Bladder Cancer (Article 20 procedure)	Europe	Ongoing	Ongoing

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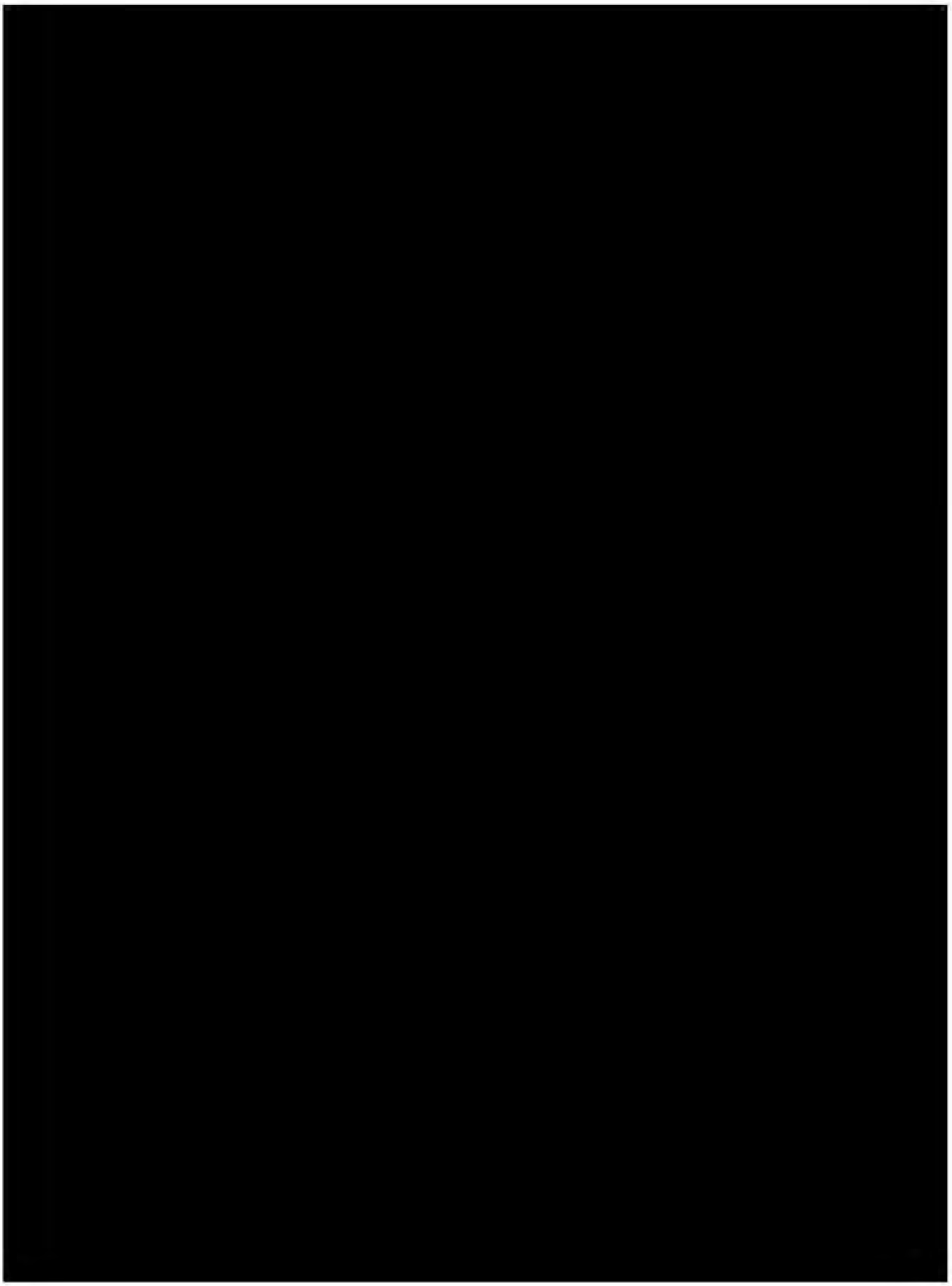

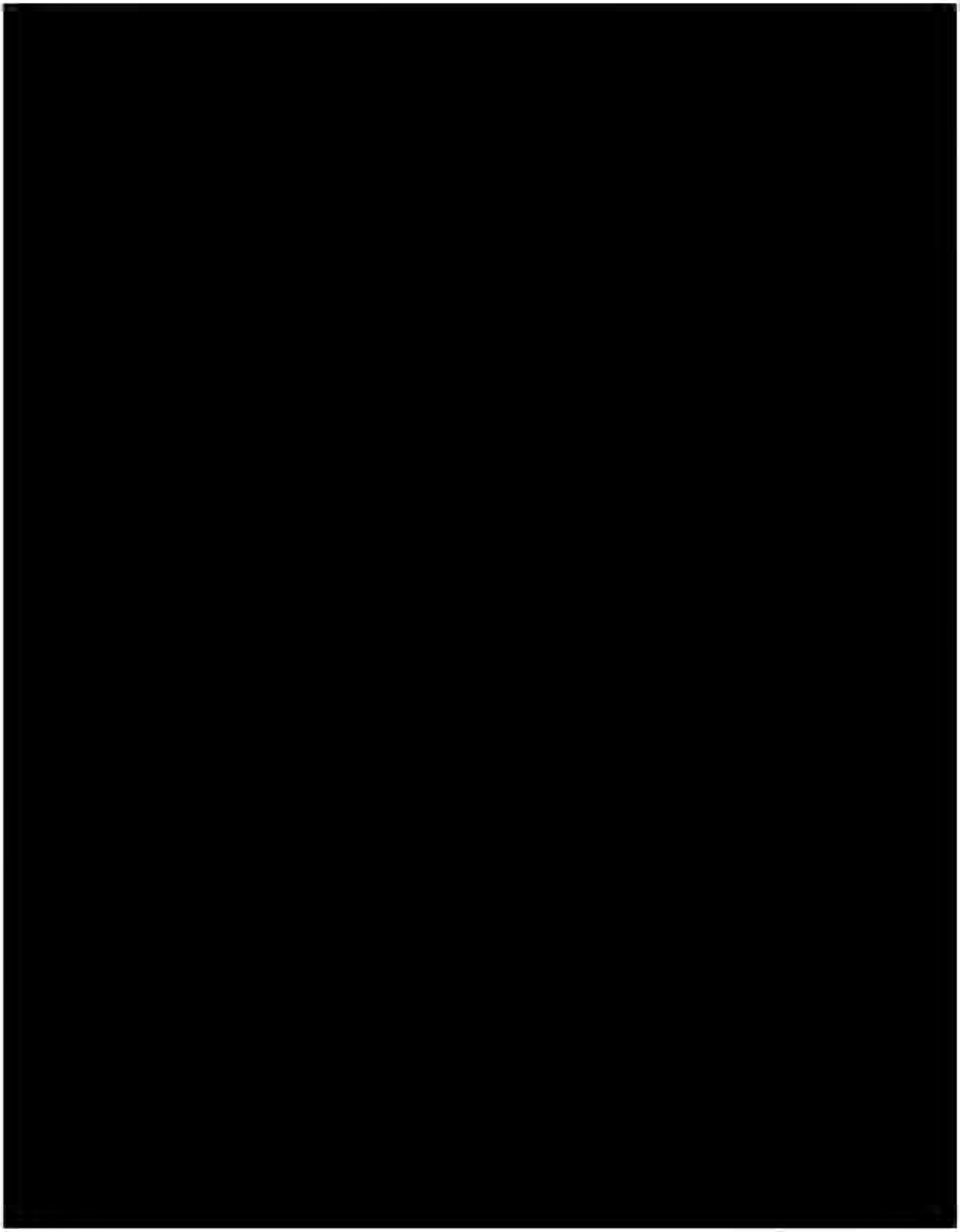

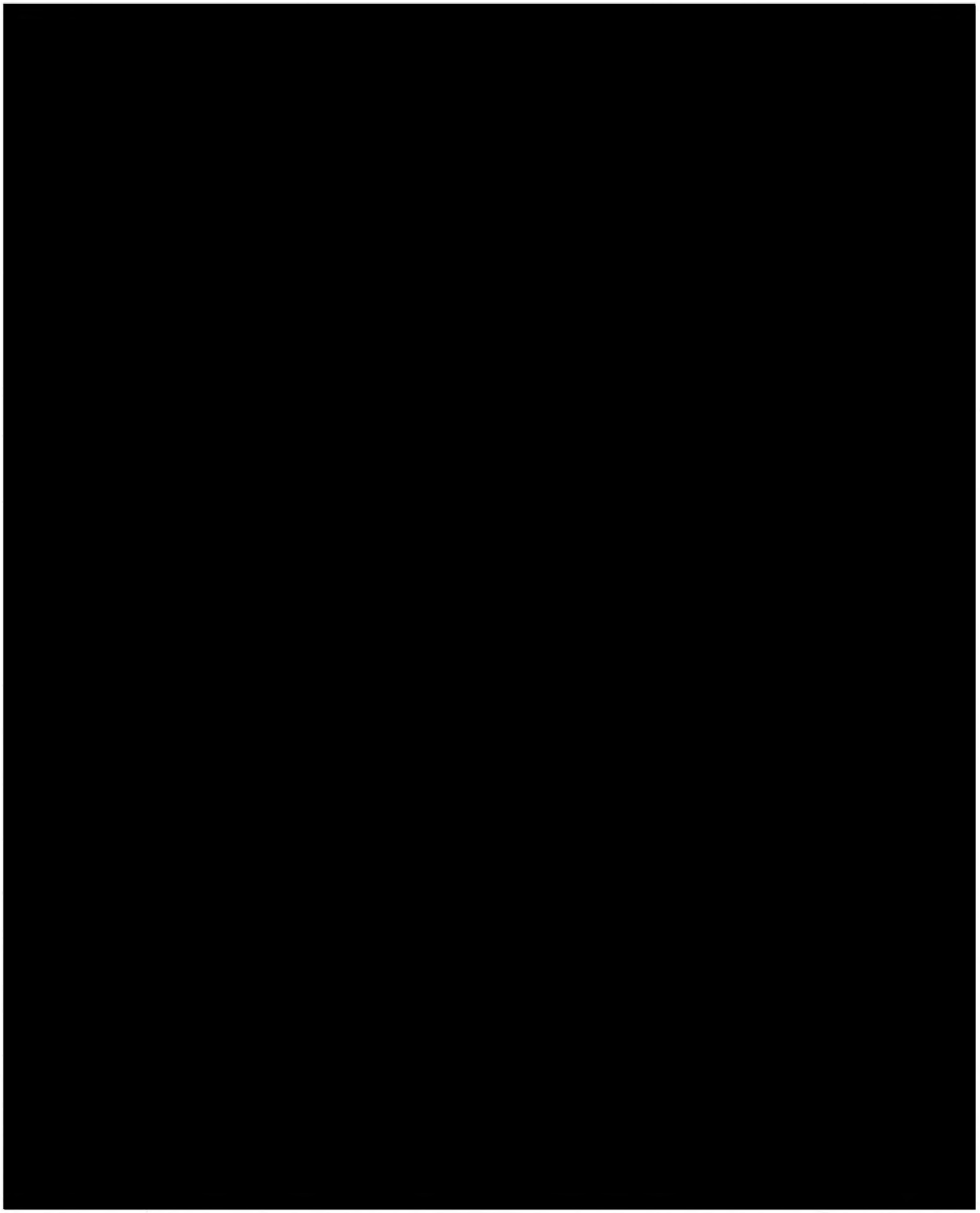

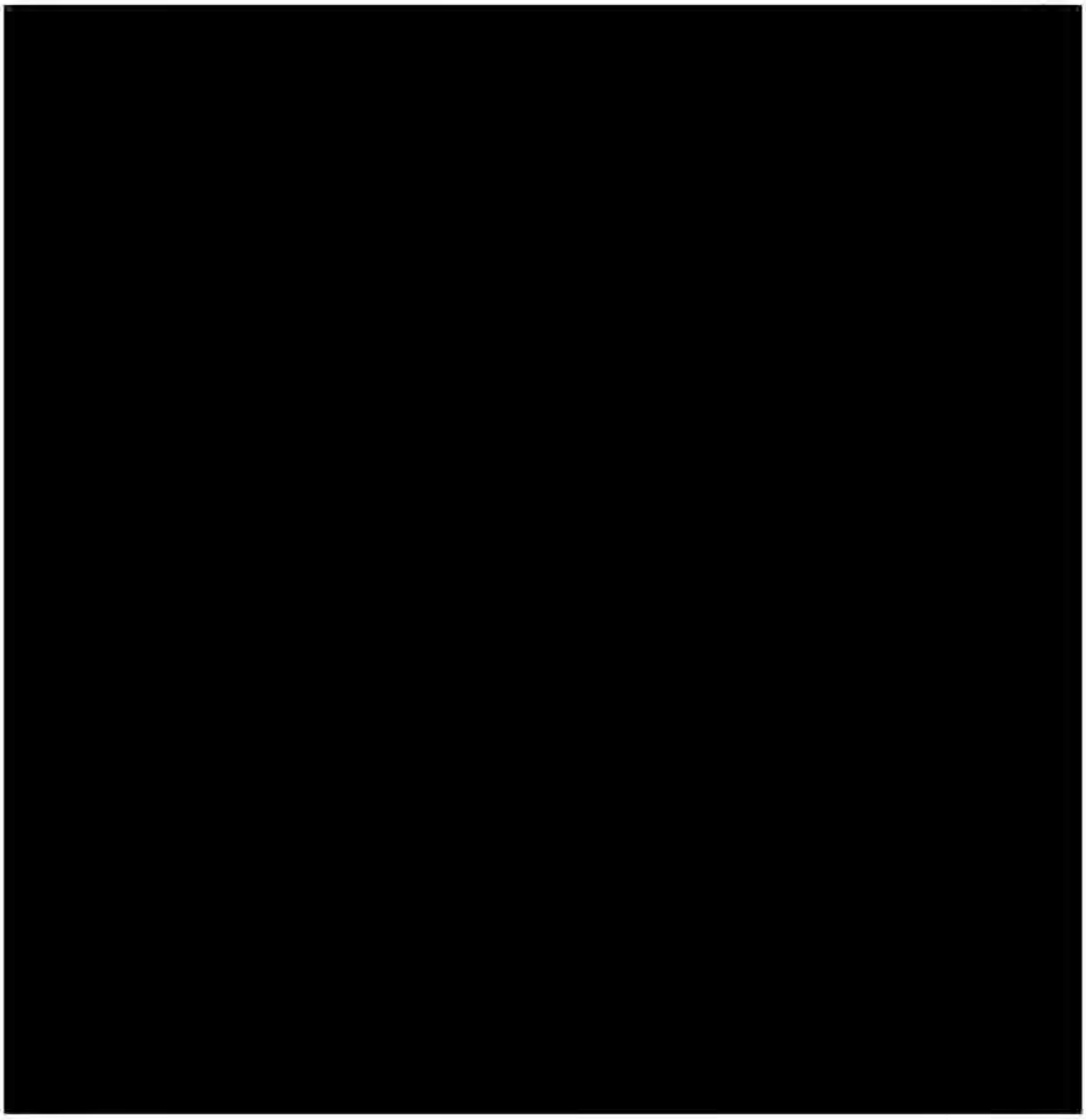

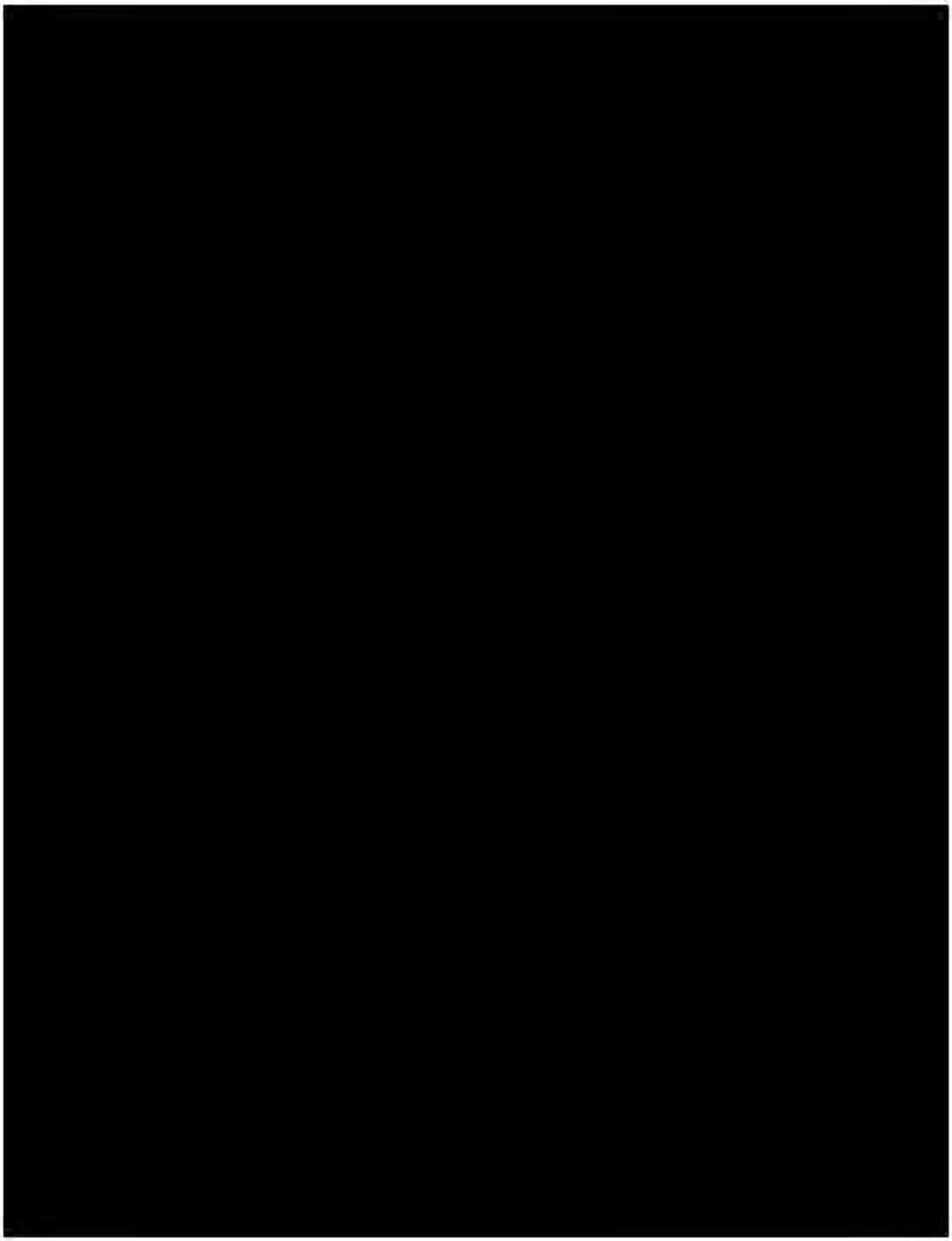

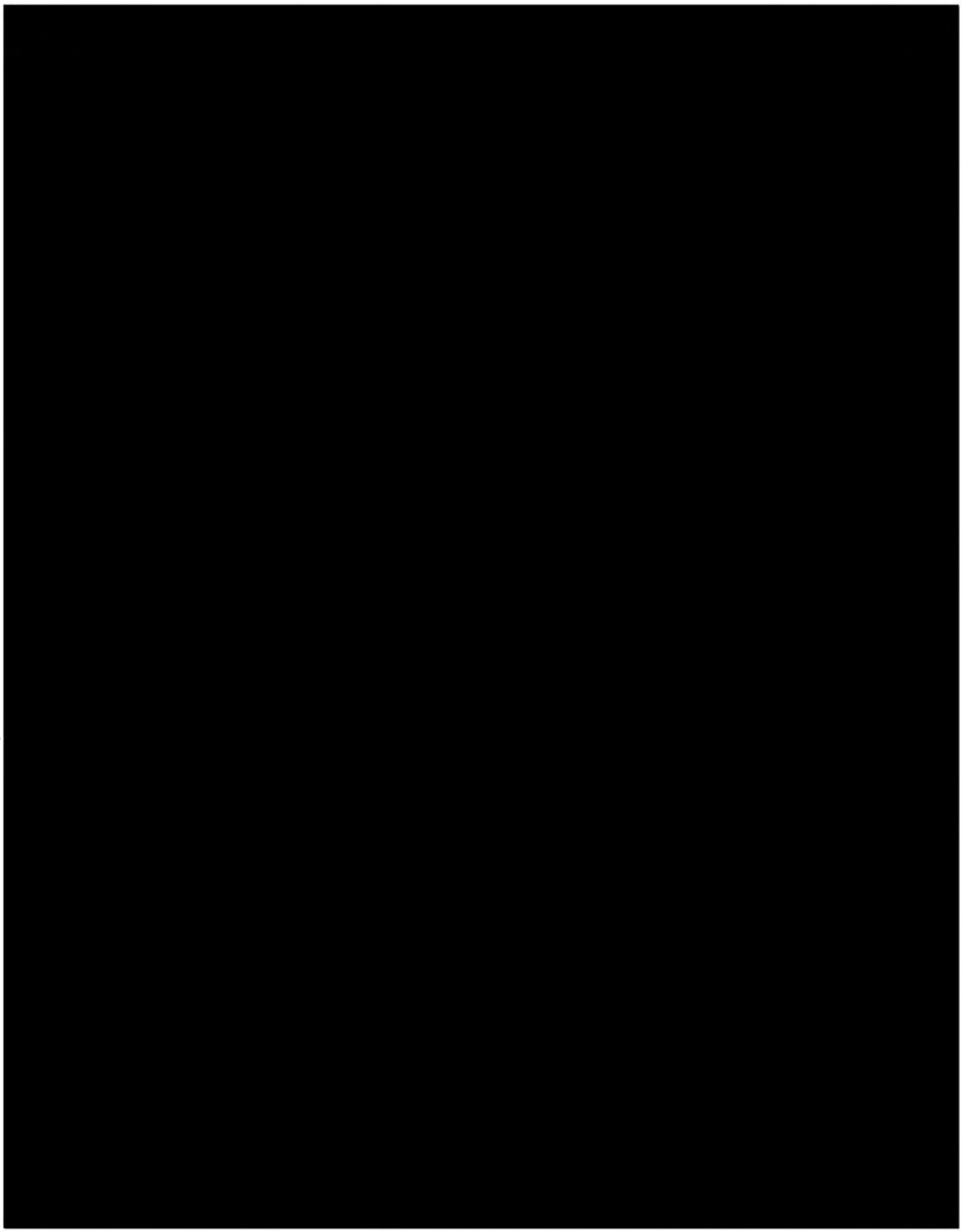

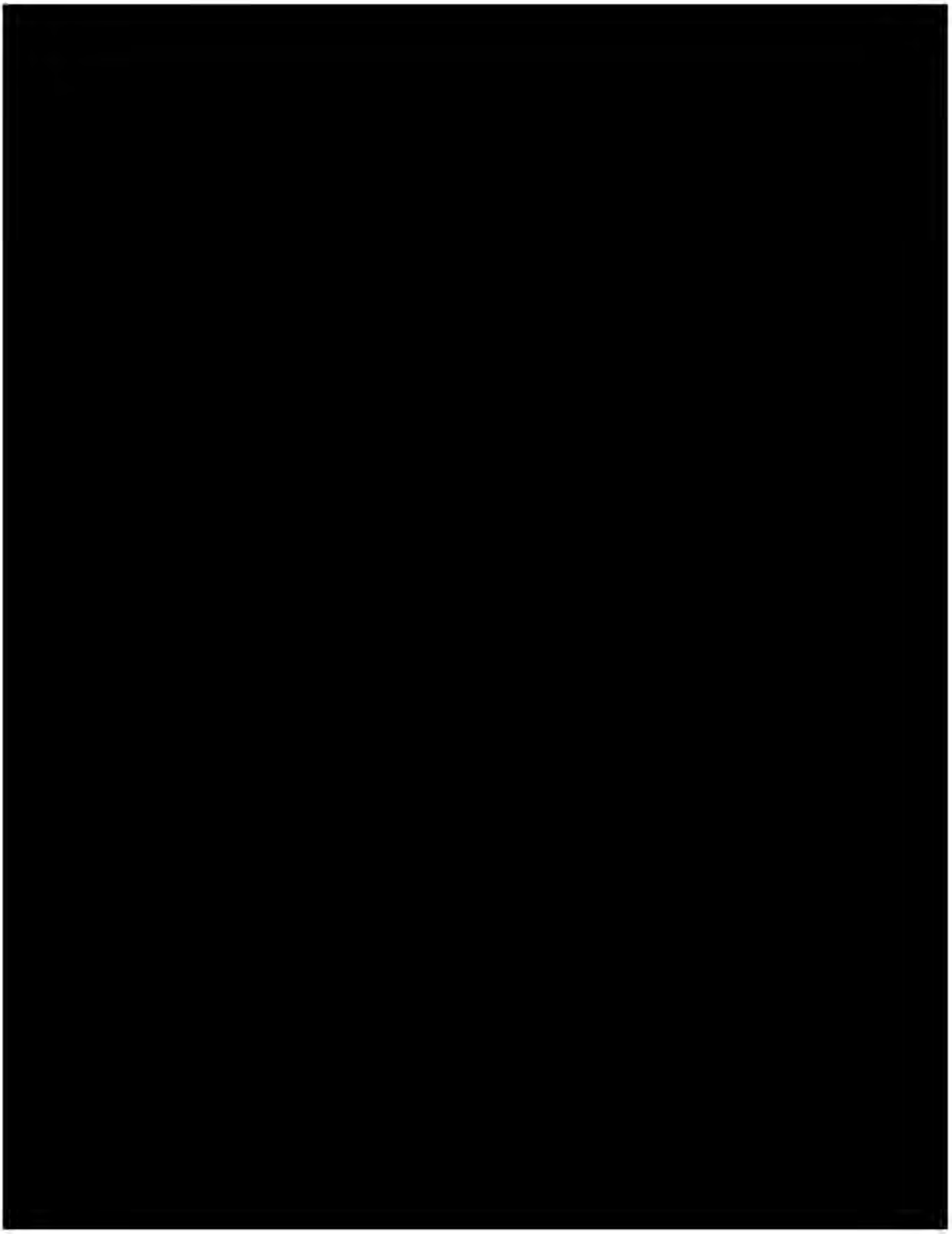

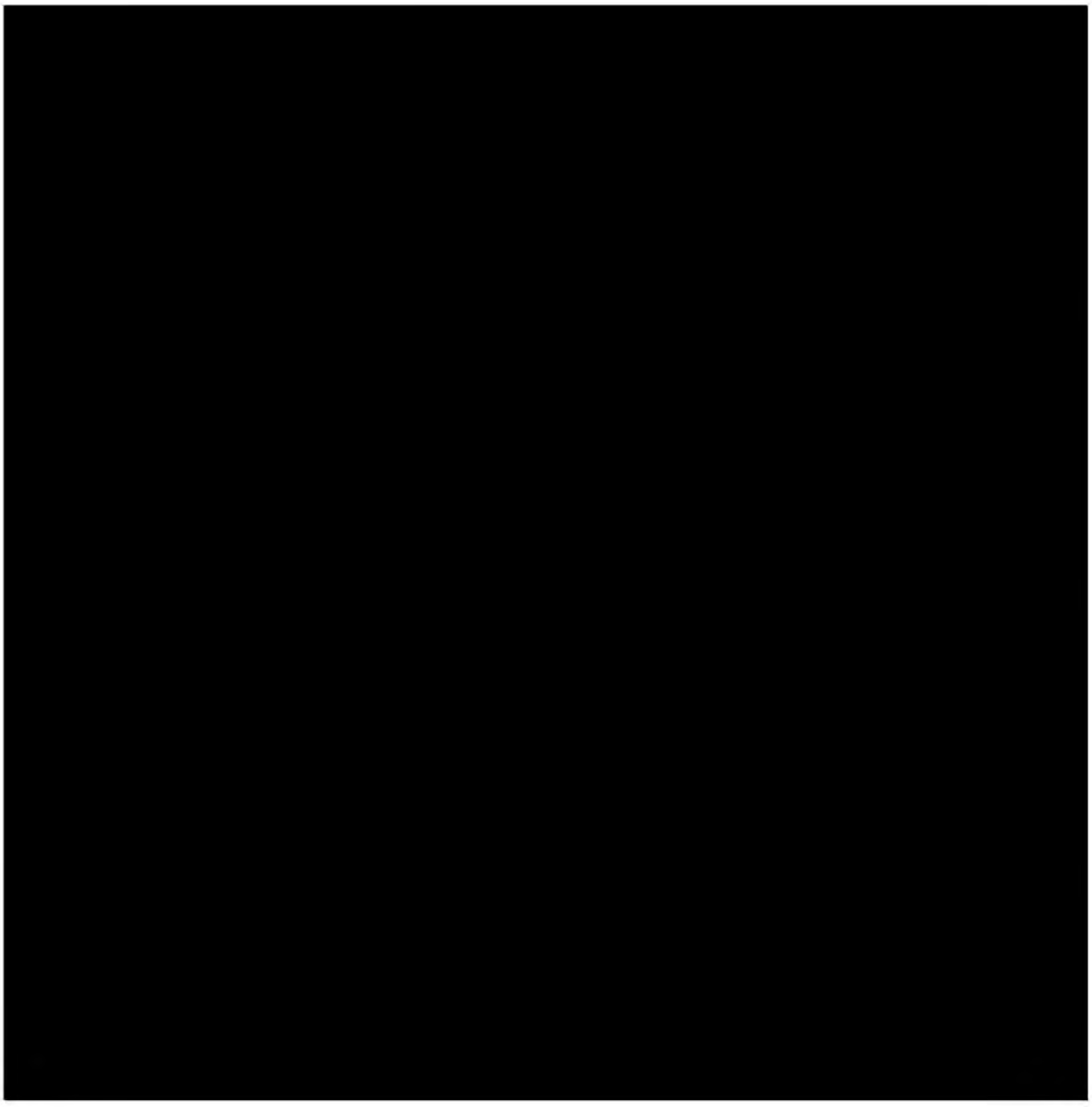

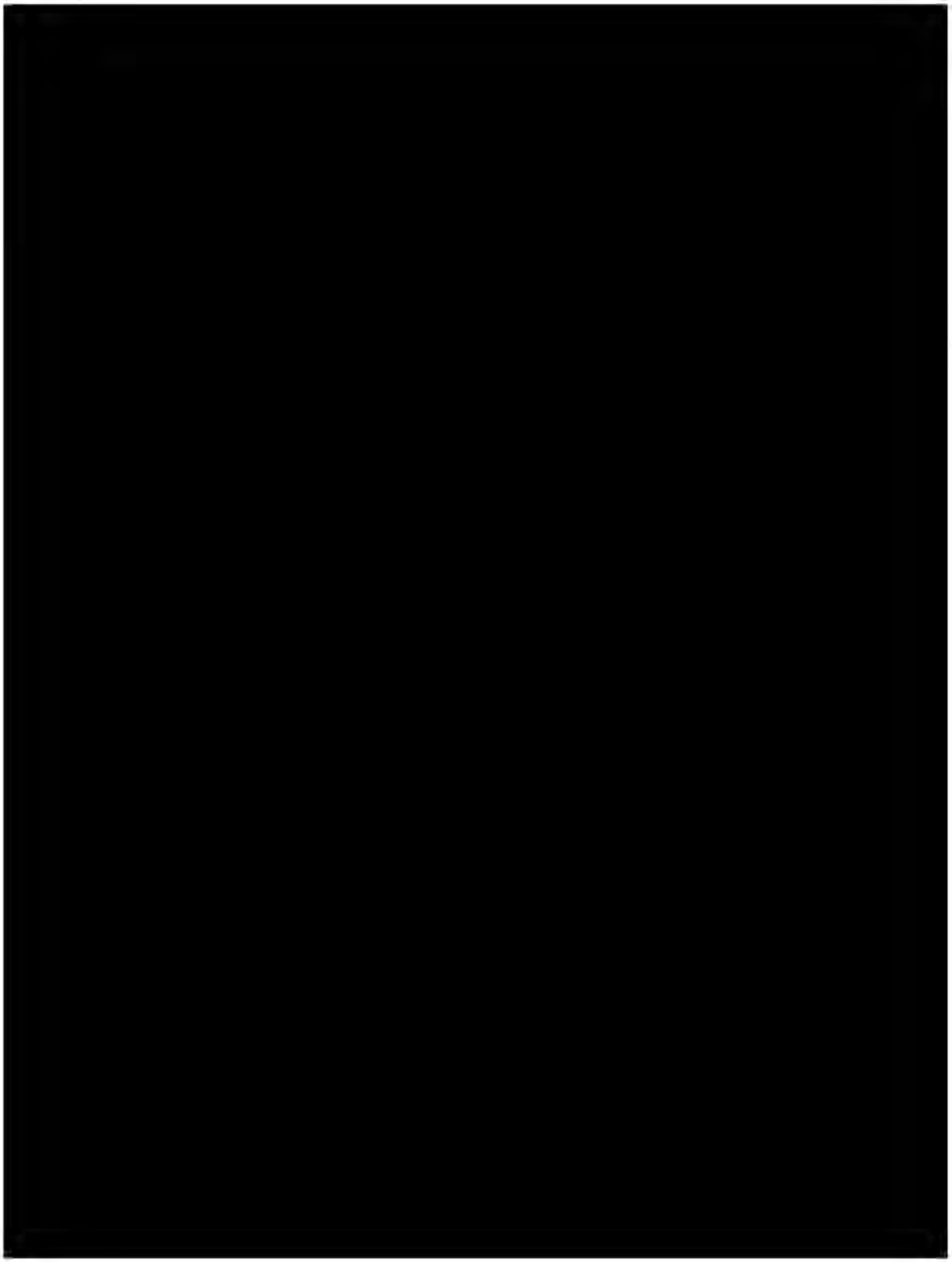

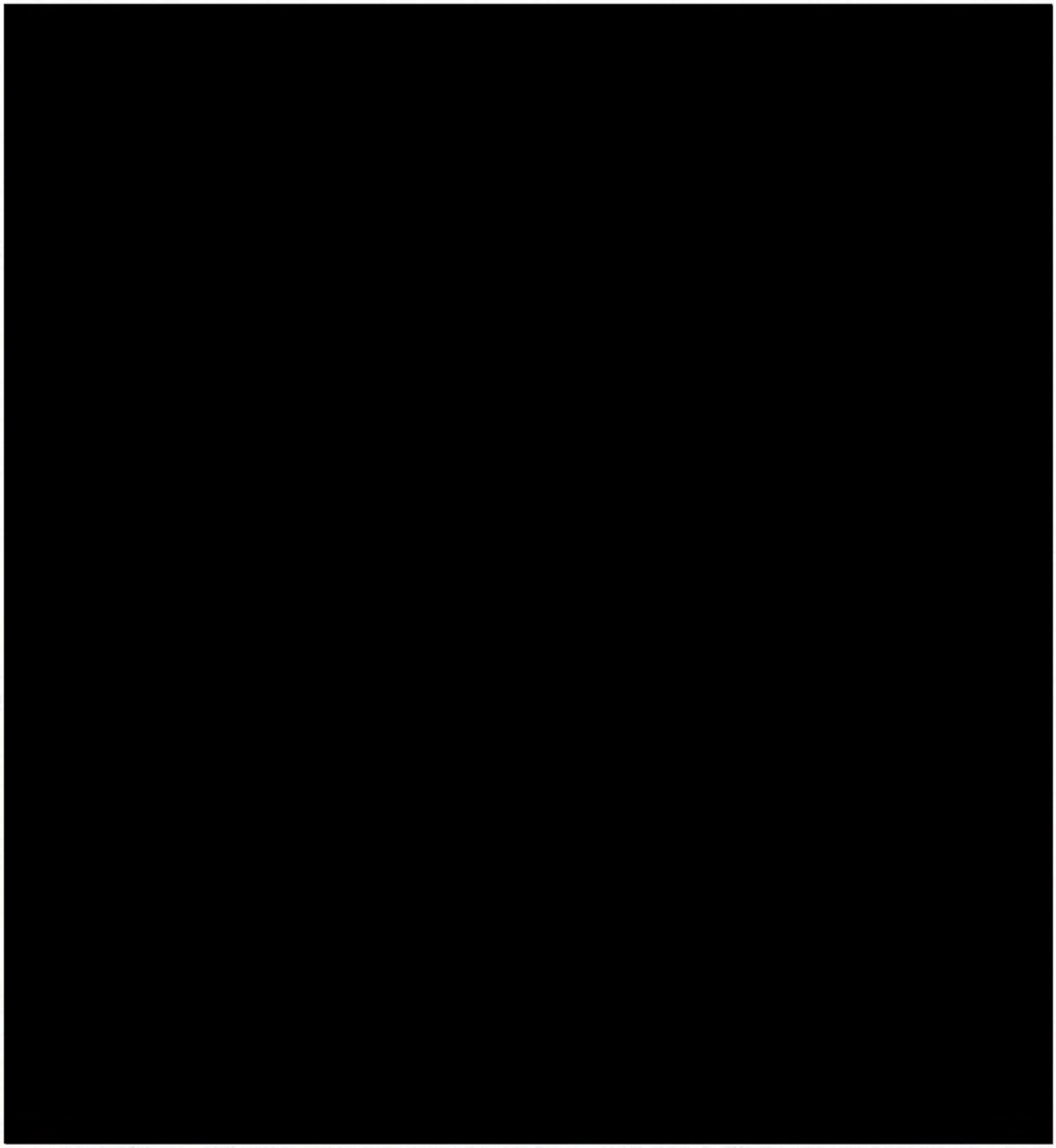

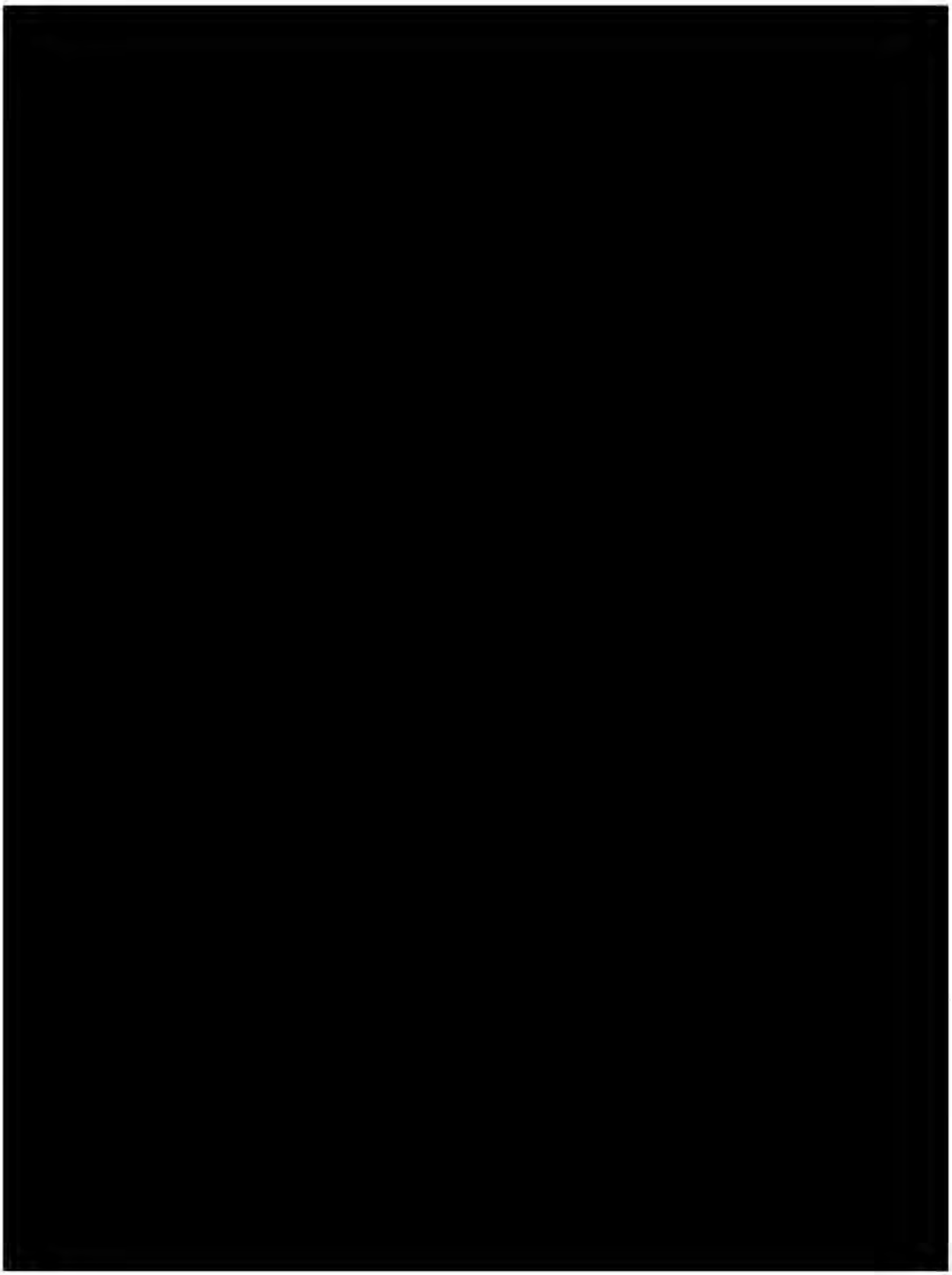

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Potential Risk	Bladder Cancer
Seriousness/outcomes	In the long-term macrovascular outcome study PROactive, the reporting of malignancies was similar in pioglitazone- and placebo-treated subjects (3.7% and 3.8%). In this elderly population (mean age of nearly 62 years) there were 2 deaths in patients who had a reported adverse drug reaction of bladder cancer. One of these was a cardiovascular death.
Severity and nature of risk	Diabetic patients appear to be at higher risk for bladder cancer, but the disease has a good prognosis if it is identified early
Frequency (Clinical Manifestations)	Clinical trial data: Data presented here are from the largest pioglitazone controlled clinical trial PROactive. Bladder cancer as being of particular interest was reviewed in detail by the data safety monitoring board of PROactive with the assistance of 2 external experts, who reviewed the data in a blind manner. After discounting for early onset (cancers occurring during the first year in the study) as biologically implausible to be related to treatment with pioglitazone and taking into account other risk factors, the remaining cases of 2 in the pioglitazone and 1 in the placebo group did not give raise for concern. During the 4-year observational follow-up study (EC445), in which over 73% of all subjects with a final visit in PROactive enrolled (pioglitazone: 1818; placebo: 1776), reports of additional malignancies were collected. At the end of the 4-year follow up period, 12/1779 (0.7%) of placebo-treated subjects and 8/1820 (0.4%) of subjects treated with pioglitazone reported new malignancies. No imbalance in the incidence of bladder malignancy between the original pioglitazone treatment group and placebo treated subjects was observed in the 4-year follow up period of the PROactive study.

Table 12 Bladder Cancers in the PROactive Study

Number (%) of Subjects		
Event	**Pioglitazone (N=2605)**	**Placebo (N=2633)**
Subjects with any malignant bladder neoplasm	**97 (3.7)**	**99 (3.8)**
Bladder (a,b)	14 (0.5)	5 (0.2)

Source: EC444 Clinical Study Report.
(a) Bladder malignacy in the 4 year observational period: pioglitazone 8/1820 (0.4%) vs placebo 12/1779 (0.7%). Note that 1case has been removed from the placebo group as the report was for a benign neoplasm
(b) Double-blind period + 4 year observational period (7 years total): pioglitazone 22/2605 (0.8%) vs placebo 18/2633 (0.7%).

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Potential Risk	Bladder Cancer
	Epidemiologic studies: As part of postmarketing pharmacovigilance commitments, the MAH is currently undertaking a number of large-scale epidemiologic studies (see Section 2.2 and Section 2.3). The prospective KPNC cohort study to investigate association of pioglitazone exposure to bladder cancer has reported 3 scheduled interim analyses in August 2005, 2007, and 2009. In these reports, patients receiving pioglitazone were not at an increased risk for the development of bladder cancer (2005: fully adjusted hazard ratio [HR] 1.2, 95% confidence interval [CI]: 0.8-1.9; 2007: fully adjusted HR 1.2, 95% CI: 0.8-1.7; 2009: fully adjusted HR 1.2, 95% CI: 0.8-1.7). However, there was weak association observed for patients treated for more than 2 years (HR 1.4, 95% CI: 1.03- 2.0). A nested case-control study in the cohort reported the first interim results in 2006 and showed that patients with bladder cancer were not more likely to have been exposed to pioglitazone than their matching controlled [redacted]
Background incidence/prevalence	Epidemiological research has shown that individuals with diabetes have an increased risk of several types of cancer, including cancers of the pancreas [28], breast [29], bladder [30-32], endometrium [33], liver [34], colon [35], and rectum [35].

[redacted]

[redacted]

Potential Risk	Bladder Cancer
[redacted]	
Regulatory action taken	SPC language. No regulatory action, but a number of CHMP commitment studies are ongoing (see Sections 2.2 and 2.3). Cumulative and periodical review and reports of malignancies are provided in the semi-annual PSURs.

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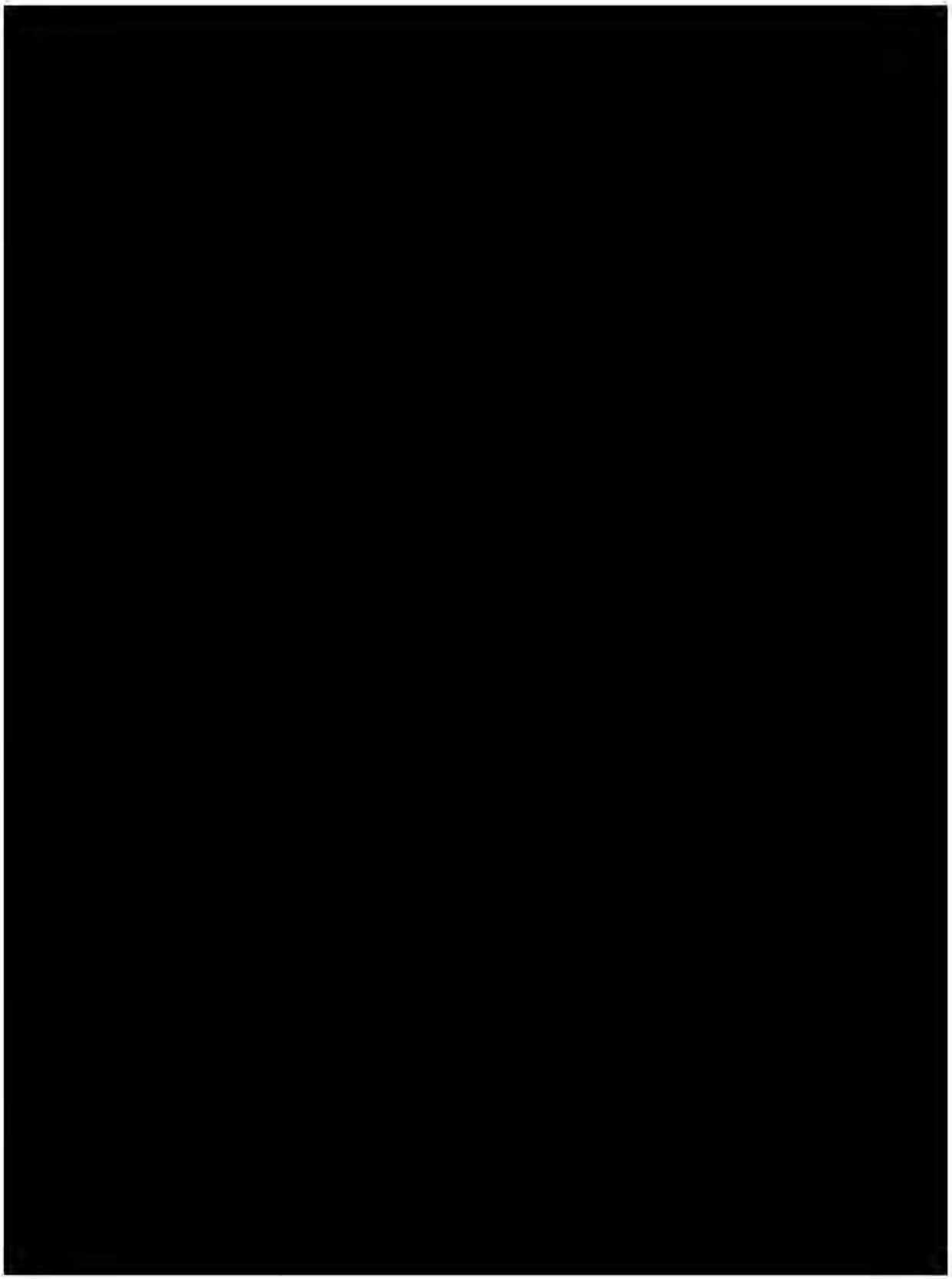

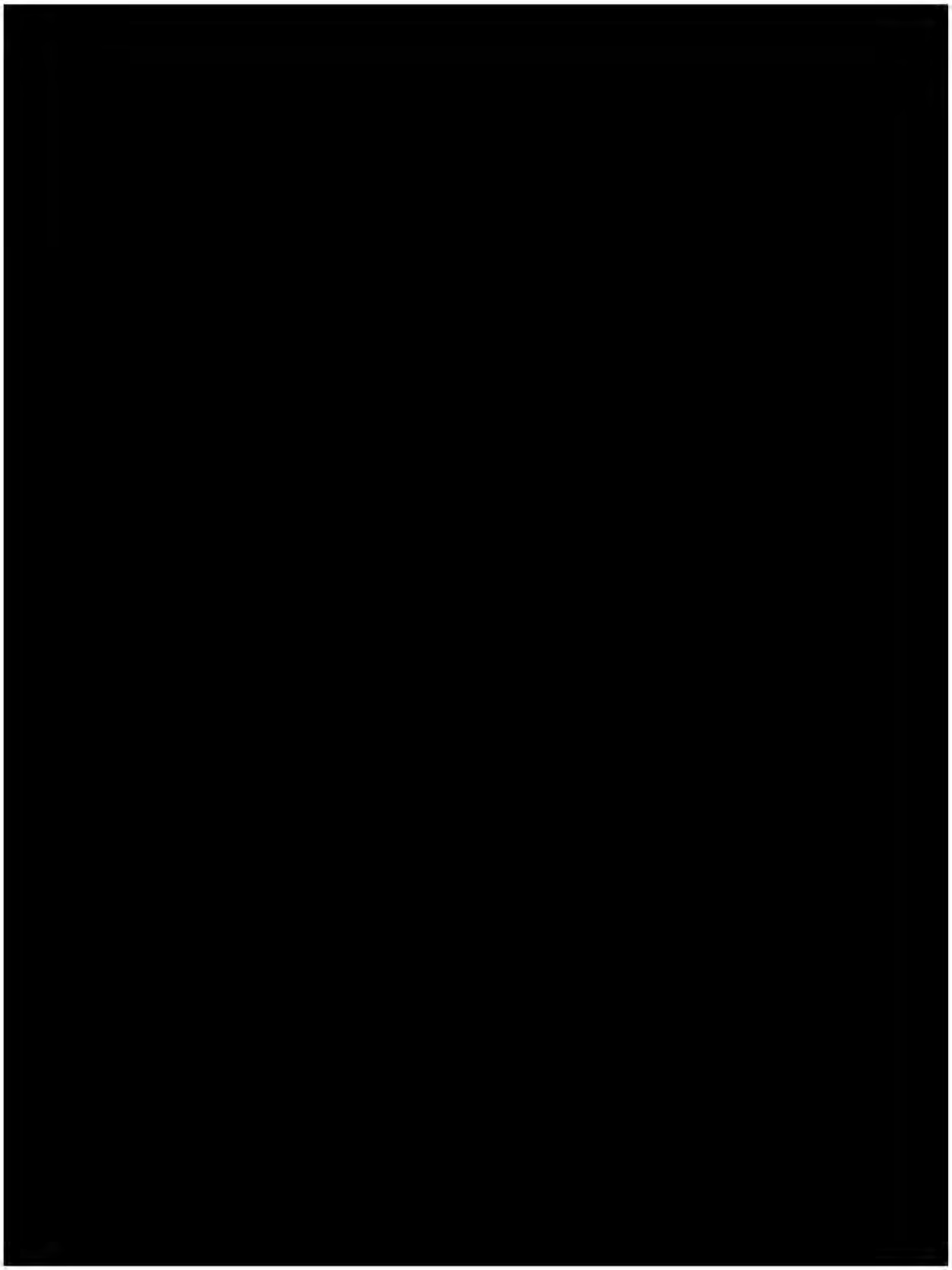

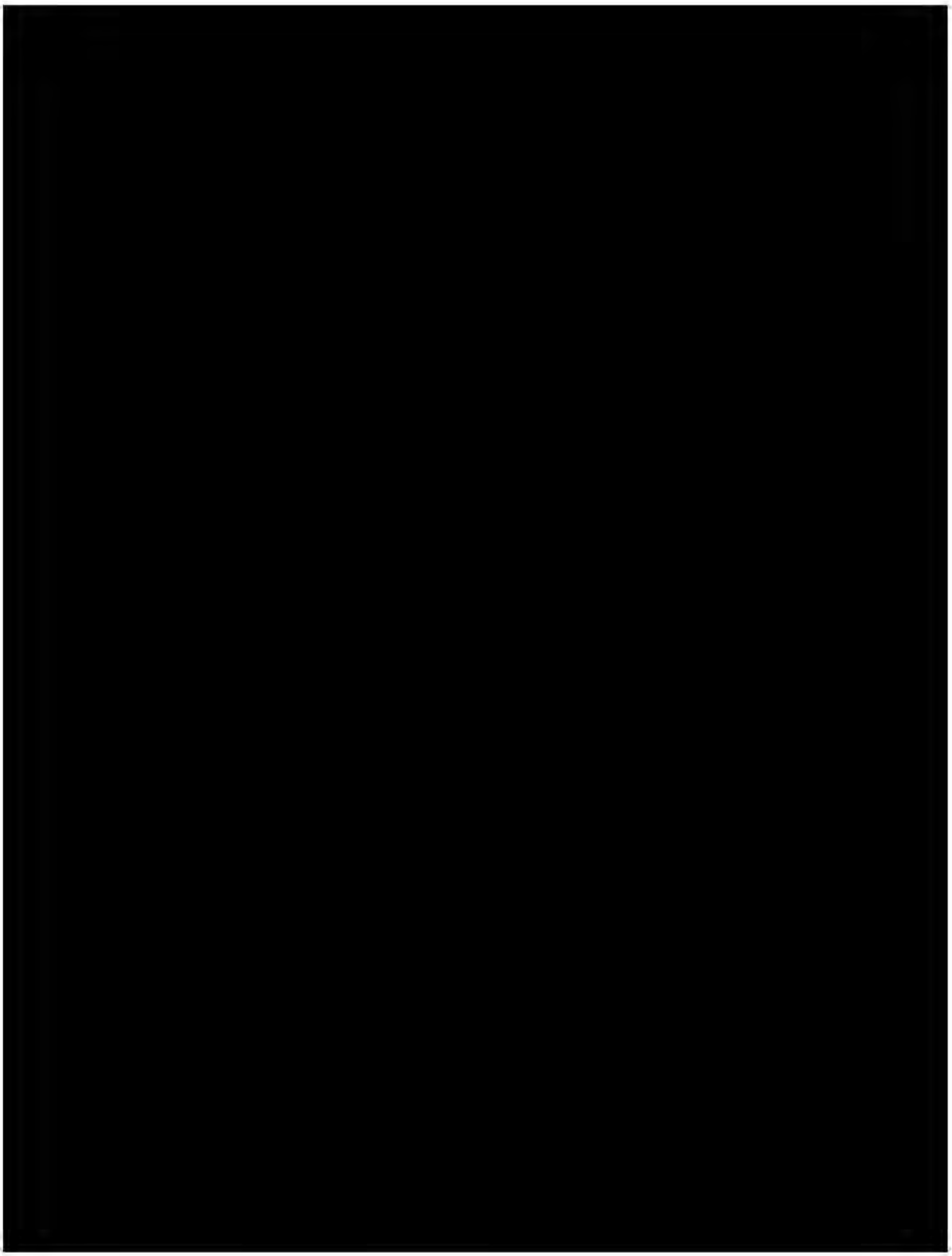

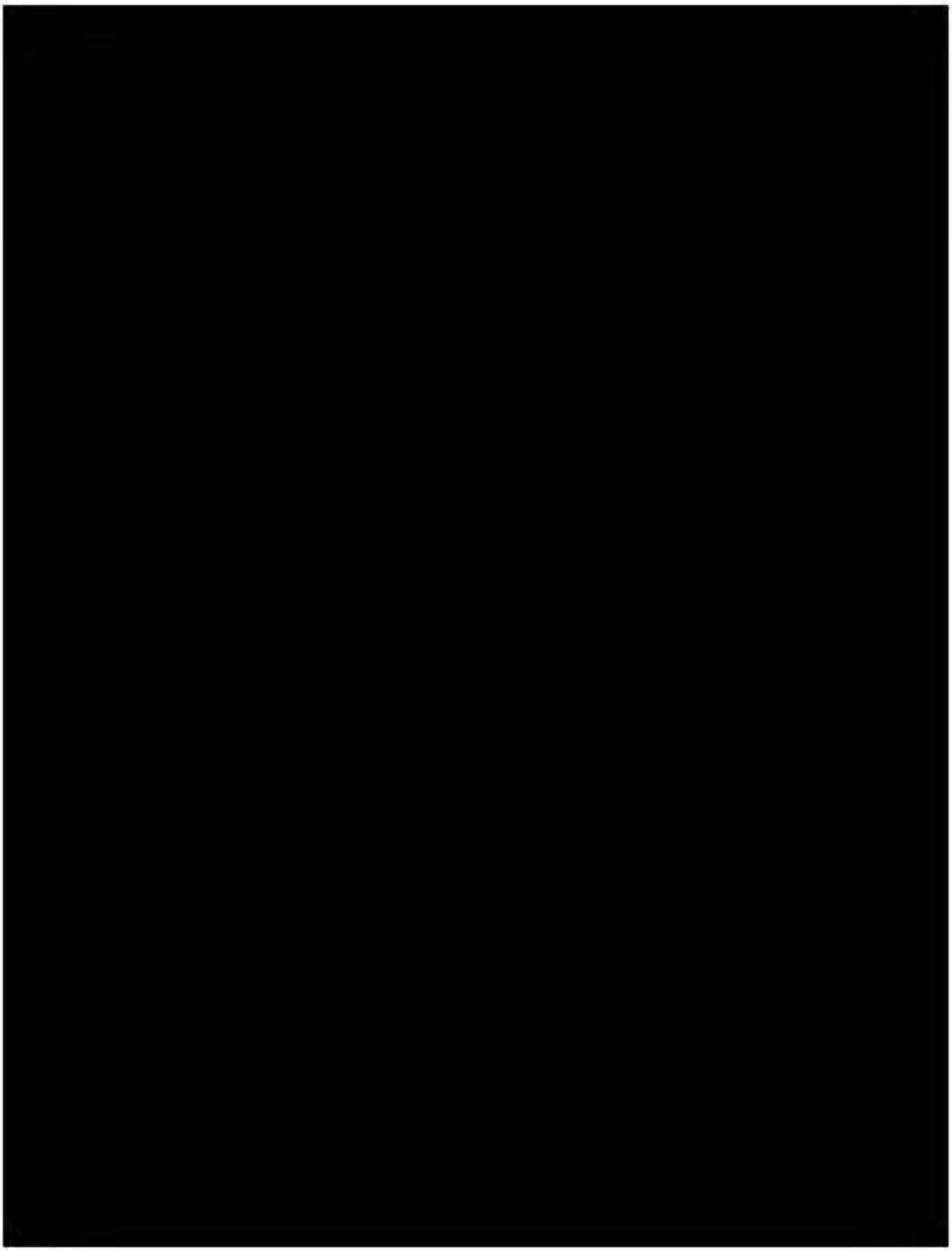

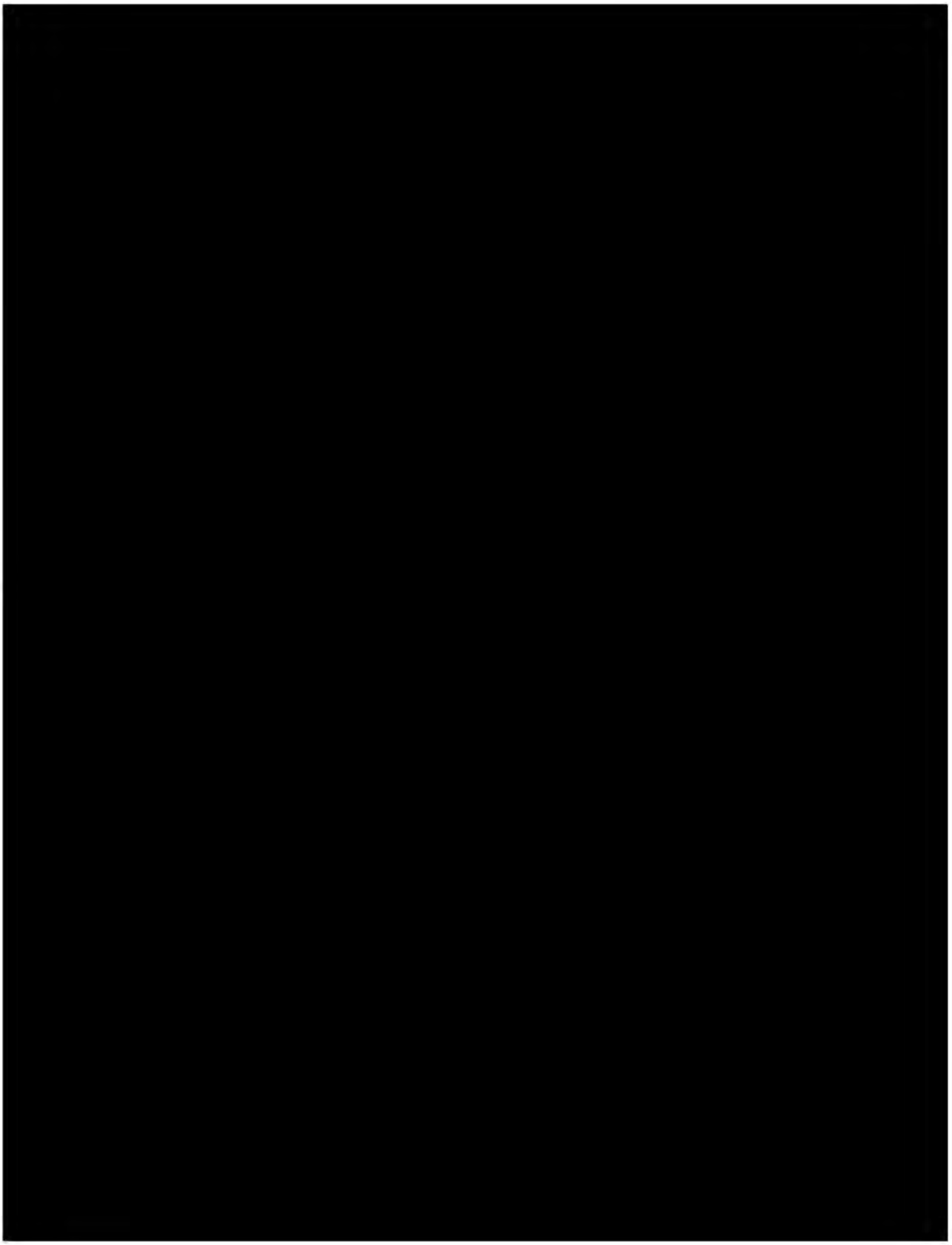

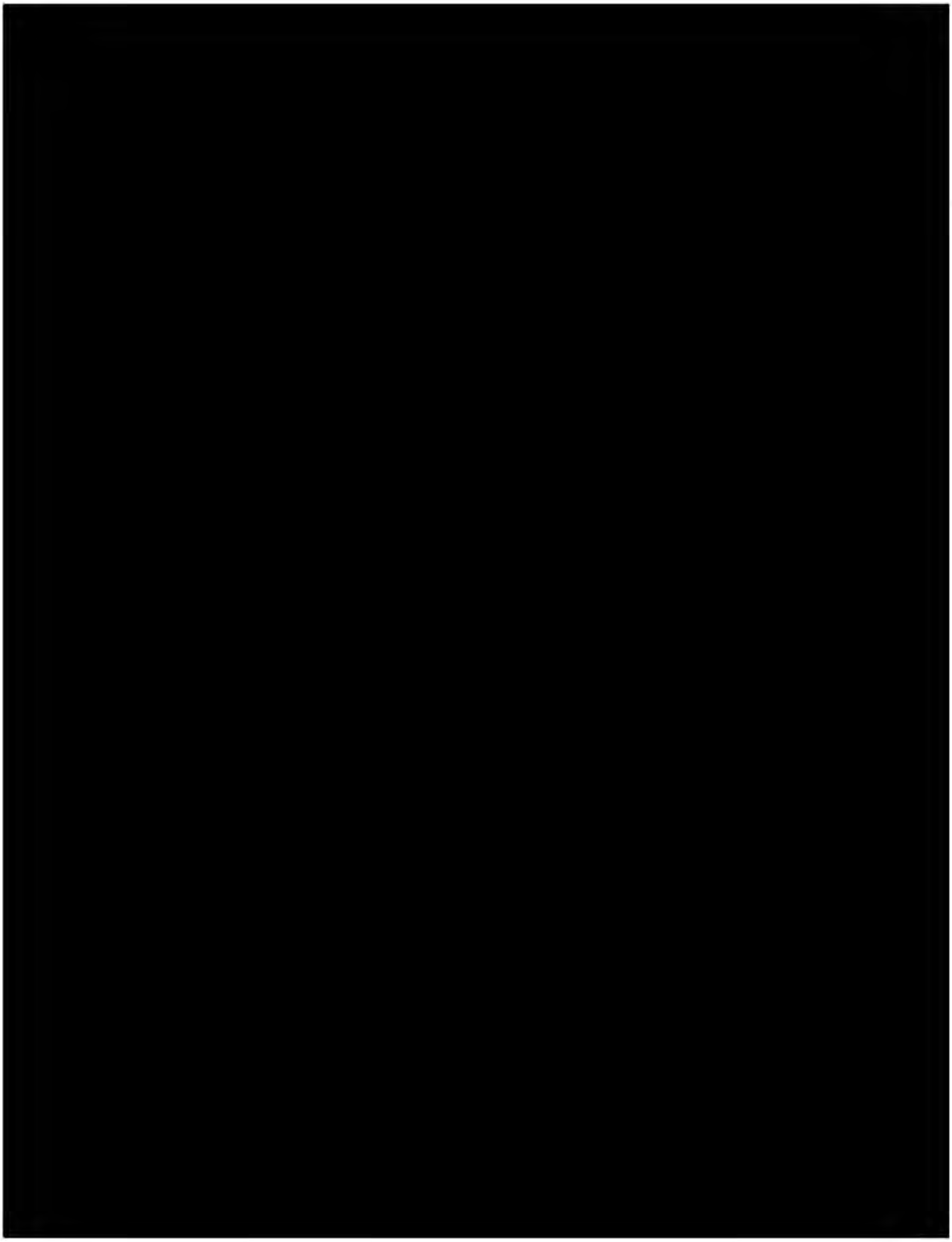

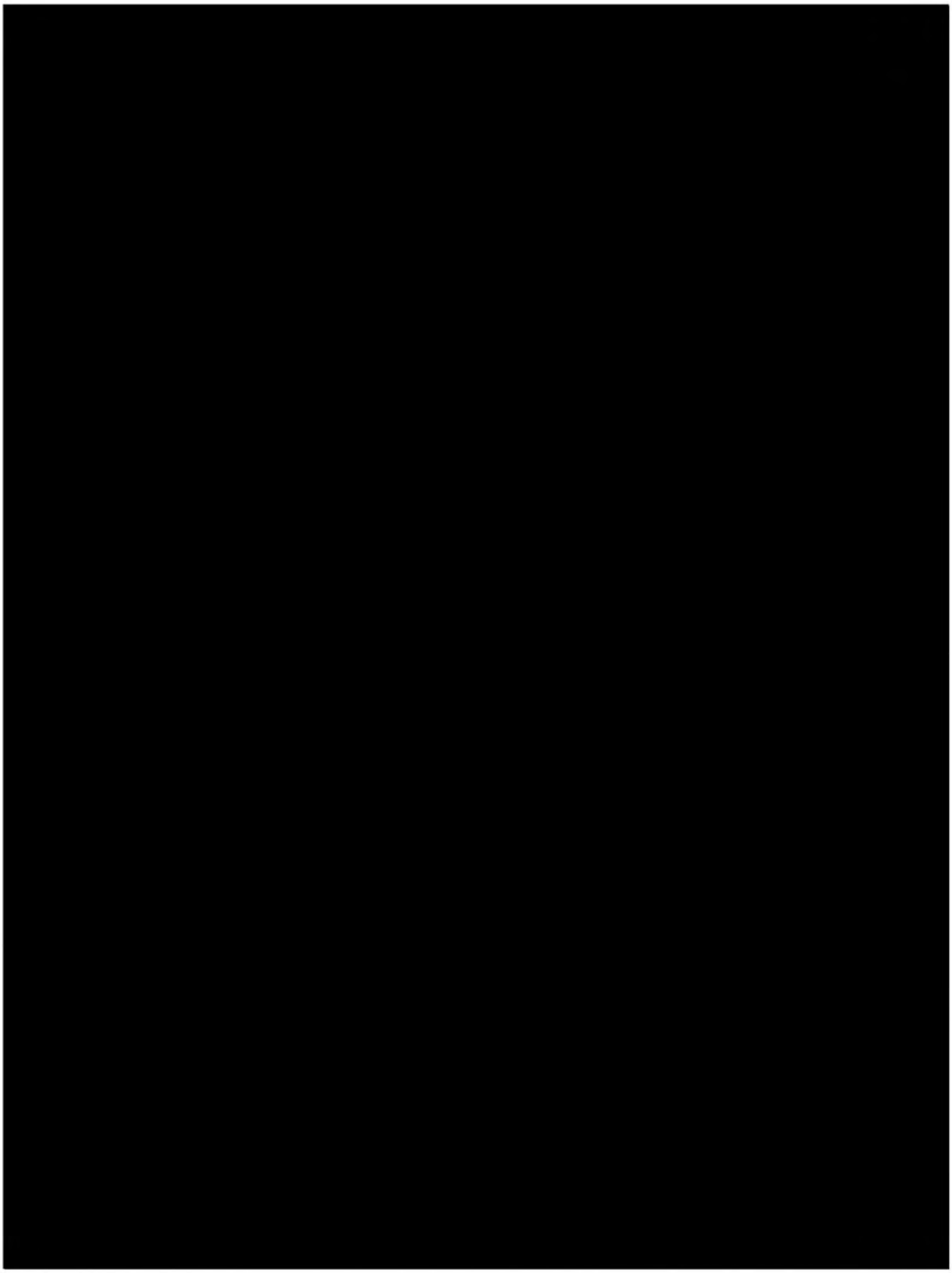

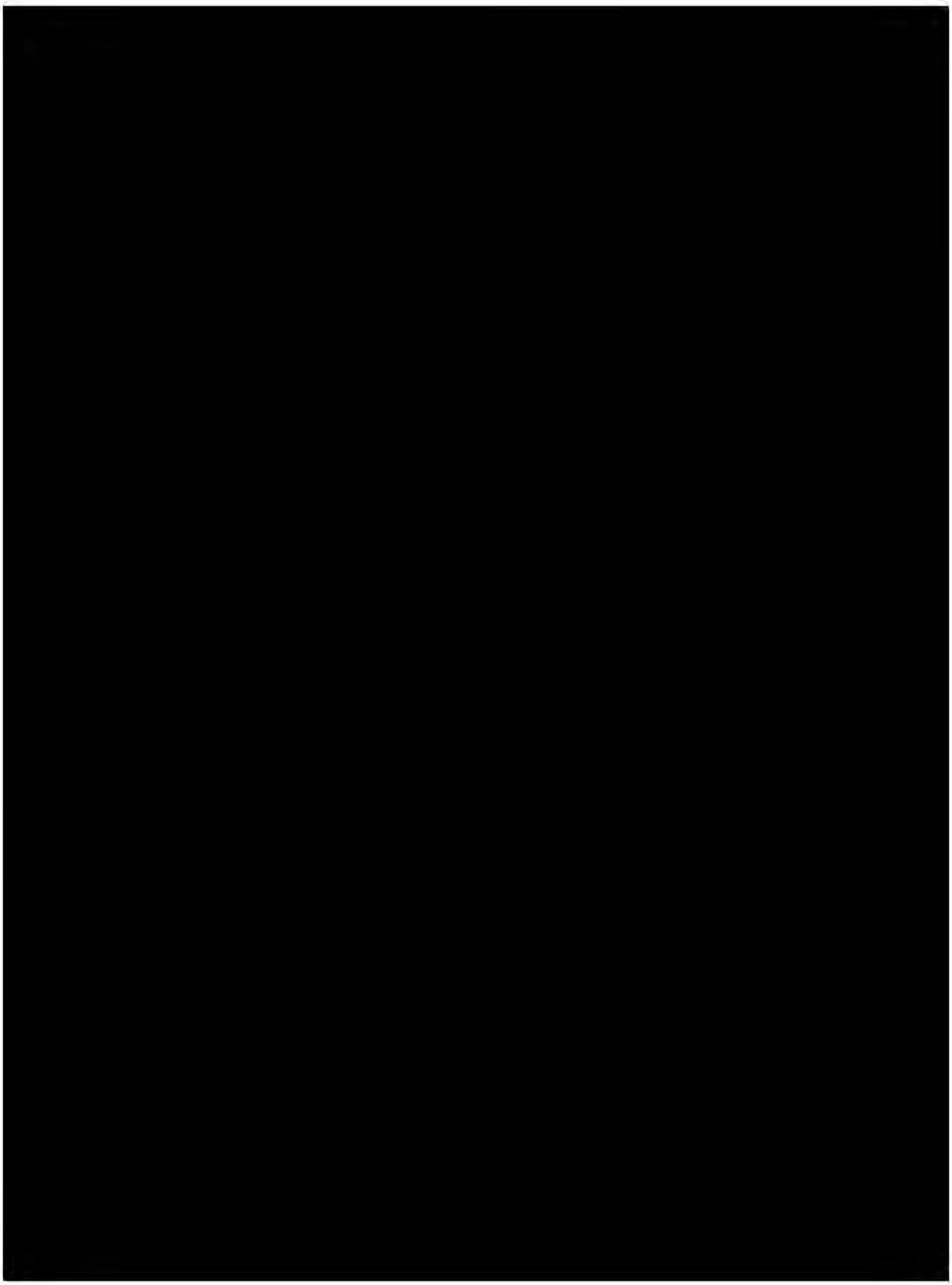

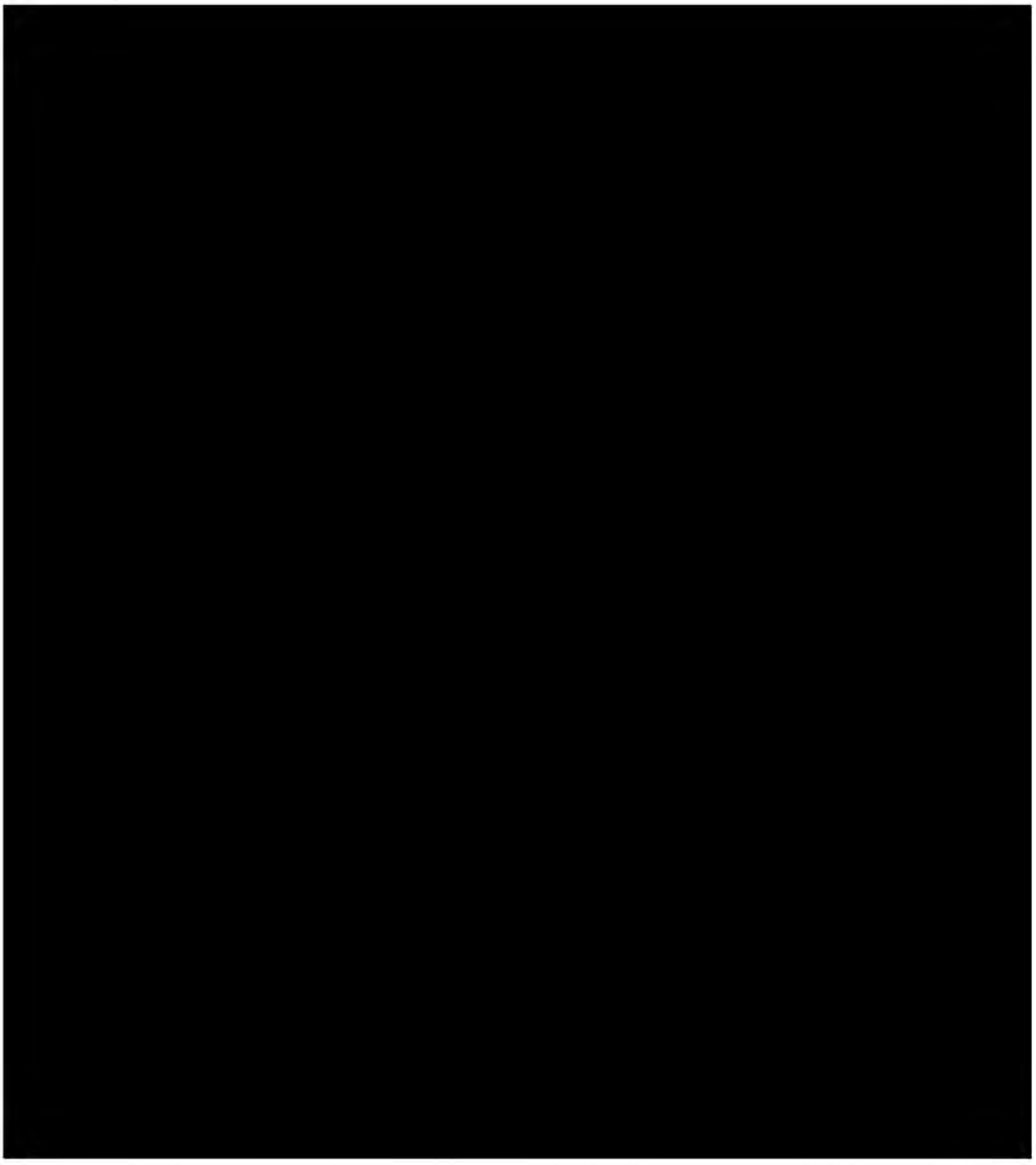

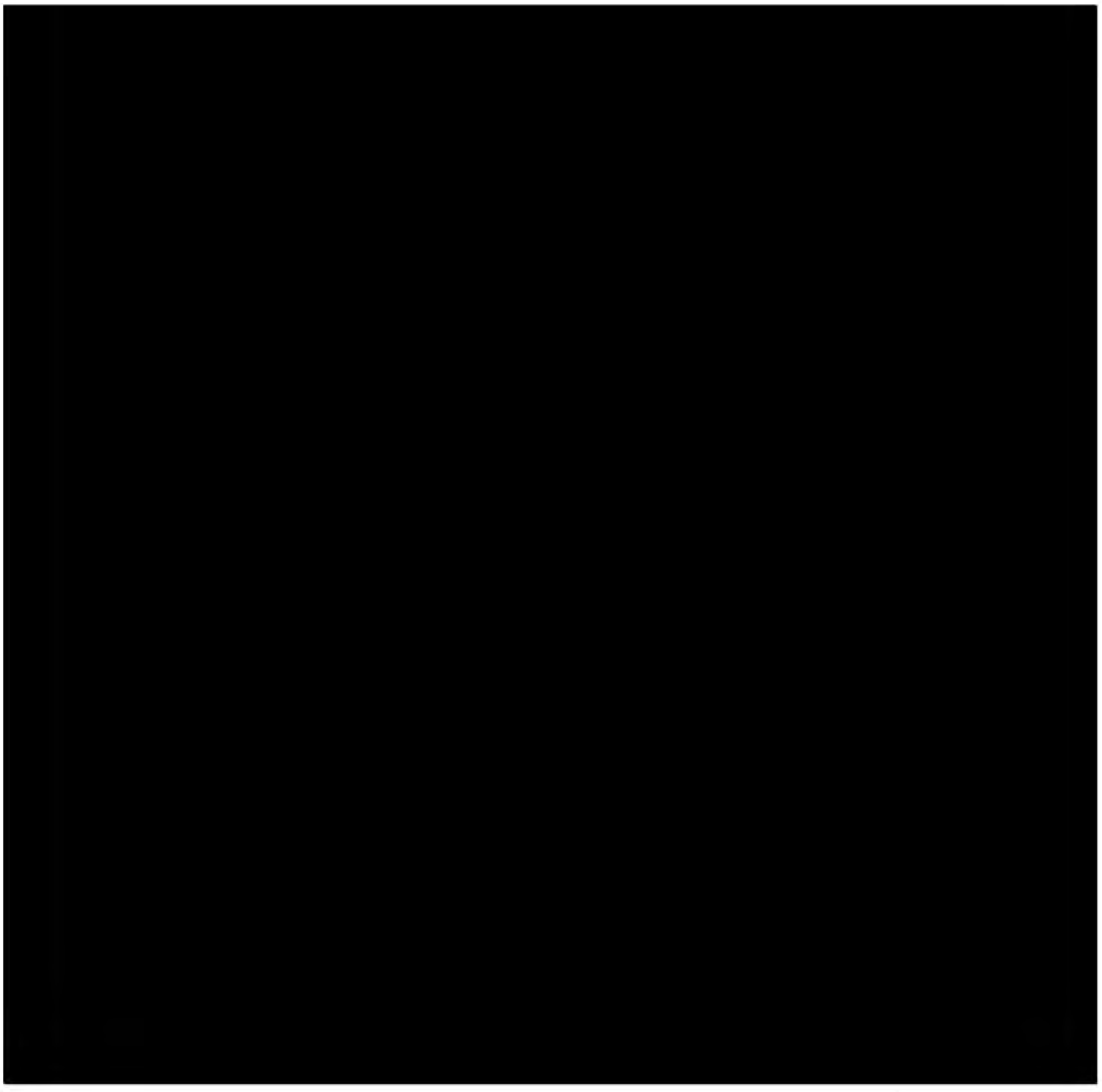

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1.6.4 Epidemiology of potential risks in the target population when unexposed to the product

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Potential risk	Bladder Cancer
Incidence of condition	Bladder cancer: An estimated 357,000 bladder cancer cases occurred worldwide in 2002, making this the ninth most common cause of cancer for both sexes combined [99]. It is relatively common in developed countries, where 63% of all incident cases occur. The incidence is highly age and gender dependent, but the overall incidence is around 10 and 25 per 100,000 per year in the EU. The incidence is increased in patients with type 2 diabetes [36], RR=1.4.
Prevalence of condition	Not known
Mortality of condition	Bladder cancer: In 2002, there were 145,000 deaths worldwide, with population-based 5-year survival rates ranging from 40% to 80%, depending on whether noninvasive lesions are included in the computation [99].

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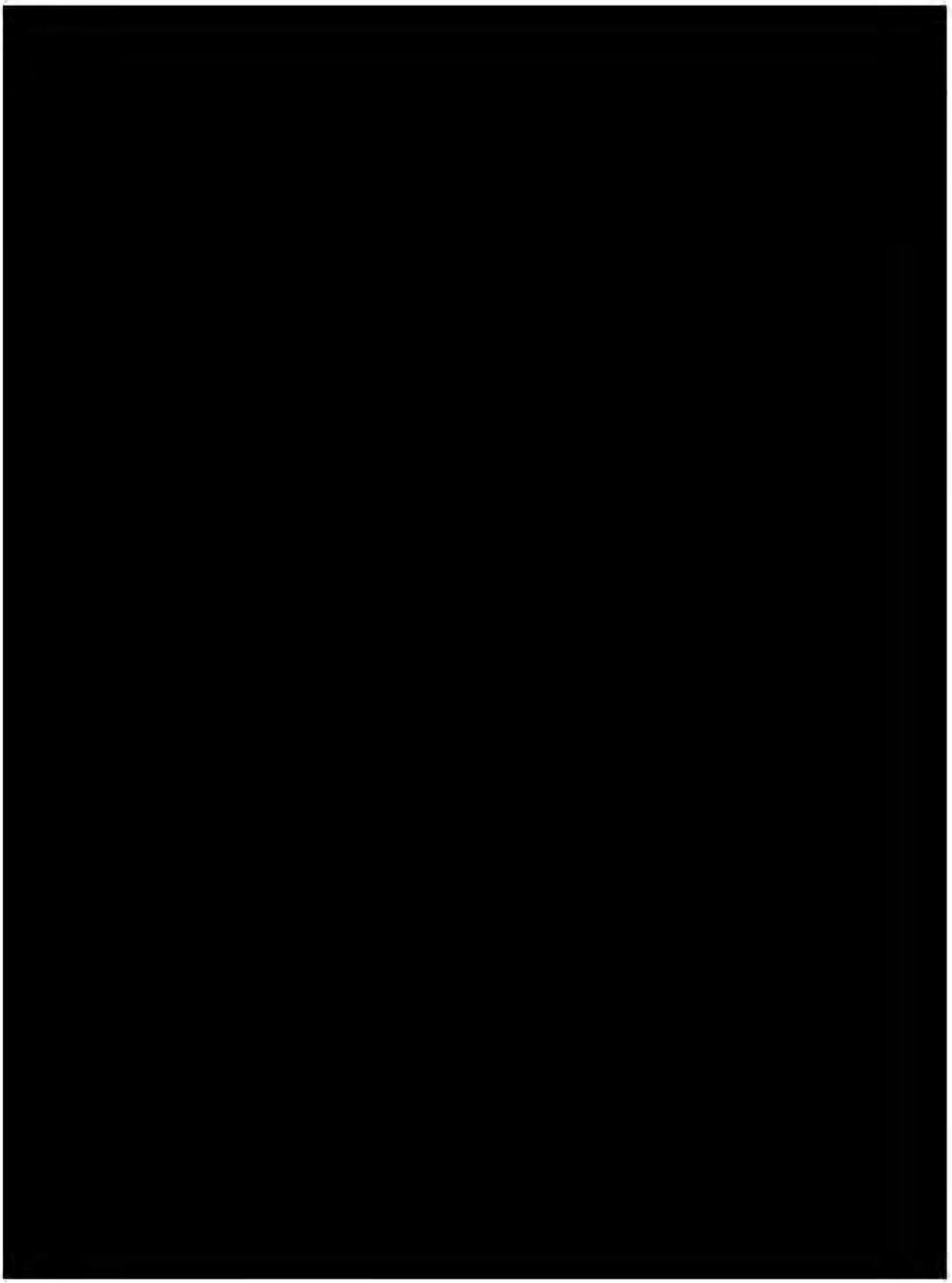

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Summary: Ongoing safety concerns

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Important Potential Risks [redacted]

Bladder cancer

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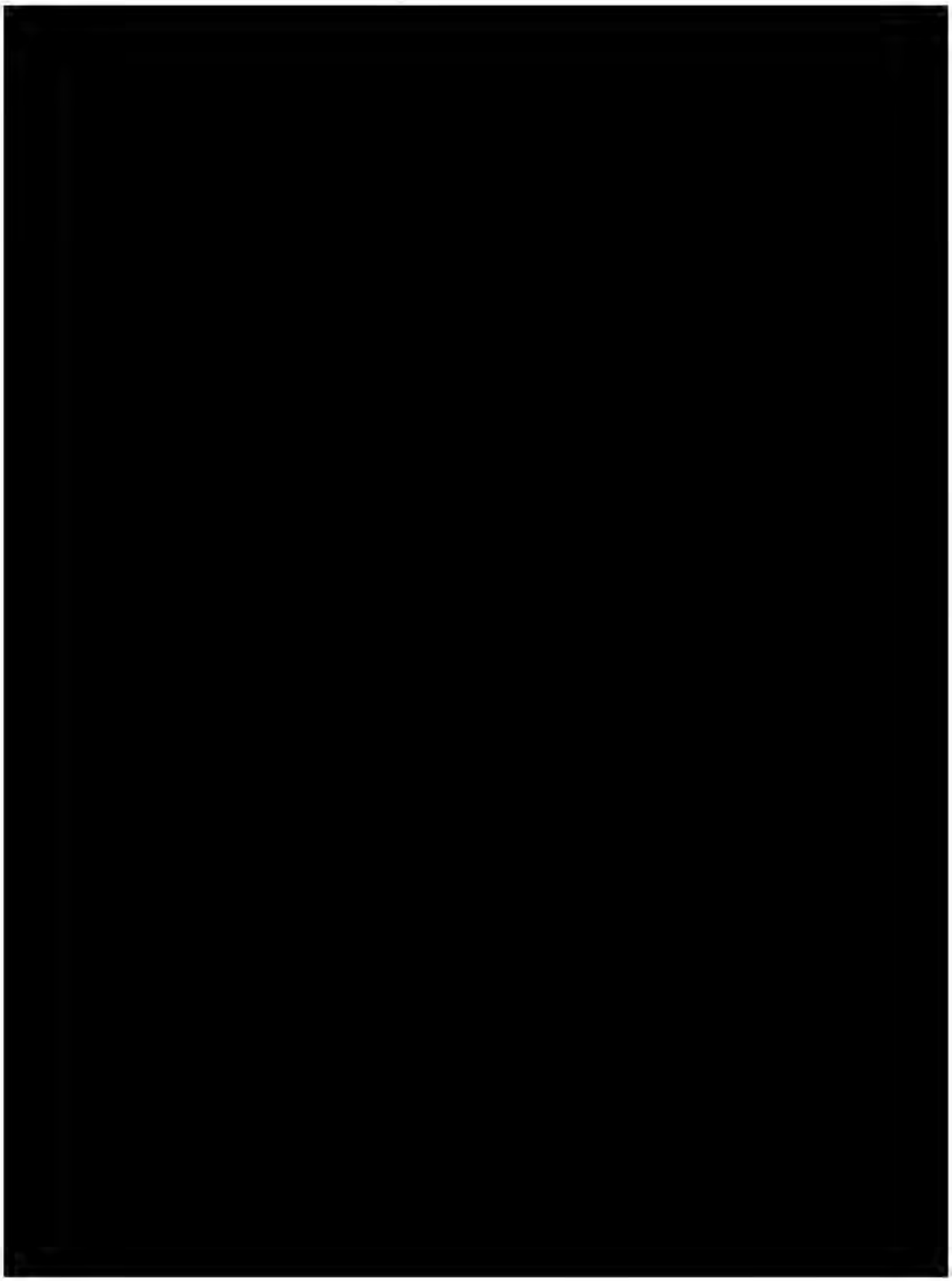

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2.2 Summary of safety concern and planned pharmacovigilance actions

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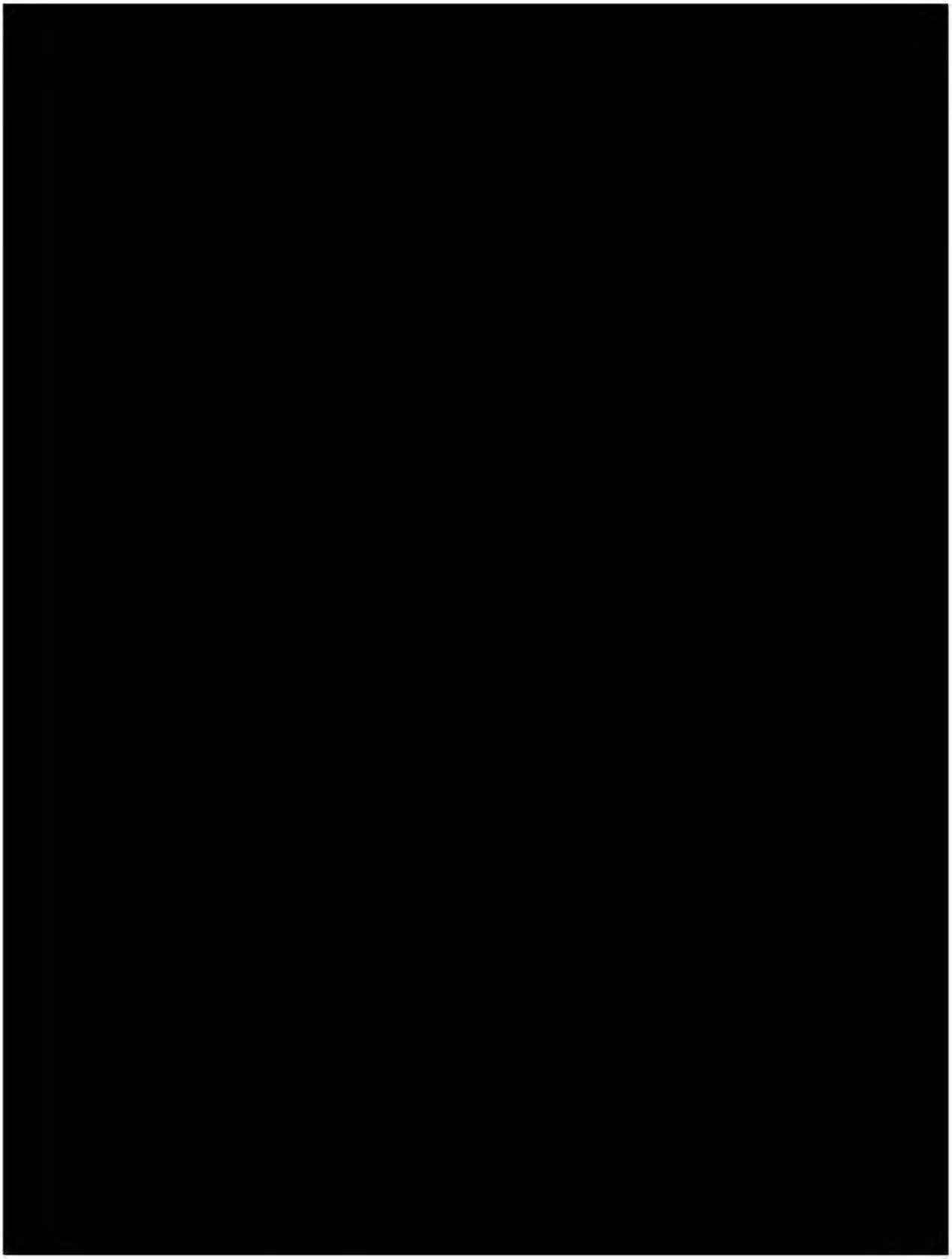
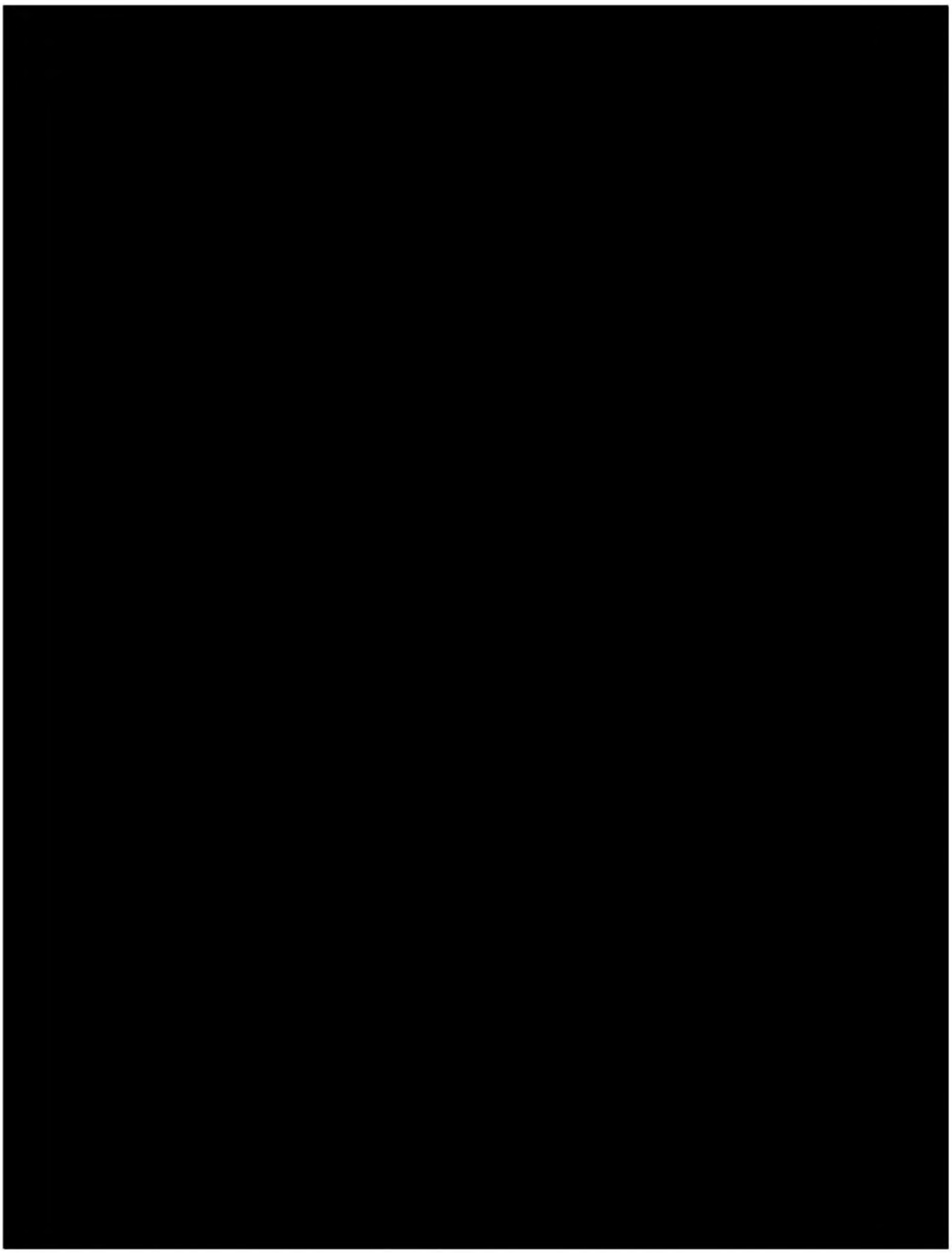
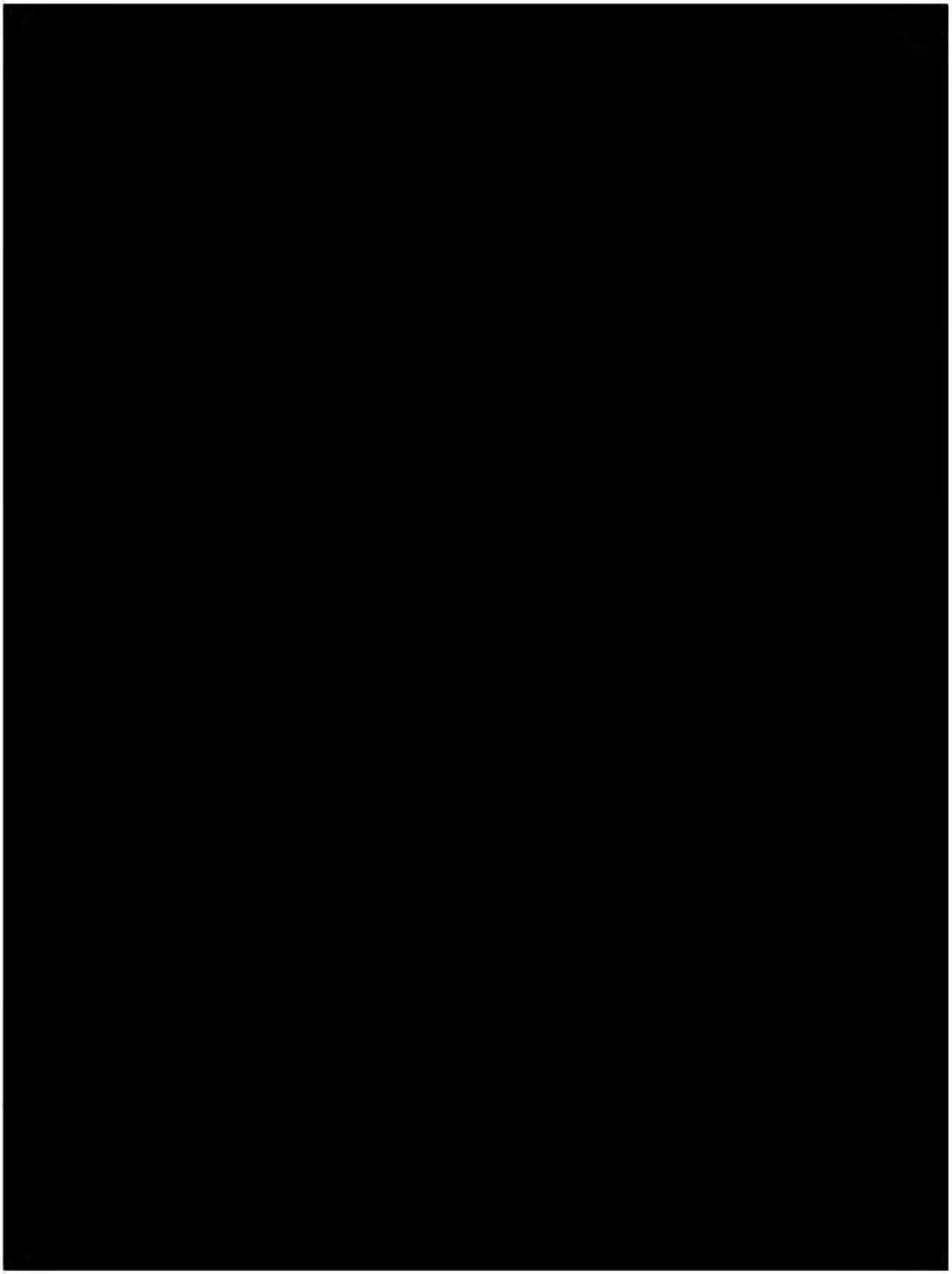
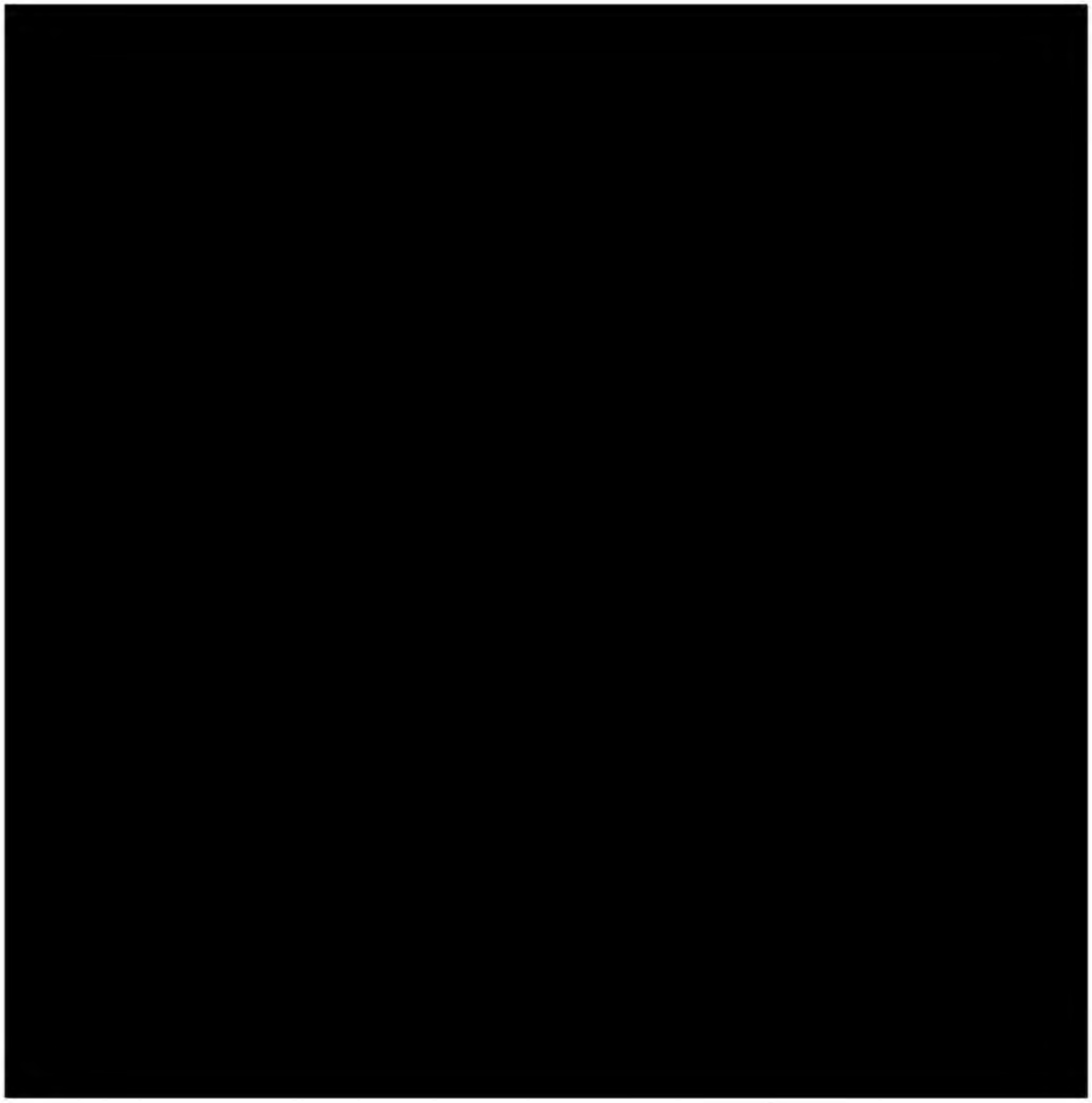
Safety Concern	Planned action (s)
[redacted]	
Bladder cancer	Ongoing epidemiologic cohort study (KPNC) on bladder cancer including a nested case-control study. Ongoing 10-year observational follow-up study from the PROactive cohort of patients collecting details on all newly diagnosed malignancies. Reporting interim results every 2 years. GPRD nested case control study conducted as part of the Article 20 review Planned EU observational study conducted in a number of EU databases with a view to conducting a meta-analysis.
[redacted]	Specific cumulative and periodical review of all cases reported from any source in the 6-monthly PSURs.

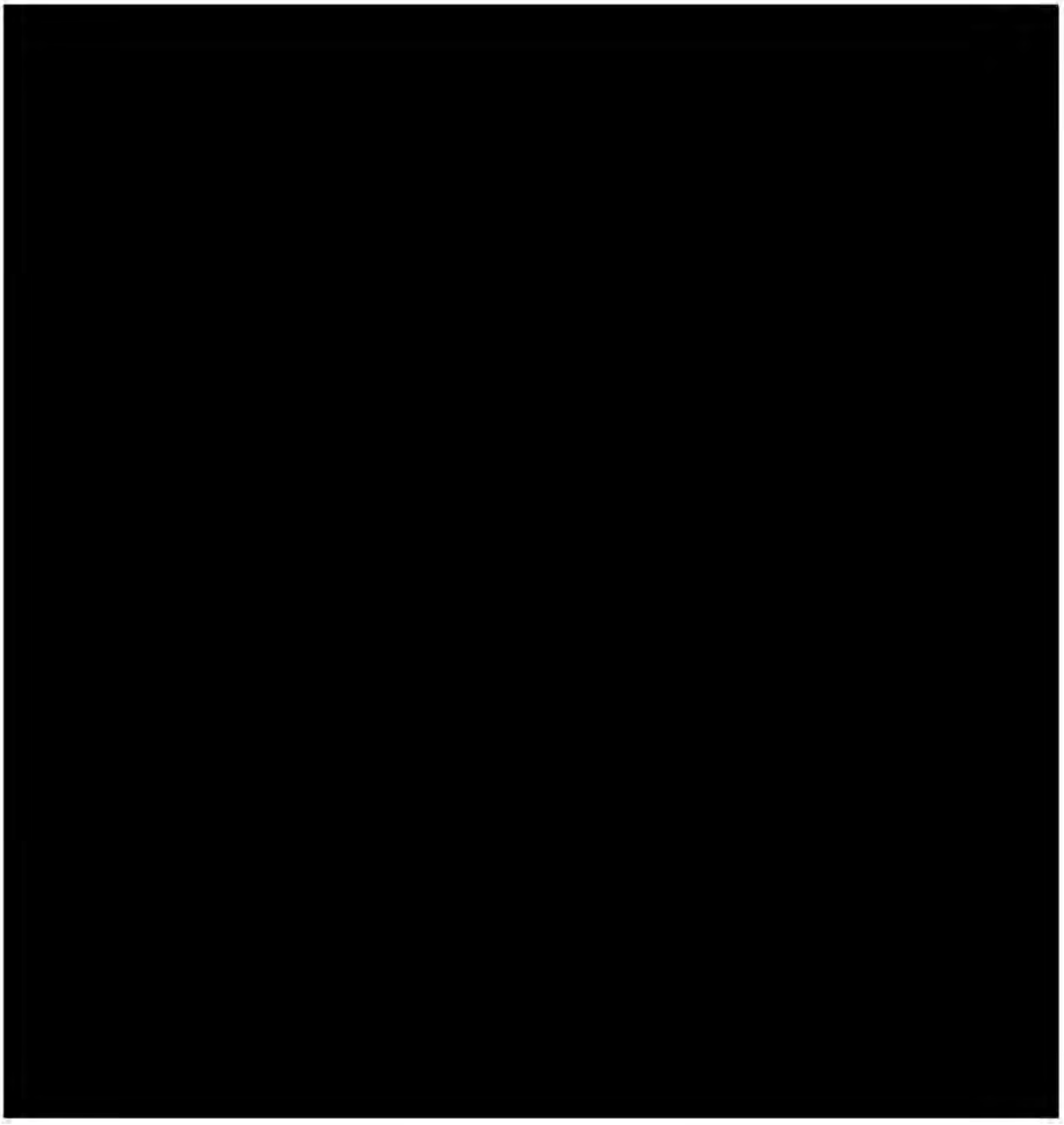
[redacted]











[redacted]

Safety concern	Bladder cancer
Grade of safety concern	Potential.
Action(s) proposed	Standard pharmacovigilance activities as stated in Section 2.1. Safety surveillance and case-series review of malignancies reported within clinical trials and as part of spontaneous reporting (including literature and regulatory reports) conducted ad hoc and within 6-monthly PSURs with a focus on bladder cancer. Interim analysis of the overall cohort and nest case-control study on bladder neoplasms using the KPNC cohort of pioglitazone patients vs matched controls (according to timetable agreed with CHMP; see Section 5.0). GPRD study: Nested case-control study of bladder cancer in diabetic patients treated with oral hypoglycaemic agents: The initial results of this study have been provided, and the study will be extended to include information on further covariates (see Annex 4 for protocol and study synopsis). A European epidemiological meta-analysis is proposed in which cohort studies will be conducted in a number of European databases to a similar protocol, with a view to conducting a meta-analysis of the results (see Annex 4 for study synopsis). [redacted]
Objective of proposed action(s)	Assess frequency and type of neoplasm associated with TZD use.
Rationale for proposed action(s)	Assessments of long-term incidence in humans (compared with no-pioglitazone diabetic controls).
Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Decisions will be based on the findings during postmarketing monitoring.
Milestones for evaluation and reporting including justification for choice of milestones	Six-monthly PSUR reports with a focus on bladder cancer. Completed final study report of the original PROactive study (2006). [redacted] Interim reports of KPNC epidemiological study on bladder malignancies (to 2012), first and second interim reports submitted in August 2005 and 2007, next report due in 2009 for cohort and nested case-control study. Final analysis due 2012. Interim and final study reports of PROactive long-term observational follow-up study (to 2015); first 2-year interim report in July 2007; thereafter in 2-year intervals until final report in 2015.
Titles of protocols	[redacted]

Completed commitments regarding bladder cancer:

1. The PEM programme by the DSRU in the United Kingdom did not identify any increased risk of malignancies (final report made available to the CHMP in February

[redacted]

[redacted]

2005). This was reviewed in the CPMP Renewal Report for ACTOS/GLUSTIN (EMEA/H/C/285-286/R1), as follows: *"Malignancies were specifically considered. There were 4 cases of carcinoma of the bladder. In 1 case the carcinoma was present before commencing pioglitazone; in a second the patient has a transurethral resection of bladder tumour several months after starting pioglitazone. In the third case the patient had been diagnosed with transitional cell carcinoma in 1994 (before pioglitazone was available) and in the final case microscopic haematuria was found on routine testing 4 months after starting pioglitazone. Later cystoscopy showed a superficial bladder tumour. One of the cases was considered to be unassessable and the other 3 were thought unlikely to be related to administration of pioglitazone. The CHMP agreed that this PEM study report confirmed the known safety profile of pioglitazone."*

2. The PROactive trial, while not a specific commitment with regard to malignancies, confirmed no overall increased risk of malignancies when pioglitazone is added to standard antidiabetic therapy, compared with placebo. However, the authors did note a slight (not statistically significant) increase in bladder malignancies, and a slight reduction in breast cancers. As outlined in Section 1.5.3.1, this was investigated by independent experts and concluded with a very small remaining imbalance that did not constitute a signal of concern.
3. The PROactive observational follow-up study provides interim analyses every 2 years and has reported the first interim results in July 2007 and the second in July 2009. In October 2009, the CHMP in its acknowledging letter recognised the limitations of this study and concurred that the study does not indicate an increased risk of malignancy.
4. The KPNC cohort study investigation association of pioglitazone treatment with incidence of bladder cancer. The first interim analysis was submitted in 2005 to the CHMP, the second in August 2007 and third in December 2009. Results are outlined in Section 1.5.3.1. For the third interim analysis, the CHMP summarized that they did not observe a significant association between any pioglitazone exposure and bladder cancer risk in their cohort study, overall. As before, the analyses addressing increasing exposure suggested an increased risk of bladder cancer among patients with the longest exposure to pioglitazone and in those with the highest cumulative dose. A post hoc analysis suggests further increased risk with even longer exposure periods. In addition, there was no evidence of a stage shift to more advanced bladder cancer among the pioglitazone exposed patients (refer to CHMP response 26 May 2010).
5. The KPNC cohort also provides patients for a nested case-control study (first interim analysis submitted to the CHMP in July 2006 and second interim analysis submitted to the CHMP in December 2009). Results are outlined in Section 1.5.3.1. The CHMP in its acknowledging letters agreed with the MAH's position (refer to CHMP

[redacted]

[redacted]

response 26 May 2010). Forthcoming analysis over the next years will provide more information and reassurance on this important topic.

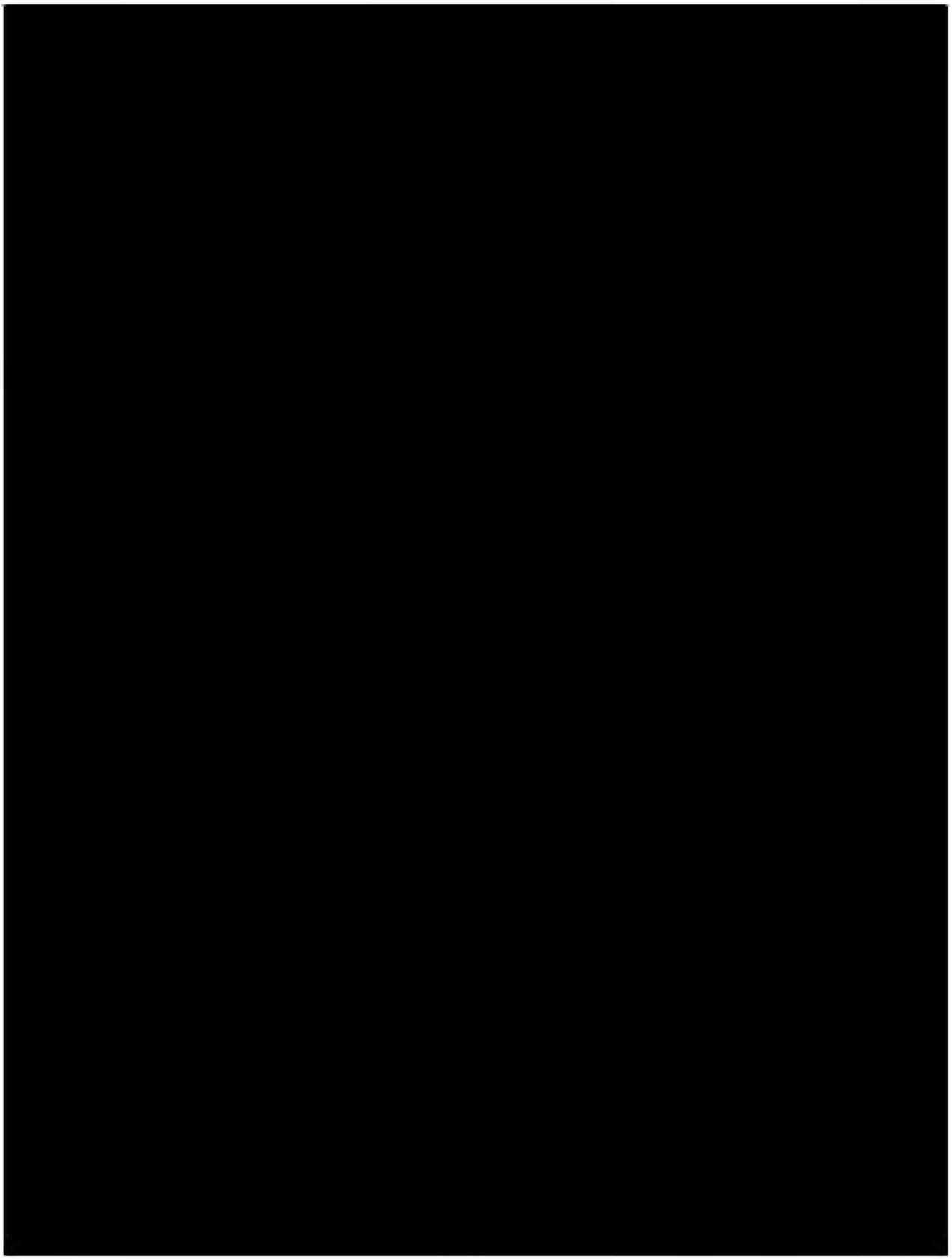
[redacted]

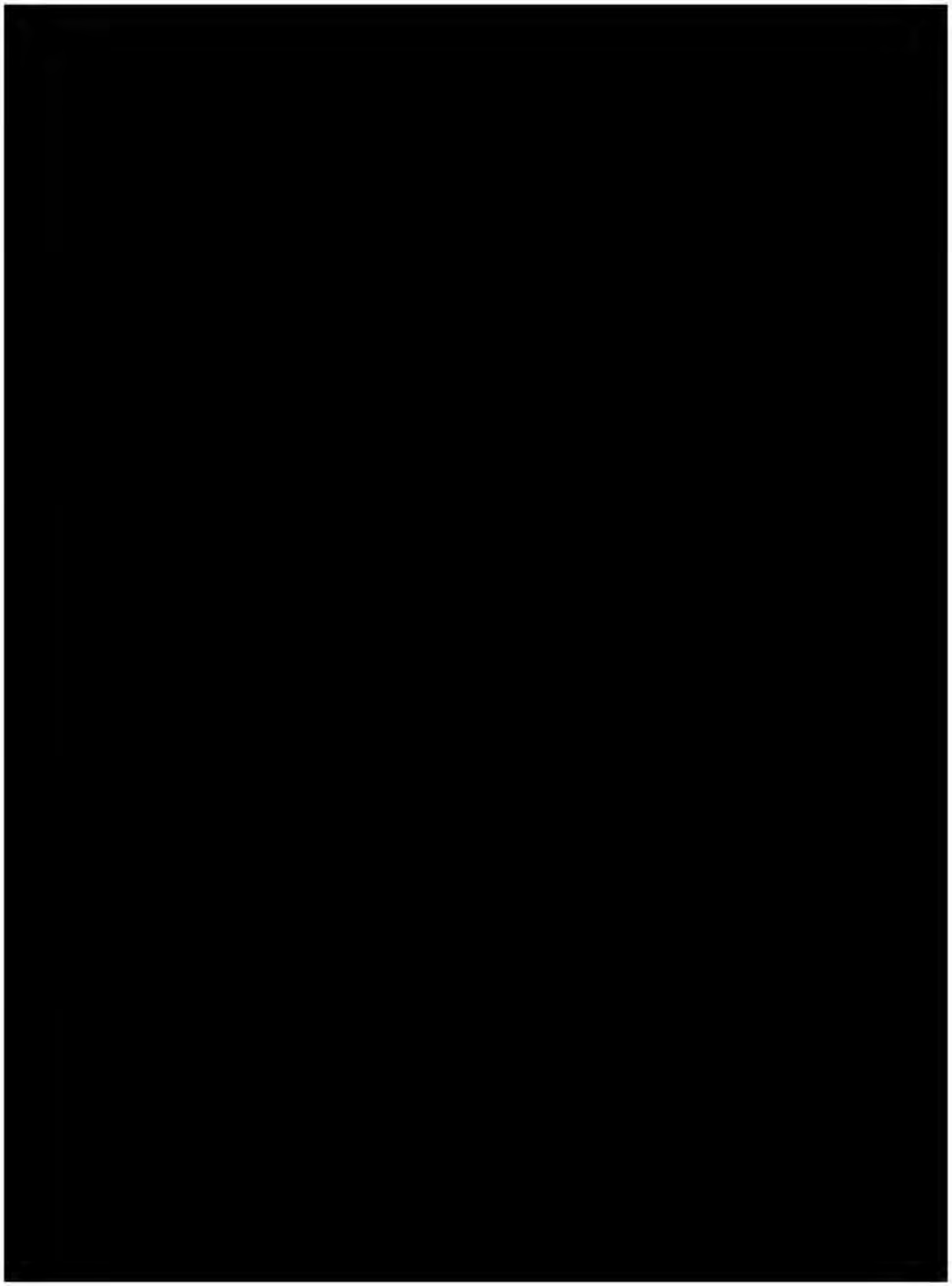
8. The results of the GPRD nested case control study requested by CHMP are provided in Annex 6, and are in line with the results seen in the KPNC study. This study was conducted under short timelines and as a result has limited information on confounders included within the analysis.

[redacted]

10. A meta-analysis has been conducted of the pioglitazone clinical trial data of bladder cancer, and the results are provided in Annex 6.

[redacted]





[redacted]

2.5 For updates to EU-RMP

As outlined in the introduction to this document, RMPs have previously been submitted for pioglitazone with respect to:

- Bladder neoplasia (specifically, May 2004).

[redacted]

[redacted]

[redacted]

2.6 Summary of outstanding actions, including milestones

Actions	Milestones/exposure	Milestones/calendar time	Study status
KPNC bladder cancer cohort study	Full prospective cohort (see Section 1.2.1.2). 1st interim report 2005; 2nd interim report 2007; 3rd interim report 2009.	Final analysis 2012. Final report expected in 2013.	Ongoing
KPNC bladder cancer nested case control	1st interim report submitted 2006; [redacted] 2nd interim report submitted 2009; [redacted] (see Section 1.2.1.2)	Final analysis 2012. Final report expected in 2013.	Ongoing

[redacted]

[redacted]

PART II

3.0 EVALUATION OF THE NEED FOR RISK MINIMISATION ACTIVITIES

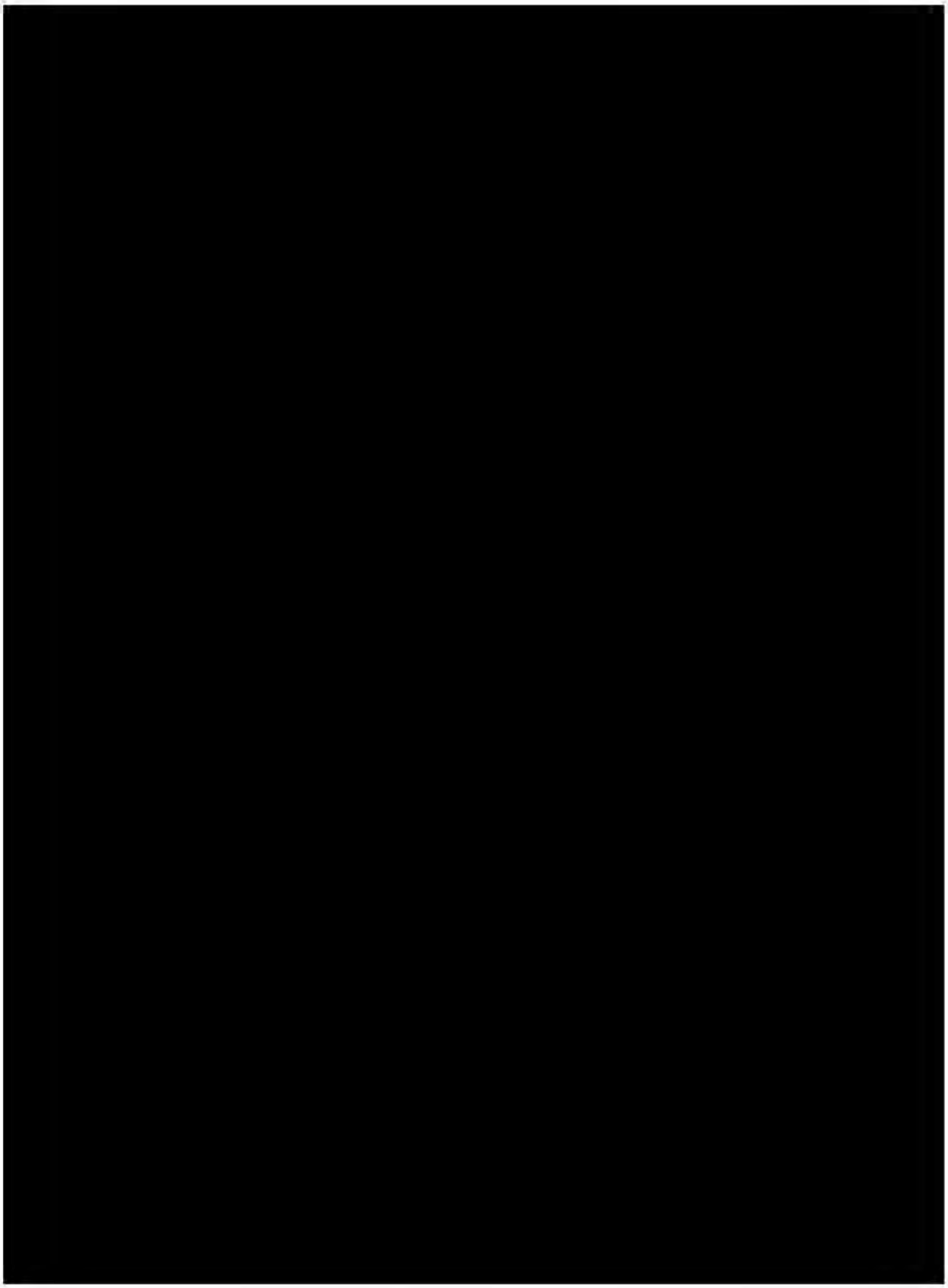
3.1 Summary table of planned actions

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide description of routine activity and justification
Important identified risks		

[redacted]

[redacted]

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide description of routine activity and justification
[redacted]		
Important Potential Risks		
[redacted]		
Bladder cancer	No	The observation of bladder hyperplasia is addressed in Section 5.3 of the SPC. The risk of neoplasia in humans is still unknown and is undergoing further evaluation. In the light of recent results from the KPNC study, the SPC and patient information have been updated to reflect the need to be vigilant for signs of bladder cancer during routine urinalysis of diabetic patients treated with pioglitazone, and the MAH proposes that a Direct Healthcare Professional communication should be issued recommending that patients be advised to contact healthcare professionals immediately in case of signs or symptoms of haematuria.
[redacted]		



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4.0 RISK MINIMISATION PLAN

Safety concern	**Bladder cancer**
Routine risk minimization activities	Wording on the risk of bladder cancer is provided in section 4.4, 4.8, and 5.3 of the SmPC, and in the patient information leaflet:

Section 4.4

Bladder Cancer

Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%). After excluding patients in whom exposure to study drug was less than 1 year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Whilst causality has not been established, patients should be advised to report haematuria promptly to their physician and appropriate investigations should be initiated.

Section 4.8 Undesirable Effects

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to< 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing incidence and seriousness.

	Frequency of adverse reactions of pioglitazone by treatment regimen				
		Combination			
Adverse reaction	**Mono-therapy**	**with metformin**	**with ulpho-nylurea**	**with metformin and sulpho-nylurea**	**with insulin**
Renal and urinary disorders					
bladder cancer	uncommon	uncommon	uncommon	uncommon	uncommon

Patient information leaflet

Bladder cancer has been experienced uncommonly (1 to 10 users in 1000) in patients taking Actos. Symptoms include blood in your urine therefore if you experience this, talk to your doctor as soon as possible.

Section 5.3

An increased incidence of hyperplasia (males and females) and tumours (males) of the urinary bladder epithelium was apparent in rats treated with pioglitazone for up to 2 years.

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A 24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

There was no tumorigenic response in mice of either sex. Hyperplasia of the urinary bladder was not seen in dogs or monkeys treated with pioglitazone for up to 12 months.

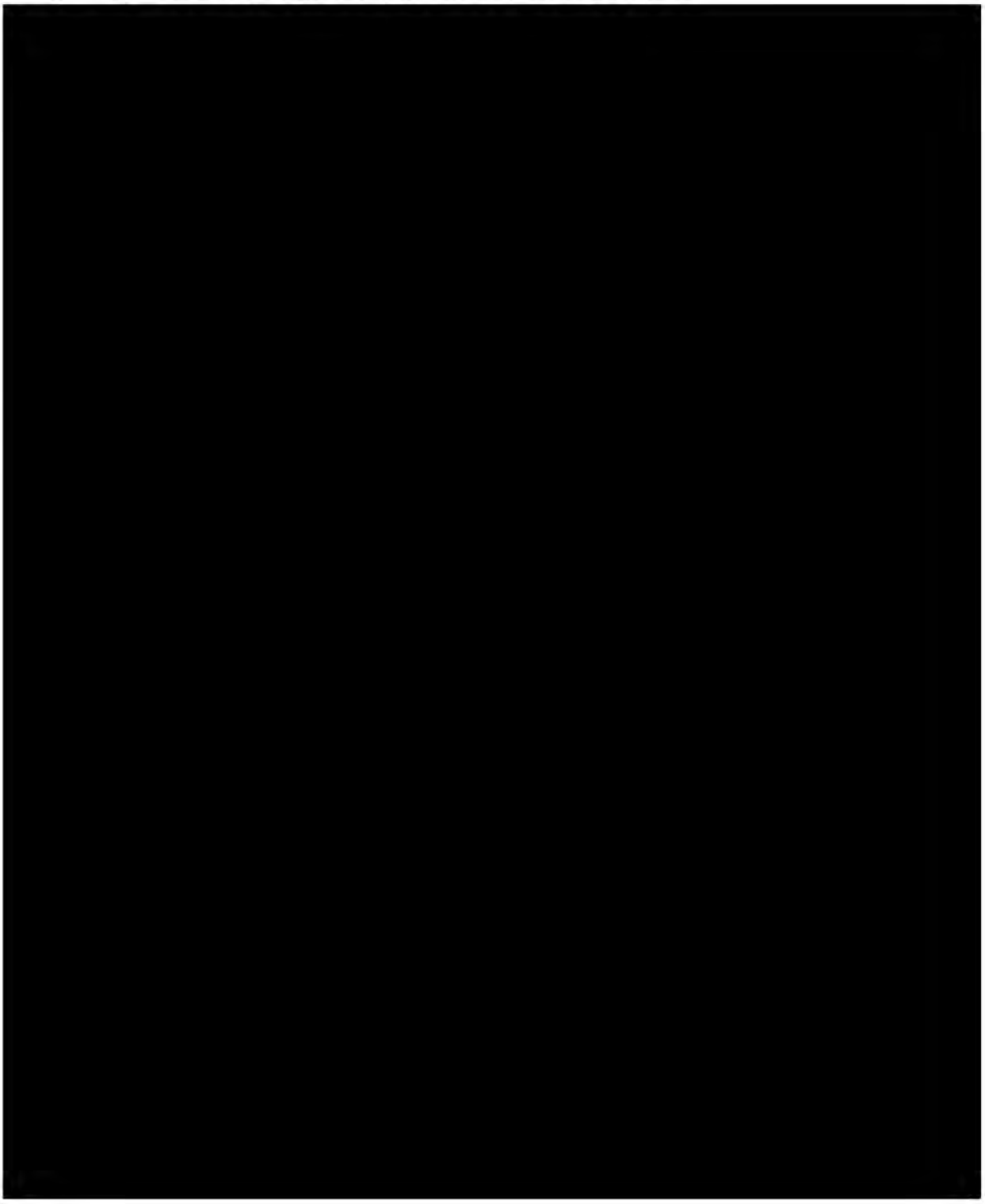
[redacted]

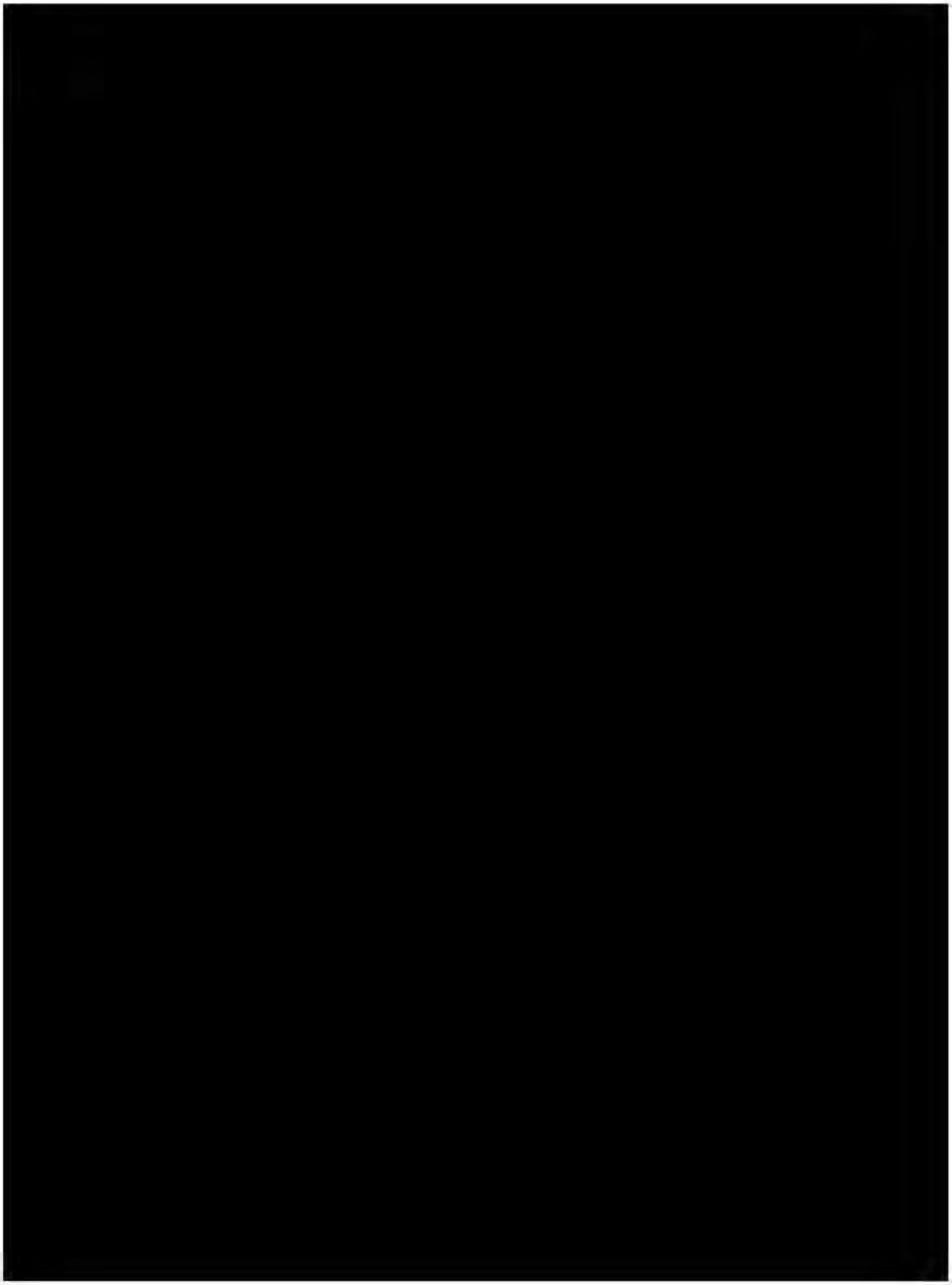
[redacted]

Safety concern	Bladder cancer
Additional risk minimization activity	Objective and Rationale: Highlight to HCPs the need to be vigilant regarding the potential risk of bladder cancer, and provide the current evidence including the absolute risk. Action proposed: Direct Health Care Professional communication (see annex 8 for proposed text) Criteria to be used to verify the success of the action: Audit prescribing healthcare professionals to assess their knowledge of the risk minimization steps. Review period: 6 months after issuing the DHPC communication

[redacted]

5.0 SUMMARY OF THE EU RISK MANAGEMENT PLAN





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Safety Concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
[redacted]		
Bladder cancer	• Safety surveillance of individual ADRs and cumulative data from all sources. • Review of all clinical trials for evidence of increased incidence of bladder cancer. • 6-monthly PSURs: Incidences of reported cases of bladder cancer and analysis of cases, including comparative incidences with background epidemiologic data. • KPNC Epidemiologic prospective cohort study on bladder cancer, (1st interim report to CHMP in August 2005; 2nd report August 2007; 3rd report 2009; final analysis 2012). • Nested case-control study of bladder cancer within the cohort study of bladder cancer 1st report submitted to CHMP in 2006; 2nd report 2009, final analysis 2012.	• SPC Section 4.4 and 4.8 • SPC Section 5.3. • Patient information leaflet • Direct Health Care Professional communication

[redacted]

[redacted]

Safety Concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	• Observational follow-up data from PROactive study EC445) for 10 years reporting newly diagnosed malignancies every 2 years (1st interim report submitted to CHMP July 2007; 2nd interim report due August 2009; 3rd report 2011; 4th report 2013; final report 2015). • AD-4388_407 Case control study in GPRD. • Planned EU wide study using a variety of databases	

[redacted]

[redacted]

6.0 CONTACT PERSON FOR THIS EU-RMP

Names

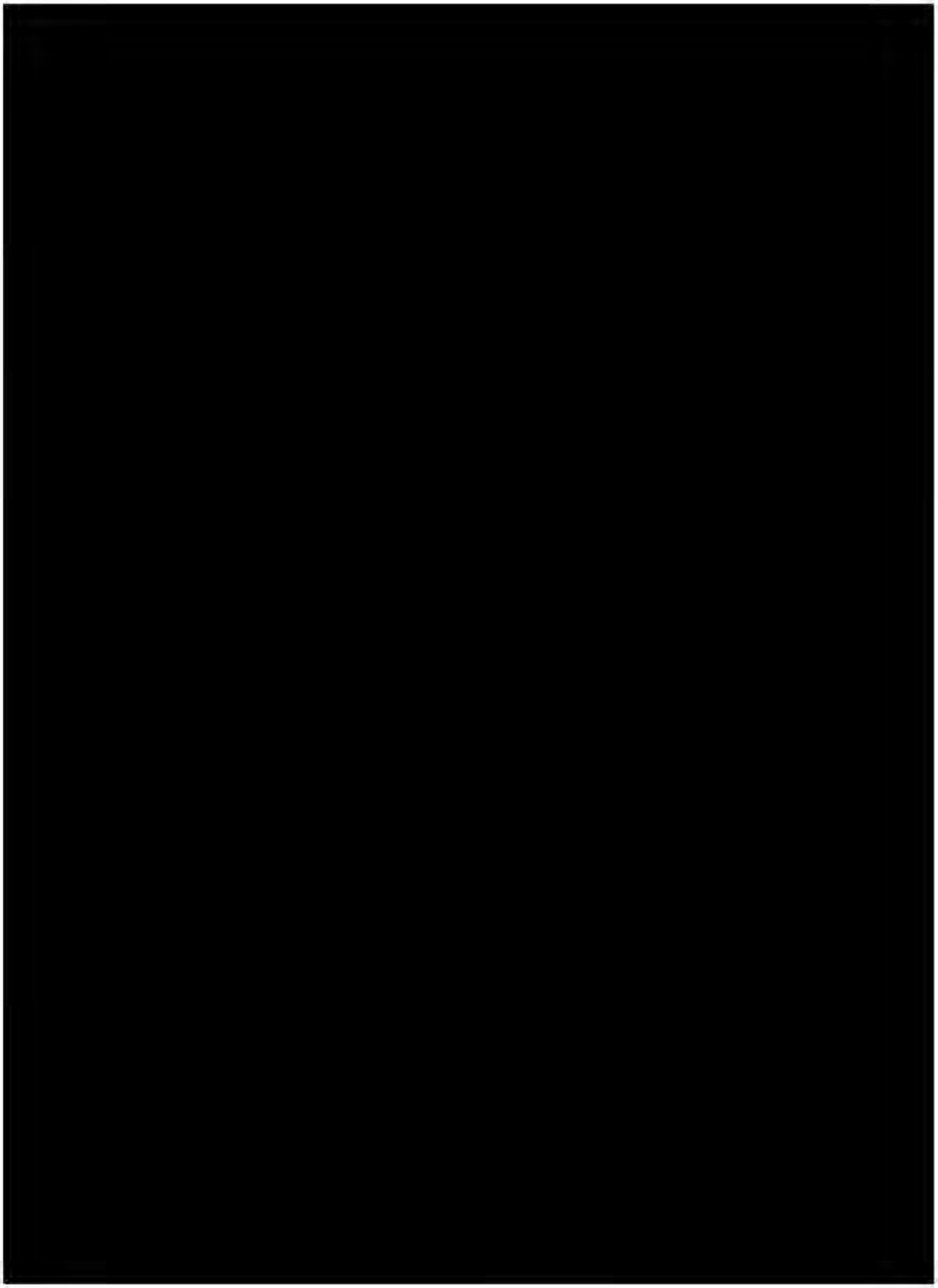
Position

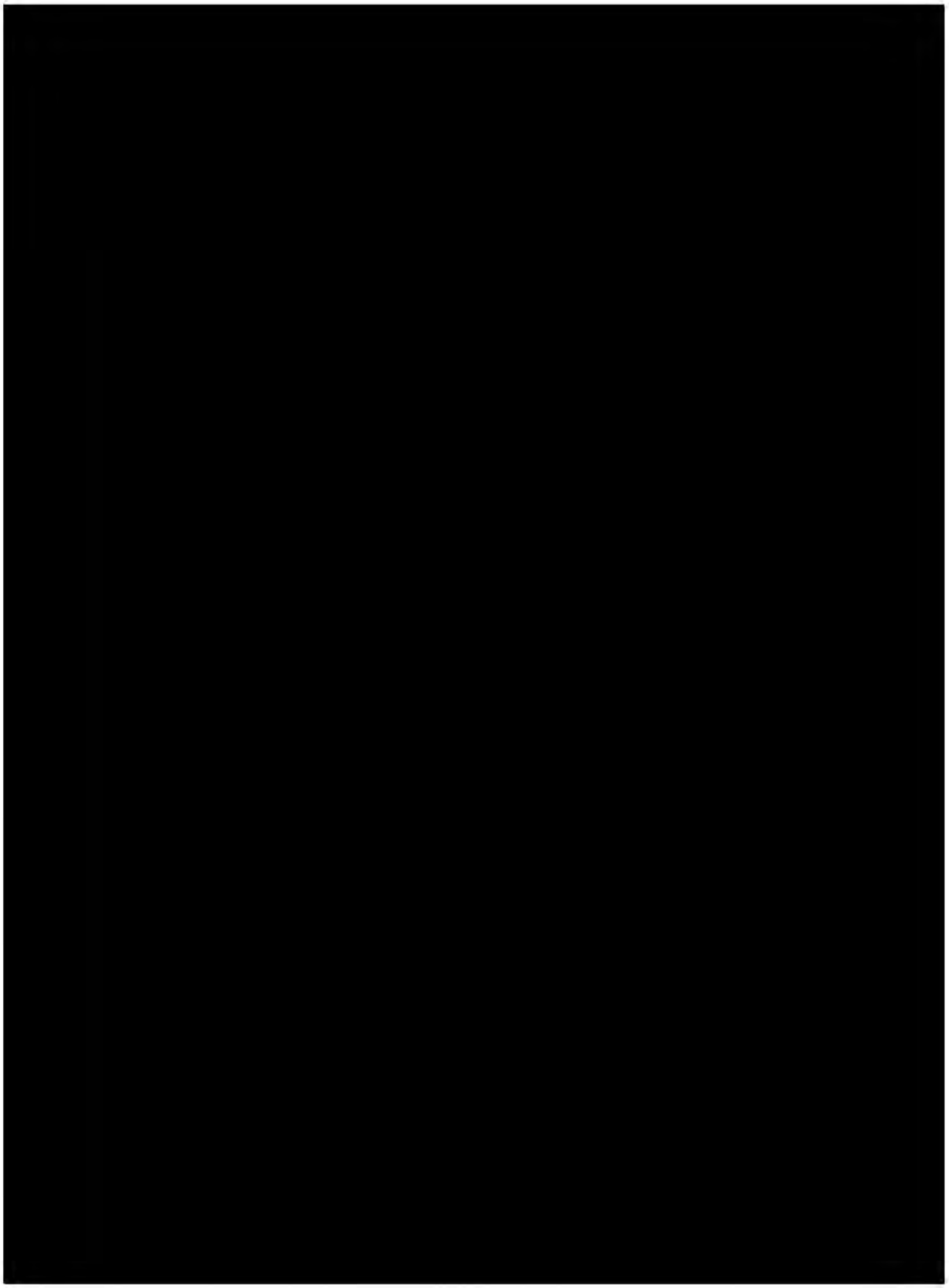
Qualifications

Signature

[redacted]

[redacted]





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36. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia 2006;49(12):2819 -23.

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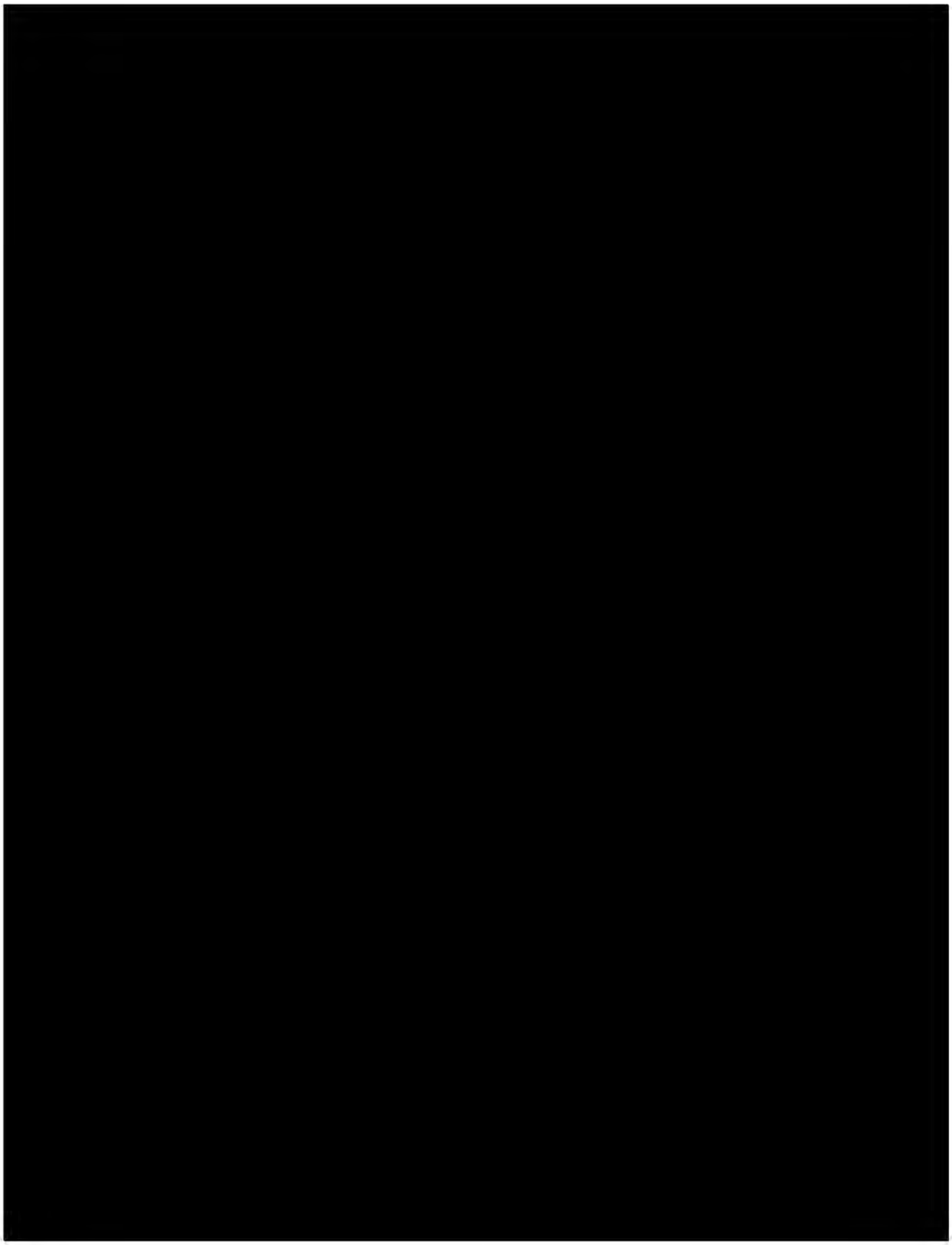

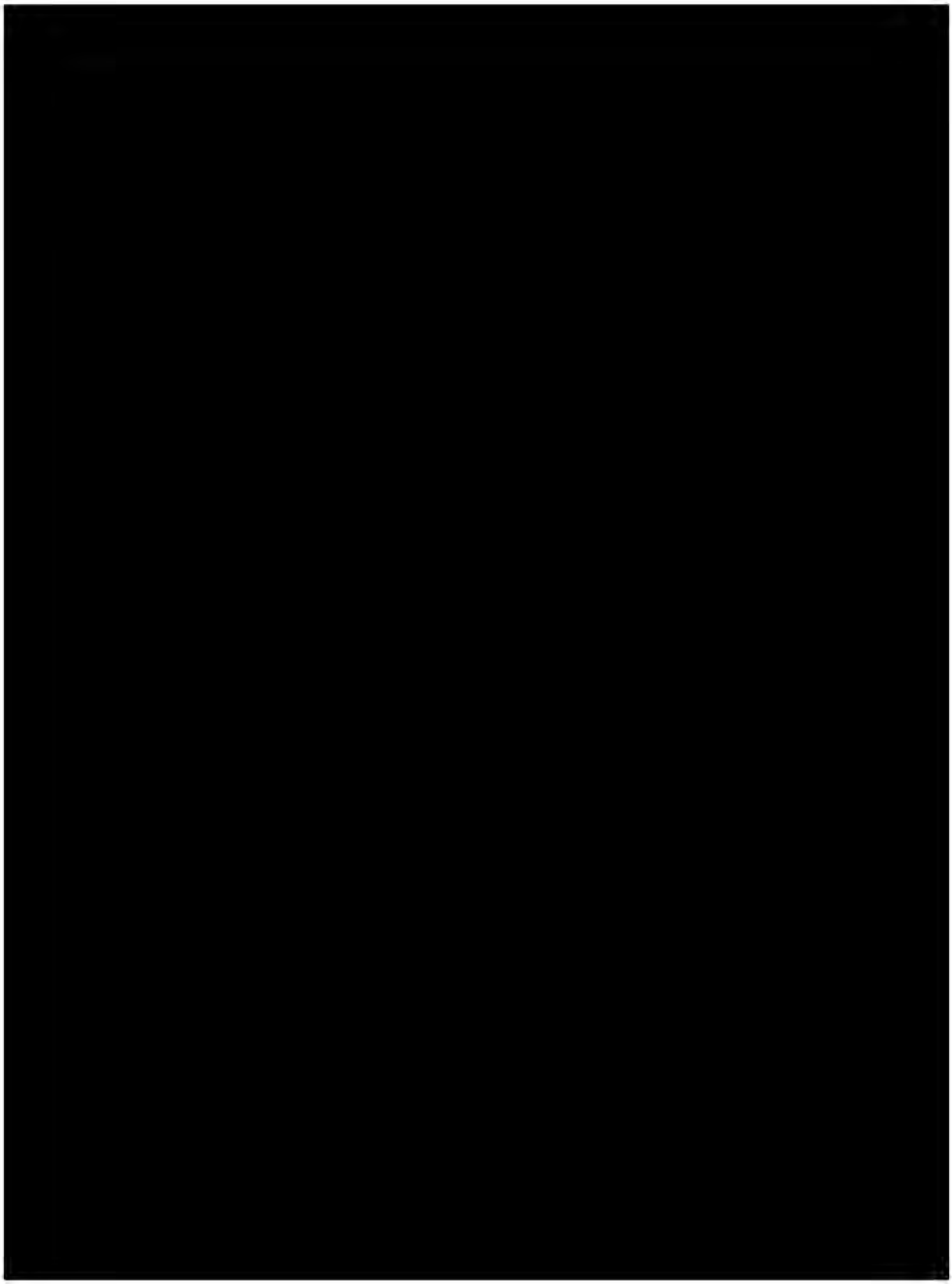

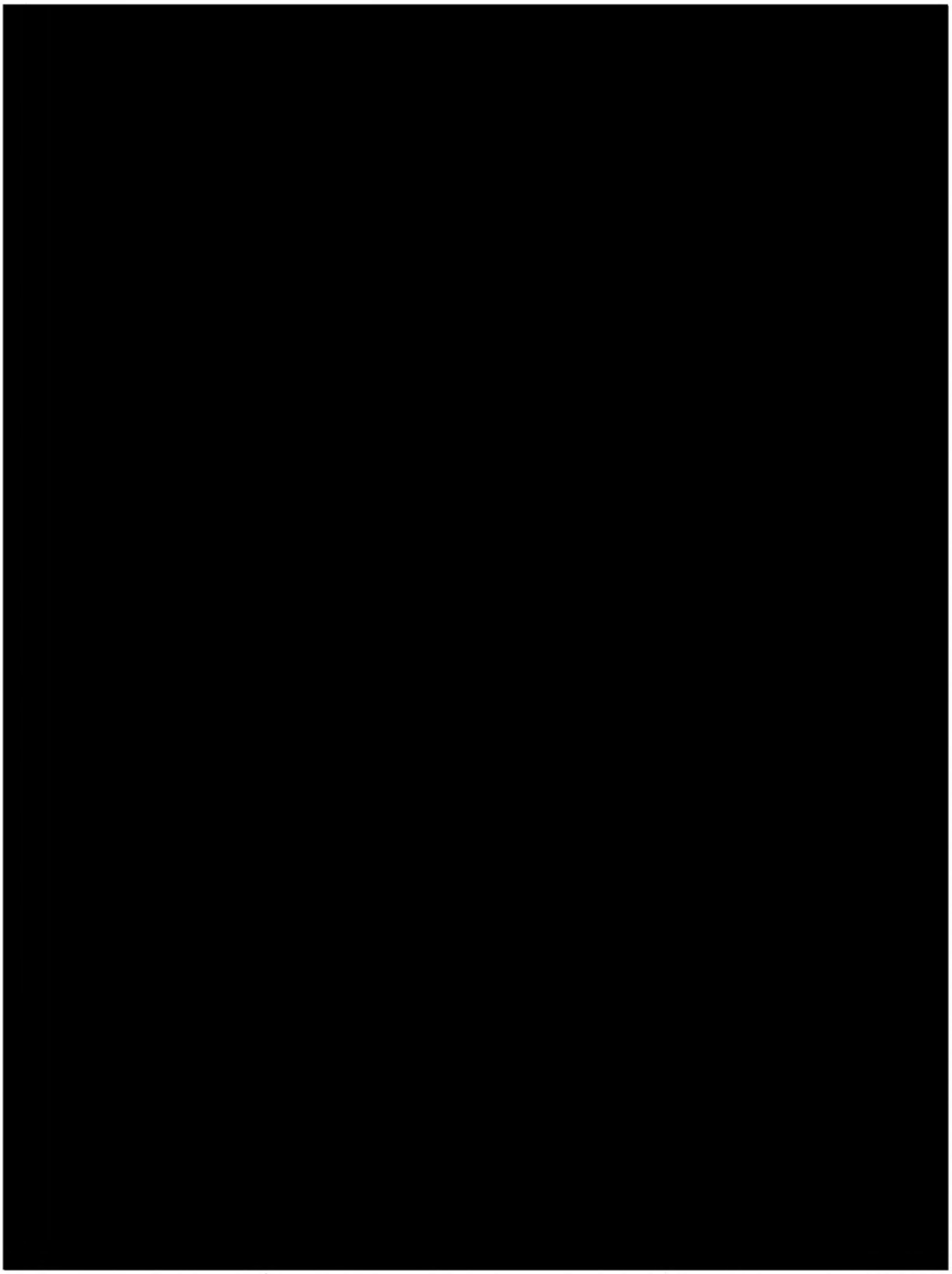

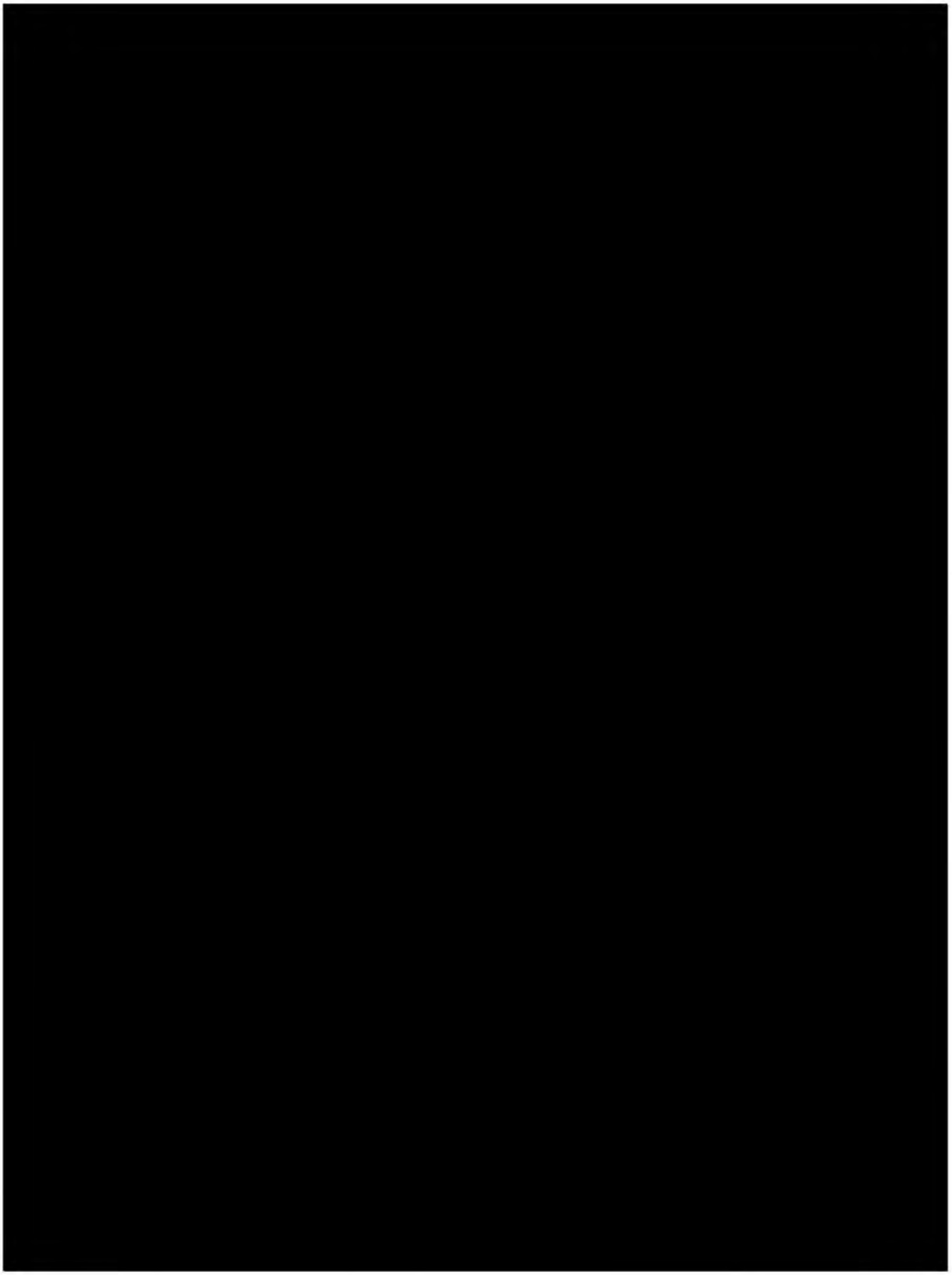

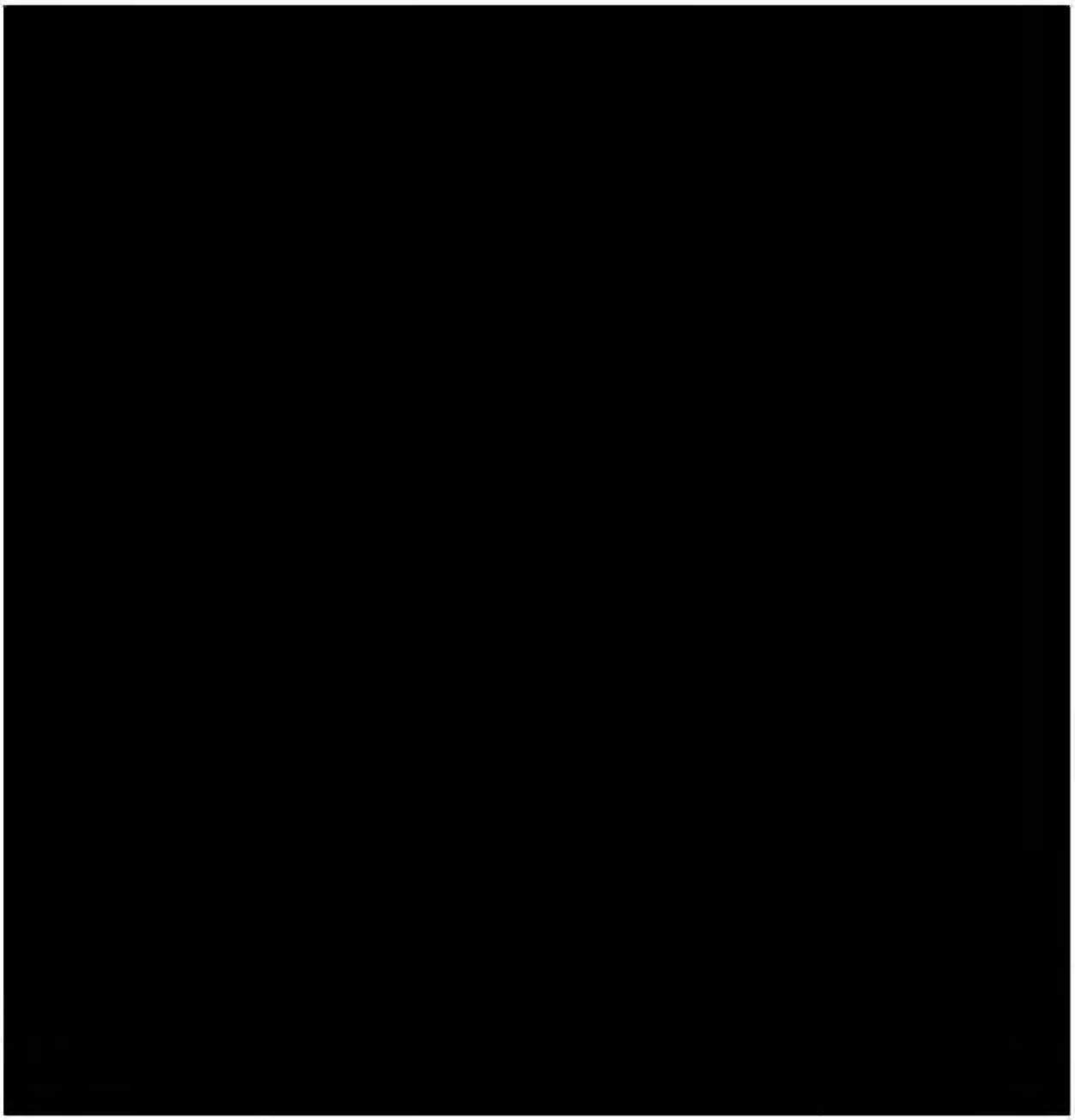

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8.0 ANNEXES TABLE OF CONTENTS

Annex No

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Annex 3: **Synopsis of ongoing and completed clinical trial programme**

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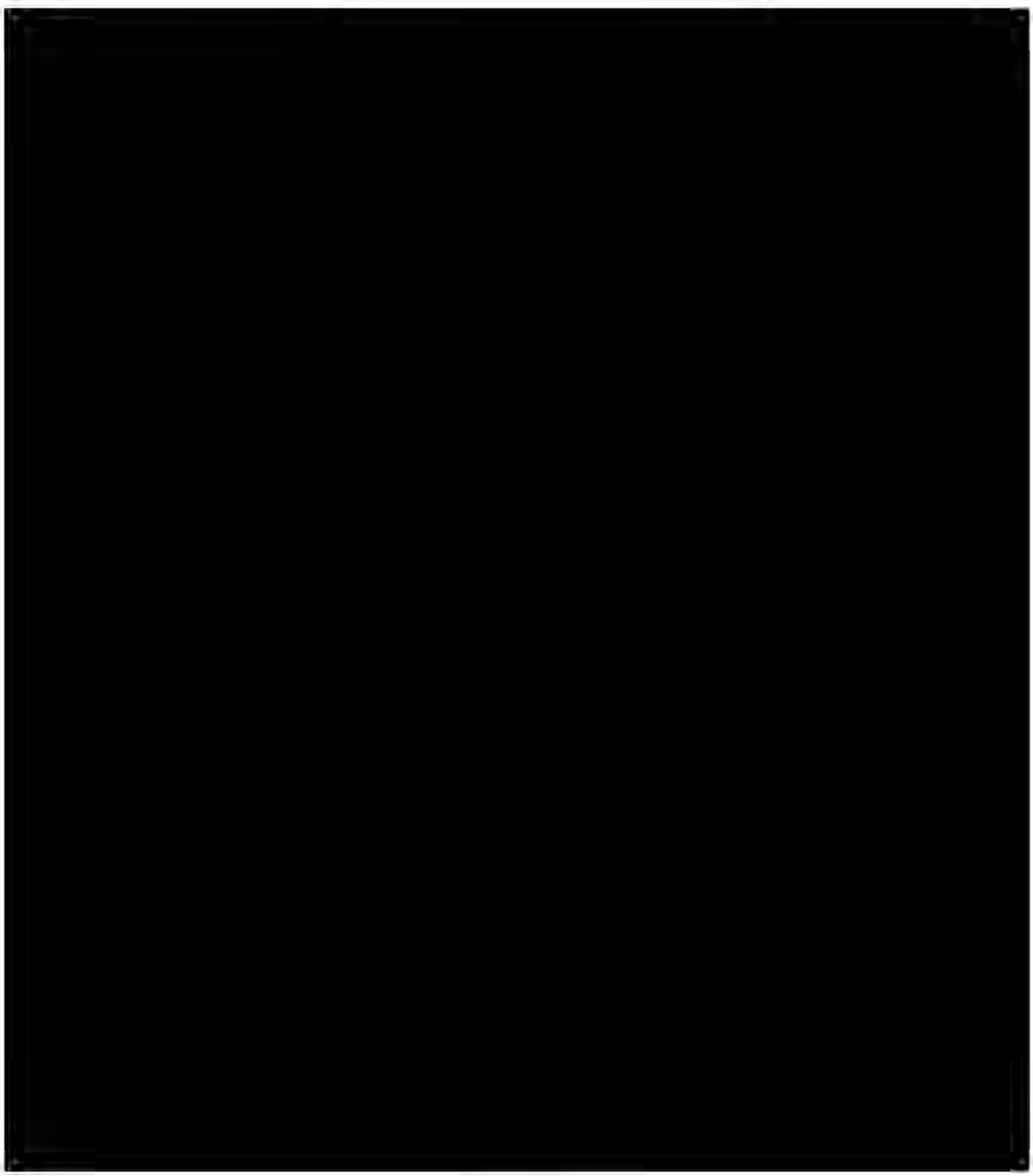

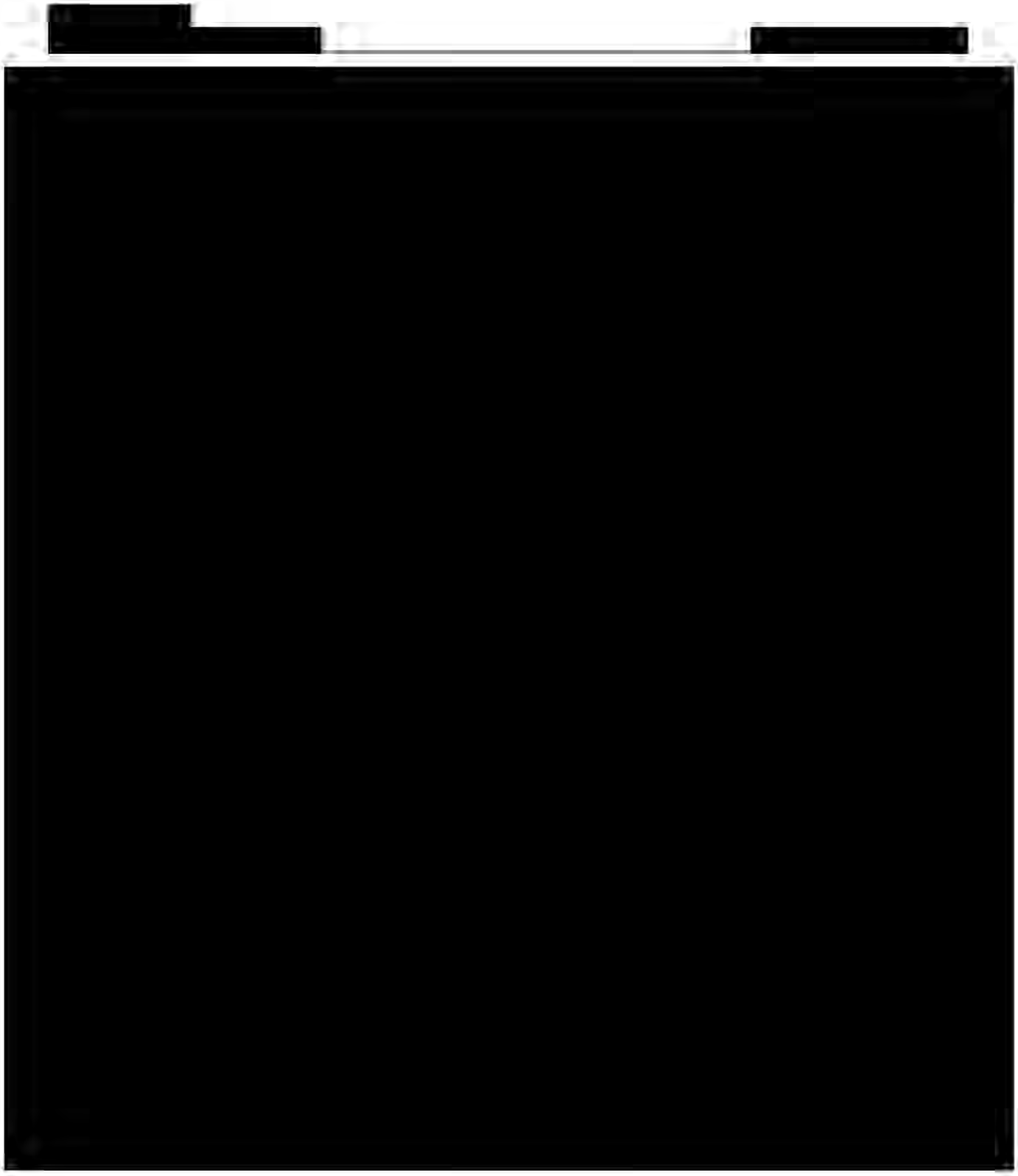

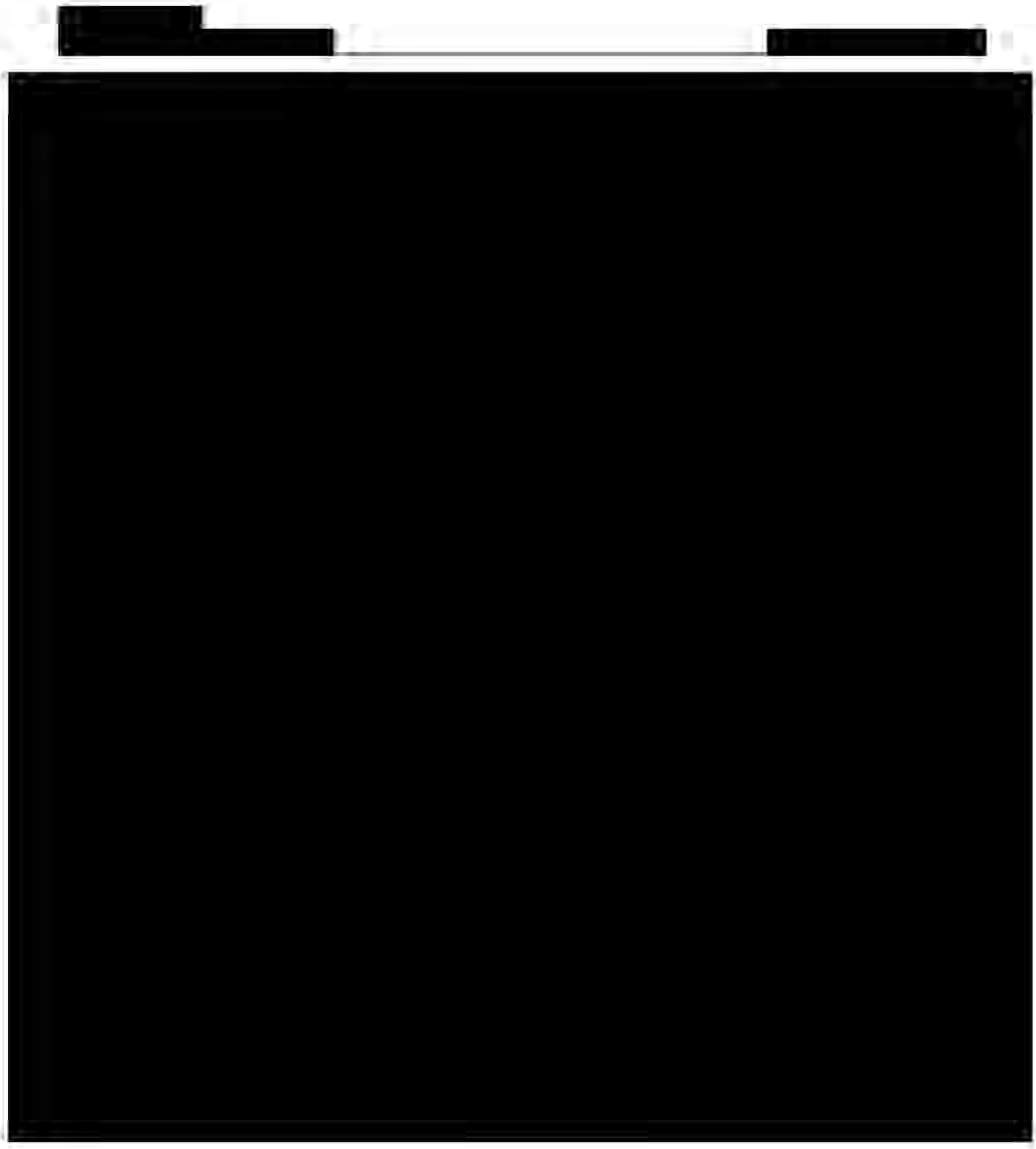

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Study no.	Study description Countries	Design No of subjects Study duration	Estimated/actual completion date
[redacted]	[redacted]	[redacted]	[redacted]
AD-4833_406	Meta-analysis of RCT data on bladder cancer	Meta-analysis	May 2011

[redacted]

[redacted]

[redacted]

Annex 4: Synopsis of ongoing and completed pharmacoepidemiological study programme

Study No. or Identifier	Description	Study design No. of patients Duration of follow-up	Estimated/actual completion date (dates when interim and final study reports are expected)
01-03-TL-OPI-524	Prospective cohort study of the incidence of bladder cancer in KPNC patients exposed to pioglitazone vs patients not exposed to pioglitazone	Observational [redacted]	First, second, and third interim analyses have been completed and submitted (Aug 2005, Aug 2007 and Dec 2009 respectively). Multiple additional analyses are planned; the last will be submitted in 2012.
01-03-TL-OPI-524	Nested case-control study of the incidence of bladder cancer in KPNC patients exposed to pioglitazone vs patients not exposed to pioglitazone (a)	Observational First interim analysis: [redacted] Second interim analysis: [redacted]	First and second interim analysis submitted in July 2006 and December 2009, respectively. Multiple additional analyses are planned; the last will be submitted in 2012.
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Study No. or Identifier	Description	Study design No. of patients Duration of follow-up	Estimated/actual completion date (dates when interim and final study reports are expected)
[redacted]			

[redacted]

Annex 5: **Protocols for proposed and ongoing studies in pharmacovigilance plan**

[redacted]

KPNC bladder cancer cohort study and KPNC bladder cancer nested case-control

[redacted]

Meta-analysis of bladder cancer (AD-4833-406)

[redacted]

[redacted]

Annex 6: **Newly available study reports**

KPNC bladder cancer cohort study and KPNC bladder cancer nested case-control

[redacted]

PROactive Extension study report

Meta-analysis of bladder cancer (AD-4833-406)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

Annex 8: **Details of proposed educational programme**

Proposed Direct Health Care Professional communication.

[redacted]

CONFIDENTIAL INFORMATION

Contains trade secret and/or confidential information, which is the property of Takeda as provided by 21 CFR § 20.61.

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Specific aims

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of transcription factors whose activities are regulated by high affinity binding of small lipophilic ligands such as steroid hormones [1]. A new class of diabetic drugs, the thiazolidinediones (TZDs), has been developed to bind to the gamma subtype of the PPARs. These medications have proved to be a valuable new therapy for type 2 diabetes mellitus. Three TZDs have been approved for marketing within the United States; two, ACTOS® and Avandia®, are currently available. Based on confidential information provided to us by Takeda Pharmaceuticals North America (TPNA), the question has arisen as to whether ACTOS use could possibly be associated with bladder cancer. Therefore, this proposal describes a method to utilize data from the Kaiser Permanente – Northern California (KPNC) diabetes registry, cancer registry, and other clinical databases to test this hypothesis. As such, the study would address the following specific aim:

1. To test the hypothesis that the risk of bladder cancer in patients with diabetes who receive ACTOS differs from that of other patients with diabetes, after adjustment for potential confounding variables.

Background

Bladder cancer

Bladder cancer is an uncommon cancer. Approximately 90% of all bladder cancers are transitional cell tumors. The incidence of bladder cancer is extremely low prior to age 40 and subsequently increases until at least age 80. The demographics of patients developing bladder cancer are similar to those of patients developing type 2 diabetes mellitus.

There are several well established risk factors for bladder cancer[2]. The disease is more common among men than women and more common among Caucasians than African-Americans. There are also several environmental exposures that are associated with an increased incidence of bladder cancer. Some of these were generally related to occupational exposures. Examples of this include aromatic amines to which workers in the dye, rubber, textile, and chemical industries may be exposed. Of note, exposure to these compounds was thought to have approximately a 20-year latency period until the development of bladder cancer.

Non-occupational exposures demonstrated or suggested to be associated with bladder cancer include cigarette smoking, chlornaphazine, phenacetin-containing analgesics, cyclophosphamide, thiotepa, melphalan, and radiation therapy. Most notable of these is cigarette smoking, which is believed to be responsible for 25% to 60% of all bladder cancers among populations in Western industrialized nations[2].

Chronic or repeated infection of the bladder is also believed to contribute to the development of bladder cancer. This is probably best demonstrated with schistosomiasis. However, frequent bacterial infections and chronic indwelling Foley catheters are believed to be associated with an increased risk of bladder cancer as well[2].

[redacted]

PPAR gamma

PPARs are members of the nuclear hormone receptor superfamily of transcription factors whose activities are regulated by high-affinity binding of small, lipophilic ligands such as steroid hormones, vitamin D, retinoids, and thyroid hormone. PPAR alpha, delta and a third subtype called gamma are related sufficiently to be considered members of a subfamily, and have similar properties including DNA binding specificity and heterodimerization with retinoid X receptor, whose ligands also activate the PPAR/RXR heterodimers. However, PPAR gamma has not been implicated in peroxisome proliferation, and although there is some overlap, PPAR gamma interacts with a different spectrum of lipophilic ligands compared with PPAR alpha. Ligands selective for PPAR gamma include Prostaglandin J_2 (PGJ_2) derivatives, such as 15-deoxy-Δ12,14-PGJ_2 (15d-PGJ_2), and anti-diabetic thiazolidinediones (TZD) compounds, including troglitazone, rosiglitazone, and pioglitazone, the latter two of which are currently in widespread clinical use for the treatment of type 2 diabetes mellitus.

Role of PPAR gamma ligands in treating diabetes mellitus

TZD PPAR gamma ligands have become an important therapy for diabetes mellitus. The currently available compounds were approved for solo and combination therapy with sulfonylureas, metformin, and/or insulin[3, 4]. An important feature of these compounds is that they increase insulin sensitivity, resulting in decreased insulin and insulin-like growth factor levels[5-8]. As such, they can be used to decrease insulin requirements in patients on insulin. Unlike sulfonylureas, TZDs do not increase insulin secretion or cause hypoglycemia when used alone. Unlike metformin, TZDs can be safely used in patients with renal insufficiency. For these reasons, the TZD PPAR gamma ligands have become an important therapeutic option for the treatment of type 2 diabetes mellitus. In general, the TZDs are well tolerated, although not indicated for use in patients with active liver disease or with advanced congestive heart failure. [3,4].

PPAR gamma and cancer

PPAR gamma is expressed in multiple tissues including adipose, liver, skeletal muscle, breast, kidney, prostate, and macrophages [9]. The function of PPAR gamma in non-adipose tissue is currently unknown. However, given that these compounds improve utilization of glucose[5-8, 10], it is plausible that these compounds could influence growth and proliferation of cells. Likewise, as an agonist for a nuclear hormone receptor, it is logical that TZDs might have the potential to influence cell proliferation and differentiation. TZDs have been shown to alter cell proliferation rates and differentiation in human liposarcoma [11], prostate cancer [12], papillary thyroid cancer [13], and breast cancer cell lines [14]. Furthermore, these compounds have been demonstrated to induce differentiation of liposarcoma in human patients [15]Thus, it is conceivable that these compounds could increase or decrease the risk of cancer of numerous organs; although the relationship between PPAR gamma expression and tumor initiation and progression remains to be clarified.

.Preliminary studies

The following preliminary studies were performed using electronic data from Kaiser Permanente Northern California (KPNC) for the purpose of demonstrating the feasibility of this research project. The following data are considered confidential.

[redacted]

The Kaiser Permanente Northern California Diabetes registry

[redacted]

[redacted]

To determine the size of the potential cohort from which we could select patients for the proposed study, we analyzed data from the KPNC diabetes registry. The diabetes registry identifies patients primarily from four data sources: primary hospital discharge diagnoses of diabetes mellitus (since 1971); two or more outpatient visit diagnoses of diabetes (since 1995); any prescription for a diabetes-related medication (since 1994); or any record of an abnormal Hb A1c test (>6.7%) (since 1991) (Table 1).

[redacted]

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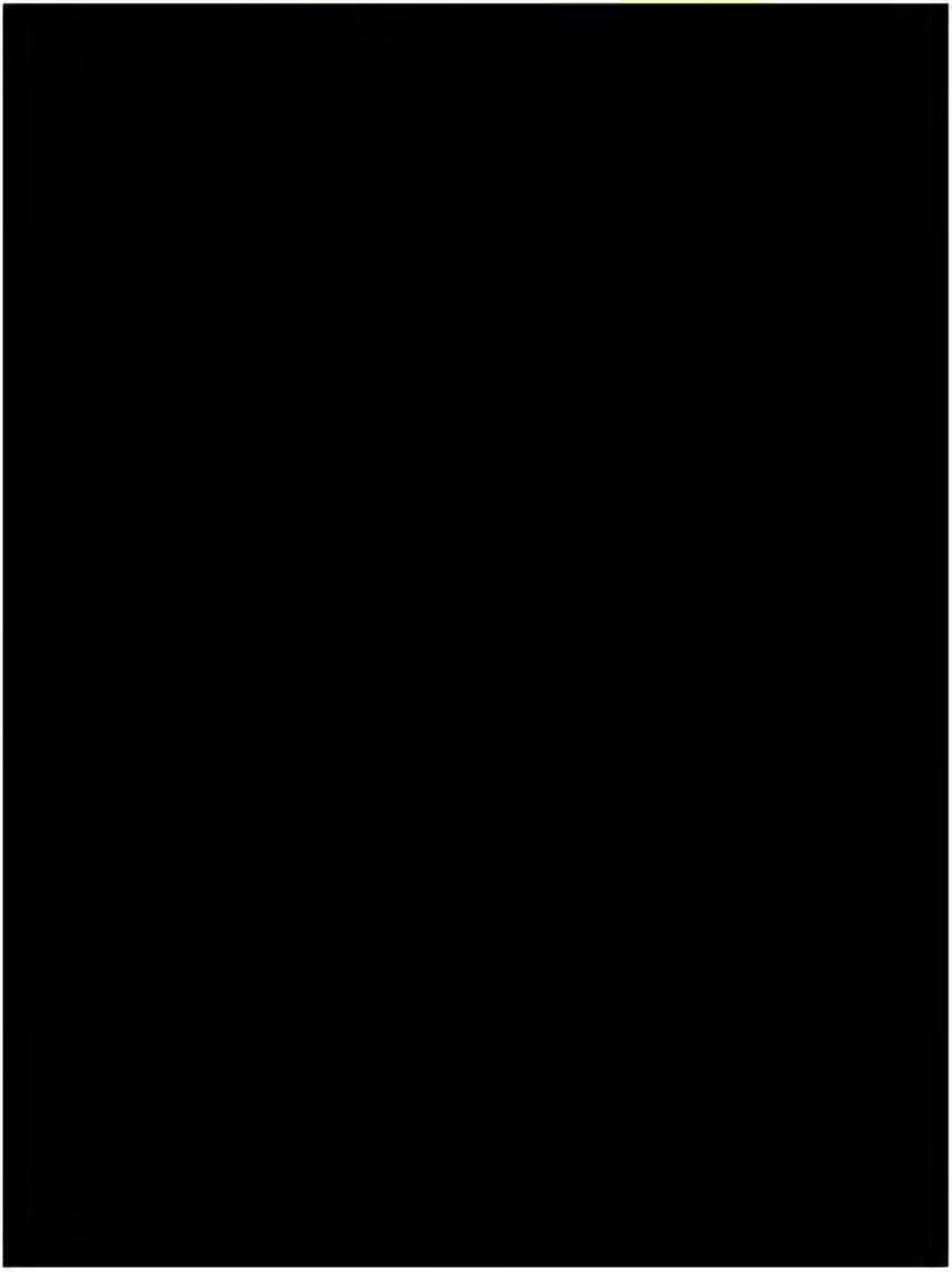

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Methods

Overview

The primary study being proposed is a cohort study in the KPNC diabetes registry cohort that will compare the incidence of bladder cancer in persons exposed to ACTOS with that of diabetic persons not so exposed. Follow-up begins in 1997 (to capture exposure to earlier TZDs) and will continue through 2012. All data will be derived from the automated KPNC diabetes registry, KPNC cancer registry, and other electronic clinical databases. Electronically available data will be used to identify endpoints, to

[redacted]

identify and quantify exposure to ACTOS and other diabetes therapies; and to adjust for a variety of potential confounding variables (glycemic control; disease severity; other diabetes therapy; and comorbid conditions). The only primary data collection is review and validation of cancer cases not already reviewed by the SEER registry.

In order to obtain more complete measurement of race, diabetes duration, and to measure additional potential confounders (especially lifetime smoking history and occupational exposures), we also propose a nested case-control study using recent cases from the cohort (2002-2007) and matched controls also drawn from the registry. Only recent cases will be selected so as to minimize potential bias from loss to follow-up and impaired recall of prior exposures. Data collection for the case-control study will use computer-assisted telephone interview (CATI) methods.

The use of the KPNC Diabetes registry data to create and follow this large cohort has multiple important advantages, including the enrollment of an unbiased and unselected cohort; the ability to enroll users retrospectively, increasing duration of follow-up; and markedly greater efficiency.

The use of the nested case-control design gives the efficiency advantages of case-control studies for variables that require primary data collection, while protecting against two major weaknesses of non-nested case-control studies, i.e., possible selection bias due to the method used to select the control group, and information bias due to inaccurate and incomplete ascertainment of antecedent drug use. In addition, the resources of KPNC allows for efficient recruitment of case and control subjects for the nested case-control study.

Data source

The KPNC Diabetes registry, described above, gathers data from a variety of KP electronic databases to build and follow the registry cohort across time. These data have been widely employed in prior epidemiological studies[16]. The health plan currently serves over 3.0 million subscribers and covers approximately 30% of the general population in the geographic areas covered[16]. Each record in all KP databases includes the member's unique medical record number. These numbers are assigned sequentially at initial joining and are never re-used.

The KPNC Cancer Registry

The Division of Research (DOR) maintains KPNC's cancer registry. All medical facilities in California are required by law to report all newly diagnosed cases of cancer to the California Cancer Registry (CCR), through a network of 10 regional registries that together capture the cancer incidence experience of the entire state. These include the San Francisco Bay Area SEER registry. All registries follow SEER practices in verifying and coding incident cancers. KP data abstractors use the same State of California-supported and SEER approved C/NET software used by the CCR elsewhere and transmit data electronically to the appropriate regional registry, where visual and computer editing of all cases is performed.

DOR consolidates all cancer incidence and follow-up data for KP members in the KP Northern California Cancer Registry. Unfortunately, data are not complete for more than 1 year after incidence. We will therefore use the KPNC registry to identify incident bladder cancers occurring between 1997 and 2001, but will use chart review and verify all potential cases occurring from 2002 forward using identical review forms and

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instructions identical to that of the KPNC registry. Our research staff will be trained by the registry abstractors. Note that identification of bladder cancers occurring between 1997 and 2012 is necessary for the cohort analyses; only those bladder cancers occurring from 2002 to 2007 will be used in the nested case-control analyses described below. A decision regarding the need to extend the case control study beyond 2007 will be made after reviewing the data through 2007.

Patient Demographics files

The patient demographics file contains information on patient date of birth, sex and address. This database is linked to the Length of Enrollment database, which contains membership information on each enrollment period for all current and past KPNC members. These databases allow us to censor on a monthly basis members who die or leave the health plan.

Outpatient and Inpatient diagnostic databases

Diagnostic databases will be one source for rapidly identifying potential new (incident) cases of bladder cancer. The Outpatient Services Clinical Record (OSCR) database captures physician-entered diagnoses and procedures at all outpatient visits. The database contains multiple diagnoses/procedures per visit. Both diagnoses and procedures are coded using International Classification for Disease (ICD-9) codes. OSCR became fully operational in May 1995.

The Admitting, Discharge, and Transfer System (ADTS) database records abstracted information (similar to the UB-92 form) for all inpatient stays at each of the 17 KPNC hospitals. This database has been computerized since 1971. This system records admissions, discharges and transfers as they occur. Data elements include patient name, KP medical record number, provider name, admission and discharge dates, principal and secondary diagnoses, and principal and additional procedure codes.

A similar system, the Claims Adjudication Tracking System (CATS) captures identical information for the 10% of hospitalizations of KP members that occur at non-KP hospitals.

Dispensed medications

As mentioned above, the Pharmacy Information Management System (PIMS) includes information on each outpatient prescription dispensed at any Kaiser pharmacy. Records include the patient member number, the drug name and strength, treatment regimen, date dispensed, and days supply. This database was on-line at all Northern California pharmacies by January, 1994. Approximately 95% of all KP members, including all those aged 65 years and above enjoy a KP pharmacy benefit. This means we are highly likely to capture all pharmacy utilization for these members because having the benefit makes it unlikely that patients would fill prescriptions at non-KP pharmacies (and be misclassified on exposure), and our database captures all prescriptions filled at any of 108 KP pharmacies. To decrease misclassification further, we often repeat analyses after deleting the 5% of members without the benefit.

Prior research has demonstrated that 80% to 85% of KPNC members fill all of their prescriptions at Kaiser pharmacies[16]. Furthermore, since the medications of interest in this study are relatively expensive, it is likely that the rate of utilization of Kaiser pharmacies is even higher.

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Electronic pathology reports

RAPTORS System: This is part of the Laboratory Utilization and Reporting System. Since 1997, it has captured coded pathology reports on every specimen (inpatient or outpatient) examined by KP pathologists. Information includes date and type of specimen, and histologic/pathologic diagnosis. Pathologic diagnoses are coded as SNOMED codes (which are the same as ICD03 morphology codes). Our KPNC cancer registry analyst searches this database monthly and will generate lists of new diagnoses of bladder cancer.

Electronic laboratory data

Laboratory Utilization and Reporting System (LURS) includes the performance and results of all laboratory tests conducted at either KPNC's central laboratory or any of the 17 hospital based laboratories. It is used for both clinical, quality control, and administrative purposes, and is considered to be the gold standard for laboratory results. Data items include ID number of provider who ordered the test, Kaiser medical facility, patient name, medical record number, test/procedure name, type and category, Current Procedural Terminology codes (CPT4), College of American Pathologists (CAP) codes for test/procedure, date test ordered and completed, and test result. This database will be utilized particularly to measure glycosylated hemoglobin concentration in an ongoing manner.

The Cohort Study

Cohort Inclusion criteria

The study cohort will include all patients who are in the KPNC Diabetes Registry and who are age 40 or older as of January 1, 1997; all additional registry members who reach age 40 at any point before December 31, 2002; patients age 40 or older who enroll in KPNC between January 1, 1997 and December 31, 2002 and who are identified as having diabetes; and all KP members age 40 or older who develop diabetes during this time period. Follow-up for bladder cancer begins for each person when they become eligible (i.e., on January 1, 1997, or a subsequent date when they are first identified as having diabetes and being 40 years of age).

We have elected to require enrollment in the diabetes registry between January 1, 1997 and December 31, 2002 for several reasons. Firstly, TZD PPAR gamma ligands were first marketed in the United States in 1997. It is possible that if there is an association between ACTOS and bladder cancer it could represent a class effect rather than solely an association with ACTOS. As such, it will be important to have subjects who are exposed to troglitazone and rosiglitazone, with and without subsequent ACTOS exposure. We have elected to stop enrollment as of December 31, 2002 so that all members of the cohort will have at least one year of follow-up time prior to the first analyses of data through December 31, 2003.

The lower age limit of 40 years helps to exclude Type 1 patients who are not apt to be exposed to TZDs. Moreover, bladder cancer is extremely rare prior to age 40 and such a diagnosis before age 40 may reflect patients with unusual cancer syndromes.

We will include all diabetes patients regardless of diabetes therapy at the onset of observation (i.e., those on diet therapy, oral hypoglycemic medications, insulin, or any combination of these). Medical therapy for type 2 diabetes is dynamic. We wish to

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capture all ACTOS exposure (and all exposure to other diabetes therapies). The planned study will extend over many years. Some patients initially treated with only diet control will later require oral medications, including ACTOS, or insulin. Likewise, patients initially requiring insulin will occasionally be switched to oral hypoglycemic regimens including ACTOS. By including all patients with type 2 diabetes mellitus, we will maximize the numbers of patients who are ever treated with ACTOS, increasing our statistical power and precision. Inclusion of persons who begin using ACTOS in later years will also increase the variability of exposure duration. Having some persons with only brief exposure to ACTOS will figure prominently in our analytic plans for examining the possibility that observed associations are confounded.

For all cohort members, follow-up will terminate with the earliest of the following events: 1) diagnosis of bladder cancer, 2) death from any cause, or 3) transfer out of KPNC for any reason, or 4) the end of study follow-up.

Cohort Exclusion Criteria

The only exclusion criteria are: age < 40 years and a diagnosis of bladder cancer recorded in the KPNC cancer registry prior to initiation of observation or within 6 months of entry into KPNC. In some analyses, patients without KP prescription benefits will also be excluded to check for possible misclassification (of exposure) bias, since their exposures may not be fully captured in KPNC's pharmacy database.

Determination of Exposure to ACTOS and other diabetes therapies

Within this cohort, study patients will be categorized as exposed to ACTOS (and also to any other diabetes medications) if they have ever received at least two prescriptions for the drug within a 6-month period. Requiring the second prescription helps to exclude the small fraction of patients who may fill a prescription but never actually take the medication. Filling two prescriptions within a reasonably brief period (6 months) seems, almost certainly, to be an indication that the medication is being used.

Identification of Outcomes

In the cohort study analyses, endpoints include all new, initial cases of bladder cancer occurring during observation of eligible patients. For cancers occurring through 2001, KPNC's cancer registry contains all incident cases. Each case has been reviewed and confirmed to be new and to be bladder cancer through the California Cancer Registry (i.e., SEER) review process. For cases occurring after 2001, we will augment registry efforts with our own chart reviews. This is necessary both for the timely calculation of cohort incidence rates and for rapid ascertainment of bladder cancer cases for recruitment to the nested case-control study. Initial identification will come from monthly reviews of pathology files, hospital discharge abstracts, and outpatient diagnoses. Chart review includes examination of all pathology reports, surgical reports and other procedure reports (e.g., cystoscopy) as well as discharge summaries and outpatient notes. SEER requirements include categorization of histopathology (transitional cell carcinoma, cloacogenic carcinoma, other), invasiveness, tumor size, extension, and lymph node involvement. Appendix A illustrates coding instructions from the SEER manual, which will be used for this study.

A small number of diabetic patients transfer out of KPNC each year. For example, in 1999, excluding those patients who died, approximately 5.2% of diabetics transferred out

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of the health system. Some of these patients will remain in California, while others will have moved out of the state. For those who remain in California, we can track their outcomes by searching the California cancer registry. This search will be performed in the fifth and the tenth year of the study for inclusion in the cohort analyses described below.

Cohort Data analyses

Calculating Incidence Density Ratios:

The first portion of the analysis will use descriptive statistics to describe the characteristics of the cohort. The primary analysis will then focus on the risk of bladder cancer as a function of exposure to ACTOS (and other diabetes medications). Crude incidence densities (events/# person-years) for bladder cancer and Poisson 95% confidence intervals will be calculated separately for persons ever exposed to ACTOS, other TZDs, sulfonylureas, metformin, other oral agents, and insulin. Persons can contribute person-time to multiple exposure groups. The rates for each exposure group will be compared by calculating incidence density ratios (IDR) and 95% confidence intervals [17], in which the denominator rates are for all person-time "not exposed" to the drug of interest, including persons never exposed as well as person-years prior to initial exposure.

In subsequent analyses, we will stratify all exposed follow-up time by quantity of total exposure (i.e. <1 year, 1-2 years, >2 years). In these analyses, individuals can contribute follow-up to more than one interval if they have used the drug for more than 1 year, i.e., they would contribute their first year to the first stratum, their second year to the second stratum, etc.

Multivariate modeling

The Cox regression model will be used for most of the analyses in this study. It allows adjustment for variation in time of cohort entry, exit, and total follow-up time. Coefficients from these models yield estimates of the relative hazard (HR), or risk for bladder cancer in a group of interest compared with that in a reference group (for example, the risk in persons ever exposed to ACTOS compared with that of persons never exposed; or the risk in persons exposed for more than 2 years to that of persons exposed for 1 year or less). The outcome variable will be time from entry into the cohort until the earliest of the following: diagnosis of bladder cancer, death, end of membership in KPNC, or end of study follow-up. For those who develop bladder cancer, this will be the time-to-event. For all others, this will be the censoring time. For each independent variable in the model, assumption of proportional hazards will be tested, and if it is not met, alternative methods will be used. Diabetes therapy will be included as a set of time-varying covariates. Results of the Cox regression models will be reported as HRs and their 95% confidence intervals (unless otherwise noted).

Adjusting for confounding and differential follow-up

As described in the background information, there are few known potential confounders in this study[2]. Importantly, because all comparisons in this study are made to other patients with type 2 diabetes mellitus, diabetes itself cannot confound the analyses.

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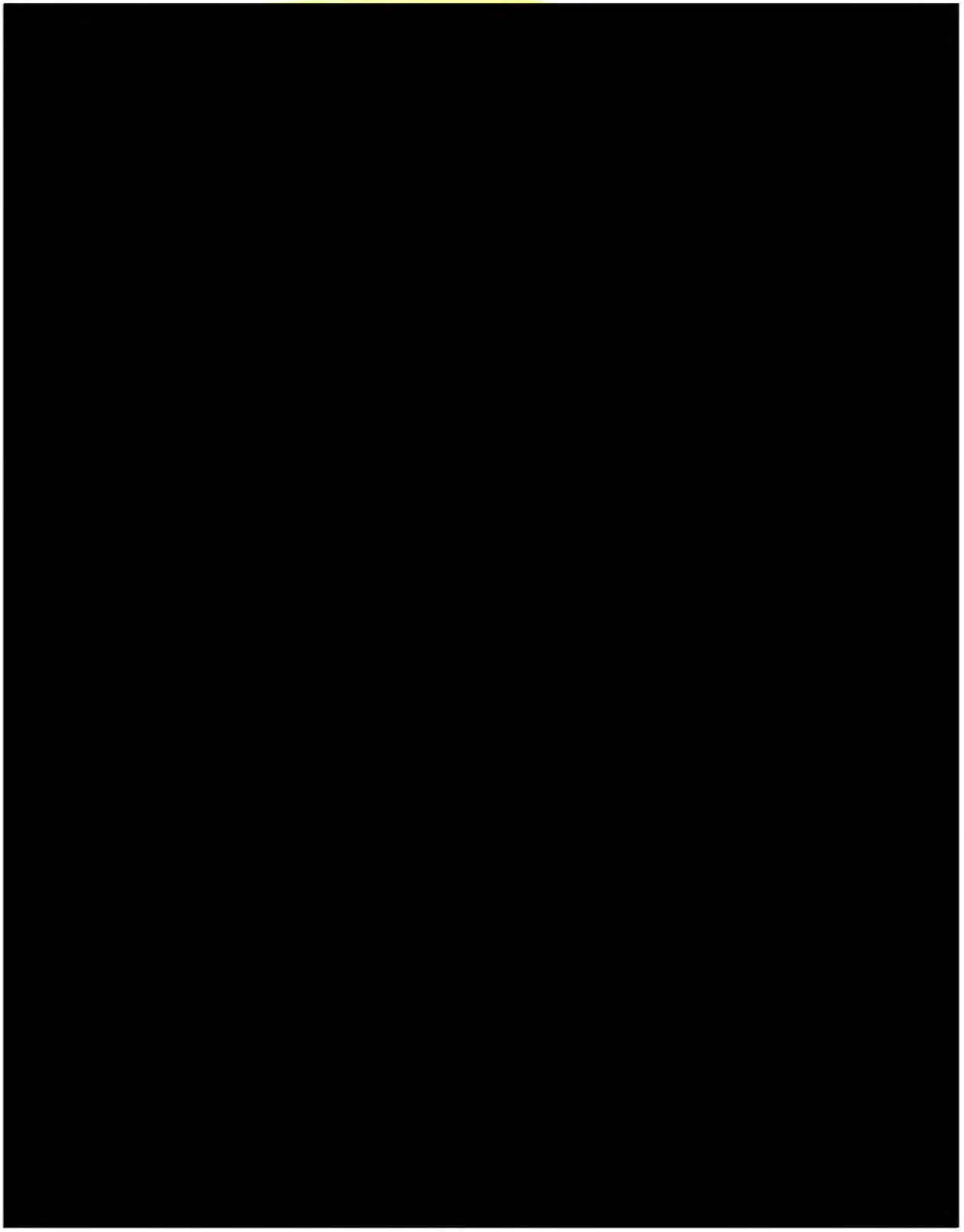

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Further Comments on Several Confounders

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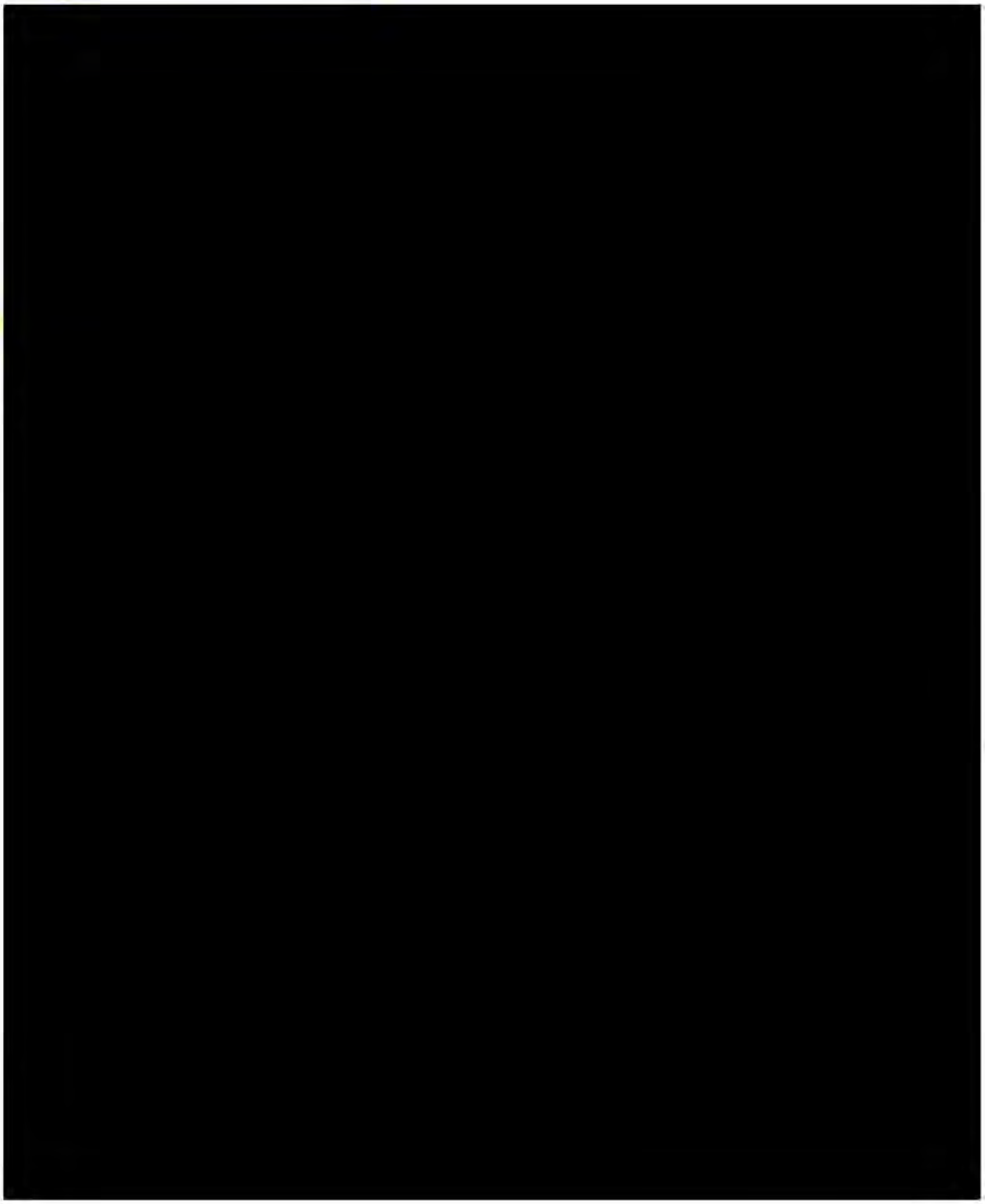

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Effect of duration of exposure

Our primary analyses will consider a person as exposed during all subsequent observed follow-up ("ever exposed" analyses). For these analyses, patients may contribute both unexposed and exposed follow-up time, the latter beginning with the date of filling the first prescription for the drug. Event rates are calculated using all observed exposed person-time after exposure begins.

The reason for conducting both "ever exposed" and "dose-response" analyses of exposure is that there is no good hypothesis at this point as to how ACTOS might be associated with bladder cancer risk. If it functions as a cancer "initiator", even brief exposures may be crucial; if as a promoter, the amount of exposure may be more important.

Duration of exposure includes two factors that may be related to risk for carcinogenesis: time since first exposure, and total exposure dosage. Time since first exposure is likely to be important simply because the carcinogenic process typically takes years to decades. It is plausible that there may be no increased risk expected until 5 years or even later. Analyses of earlier follow-up will predictably be negative and may simply dilute analyses that include later follow-up.

Duration of exposure is also related to the total dosage consumed. If repeated exposure is necessary to drive the carcinogenesis process, cumulative time of actual use may be more important than time since first use. For example, a person who use a carcinogenic medication ten years ago but used the medication for only 3 months may have a higher, lower, or comparable risk of cancer as someone who started the medication 3 years ago and used it for two full years.

Although the primary analysis will examine "ever exposure" to ACTOS, we will conduct additional analyses that account, one at a time, for these two aspects of exposure. We hypothesize that a true biological effect would be greatest among long-term users and expect to see a greater effect in patients who began the medications longest ago. The interval from initial exposure to end of follow-up will be examined by replacing the 'ever exposed' variable with a time-varying variable with the following levels of time since first exposure: "recent starter" (<18 months prior to index date), "less recent starter" (18 to 36 months prior to the index date), "distant starter" (>36 months prior to the index date), and "unexposed". We will then compare each level of time back to the no exposure level. For instance, we will focus some analyses on follow-up of > 3 years, acknowledging that cancer incidence during the first three years of exposure is unlikely to be causally related to the exposure. If we see an association of ACTOS use with bladder cancer during the first 1-2 years of exposure, this would suggest that we are observing a confounded association rather than a causal relationship.

Dosage will be examined separately from the interval since first exposure. These analyses will use all follow-up, and will determine dosage from the pharmacy database, using the number, timing, quantities and dosing instructions for ACTOS and other medications. We will be able to determine the total quantity of ACTOS received during all of follow-up. Most prescriptions are issued for 3-month pill supplies. We will make the frequently used assumption that exposure continues for four months after a 3-month prescription is dispensed. Intervals longer than 4 months constitute a gap in exposure; and for calculating quantitative exposure, subsequent person-time will not be used until another prescription is filled. In analyses similar to those for pack–years of cigarette

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smoking, we will test for a trend of increasing bladder cancer risk in relation to increasing total dose of ACTOS. To address dosage, we will create two time-varying covariates which again will replace the 'ever exposed' variable. These variables will be updated within the Cox model each time the patient fills a prescription for ACTOS. The first will be for total time of exposure, and it will have the following levels: never exposed, less than one year, 1-2 years, >2 years. The second will be for quantity of drug taken, taking into account the dosage and number of pills prescribed each time a prescription is filled. These two dosage variables will be included separately in Cox regression models.

Potential for left censoring

Although unlikely to be important in this study, left censoring is a common concern in pharmacoepidemiology studies using administrative data. Left censoring refers to bias resulting from missing data that occurred prior to the start of the administrative data. In this study, the concern would be that patients may be misclassified as unexposed if they previously started and discontinued ACTOS prior to enrolling in KPNC. Several features of this study make this unlikely. Firstly, most users of ACTOS are long-term users. Secondly, we will not enroll new patients after December 31, 2002. Thus this form of left censoring could only apply to patients who enroll in KPNC with an existing diagnosis of type 2 diabetes mellitus between the release of ACTOS onto the market and December 31, 2002, a relatively short time window.

Nonetheless, we have designed a sub-analyses specifically to assess the potential impact of left censoring. In this analysis, we will exclude from our cohort any patient who enrolls in KPNC with an existing diagnosis of type 2 diabetes mellitus between the release of ACTOS onto the market and December 31, 2002. Missed ACTOS therapy should not be possible among those remaining in this analysis.

Secondary analysis according to date of registration and diagnosis with diabetes

There is a small possibility that the results of the study could be biased by prescribing patterns if duration of diabetes is related to bladder cancer risk. To account for this possibility, we will perform two sub-analyses including only patients enrolled in KPNC prior to the date that TZDs were first marketed. Within this group we will first study those patients diagnosed with diabetes prior to 1997 and in a second analysis we will study those patients diagnosed with diabetes after 1997. Of course, this will considerably reduce our sample size in these subanalyses.

Repeated analyses of the cohort study

The described cohort analyses can first be conducted on patients in the database who meet inclusion criteria as of December 31, 2002 using data through December 31, 2003. We propose to repeat this analysis at two-year intervals thereafter until 2007. Thus, we will plan to complete analyses using data through 2003, 2005, and 2007. Additional analyses are planned in 2013, using data through 2012.

Nested case-control study

Because some potentially important confounders, particularly race/ethnicity and quantitative smoking data are not routinely recorded in the electronic records at KPNC, it

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will be necessary to conduct some primary data collection to determine whether these variables are confounders of the association between ACTOS and bladder cancer in a nested case-control study. A nested case-control study preserves the "cohort-based" nature of the analyses (i.e., it avoids selection biases that may arise in non-nested case-control studies).

Selection of case and control subjects for the nested case-control study

In the nested case-control study, all cases of bladder cancer within the cohort will be compared to a random sample of subjects without bladder cancer from the cohort. Each patient with bladder cancer will have an index date assigned that is the date of the first recorded diagnosis of bladder cancer. Selection of controls will be performed using incidence density sampling with the date of the matched case patient's first diagnosis with bladder cancer serving as the index date for the control. One control patient will be selected for each case patient. Control patients will be matched to the case patients on sex, age (± 2.5 years), and time from entry into the diabetes registry to index date (± 6 months). Because we will collect case and control patients prospectively, it is possible (but not problematic) that a patient could be included as a control subject and later as a case subject; this is inherent in incidence density sampling.

All cases will come from the cohort; rapid case ascertainment methods are the same methods described above for the cohort analyses. There should be ample cases to allow selection of just one control per case, which is the most efficient case-control design, although if it were necessary the numbers of controls could be increased. To increase the likelihood that cases are alive, still in the health plan, and able to participate, we will attempt to recruit patients within 3 months of diagnosis. Thus, most of the case-control recruitment will be performed prospectively. However, to augment the sample size, we will also recruit patients diagnosed in 2002-2003. Because mortality is low in bladder cancer, we expect that we will be successful in recruiting these patients as well. Importantly, by recruiting cases diagnosed between 2002 and 2003, we should have substantial power for preliminary analyses required by the FDA at the time of our first analyses.

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Primary definition of exposure to ACTOS in the case-control study

We will use identical definitions of exposure in the case-control study as in the cohort study. Thus for the primary analyses, we will consider a patient exposed to ACTOS if they have filled at least two ACTOS prescriptions within a 6 month period.

Analysis of the case-control study

The modeling for this part of the study will be done using conditional logistic regression[18]. The exposure of interest will still be ACTOS use. Results will be reported as odds ratios (OR) and their 95% confidence intervals (unless otherwise noted). Possible confounders will be identified in the same manner as was explained for the cohort study.

Secondary analyses of the case-control study

In secondary analyses of the case-control study, we will use varying definitions of exposure to further assess the association between duration, recency, and dose of

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exposure and risk of bladder cancer. These analyses in essence reproduce the similar analyses described for the cohort study, but allow for adjustment for potential confounders that are only collected in the case-control study. The variables for duration and exposure will be cumulative over the entire follow-up period as opposed to time-varying as they were in the cohort analysis.

The variable for dosage will be calculated slightly differently than in the cohort study. We will determine the total dispensed mg of ACTOS for each patient. This total dose will then be divided by the total number of days from the first prescription to the end of the last filled prescription (e.g., if first prescription was filled on 1/1/00 and the last prescription was for 31 days and was filled on 12/1/00, the total exposure period would be 365 days). This will determine the average daily dose. The average daily prescribed dose will be compared between cases and controls who are "users" of ACTOS using the Student's t-test. Average daily prescribed dose also will be subdivided into tertiles in order to create a categorical variable, and this measure of dosage exposure will be used in the logistic regression model.

To further assess the relation between duration and recentness of exposure, we will perform one final set of analyses. In these analyses, we will examine the interaction between recentness of exposure and duration of exposure and the interaction between recentness of first exposure and duration of exposure. If ACTOS truly increases the risk of bladder cancer, we would expect to see the strongest effect in long-term continuous users.

Additional models will be run after excluding the "non-users" to ensure that any trend we find in dosage is not simply testing "any" exposure versus no exposure. That is, the exclusion of "non-users" answers the question, "given any ACTOS exposure, does increasing dose increase the risk of bladder cancer still further?" Multiple logistic regression will also be performed to determine fully adjusted ORs for each of these dose categories.

Left censoring

Like with our cohort analyses, we will perform a subgroup analysis of our nested case-control study limited to cases and their matched controls who were enrolled in KPNC prior to the release of ACTOS on the market. For these subjects, all exposure to ACTOS should be completely recorded in the pharmacy data.

Comparison of non-participants to participants in the case-control study

Although we expect a high participation rate in the case-control study, it is possible that participants differ from non-participants. To address this, we will compare the participants to the non-participants on the available electronic data (table 3). These analyses will be performed separately for cases and controls.

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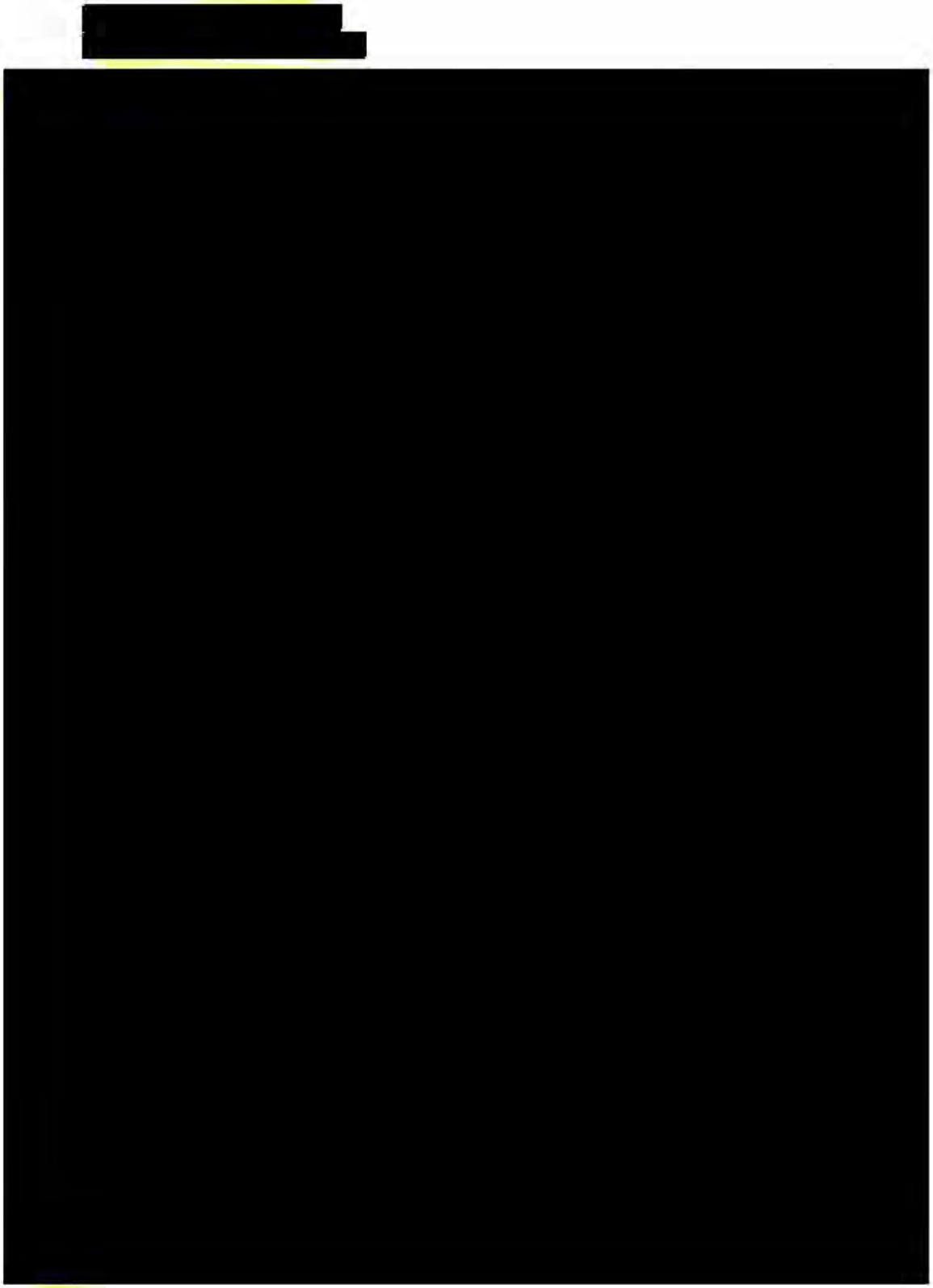

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Logistics

Data management

All data will be collected, managed, and analyzed at the Division of Research. DOR programmers, particularly, [redacted], are extremely familiar with the features of the data bases that will be used. Data analyses will be conducted under the oversight [redacted], and with input from the research team [redacted].

Electronic data

The obvious advantage of the KP setting for conducting this study is the efficiency derived from having multiple clinically relevant databases on very large numbers of persons with diabetes. However, execution of the study using these databases represents a substantial data management challenge. This complexity stems from the need for careful operationalization of definitions of cohort inclusion and exclusion criteria, case identification and verification, measurement and construction of a large number of covariates; careful quantification of exposure to each diabetes medication, and cohort follow-up to identify both endpoints and censor dates. Each of these tasks requires meticulous attention to details in programming. As has been previously described, each of these databases is independent of the others, although they are linked by unique identifiers. Data management will be an ongoing process during the entirety of the study and will be completed in a stepwise fashion.

Chart Review of Case Verification Data

The medical records, particularly the pathology reports, surgical reports, and hospital discharge summaries will be reviewed by a professional medical records analyst, with initial direct training by the KP cancer registry coder. An ongoing 5% sample of all cases reviewed will be re-reviewed by the project coordinator for quality assurance purposes. Disagreement rates >5% will trigger re-training of the records analyst. In addition, [redacted] will be the final arbiter of any cases where there is uncertainty after reviewing the pathology and clinical data as to whether the patient truly has bladder cancer.

Data from the chart reviews will be entered onto chart abstraction forms. Double data-entry with automated range and logic checks, will be conducted in the DOR's data entry department.

CATI Data from Case-control Study

The CATI interviews will be conducted a research assistant at the DOR, who will be supervised by the project coordinator. Interview data will be directly entered via a graphics interface into a SAS data set. These data will be reviewed for range and logic errors by [redacted] When cleaned, these data will be merged with data from the cohort on drug exposures, comorbidity indices, and other confounders.

Timeline

First five years of the study

The timeline presented here describes the first five years of work. The targeted start date for this study is mid 2004. During the first six months we will hire and train the project manager and the interviewers. We will develop the telephone questionnaire to be

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used in the nested case-control study. The questionnaire will be pilot tested on members of the research team and on persons with diabetes who are not eligible for the study. By September 1, 2004 we should be ready to apply the questionnaire to patients eligible for the study.

Much of the first 6 months will also be used to refine our algorithm to identify eligible patients with bladder cancer and matched controls. During the entirety of the first year, we will be actively generating computer programming to extract relevant data from the electronic resources of KPNC.

Creation of the first analytic data sets for the cohort analyses will be completed in mid 2004. This will allow for the first cohort analyses to be completed in late 2004 for a report to the FDA by the beginning of 2005. Importantly, however, we will not be able to complete a fully powered nested case-control analysis until we have collected data through approximately December 2005. Thus, we will target completion of our first analysis of the case-control data and creation of a report describing this analysis for July 1, 2006.

Repeated analyses of the cohort study are planned in 2006 (using data through 2005) and in 2008 (using data through 2007). A repeat analysis of the larger case-control data is planned for 2008 as well. Subsequent analyses of cohort data collected through 2012 are planned in 2013. If the distribution of potential confounders that are only available through patient interview does not differ among ACTOS users and non-users in the 2008 analyses, repeat of the nested case-control study may not be necessary for the 2013 analyses.

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Conclusions

This study is designed to assess the relative risk of bladder cancer among persons exposed to ACTOS therapy for type 2 diabetes mellitus. The study uses an efficient cohort design, incorporating the advantages of the existing electronic data sources at KPNC; in addition, the nested case-control study takes advantage of the ability of the KPNC's Division of Research to rapidly perform patient interviews to collect data not routinely recorded in the electronic medical record. Perhaps equally as important, within the proposed design, the study cohort can be followed forward at pre-defined intervals, allowing for the efficient completion of repeated analyses after longer periods of exposure.

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CLINICAL STUDY REPORT

AD-4833_406

Long Title:	Meta-Analysis of Bladder Cancer Reported During Randomized Controlled Clinical Trials of Pioglitazone HCl (ACTOS)
Sponsor:	Takeda Global Research & Development Center, Inc. One Takeda Parkway Deerfield, IL 60015
IND Number:	Not applicable **EUDRACT Number:** Not applicable
NCT Number:	Not applicable
Study Drug:	Pioglitazone HCl
Indication Studied:	Not applicable
Study Phase:	Not applicable
Study Dates	Not applicable
Early Study Termination Date:	Not applicable
Sponsor's Responsible Medical Officer:	Not applicable
Report Date:	13 May 2011

This study was performed in accordance with Good Clinical Practice.

3.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

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* No content exists for this appendix.

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4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
BMI	body mass index
CI	confidence interval
CV	cardiovascular
EMA	European Medicines Agency
HbA1c	glycosylated hemoglobin
HR	hazard ratio
KPNC	Kaiser Permanente Northern California
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MTD	maximum tolerated dose
RR	risk ratio
PPAR	peroxisome proliferator-activated receptor
SAP	statistical analysis plan
SU	sulfonylurea
T2DM	Type 2 diabetes mellitus
TGRD	Takeda Global Research & Development Center, Inc.
TZD	thiazolidinedione

[redacted]

5.0 ETHICS

All studies included in the meta-analyses were conducted with respect for the individual participants (ie, subjects), according to the protocol, the World Medical Association Declaration of Helsinki, the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice, and other applicable regulatory requirements. Conduct of the individual studies was governed by the appropriate Ethics Committee or Institutional Review Board. Prior to undergoing any study procedures, subjects were required to sign and date a subject informed consent form. Subjects were free to withdraw from the study at any time without having to provide a reason.

[redacted]

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Not applicable.

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7.0 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by insulin resistance and defective insulin secretion, causing abnormalities in glucose and lipid metabolism. Comorbidities of microvascular and macrovascular disease are common with T2DM, placing a high burden on healthcare.

The association between diabetes and risk of development of bladder cancer and other cancers has been investigated in several recent epidemiological studies [1,2]. A recent publication by the Emerging Risk Factors Collaboration [2] showed an increase in the risk of death from bladder cancer in patients with diabetes at baseline compared to those without diabetes at baseline (hazard ratio [HR]=1.4, 95% confidence interval [CI]: 1.01, 1.96). In addition, a meta-analysis of data from published studies that specifically evaluated the association between diabetes and the risk of bladder cancer was conducted in 16 studies (7 case-control studies, 3 cohort studies, and 6 cohort studies of hospitalized diabetic patients). Analysis of all 16 studies revealed that diabetes was associated with a statistically significant increased risk of bladder cancer compared with no diabetes (risk ratio [RR]=1.24, 95% CI: 1.08, 1.42). Between-study heterogeneity was statistically significant (P<0.0001). Cigarette smoking has previously been established as a risk for bladder cancer, and 7 studies controlled for history of smoking. After controlling for this major confounder, these studies showed a statistically significant positive association between diabetes and the risk of bladder cancer. Overall, results of this meta-analysis suggest that diabetes is an independent risk factor for bladder cancer [1].

Pioglitazone is a thiazolidinedione (TZD)-type peroxisome proliferator-activated receptor-gamma (PPAR)γ agonist that increases transcriptional activity of genes encoding proteins involved in lipid metabolism, glucose utilization, and insulin sensitivity [3], used in the treatment of T2DM. Pioglitazone is indicated as an adjunct to diet and exercise to improve glycemic control, however, it is generally not used as a first line therapy [4].

[redacted]

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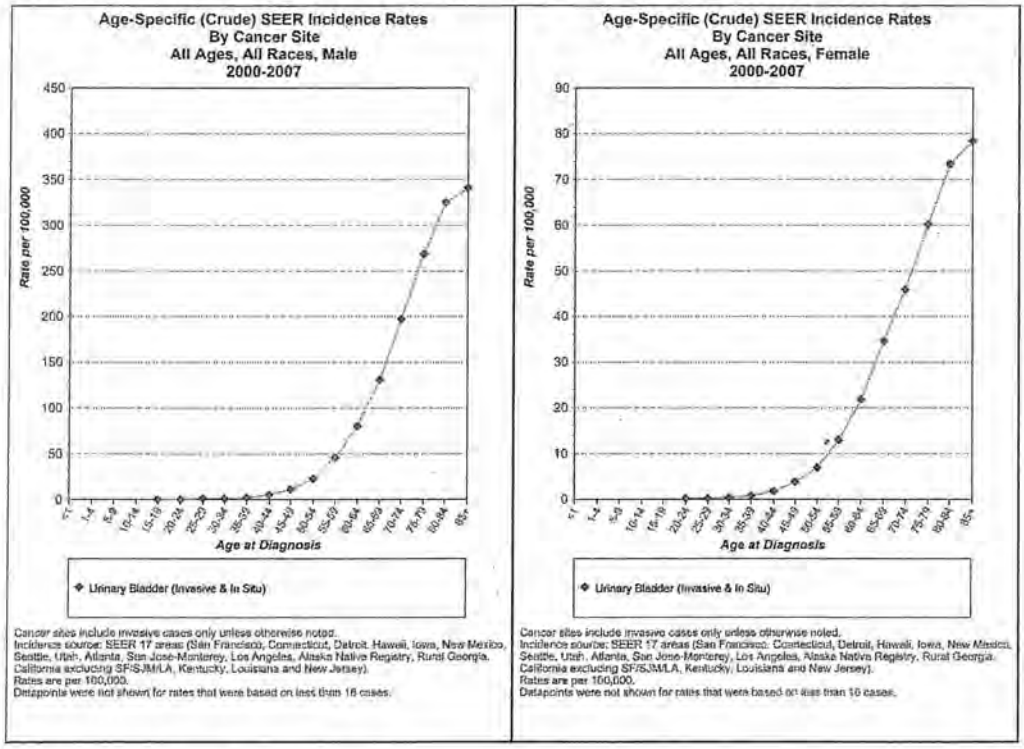
Demographically, bladder cancer is approximately four times more common in males than females, and the incidence increases rapidly with increasing age as shown below in Figure 7.a.

Figure 7.a Incidence of Bladder Cancer by Age



Source: SEER (http://seer.cancer.gov)

An ongoing epidemiological study is being performed on patients in the Kaiser Permanente Northern California (KPNC) database with interim results showing that there is no overall statistically significant increased risk of bladder cancer among patients ever treated with pioglitazone [7]. However, analyses addressing increasing exposure to pioglitazone suggest an increased risk of longer-term therapy.

The present meta-analysis was conducted at the request of the European Medicines Agency (EMA) to provide additional information on pioglitazone and bladder cancer.

[redacted]

8.0 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this meta-analysis was to evaluate the risk of bladder cancer in subjects with T2DM treated with pioglitazone vs. comparator (placebo or active control) in randomized, controlled clinical trials in the pioglitazone clinical database, excluding subjects with bladder cancers with onset date less than one year (<365 days) after the first dose of study drug.

The decision to exclude subjects with a diagnosis of bladder cancer in the first year was based on the long latency period between initial exposure to a compound and the detection of the outcome. In fact, for most agents the latency for the development of bladder cancer is usually 10 years and frequently longer than 20 years [8], and even after exposure to the most potent known human bladder carcinogens, cyclophosphamide and aristolochic acid, tumors rarely appear before 4 years and never before 1 year. The plan to exclude subjects with an early diagnosis of bladder cancer (within 1 year of randomization) for the primary objective is consistent with the recommendation of the independent review committee used to examine the cases of bladder cancer in the PROactive study (EC444) [9]. In their blinded assessment of causality of the bladder cancer cases in PROactive, the experts independently eliminated cases that were reported within 1 year of randomization because of a lack of pharmacological plausibility.

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9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Description

All Takeda Global Research and Development (TGRD) phase 2 through 4 comparator-controlled studies with patient level data available were included in the summaries and analyses (Table 9.b). All studies included in this meta-analysis were from the pioglitazone clinical trials database in which subjects with T2DM were evaluated. In order to maximize comparability and reduce bias, the studies included in the meta-analysis must have fulfilled the following two criteria:

- randomized.
- controlled (placebo or active control).

For the purpose of this meta-analysis, bladder cancer was identified from the Medical Dictionary for Regulatory Activities (MedDRA) classification of investigator adverse event (AE) reports. The list of preferred terms classified as "bladder cancer" is provided in Table 9.a.

Table 9.a List of Preferred Terms for Bladder Cancer

Endpoint Event: Bladder Cancer			
Bladder adenocarcinoma recurrent	Bladder cancer recurrent	Bladder squamous cell carcinoma recurrent	Bladder transitional cell carcinoma recurrent
Bladder adenocarcinoma stage 0	Bladder cancer stage 0, with cancer in situ	Bladder squamous cell carcinoma stage 0	Bladder transitional cell carcinoma stage 0
Bladder adenocarcinoma stage I	Bladder cancer stage 0, without cancer in situ	Bladder squamous cell carcinoma stage I	Bladder transitional cell carcinoma stage I
Bladder adenocarcinoma stage II	Bladder cancer stage I, with cancer in situ	Bladder squamous cell carcinoma stage II	Bladder transitional cell carcinoma stage II
Bladder adenocarcinoma stage III	Bladder cancer stage I, without cancer in situ	Bladder squamous cell carcinoma stage III	Bladder transitional cell carcinoma stage III
Bladder adenocarcinoma stage IV	Bladder cancer stage II	Bladder squamous cell carcinoma stage IV	Bladder transitional cell carcinoma stage IV
Bladder adenocarcinoma stage unspecified	Bladder cancer stage III	Bladder squamous cell carcinoma stage unspecified	Metastatic carcinoma of the bladder
Bladder cancer	Bladder cancer stage IV	Bladder transitional cell carcinoma	Bladder neoplasm

Note: Based on MedDRA Version 13.1.

[redacted]

[redacted]

Table 9.b Studies Included in the Meta-Analysis

[redacted]

9.2 Selection of Study Population

The subject population was screened using predefined inclusion and exclusion criteria in each study to select subjects who did not have conditions that would present undue safety risks, interfere with the absorption or metabolism of study drug, confound the efficacy and safety analyses or interpretation of data, or otherwise interfere with the study objectives. All studies included adult subjects who had a previous diagnosis of T2DM and inadequate glycemic control.

9.2.1 Method of Assigning Subjects to Treatment Group

All studies included in the meta-analyses included a treatment randomization procedure. The randomization codes, subject identifiers, and treatments assigned to each subject are listed in the appendices of the individual study reports.

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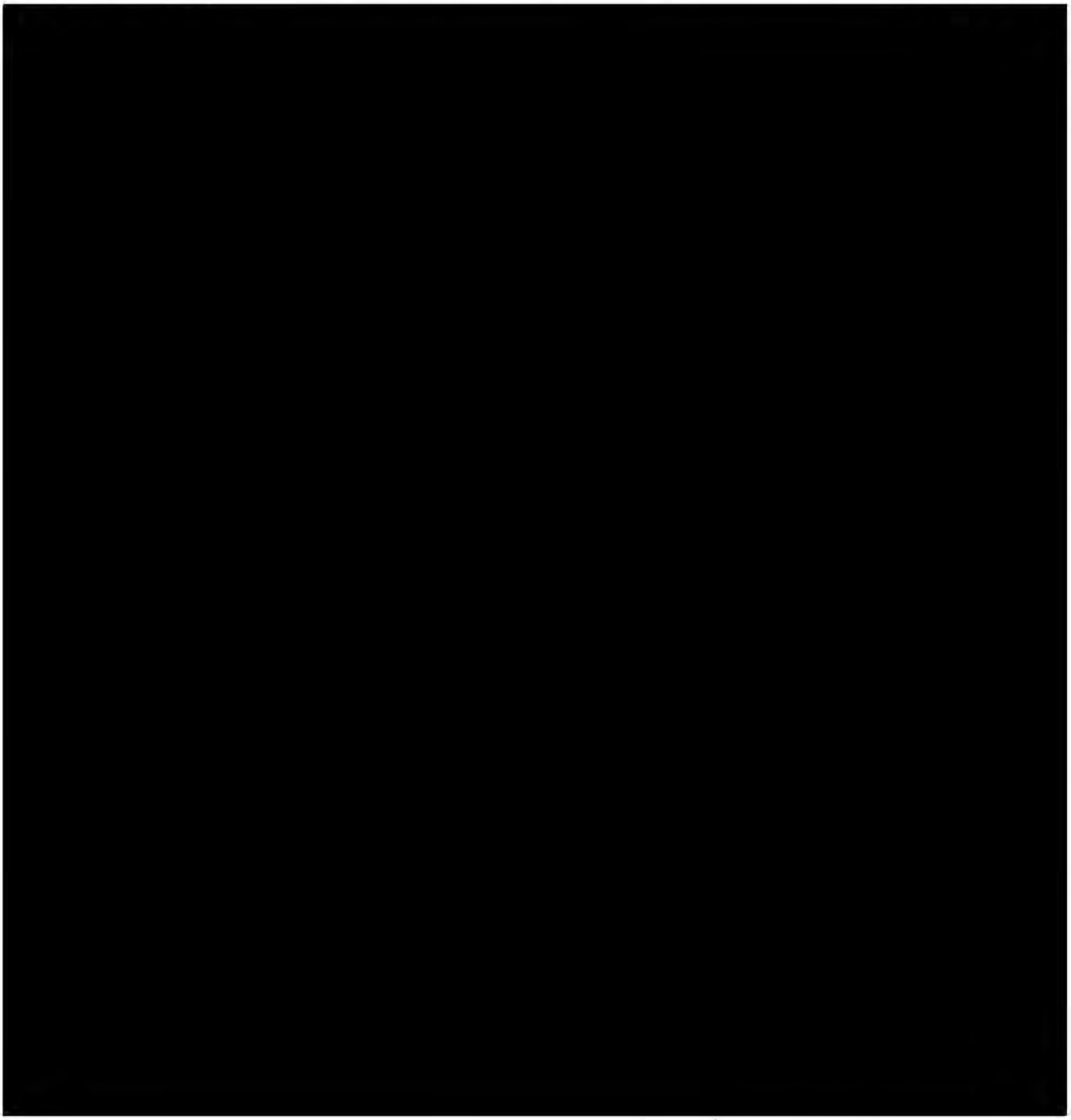

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9.2.3 PROactive (EC444)

PROactive was a double-blind, randomized, placebo-controlled cardiovascular (CV) outcomes study conducted by TGRD Europe, involving subjects with inadequately controlled T2DM and

[redacted]

established history of macrovascular disease as defined in the protocol. Pioglitazone was force-titrated from 15 mg (or matching placebo) to the maximum tolerated dose (MTD) up to 45 mg (or matching placebo) by the Month 2 visit; subjects continued on the highest tolerated dose throughout the treatment period (up to 3.5 years). Concomitant antidiabetes medications and CV medications were adjusted throughout the study with the goal of achieving and maintaining target HbA1c, blood pressure, and lipid levels and reducing CV risk. The subject population for PROactive differed from other clinical trials in the database in that the subjects were older, had a longer duration of diabetes prior to randomization, and were at risk for a CV event.

The primary objective of PROactive was to test the hypothesis that pioglitazone reduces total mortality and cardiovascular morbidity in high-risk subjects. The primary efficacy variable for PROactive was a composite of all-cause mortality, nonfatal myocardial infarction (MI) (including silent MI), stroke, acute coronary syndrome, cardiac intervention (including coronary artery bypass graft or percutaneos coronary intervention), major leg amputation, and bypass surgery or revascularization in the leg. All endpoint events were specifically adjudicated by a blinded, centralized committee of experts, as specified in the protocol.

In PROactive, a total of 5238 subjects were included in the safety analysis set, with 2605 in the pioglitazone arm and 2633 in the placebo arm.

9.3 Analysis Variables for the Meta-Analysis

The primary analysis (primary endpoint) for the meta-analysis was the time (days) from date of first study dose to the date of first occurrence of an event of bladder cancer at any time.

If a subject did not experience bladder cancer, the subject was censored with the time-to-event set to equal to the number of days from the date of first study dose to the date of the end of study.

9.4 Statistical Methods

A summary of the primary statistical methods used in this meta-analysis are summarized below, and the complete Statistical Analysis Plan (SAP), dated 08 April 2011, is provided in Appendix 16.1.9.

The primary analysis is the analysis of time (days) from the first dose of study medication to the first occurrence of an event of bladder cancer, using stratified Cox proportional hazard methodology to estimate the hazard ratio of pioglitazone versus comparator and its 95% CI, where the stratification factor is study. Since the underlying assumption of proportional hazards may not be realistic across all the studies due to the inherent differences among the studies (eg, study design, patient populations), the stratified analysis is deemed a more appropriate approach since it does not require the proportional hazards assumption with respect to study. Additional covariate variables in the model are: (1) age (age at baseline), (2) gender (male vs female), (3) smoking status, and (4) cancer (whether a subject had any prior cancer). A covariate for cancer causing agents was considered but ultimately was not included since the use was very infrequent and no subjects with bladder cancer took a cancer causing agent. A list of cancer causing agents considered is included in the SAP.

[redacted]

The primary analysis was performed excluding subjects with early diagnosis of bladder cancers (ie, with onset date < 365 days after first dose). The decision to exclude subjects with a diagnosis of bladder cancer in the first year was based on the long latency period (years) for development of bladder cancer [8].

The events of bladder cancer in this meta-analysis were identified based on investigator AE reports (preferred terms) using the list of MedDRA preferred terms in Table 9.a.

The AEs summarized in this meta-analysis were coded at the preferred term level according to MedDRA Version 13.1, regardless of the version used to code AEs in the original protocol.

The assumptions of proportional hazards in the time-to-event analysis were examined, and the results in SAS outputs are included in Appendix 16.1.9.2. There was no violation of assumptions of proportional hazards detected in the fitted models for Table 2.2.1 through Table 2.3.4.

9.4.1 Determination of Sample Size

Not applicable.

9.5 Changes in the Conduct of the Study or Planned Analyses

The original SAP was dated 08 April 2011, and the following corrections and analyses were added after the SAP approval.

1. Corrected the misclassification of 2 studies (SYR-322OPI-001 and SYR-322OPI-002) in Table 5.a in the SAP. The 2 studies were both 26-week studies, and were classified as studies with duration of "≥1 year and <2 years". The correction did not have impact on the analysis results, as the classification was not used as a factor in the analysis.
2. Added "Cancer-Related Mortality" and "CV-Related Mortality" to Table 4.1, 4.2 and 4.3. The HR, their CIs, and P-values based on Cox proportional hazard models were also added.

[redacted]

The objective of the additional analysis is to put the analysis of risk of bladder cancers into a broader perspective of risk-benefit assessment of pioglitazone.

3. An analysis of bladder cancer in subjects in the PROactive study excluding subjects with early diagnosis of bladder cancer (Table 2.2.4 and 2.3.4) was added to the secondary analysis.

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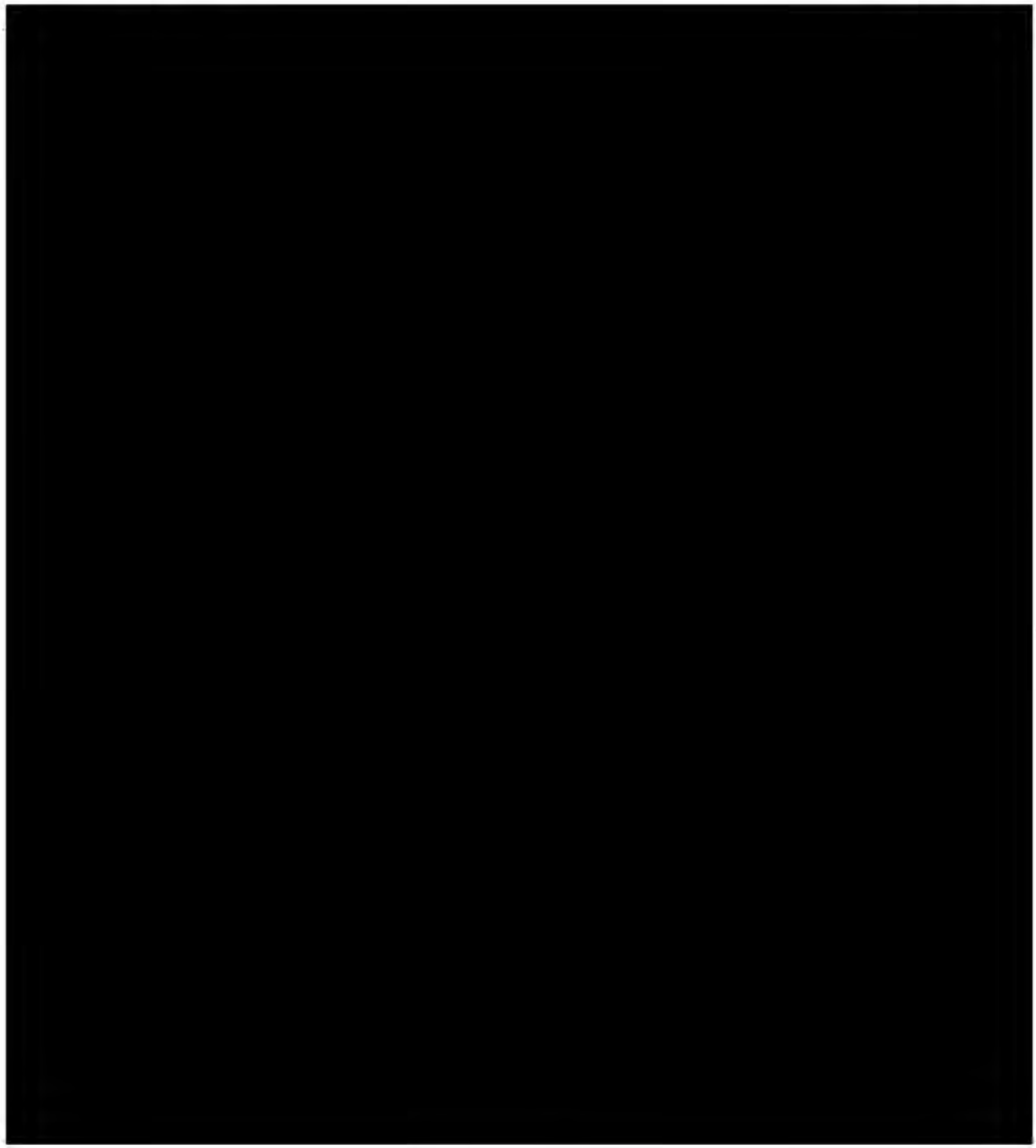

11.0 BLADDER CANCER META-ANALYSIS

11.1 Data Sets Analyzed

Analyses for bladder cancer were performed on the following groups of subjects (performed on subjects who took at least 1 dose of study drug [Safety Population]):

- Primary Analysis: All subjects in all controlled studies, excluding subjects with bladder cancer with onset date less than one year (<365 days) after the first dose of study drug

[redacted]

11.1.1 Data Presentation

For all tables, an early diagnosis of bladder cancer is defined as onset date less than 1 year after first dose of study drug (<365 days). In addition, AEs are in MedDRA version 13.1 and AEs with an onset date on or after the first dose of study drug are included in the analysis. The list of preferred terms classified as "Bladder Cancer" is presented in Table 9.a.

11.2 Demographic and Other Baseline Characteristics

11.2.1 Demographic Characteristics

Demographics and other baseline characteristics are presented for all controlled studies (excluding subjects with early diagnosis of bladder cancer) in Table 1.2.1 and summarized in Table 11.a. Demographics and other baseline characteristics are presented for subjects with early diagnosis of bladder cancer in Table 1.2.2 and for all subjects in PROactive in Table 1.2.3.

[redacted]

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11.3 Bladder Cancer Meta-Analysis Results

11.3.1 Primary Analysis

The primary analysis was the analysis of time (days) from the first dose of study medication to the first occurrence of an event of bladder cancer, using stratified Cox proportional hazard methodology to estimate the HR of pioglitazone versus comparator and its 95% CI, where the stratification factor is study.

Results of the primary analysis for all controlled studies (excluding subjects with an early diagnosis of bladder cancer) are displayed as a Kaplan-Meier curve in Figure 2.2.1.

The risk analysis for bladder cancer is presented for all study groups (excluding those with an early diagnosis of bladder cancer) in Table 2.2.1 and summarized in Table 11.c.

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[redacted]

In PROactive, 14 subjects in the pioglitazone group and 5 subjects in the comparator group had an event of bladder cancer. When subjects who had a diagnosis of bladder cancer in the first year were excluded, 6 subjects in the pioglitazone group and 2 in the comparator group had an event of bladder cancer. When all subjects were included in the secondary analysis, there was a suggestion of an increased risk for bladder cancer among subjects treated with pioglitazone versus comparator group; however, this did not reach statistical significance (P-value=0.053). The HR was 2.739 (95% CI: 0.986, 7.605). When subjects with an early diagnosis of bladder cancer were excluded, the HR was 2.963 (95% CI: 0.598,14.482) with P-value = 0.184.

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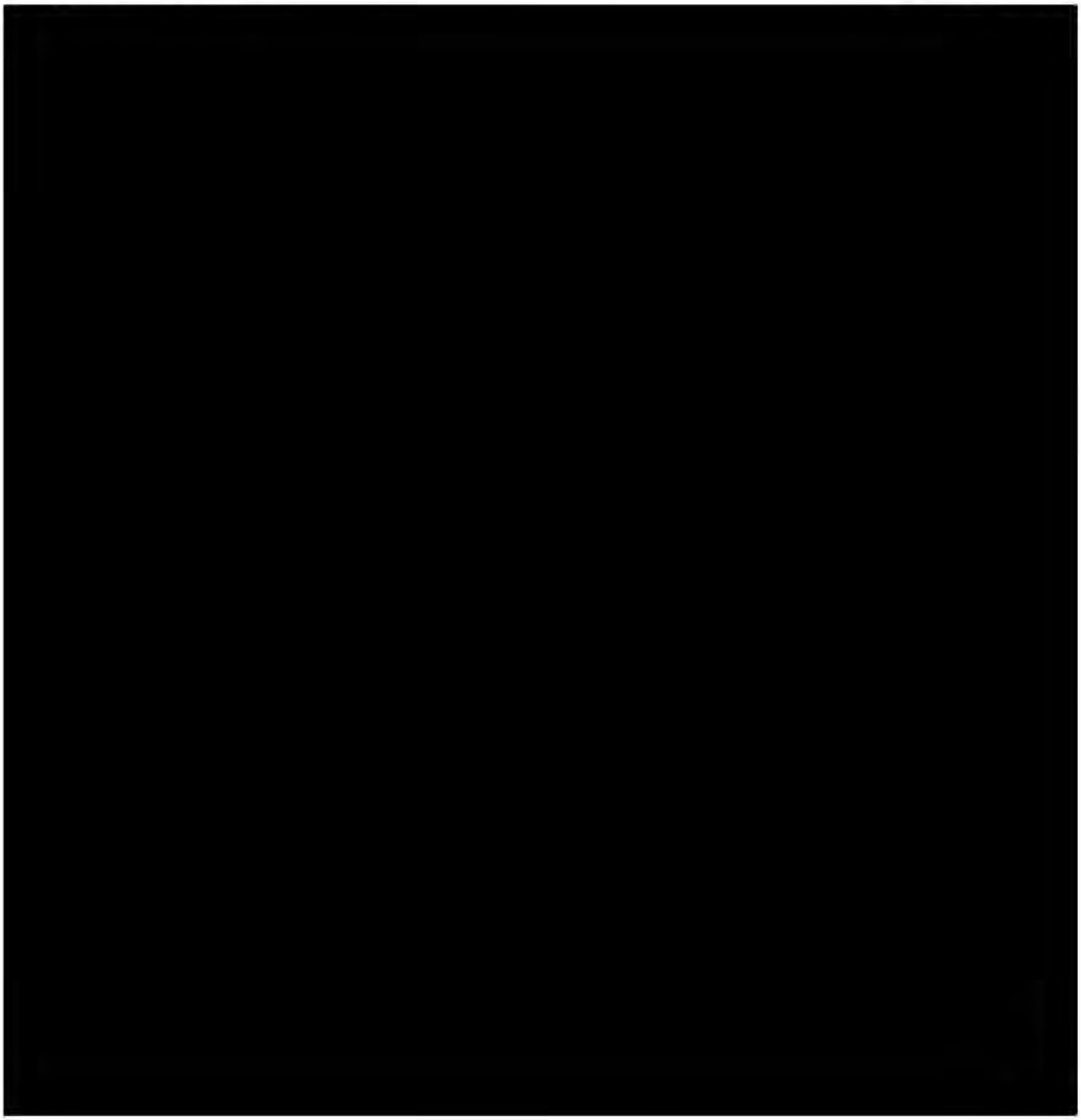

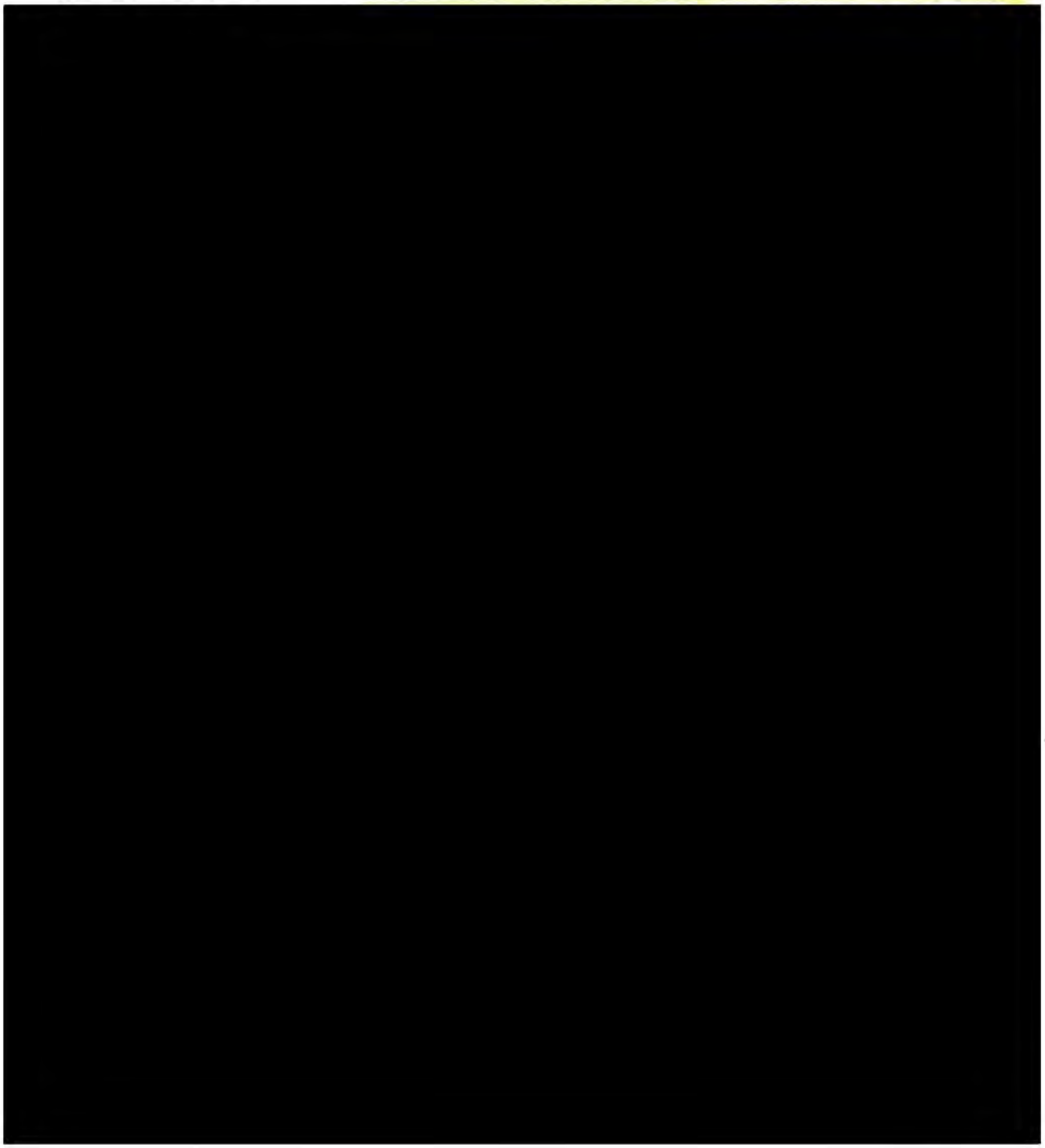

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11.3.5 Bladder Cancer Meta-Analysis Conclusions

Overall, the current pioglitazone meta-analysis demonstrated the following results:

- For the primary endpoint, there was no statistically significant increased risk for bladder cancer among subjects treated with pioglitazone vs comparator (P-value = 0.120) (HR: 3.481, 95% CI: 0.723, 16.755).

[redacted]

[redacted]

[redacted]

[redacted]

12.0 SAFETY EVALUATION

The focus of the current meta-analysis is the evaluation of pioglitazone in bladder cancer. Therefore, the data presented in this section is provided within the context of bladder cancer.

[redacted]

12.2 Treatment-Emergent Adverse Events

12.2.1 Brief Summary of Treatment-Emergent Adverse Events

Adverse events of bladder cancer are presented in Section 12.2.2. Case narratives for subjects with AEs of bladder cancer including a discussion of potential risk factors are presented in Section 15.

12.2.2 Analysis of Treatment-Emergent Adverse Events

12.2.2.1 Treatment-Emergent Adverse Events of Bladder Cancer

Adverse events of bladder cancer in all of the controlled studies (excluding subjects with early diagnosis of bladder cancer) are presented in Table 3.1 and shown in Table 12.c. Adverse events of bladder cancer in all of the controlled studies (all subjects) are presented in Table 3.2 and shown in Table 12.d. Adverse events of bladder cancer in the PROactive study are presented in Table 3.3 and shown in Table 12.e.

[redacted]

[redacted]

[redacted]

[redacted]

13.0 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

Controlled clinical trials from the TGRD database were examined in the form of a meta-analysis using bladder cancer as an endpoint. Important differences exist between the controlled clinical trials, most notable length of treatment; ranging from short-term studies of less than 1 year to long-term studies of 2 years or more (Table 9.b). It is important to point out that none of the controlled clinical trials were designed to examine bladder cancer.

In the present meta-analysis, bladder cancer cases diagnosed in the first year were excluded from the primary analysis, but an additional sensitivity analysis, in which all cases were included regardless of the time to detection, was also performed. The reason for this approach follows considerations of the biological plausibility of a causal relationship: the latency for the development of bladder cancer, from the start of changes in the bladder epithelium to transformation to tumours and development of symptoms (haematuria) is usually around 20 years [8]. Even after exposure to the most potent known human bladder carcinogens, cyclophosphamide, and aristolochic acid, tumours rarely appear before 4 years and never before 1 year. Consistent with this, in their blinded assessment of causality of the bladder cancer cases in PROactive (EC444), the experts on the independent review committee independently eliminated cases of bladder cancer that were reported within 1 year of randomization because of a lack of biological plausibility.

The primary analysis was the analysis of time (days) from the first dose of study medication to the first occurrence of an event of bladder cancer, excluding subjects with an early diagnosis of bladder cancer. For the primary analysis, the point estimate for the hazard ratio (HR) was 3.481 (95% confidence interval [CI]: 0.723, 16.755), which did not reach statistical significance (7 cases in the pioglitazone group [0.06%] vs 2 cases in the comparator group [0.02%]). For the sensitivity analysis, which included all subjects in the controlled clinical studies, the point estimate for the HR was 2.642 (95% CI: 1.106, 6.31), which was statistically significant (19 cases in the pioglitazone group [0.15%] vs 7 cases in the comparator group [0.07%]). Thus, there was a statistically significant increased risk for bladder cancer among subjects treated with pioglitazone vs comparator, when all subjects were included. It should be noted that the overall number of bladder cancers was low, and therefore it is difficult to draw meaningful conclusions.

[redacted]

[redacted]

Potential risk factors for bladder cancer from the clinical database were included as covariates in the Cox proportional hazard model analyses (age, gender, smoking status, and prior cancer history). Additional potential risk factors not adequately captured in the clinical database were assessed based on CIOMS reports for the patients who reported bladder cancer, including prostatic disease, recurrent bladder infection, family history of cancer, exposure to industrial chemicals, kidney stones, symptoms prior to treatment, and a previous history of bladder cancer. Notably, 2 patients in the pioglitazone group and none in the placebo group had a history of bladder cancer. In general these risk factors occurred with a similar frequency in the 2 treatment groups among patients with bladder cancer, but interpretation is limited based on the low incidence of events and lack of data for these risk factors in patients who did not have bladder cancer. Although randomization should have balanced out any confounding factors, slight imbalances in rare risks at baseline could have provided spurious results.

Overall, the number of bladder cancer cases was low, with 26 cases of bladder cancer reported in the controlled clinical trial database which contains over 22,000 patients (19 pioglitazone, 7 placebo). When subjects were excluded that were diagnosed with bladder cancer in the first year (based on a lack of biological plausibility), the number of cases dropped to 9 (7 in the pioglitazone group and 2 in the placebo group). Given the low overall incidence of bladder cancer and biologic implausibility of developing bladder cancer within 1 year of treatment, it is difficult to draw meaningful conclusions. Nonetheless, the results from the present meta-analysis do not exclude the possibility that there is an association between pioglitazone and bladder cancer. However, several factors (as discussed below) suggest that this finding may be spurious.

Firstly, results from the 6-year interim analysis of EC445, the observational extension of EC444, do not suggest an increased risk over time. In fact, the results during the observational period show more patients with bladder cancer in the comparator arm than for the pioglitazone arm. When the controlled and observational data are analyzed together including both the 3.5 year controlled period and the 6-year follow up, bladder cancer was reported in 25 patients (0.9%)

[redacted]

treated with pioglitazone during EC444 or EC445 and 20 patients (0.8%) for the comparator arm, ie, never took pioglitzaone (HR 0.98, 95% CI: 0.6, 1.8) (see Response to Questions: Question 4 for additional information on the PROactive extension [EC445]). Although most exposure to pioglitazone occurred during the double-blind portion of the PROactive study (average duration of approximately 2.5 years), this analysis suggests a lack of residual effect of pioglitazone following discontinuation of therapy.

Secondly, limitations of this meta-analysis need to be taken into account when evaluating the results. The meta-analysis was a post-hoc analysis of the database, and as already mentioned, none of the studies were designed to examine bladder cancer. Patients in the controlled studies were not excluded if they had a previous history of bladder cancer. In addition, in most studies subjects were not screened for bladder cancer. Therefore, subjects could have been enrolled who were already developing bladder cancer, which raises the possibility that if potential subjects had been screened for bladder cancer there would have been even fewer cases. Although randomization should have balanced cases, when measures were taken to exclude patients with unexplained haematuria or previous diagnosis of bladder cancer in clinical studies (as was implemented in OPI-516 and OPI-518; both 72-week studies), only 2 subjects total reported bladder cancer (1 in the pioglitazone group and 1 in the comparator group).

Cancer is linked to mortality; therefore examining the outcome of mortality is important in evaluating the overall risk-benefit. Bladder cancer has different outcomes depending on the stage of cancer, with suspected in situ cancer having a better prognosis than regional, distant, or invasive cancer. In this meta-analysis, histology (including staging) was not available for all subjects with bladder cancer so the only available outcome was mortality. For this reason, mortality was examined and broken down into all-cause, mortality of cancer (in general), and mortality of cardiovascular (CV) events (the most prevalent cause of death in subjects with type 2 diabetes mellitus in this meta-analysis). All-cause, CV-related, and cancer-related mortality was similar (but numerically lower) between the pioglitazone group and the comparator group. Thus, the potential association between pioglitazone and bladder cancer does not translate into an increase in mortality. For all subjects, the majority (over 70%) of the deaths in both the pioglitazone group and the comparator group were CV-related. Deaths related to cancer comprised less than 20% of all deaths in both groups. This is consistent with results from The Emerging Risk Factors Collaboration [2], in which the ratio of estimated years of life lost to diabetes for a man between the ages of 40 and 50 years (the demographic group most represented in this meta-analysis) for CV vs cancer death is approximately 3 to 1.

13.2 Conclusions

- There was no statistically significant increased risk for bladder cancer among subjects treated with pioglitazone vs comparator from the analysis (primary endpoint) excluding subjects with bladder cancer diagnosed in the first year after starting treatment.
- There was a statistically significant increased risk for bladder cancer among subjects treated with pioglitazone vs comparator from the analysis including all subjects.

[redacted]

- Results from analyses by pioglitazone dose are difficult to interpret due to the limited exposure at the 2 lowest doses of pioglitazone (15 and 30 mg), but do not indicate a dose-response relationship.
- No increase in all-cause, CV-related, and cancer-related mortality was observed in the pioglitazone group compared with the comparator group, with the majority of deaths being CV-related in both groups.
- Results from the meta-analysis of controlled studies and the combined PROactive and EC445 (observational extension of PROactive) does not reveal a residual risk over time.
- Interpretation of this data is limited by the nature of short-term clinical trials, which are not optimal for examining long-term rare safety outcomes such as bladder cancer, and this may be compounded by meta-analysis of these trials.
- The clinical trial meta-analysis suggests a signal of association of pioglitazone and bladder cancer, which needs further clarification from other data sources.

[redacted]

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[redacted]

Pioglitazone HCl (ACTOS®)

An Observational Study of Patient Cohorts Who Previously Received Long-Term (3 years) Treatment With Pioglitazone or Placebo in Addition to Existing Antidiabetic Medications (4-Year Interim Report)

EXECUTIVE SUMMARY

Marketing Authorization Holder:
Takeda Global Research & Development Centre (Europe) Ltd
61 Aldwych
London. WC2B 4AE
United Kingdom

July 2009

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[redacted]

LIST OF ABBREVIATIONS

A1c	glycosylated hemoglobin
CABG	coronary artery bypass graft
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
HR	hazard ratio
KPNC	Kaiser Permanente Northern California
MACE	major adverse cardiac event (all-cause mortality, nonfatal MI, or stroke)
MAH	Marketing Authorisation Holder
MI	myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
PPAR	peroxisome proliferator–activated receptor
RR	relative risk
T2DM	type 2 diabetes mellitus
TZD	thiazolidinedione

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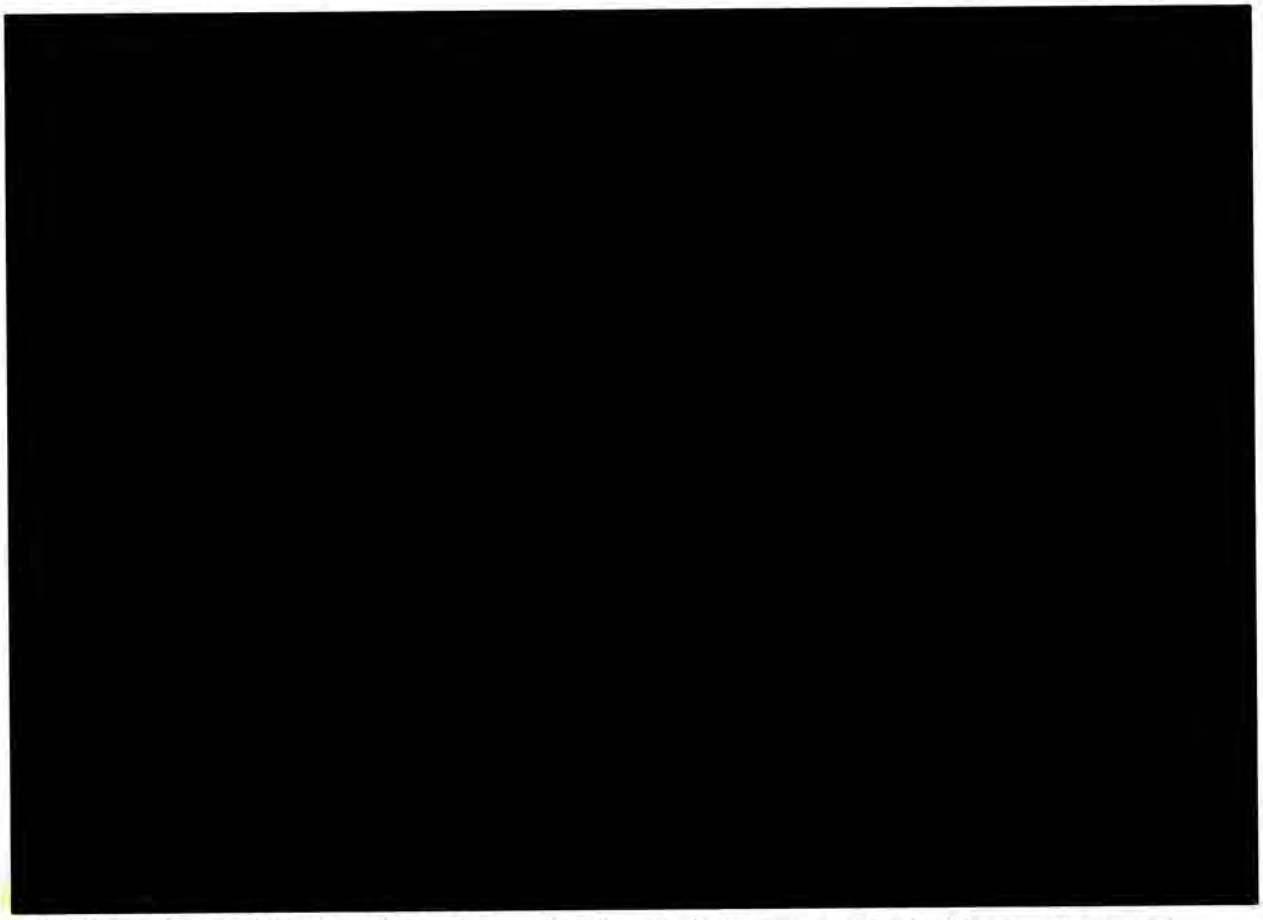
[redacted]



Another primary objective of this observational study is to compare the incidence, nature, and pattern of newly diagnosed malignancies between cohorts (prior pioglitazone vs prior placebo treatment). This aspect of the observational study forms part of the MAH's Risk Management Plan for pioglitazone-containing products. Of particular interest was to investigate whether the higher incidence of newly diagnosed bladder cancer in subjects receiving pioglitazone during PROactive would persist after therapy cessation.

In accordance with the agreed nonclinical and clinical programs, described in a 26 May 2005 letter to the MAH (EMEA/1786875/2005), the MAH committed to provide follow-up data at 2-year intervals (starting July 2007) for up to 10 years on the long-term incidence of all malignancies in pioglitazone- and placebo-treated subjects previously enrolled in PROactive. Thus, the AD-4833/EC445 4-year Interim Clinical Study Report along with this Executive Summary are hereby submitted.

2.0 STUDY DESIGN

2.1 Design Overview

This is an ongoing European, multicenter, observational study of cohort subjects who previously completed PROactive in which subjects received pioglitazone or placebo in addition to their existing antidiabetic medication and other cardiovascular medication. This study assesses total mortality and macrovascular morbidity, as well as the incidence, nature, and pattern of newly diagnosed malignancies in high-risk subjects with T2DM. The planned total duration of the study is up to 10 years, with data being analyzed and reported every 2 years.

Approximately 75% of the subjects who completed PROactive [redacted] enrolled in this observational study and were assessed every 6 months (nominal visits at Months, 6, 12, 18, 24, 30, 36, 42, and 48). This Executive Summary provides critical review of the data collected over the first 4 years of observation after cessation of PROactive (pioglitazone or placebo) treatment.

No treatment is prescribed by this protocol, and subjects are managed in accordance with normal medical practice, including existing antidiabetic medications. Any reference to study medication or treatment groups in this summary refers to treatment received during the PROactive treatment period, not the observational study period.

[redacted]

[redacted]

In addition to the information requested for all other malignancy types (above), the following data was requested for bladder cancers:

- History of chronic irritation of the bladder.
- History of schistosomiasis (bilharzia).
- History of hematuria.
- Family history of bladder cancer.
- Histological type.

Additionally, concomitant medications (antidiabetic, lipid-lowering, cardiovascular, and anti-platelet) were recorded at each assessment. For subjects who used TZDs, the drug name, total daily dose, and start and stop dates were recorded. If known, the subject's most recent glycosylated hemoglobin (A1c) value was also recorded at each assessment.

[redacted]

[redacted]

No formal statistical analysis was planned for safety data. Summaries of information pertaining to malignancies were provided for the overall incidence rate, by type of malignancy (including RRs and corresponding 95% confidence intervals [CIs] in which the frequency of malignancies was sufficient), and according to TZD exposure.

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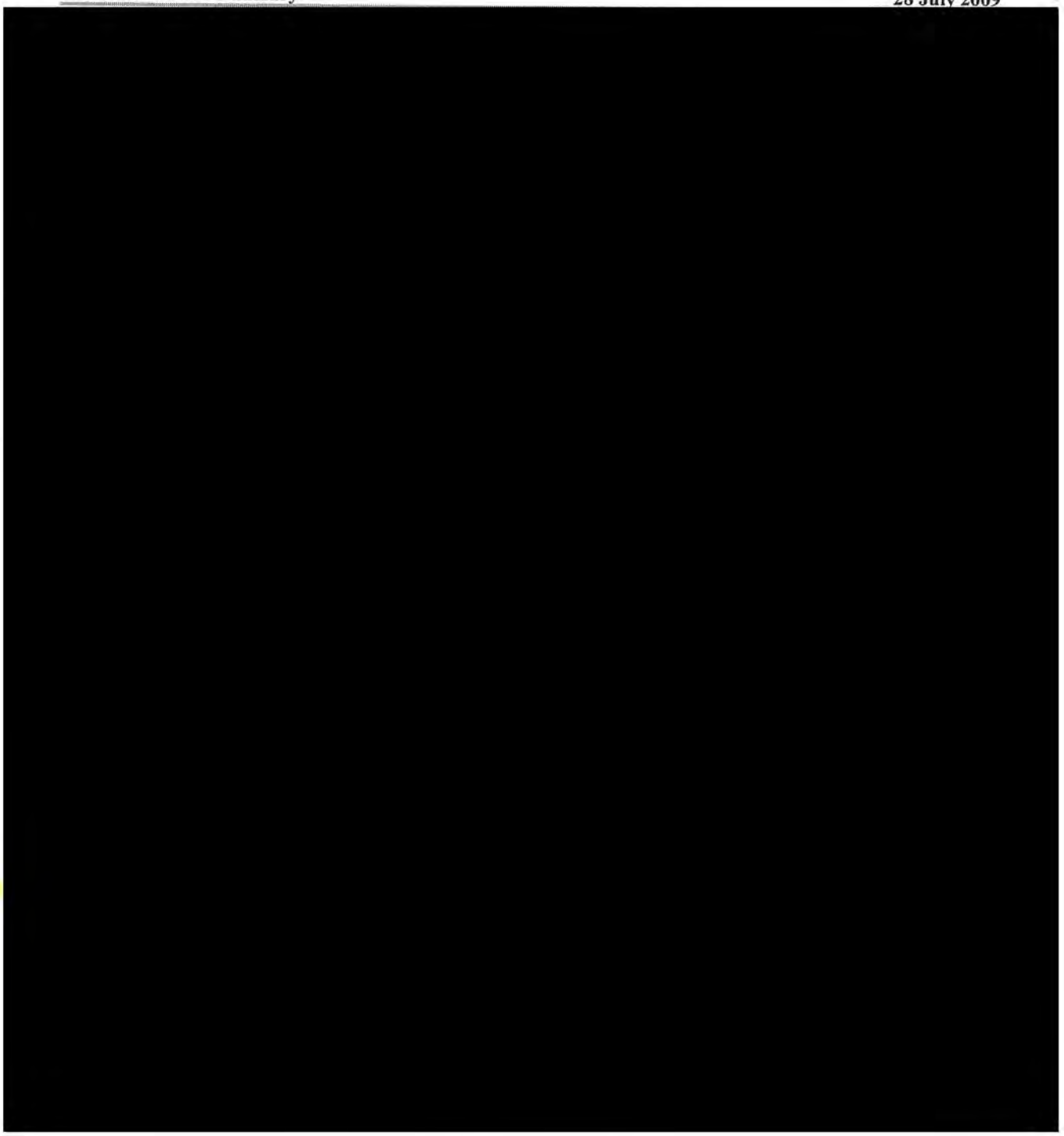

4.0 RESULTS

[redacted]

4.3 Malignancies

[redacted]

During PROactive, a higher number of bladder cancers was observed in subjects receiving pioglitazone compared with placebo: [redacted] placebo. Independent reviews were performed, and the data safety monitoring committee concluded that this imbalance did not represent an emerging safety signal for bladder cancer and that the PROactive study should be continued as previously planned.

During the first 2 years of observation, there was no difference in the incidence of newly diagnosed bladder cancer between the PROactive treatment groups, as reported in the 2-year interim report to this observational study. Thus, there was no evidence to indicate any association between pioglitazone use and the development of bladder cancer.

[redacted]

[redacted]

5.0 DISCUSSION AND CONCLUSIONS

5.1 Discussion

Safety assessments during PROactive included incidence and pattern of newly diagnosed malignancies. Overall, few malignances were newly diagnosed and incidence was similar between treatment groups. Higher incidences, however, were observed in the pioglitazone group for prostate and bladder cancers.

[redacted]

Due to the imbalance in newly diagnosed bladder cancers observed in PROactive [redacted] independent reviews were performed with the conclusion that this imbalance did not represent an emerging safety signal for bladder cancer. After the first 2 years of observation, there was no difference in the incidence of newly diagnosed bladder cancer

[redacted]

between the PROactive treatment groups [redacted] After the first 4 years of observation, newly diagnosed bladder cancer was reported more frequently in the PROactive placebo group [redacted] These results support the conclusions previously made by the independent reviewers, indicating that the risk of developing bladder cancer was not associated with pioglitazone treatment in this study.

[redacted]

As part of the ongoing pharmacovigilance and the MAH's risk management activities, a series of epidemiological studies are being performed using the Kaiser Permanente Northern California (KPNC) database to examine a possible association between pioglitazone use and the potential risk of bladder cancer. Included in the series are a prospective cohort study of bladder cancer incidence, a nested case-control study of bladder cancer incidence, and a nonbladder malignancy cohort extension study. The KPNC database contains clinical information on a large cohort of patients with T2DM served in a managed care setting. These epidemiological studies are being conducted over 5 to 10 years, and interim reports have been submitted to the European regulatory authorities.

[redacted]

[redacted]

The MAH concluded that both analyses did not show an increased risk of bladder cancer among pioglitazone users when compared with those exposed to other categories of antidiabetic medications. The CHMP concluded that the study did not suggest an association between pioglitazone and bladder cancer. The first and second interim analysis of the cohort study on the comparative incidence of bladder cancer was submitted in September 2005 (EMEA/32873/2006) and August 2007 (EMEA/540957/2007), respectively.

[redacted]

The primary analysis of this interim nested case-control study provided reassurance that pioglitazone use is not associated with a greater risk of developing bladder cancer compared with diabetic patients exposed to other categories of antidiabetic drugs. The CHMP stated that "It is agreed that the primary analysis showed no definite association between pioglitazone and bladder cancer; it is not possible to draw any definite conclusions regarding the secondary analyses presented and future analyses will provide more data." (EMEA/473068/2006).

[redacted]

[redacted]

[redacted]

5.2 Conclusions

[redacted]

- During this 4-year observational period, the incidence of newly diagnosed bladder cancer in subjects randomized to placebo in PROactive was higher than in subjects randomized to pioglitazone in PROactive. Therefore, the data from this study do not support an association between pioglitazone use and the development of bladder cancer.

[redacted]

[redacted]

6.0 REFERENCES

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[redacted]

Direct Healthcare Professional Communication on the association of Pioglitazone Hydrochloride with Urinary Bladder Cancer

As part of our continuing efforts to provide appropriate safety information to healthcare providers, Takeda Pharmaceuticals Europe Ltd. is informing you of recent safety data concerning pioglitazone-containing products. These products are Actos and Glustin (pioglitazone hydrochloride) Tablets, Competact and Glubrava (pioglitazone hydrochloride and metformin hydrochloride) Tablets and Tandemact (pioglitazone hydrochloride and glimepiride) Tablets. These products are used to treat type 2 diabetes mellitus.

Summary

There has been a recent increase in reports of urinary bladder cancer and Actos, and both the Summary of Product Characteristics (SmPc) and Package Leaflet (PL) have been updated to incorporate this information. In ongoing epidemiological studies[1] as part of the Risk Management Plan, no overall association between pioglitazone and bladder cancer has been identified and further research is ongoing.

In light of these reports, physicians are advised to investigate reasons of persistent haematuria in patients receiving pioglitazone.

Takeda concludes that the current body of evidence for pioglitazone provides a positive benefit-risk profile within approved indications.

The following additional text has been included in the SmPC:

"Section 4.4 Warnings and Precautions

Bladder Cancer

Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Whilst causality has not been established, patients should be advised to report haematuria promptly to their physician and appropriate investigations should be initiated."

Updates have also been made to Section 4.8 (Undesirable Effects) of the SmPC and Section 4 (Possible Side Effects) of the Package Leaflet consistent with the change to Section 4.4.

Further Information on the safety concern

The communication of this information has been agreed with the European Medicines Agency and National Competent Authorities

Call for Reporting

Healthcare professionals should report any adverse events suspected to be associated with the use of pioglitazone containing products to the national competent authority. Additionally, any such information may be reported to Takeda's Pharmacovigilance department at:

[*Contact details of Takeda Local Representative in Member State*]

Communication information:

The product information (SmPC and PL) has been revised to include this information and approved by the European Medicines Agency. Education materials will be updated as appropriate and will be distributed when available.

Should you have any question or require additional information, please call Medical Information at [*Contact details of Takeda Local Representative in Member State*]

Sincerely,

Dr C Baum MD

European Medical Director

Takeda Pharmaceuticals Europe Limited

Please see accompanying Complete Prescribing Information.

References

1. Lewis, JD Ferrara, A. Peng.T., et al Risk of Bladder Cancer Among Diabetic Patients Treated With Pioglitazone: Interim report of a longitudinal cohort study Diabetes Care April 2011 vol. 34 no. 4 916-922