

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Variation Form



4.2. Posology and Method of Administration

Adults and the elderly: Each measure from the dispenser is 1.25g of Oestrogel. Two measures (2.5g) of Oestrogel once daily (1.5mg 17 β -oestradiol) is the usual starting dose, which in the majority of women will provide effective relief of symptoms. If after one month's treatment effective relief is not obtained, the dosage may be increased accordingly to a maximum of four measures (5g) of Oestrogel daily (3.0mg 17 β -oestradiol).

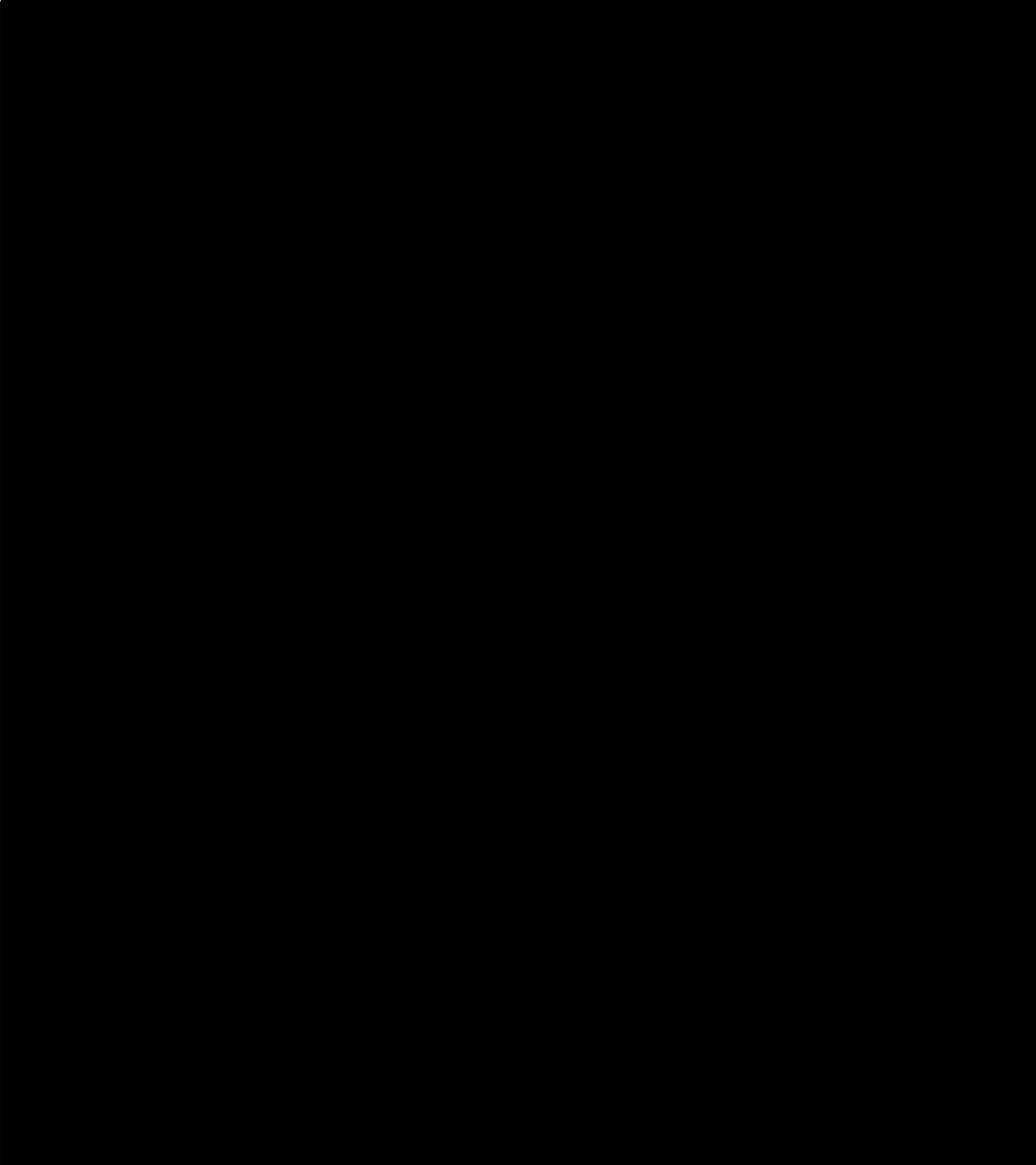
The lowest effective dose should be used for maintenance therapy. In women with an intact uterus the recommended dose of a progestogen should be administered for 12 days of each month, in accordance with the manufacturers recommendations. Oestrogel should be administered daily on a continuous basis.

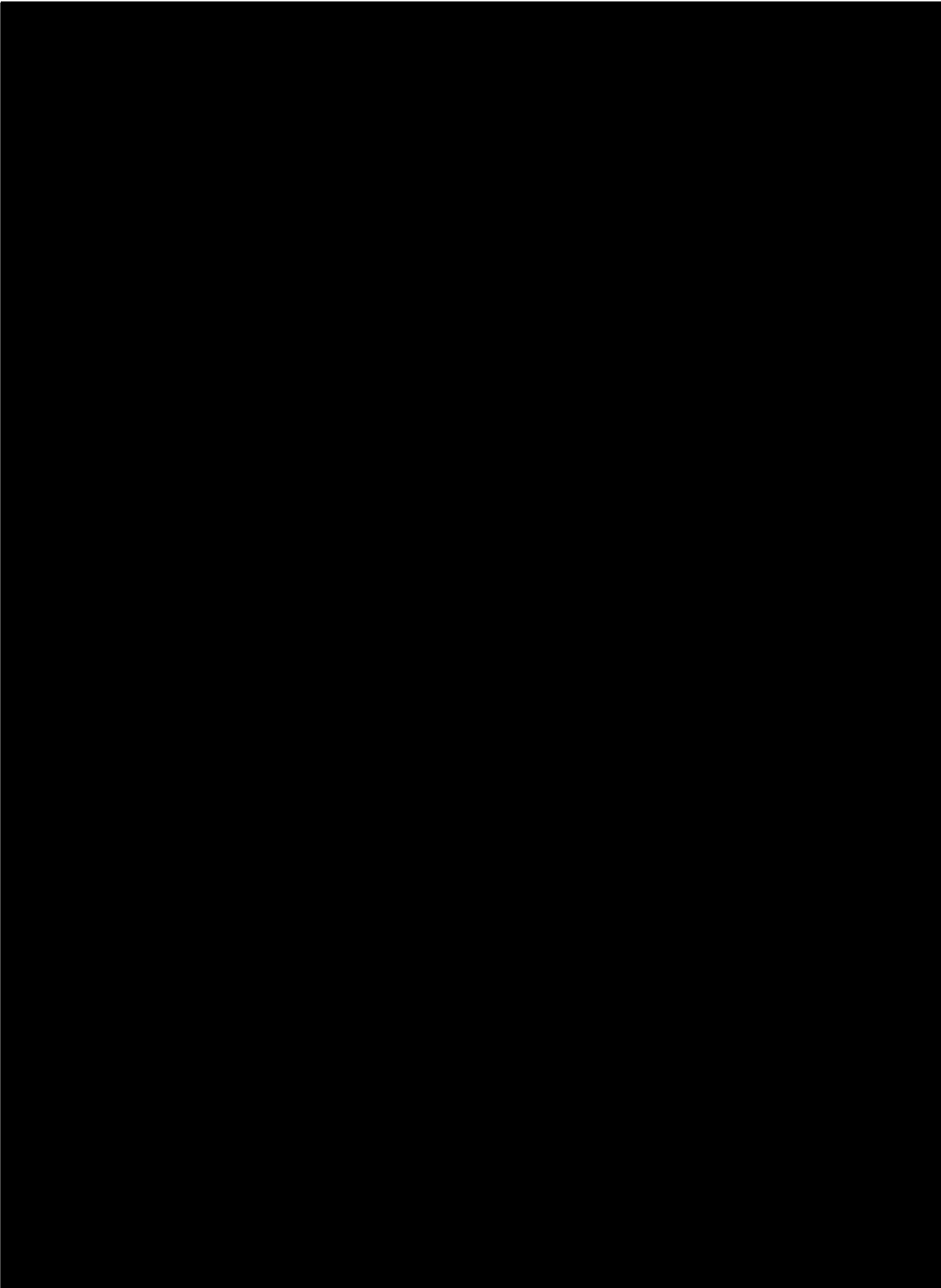
The correct dose of gel should be dispensed and applied to clean, dry, intact areas of skin e.g. on the arms and shoulders, or inner thighs. The area of application should be at least 750cm², twice the area of the template provided. One measure from the dispenser, or half the prescribed dose, should be applied to each arm/shoulder (or

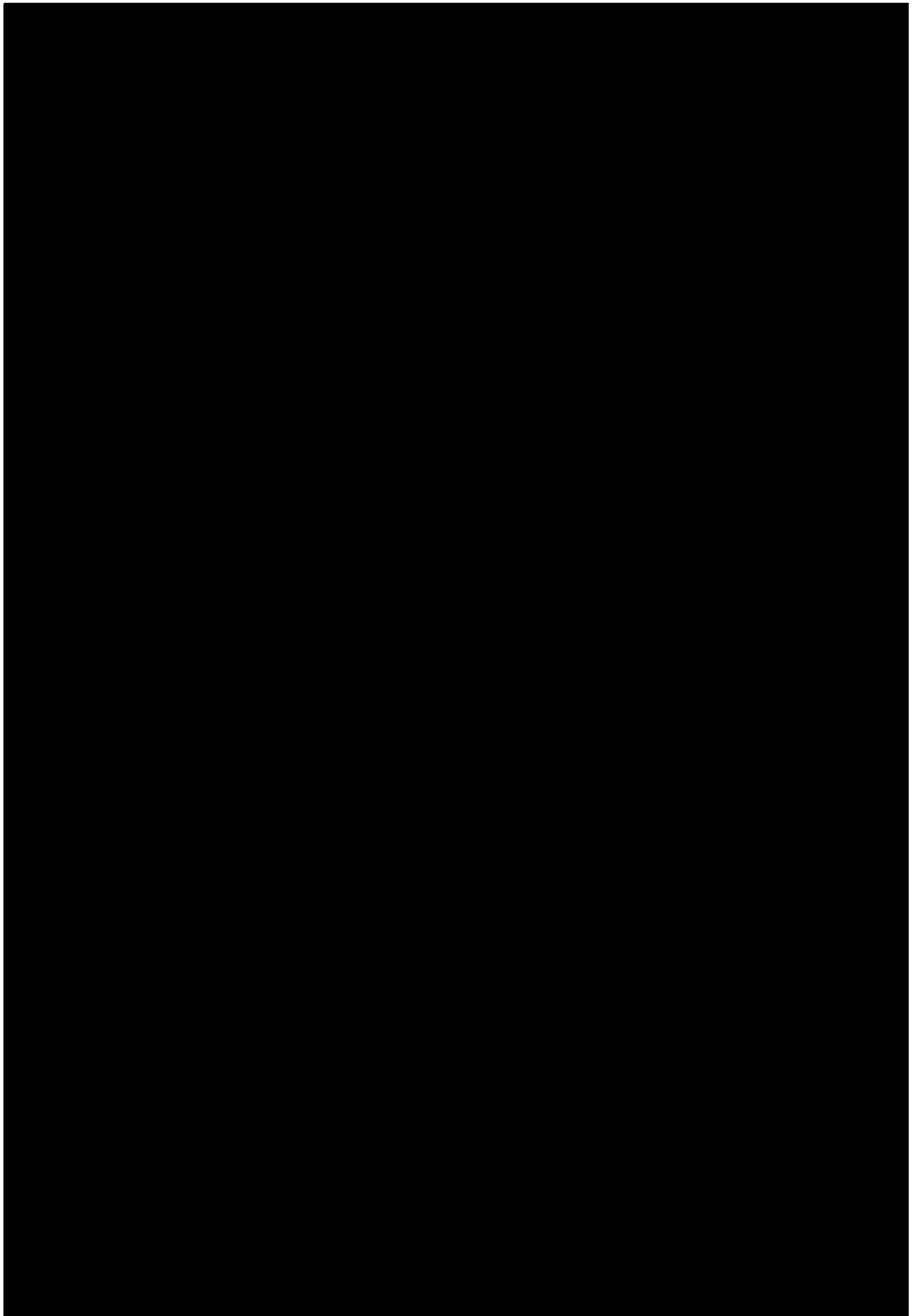
thigh). Oestrogel should NOT be applied on or near the breasts or on the vulval region.

Oestrogel should be allowed to dry for 5 minutes before covering the skin with clothing.

Children: Not recommended for children.





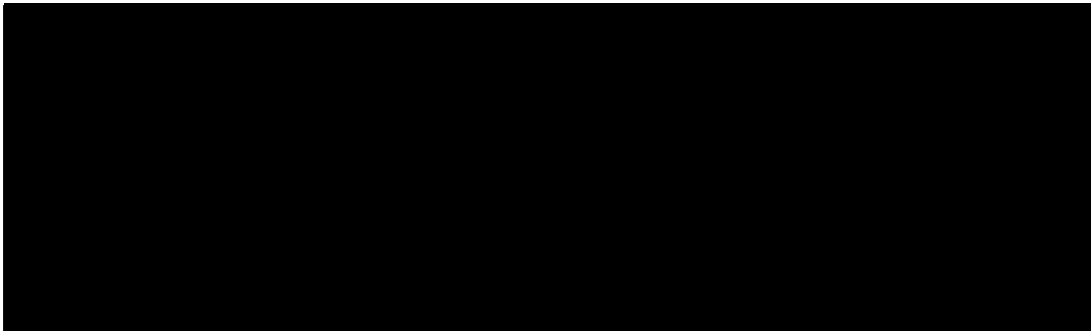




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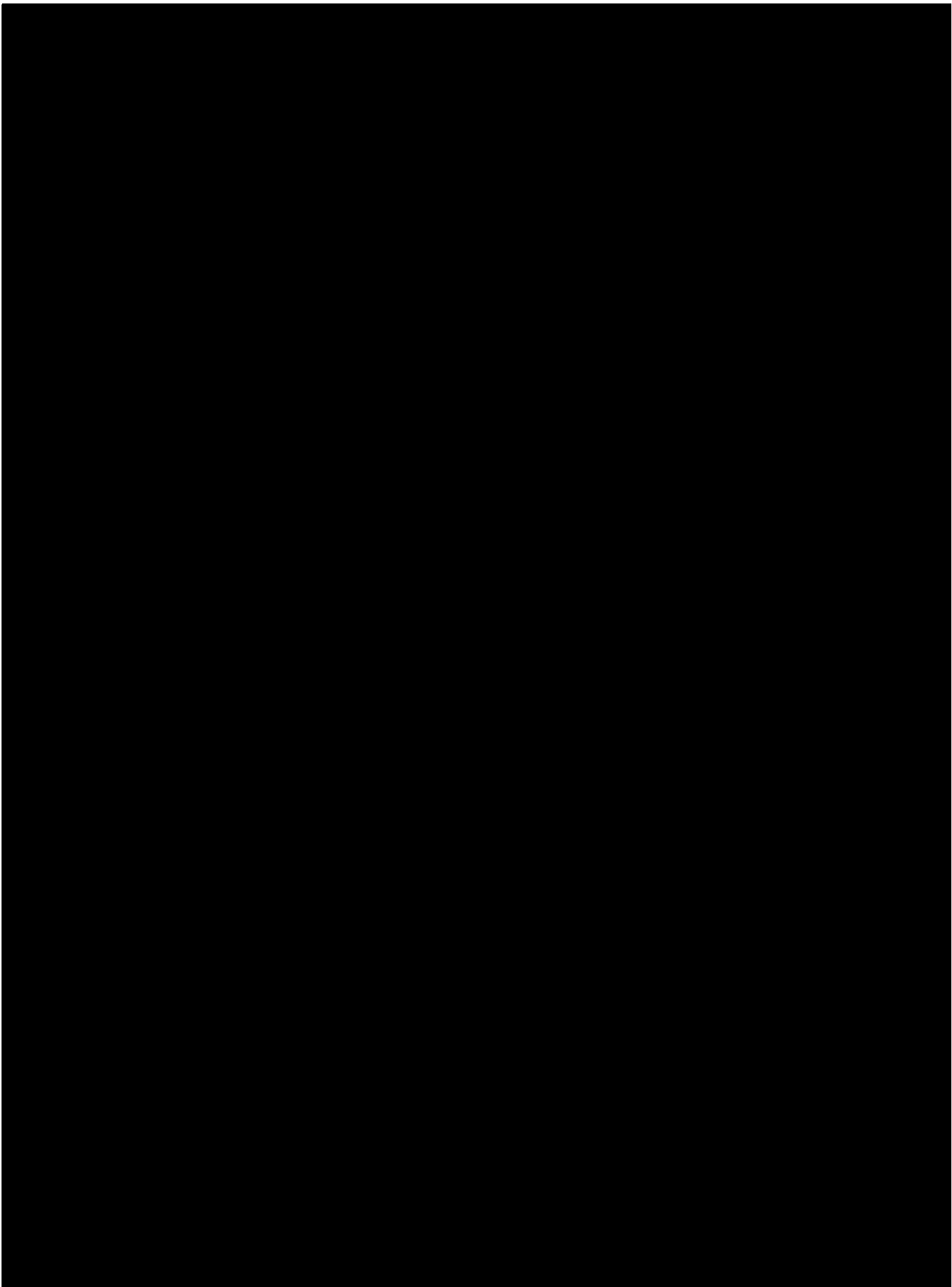


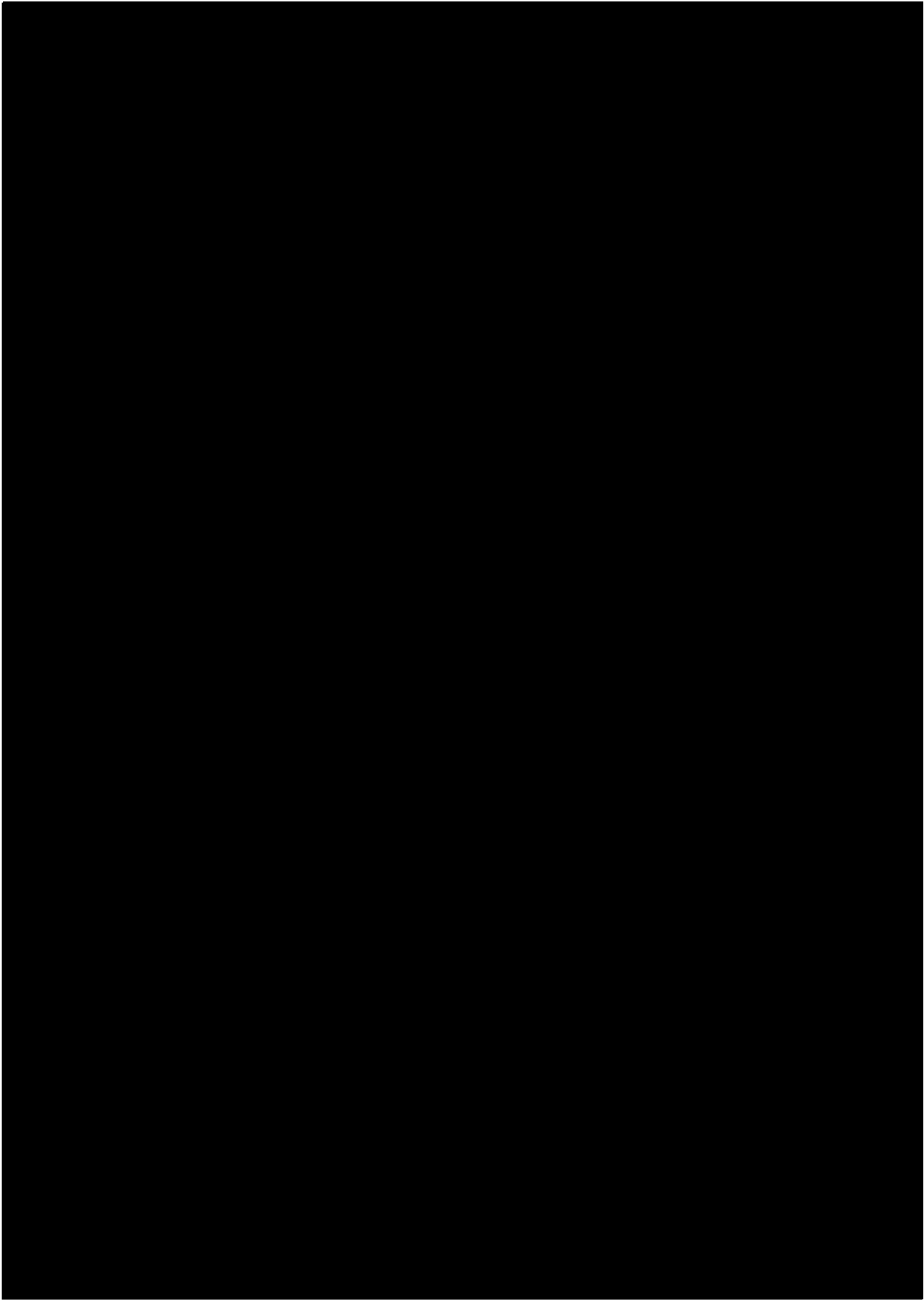
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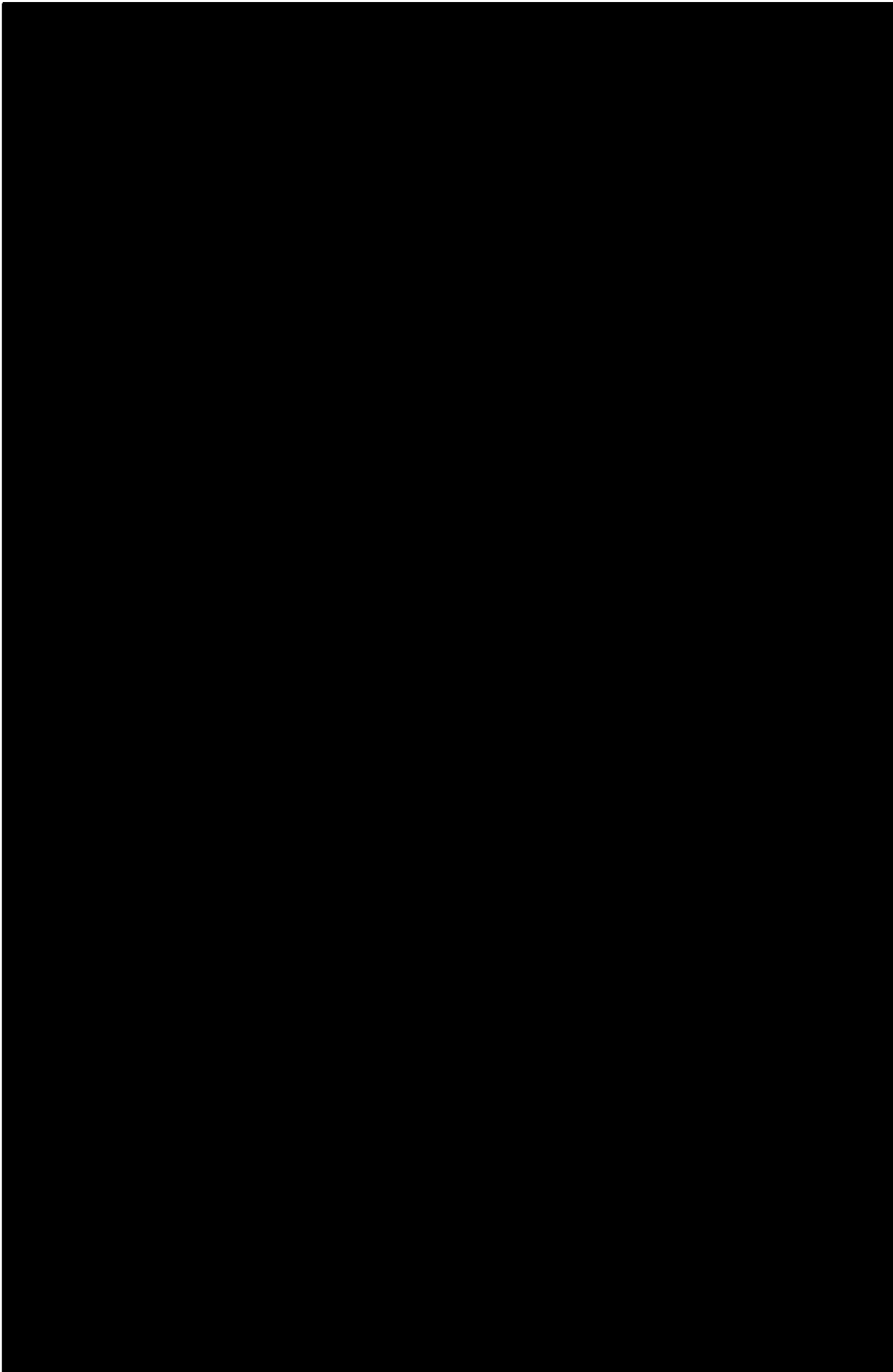


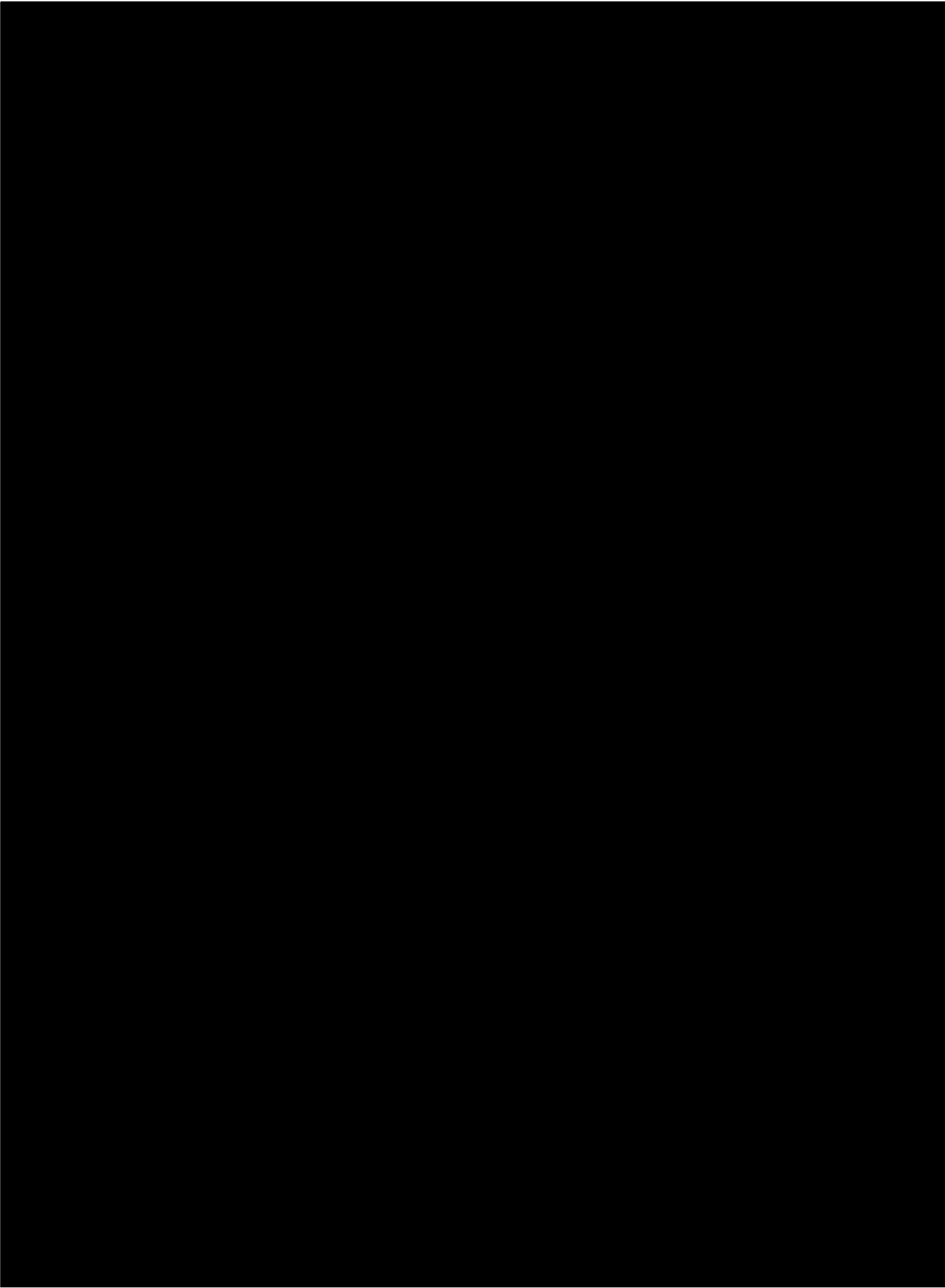
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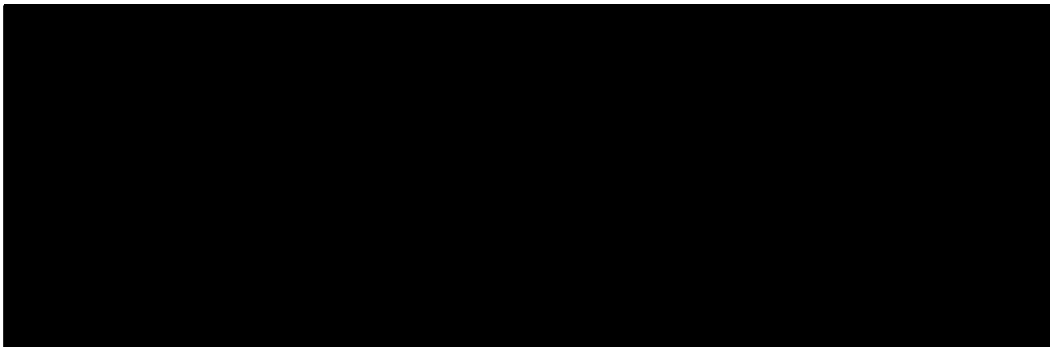


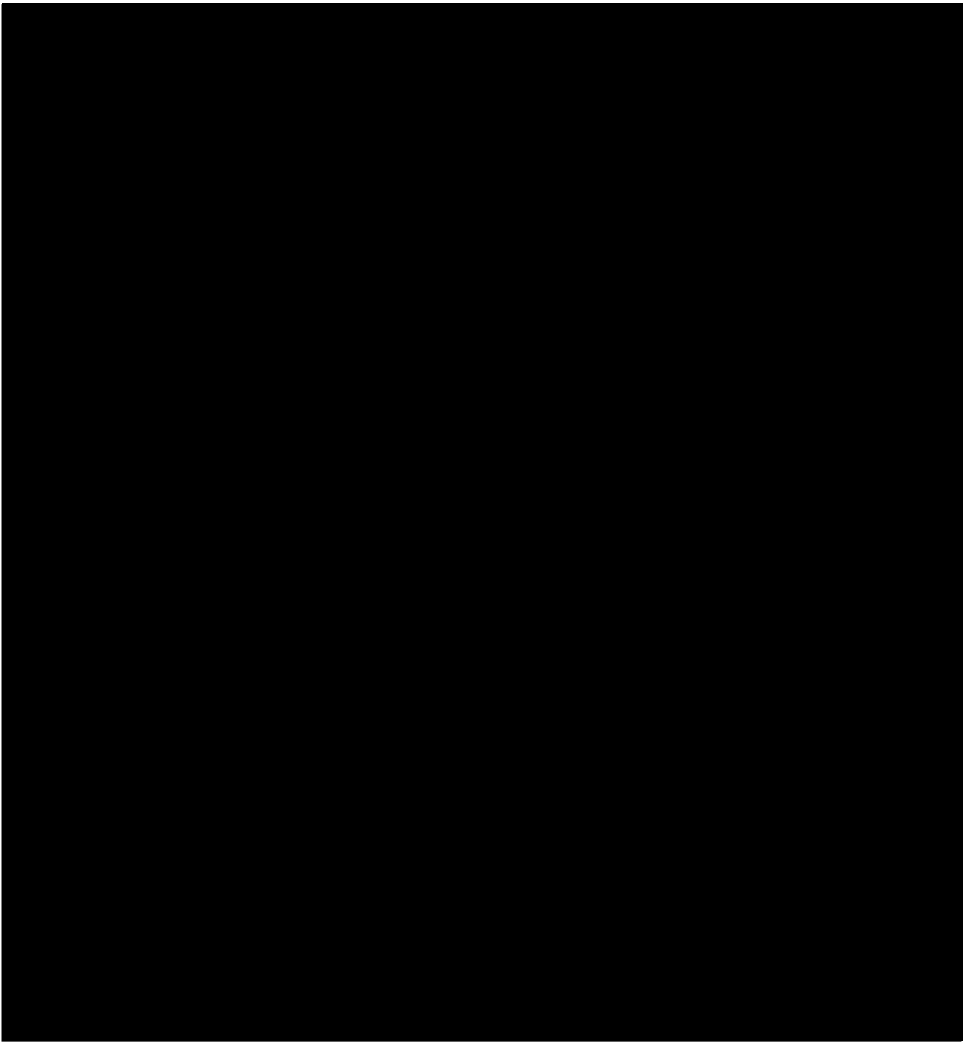


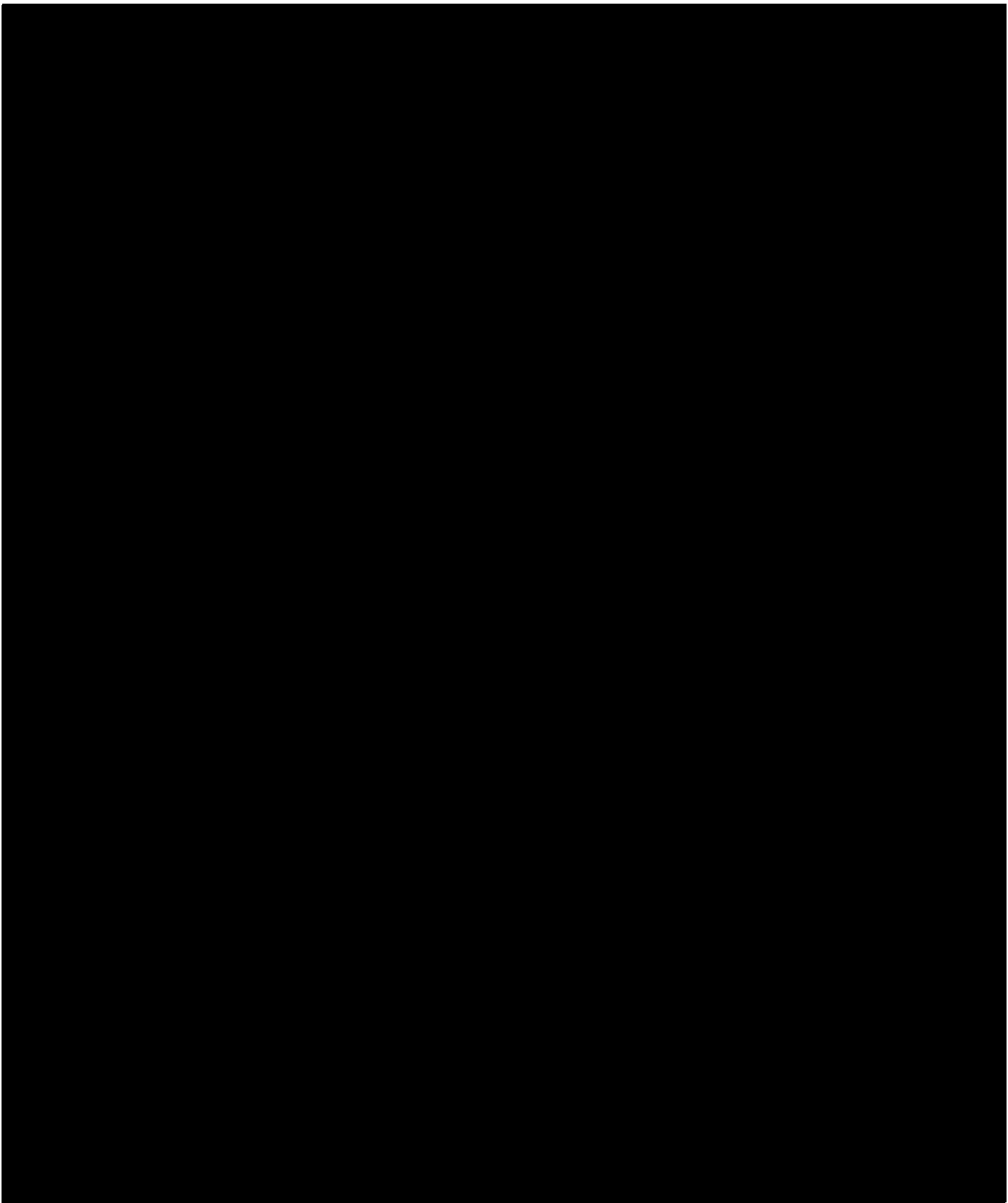


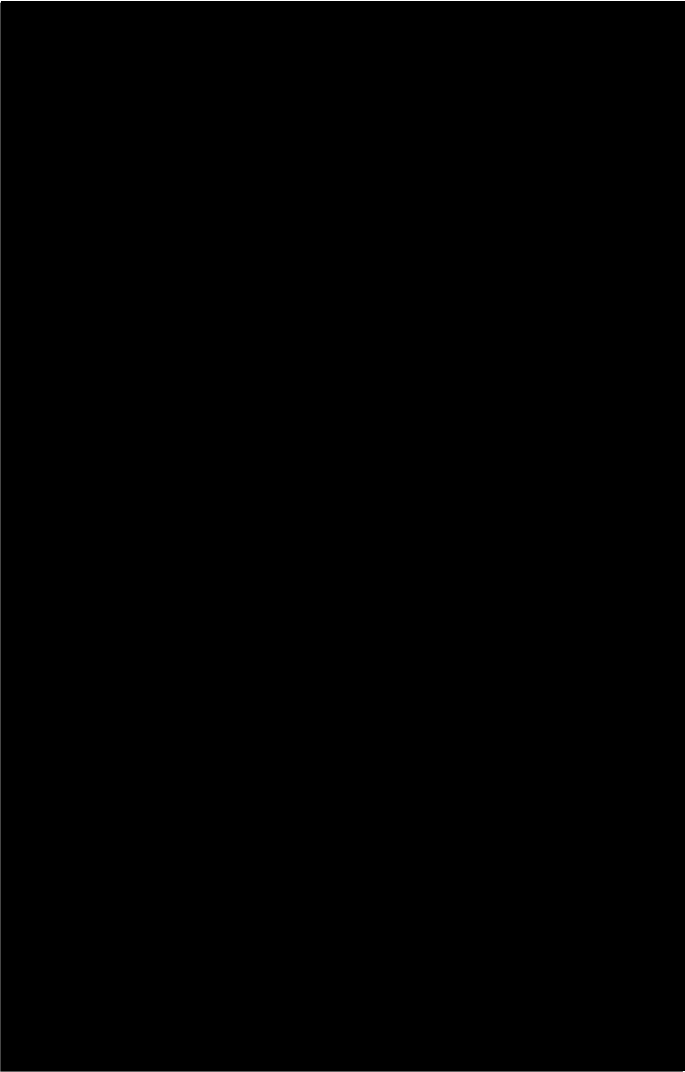


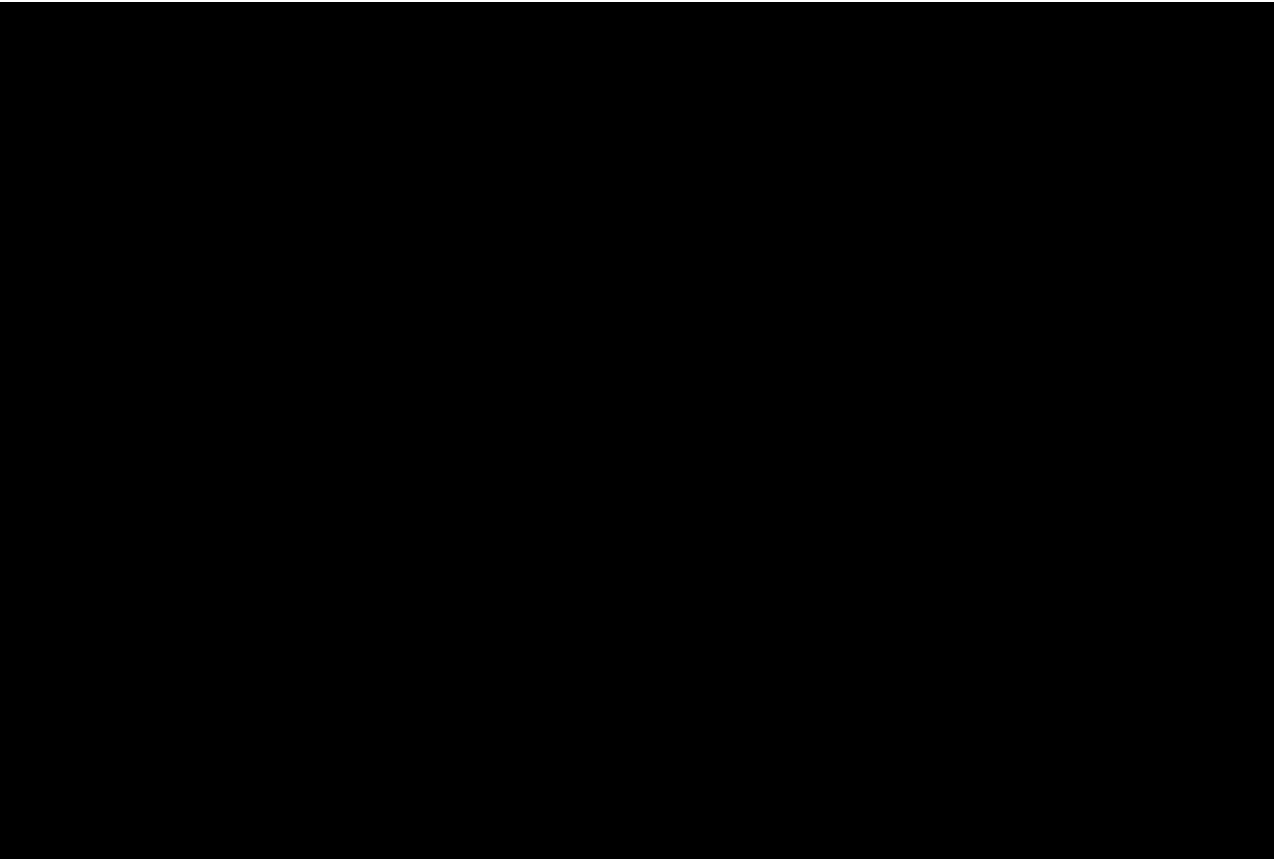










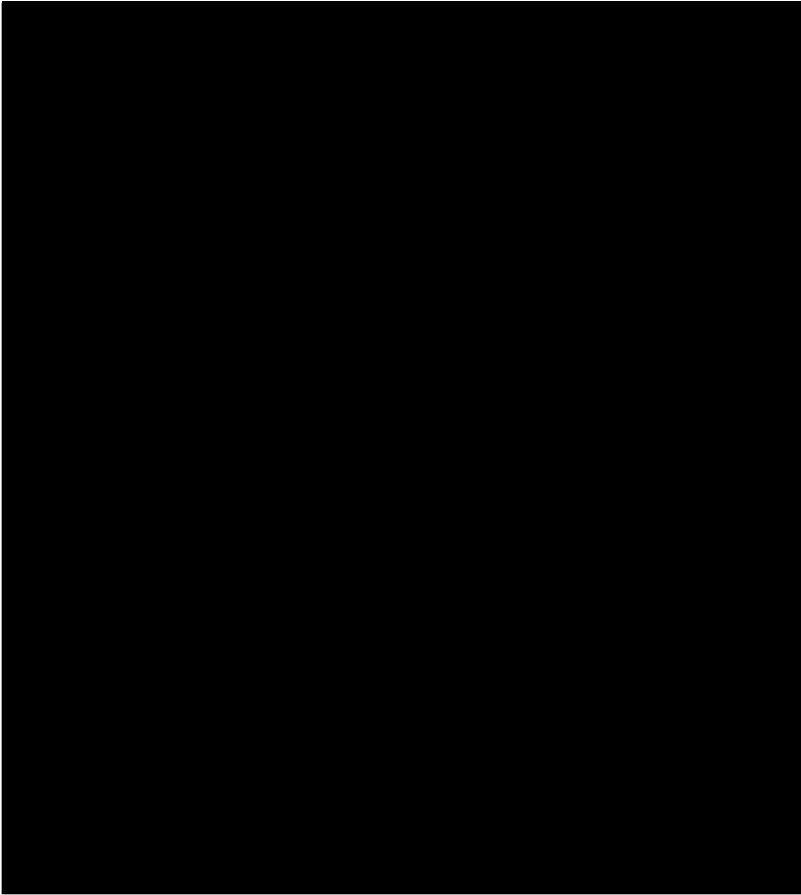


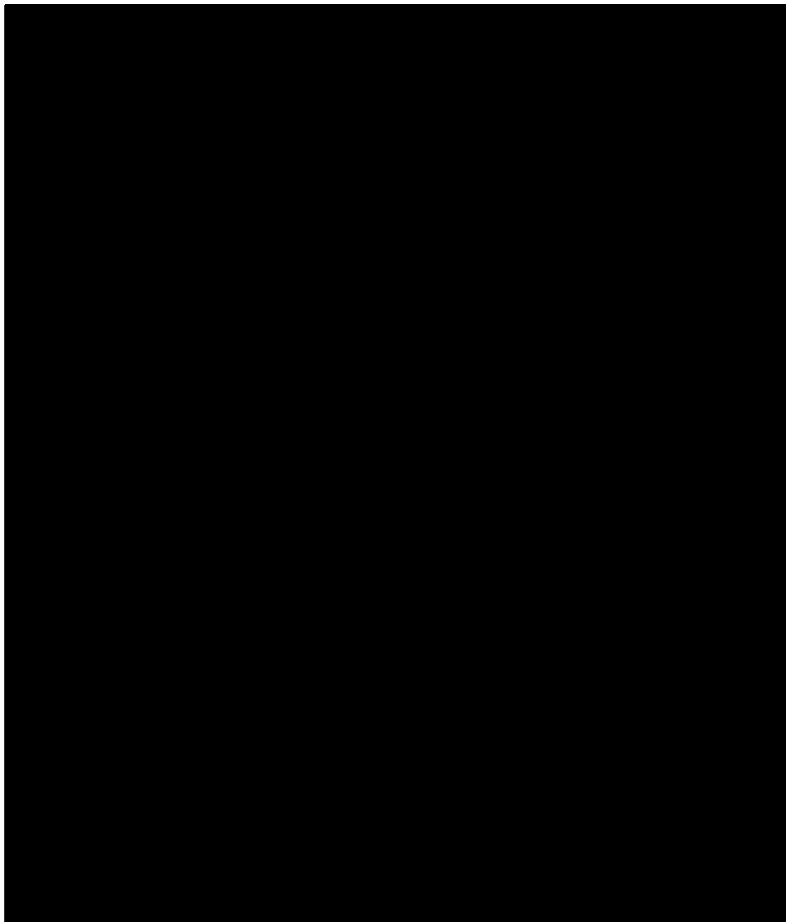


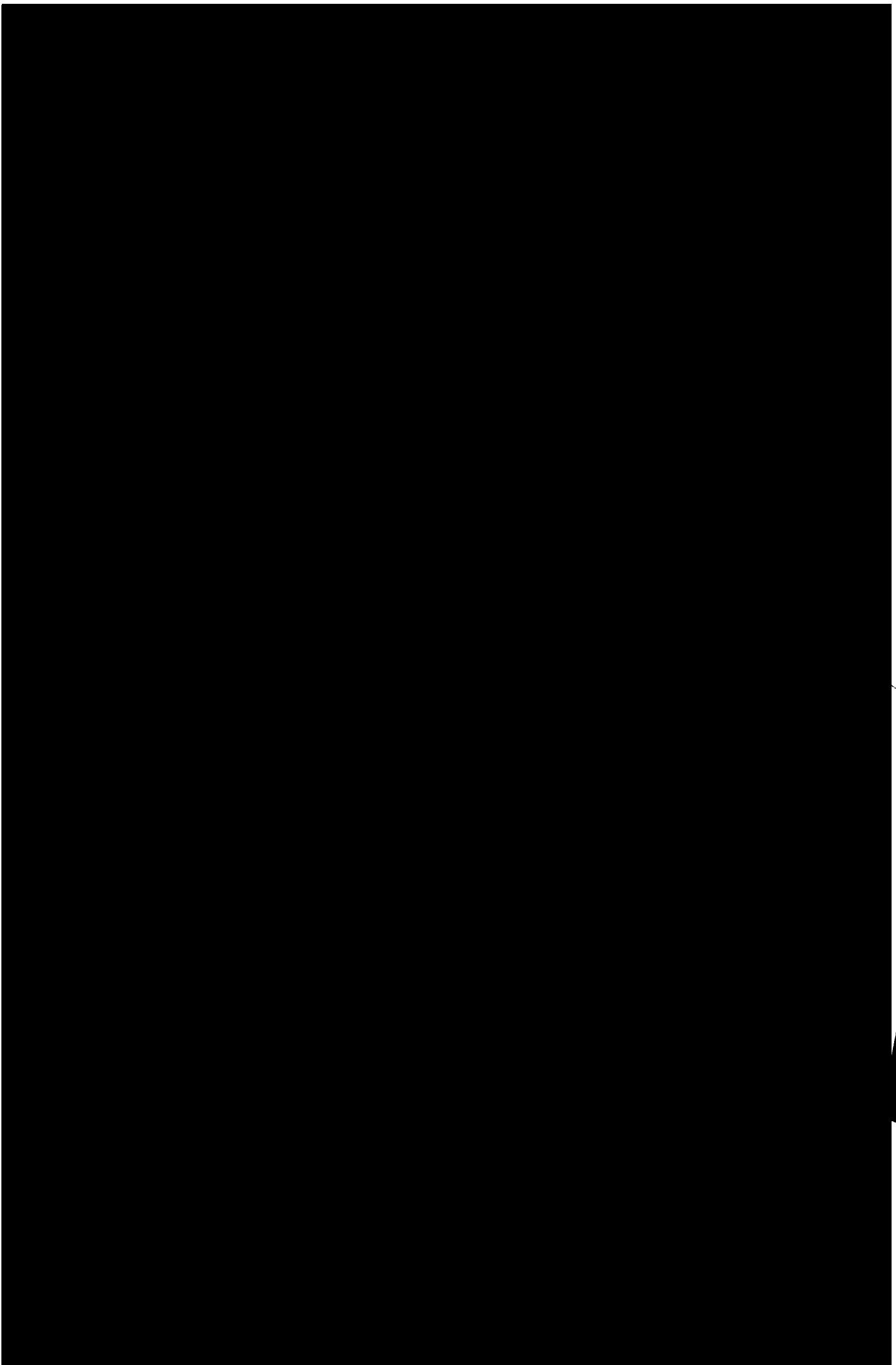
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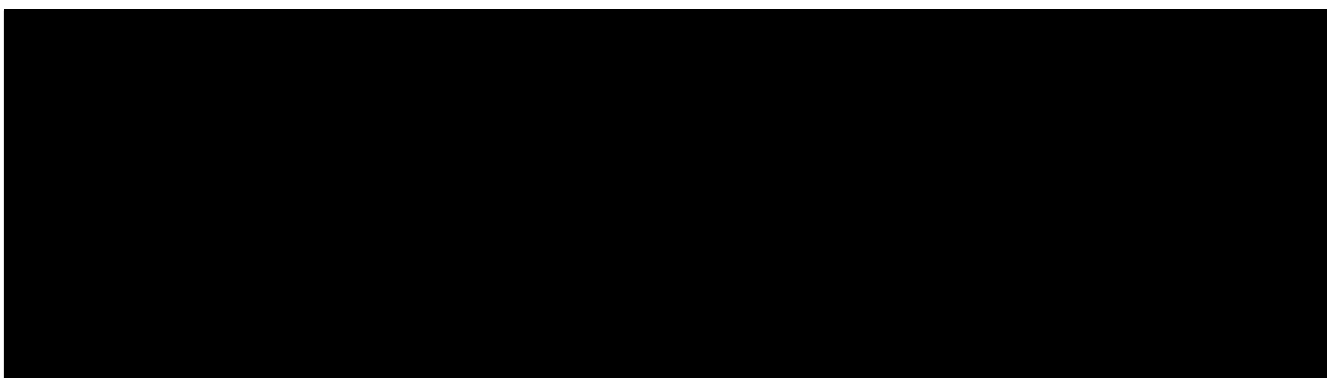
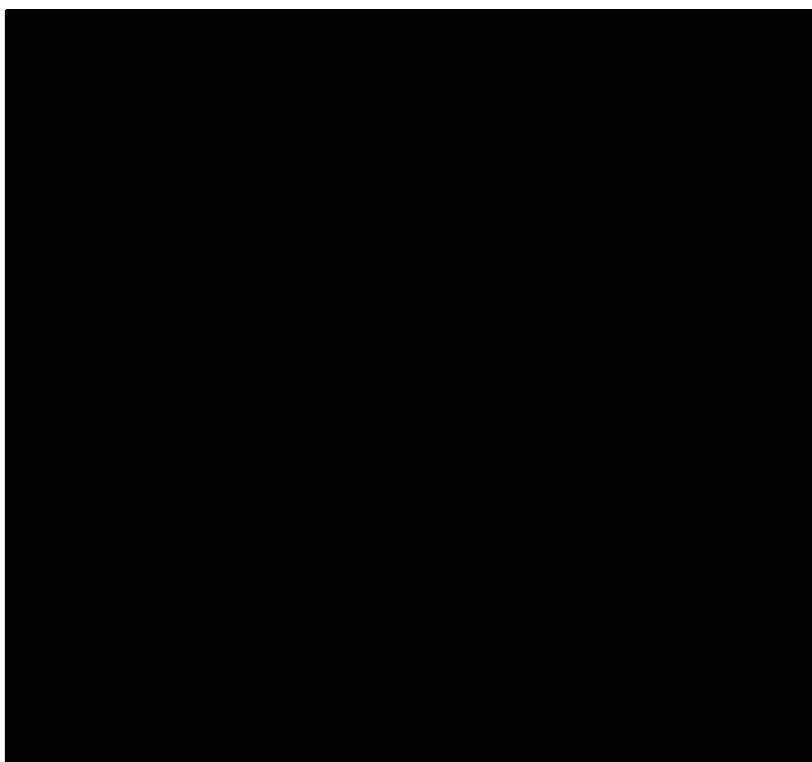
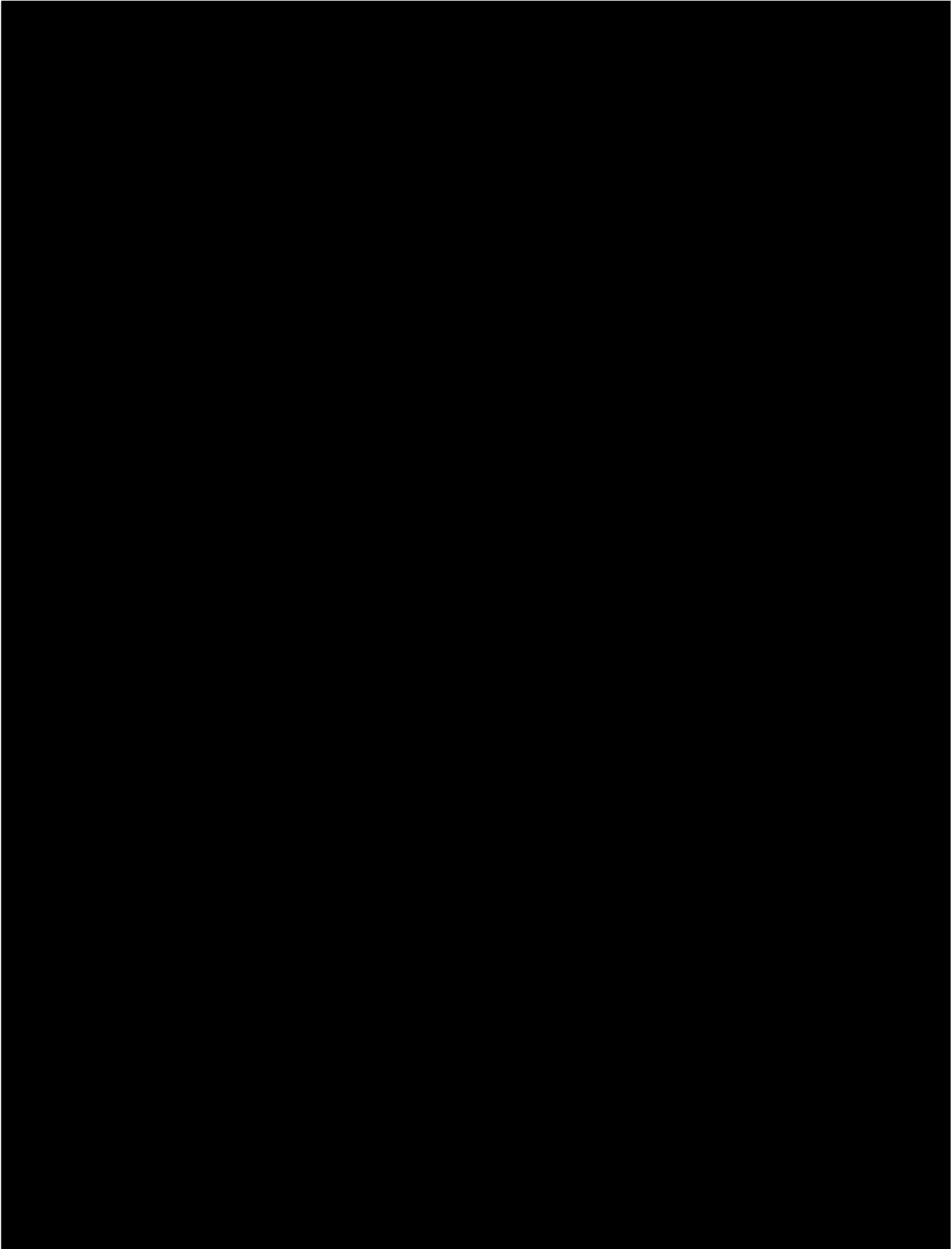
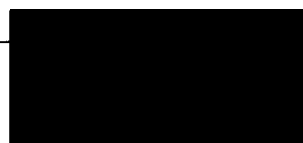
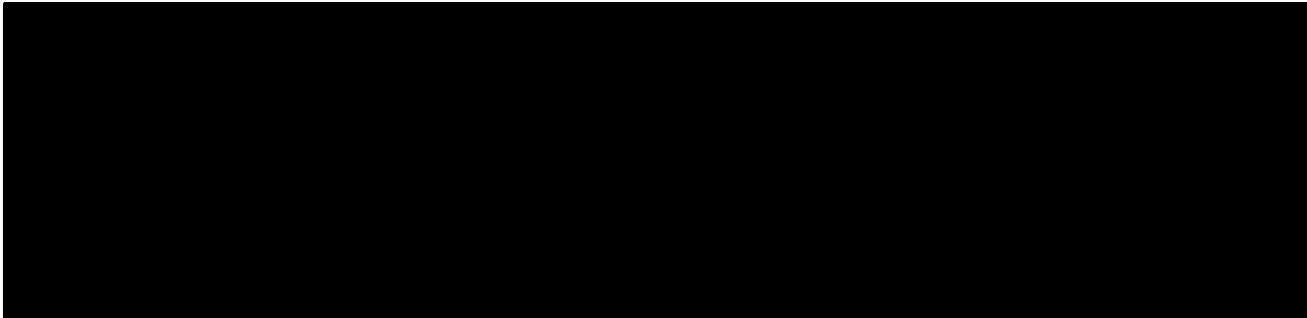


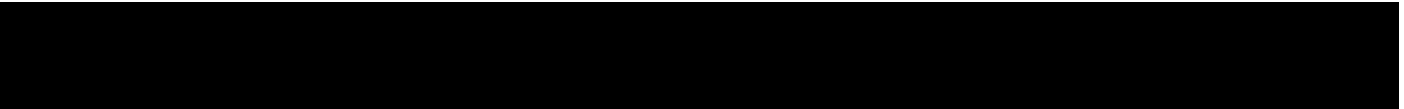
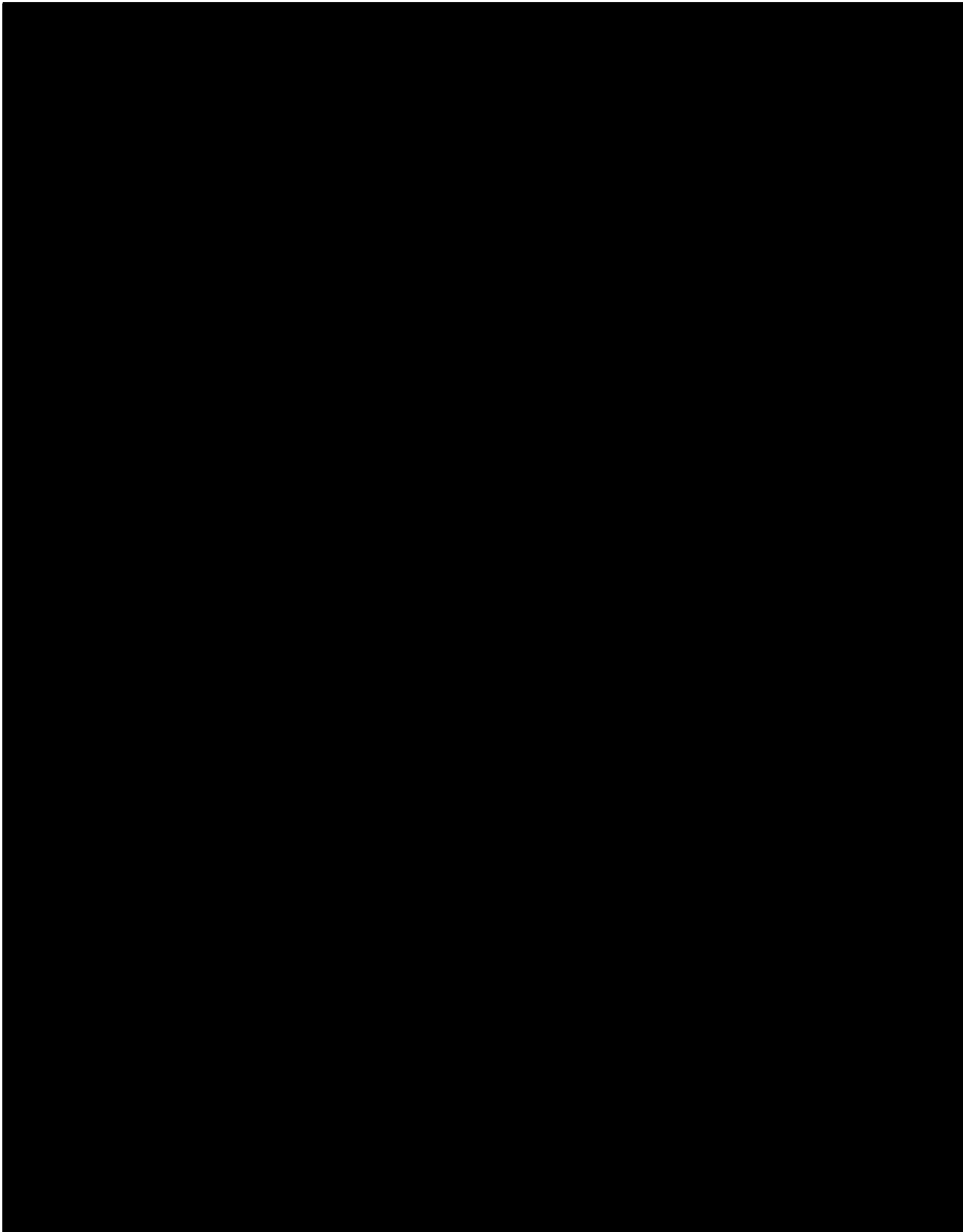
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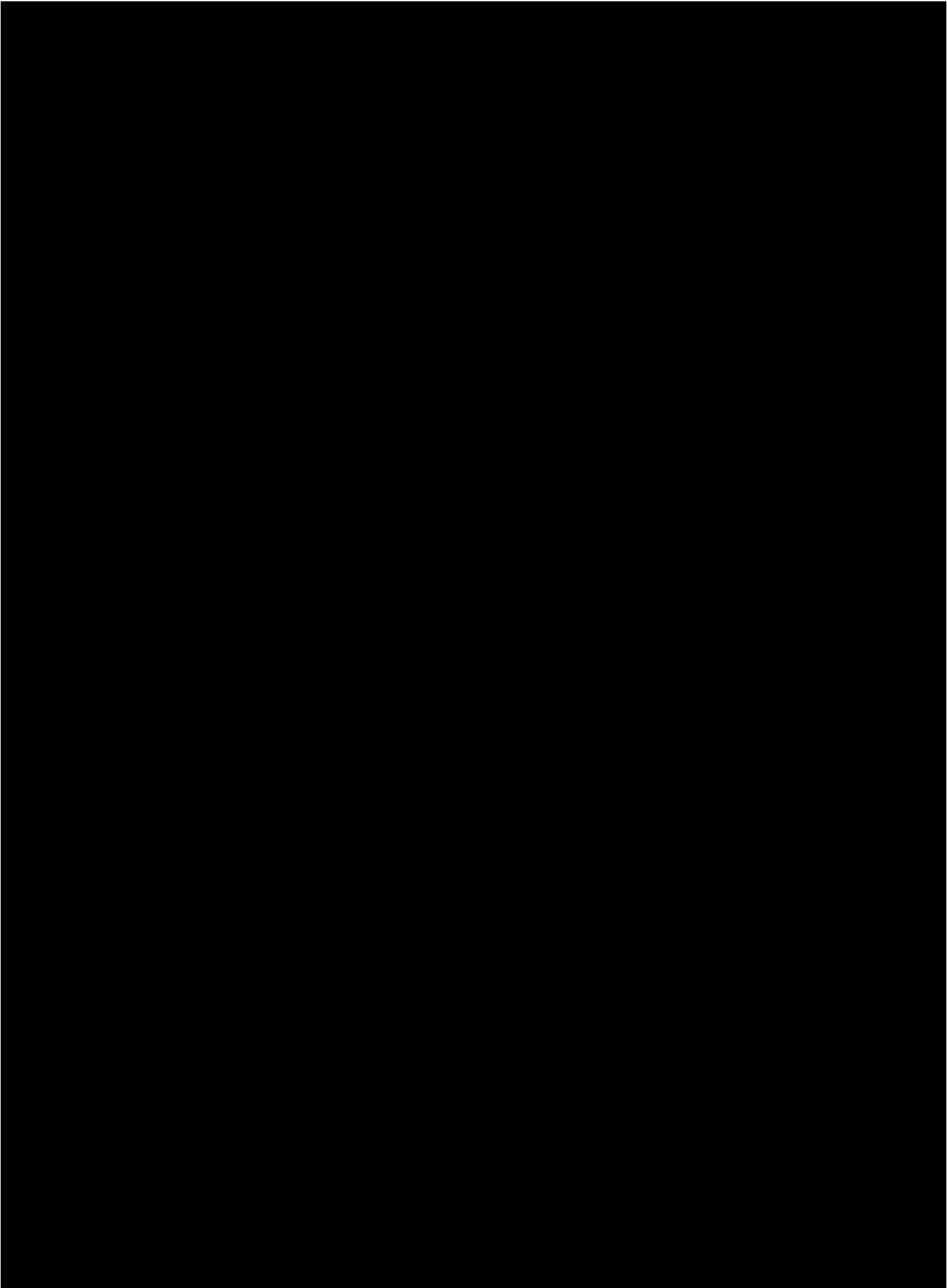
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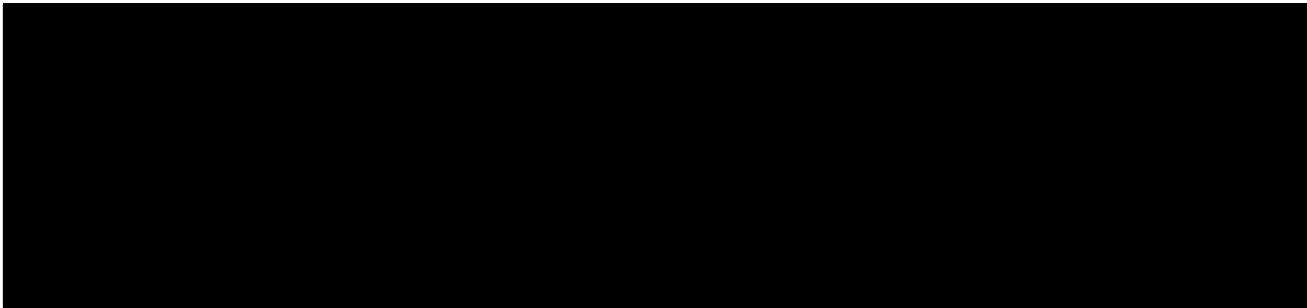






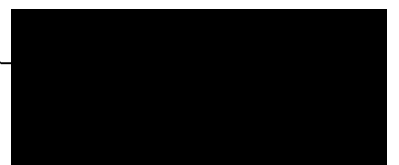




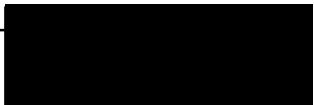
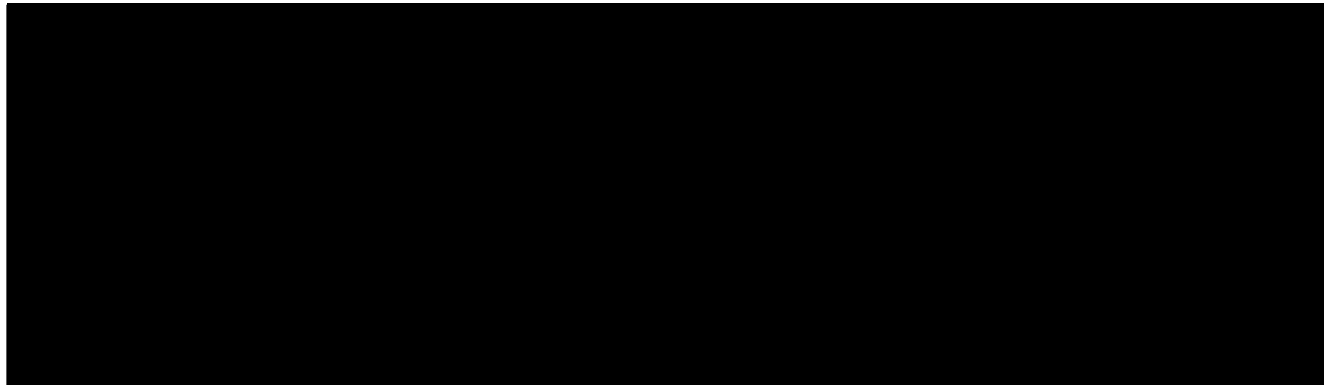








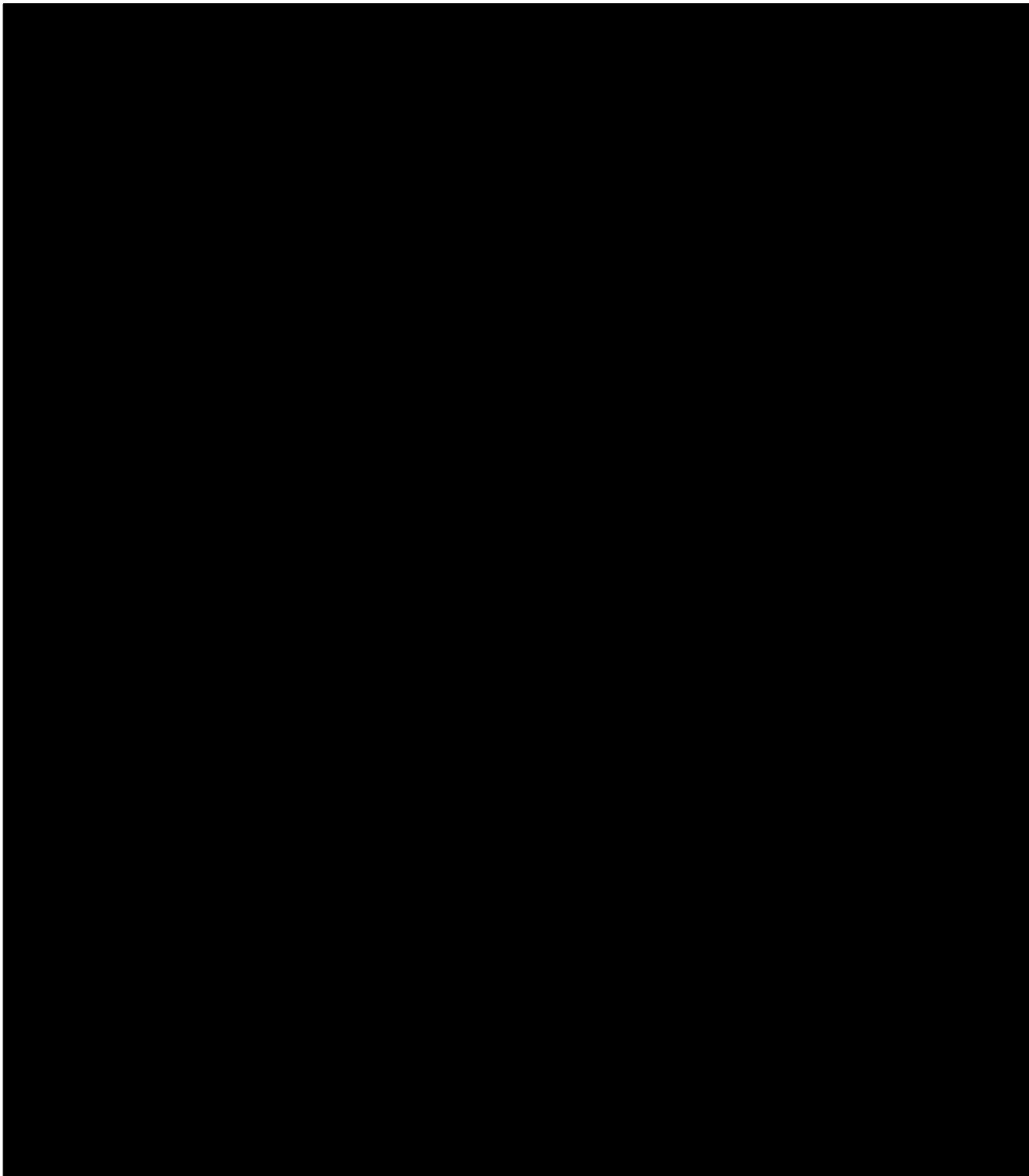
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PART IC : EXPERT REPORT ON THE CLINICAL DOCUMENTATION

PART IC

PRODUCT PROFILE

PRODUCT PROFILE

OESTROGEL PUMP-PACK PL 13402/0020

b) Chemical and Pharmacokinetic Properties

Oestrogel contains oestradiol (0.06% w/v) as the active ingredient. Pharmacokinetic studies indicate that, when applied topically to a large area of skin in a volatile solvent, approximately 10% of the oestradiol is percutaneously absorbed into the vascular system, regardless of the age of the patient. Daily application of 2.5 g or 5 g Oestrogel over a surface area of 400–750cm² results in a gradual increase in oestrogen blood levels to steady state after approximately 3–5 days and provides circulating levels of both oestradiol and oestrone equivalent in absolute concentrations and in their respective ratio to those obtained during the early-mid follicular phase of the menstrual cycle.

Avoidance of first pass metabolism by the percutaneous route not only results in a physiologic ratio of oestradiol and oestrone, but also reduces the impact on hepatic biosynthesis of protein that has been demonstrated with orally administered oestrogens.

c) Indications

Oestrogel is indicated as oestrogen replacement therapy for the relief of symptoms due to natural or surgically induced menopause, such as vasomotor symptoms, atrophic vaginitis and atrophic urethritis. Oestrogel is also indicated for use in the prevention of postmenopausal bone loss in women considered at risk of developing fractures.

The starting dose is 2.5 g Oestrogel (2 measures, 1.5 mg 17 β -oestradiol) once daily, which should provide effective symptom relief in the majority of women. If effective relief is not obtained after one month's treatment, the dose may be increased according to a maximum of 5 g Oestrogel (4 measures, 3 mg 17 β -oestradiol) daily. In women with an intact uterus, the recommended dose of a progestogen should be administered for 12 days of each month.

As the major oestrogen secreted by the human ovary, oestradiol is crucial to the development and maintenance of the female reproductive system and secondary sex characteristics, it promotes growth and development of the vagina, uterus and fallopian tubes, and enlargement of the breasts. Indirectly it contributes to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for pubertal growth spurt and its termination, growth of axillary and pubic hair and pigmentation of the nipples and genitals.

The onset of menopause results from a decline in the secretion of oestradiol and other oestrogens by the ovary resulting initially in the cessation of menstruation, followed by menopausal symptoms such as vasomotor symptoms (hot flushes and sweating), muscle cramps, myalgias, arthralgias, anxiety, atrophic vaginitis and kraurosis vulvae. Oestrogens are also an important factor in preventing bone loss and after the menopause women lose bone mineral content at an average rate of 15–20% in a ten year period.

It has been established that the effects of oestrogen on bone loss do not depend on the route of administration, but on the oestradiol plasma levels achieved. In this respect, women with plasma oestradiol levels in excess of 60 pg/ml show evidence of suppressed bone turnover. Data from

[REDACTED]

clinical studies demonstrate that a daily dose of 2.5 g Oestrogel (1.5 mg 17 β -oestradiol) allows an increase in the plasma concentration of oestradiol to greater than 60 pg/ml.

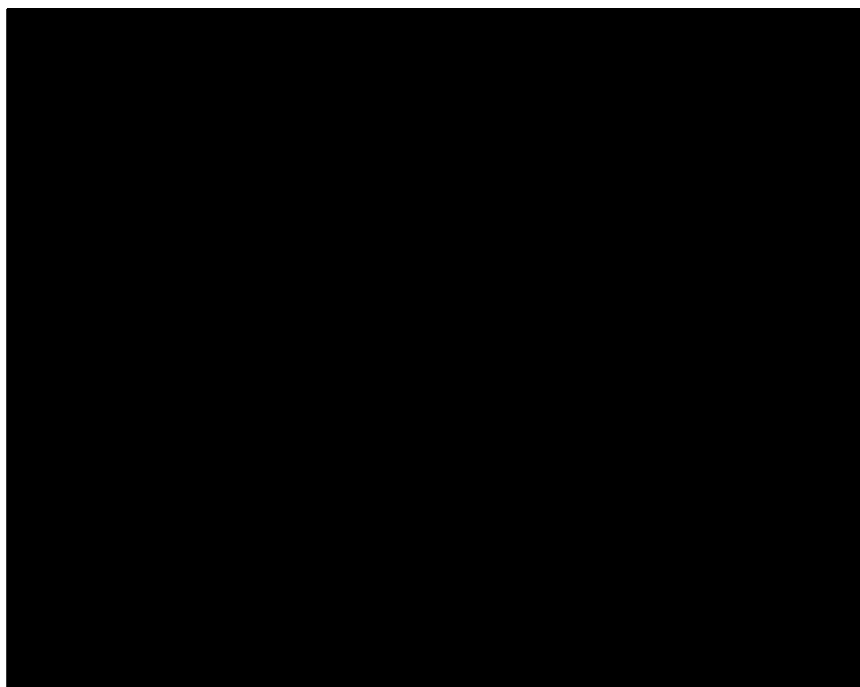
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PART IC

EXPERT COMMENTARY

**Clinical expert report on Oestrogel in the
prevention of osteoporosis.**



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1. Problem statement

The menopause occurs when the numbers of ovarian primordial follicles which develop into follicles fall to a critical level. In the early menopause the development of follicles and their activity are sporadic, and many of the perimenopausal cycles are anovulatory. 17- β oestradiol levels reflect follicular activity, being the most potent oestrogen secreted by the ovary. Periodic increases will not be opposed by progesterone in anovulatory cycles. Over time 17- β oestradiol levels gradually fall to the postmenopausal range as follicle development ceases altogether.

Peak bone mass is normally achieved by young adulthood; the subsequent rate of loss in the interval before the menopause is small as long as oestradiol levels are maintained by ovarian activity. Low circulating oestradiol levels are associated, almost certainly causally, with increases in the rate of bone turnover. The development of osteoporosis depends partly on the extent to which the rate of loss exceeds that of remineralization and partly on peak bone mass. Osteoporosis has been defined as "A disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk". WHO, 1984).

Bone derives the mechanical strength necessary for a rigid skeleton from the structural matrix framework and the mineral deposited on it. Both of these elements are in constant turnover throughout life; multiple factors control the rate of turnover in response to a variety of physiological requirements. Osteoclast mediated bone resorption is balanced by osteoblast mediated bone formation and this balance can be altered by many factors. Oestradiol deficiency leads to an increase in bone turnover involving increased bone resorption. Whilst the rate of turnover may be estimated by assessing urinary or blood resorption and formation markers, the most relevant assessment of skeletal status is bone mineral density (BMD). Although this is a representation of the mineral mass present at the measured sites it does not reflect the architectural aspects of bone. The technology for assessing BMD has gone through many refinements in the last 30 years. The best current method is dual X-ray absorptiometry (DEXA), which achieves a precision of 1 to 2%.

The greater turnover in trabecular than cortical bone has been confirmed by the rates of change of bone mineral density measurements. Trabecular bone, with its honeycomb structure and larger surface area on which osteoclasts can act, is likely to reflect changes in bone turnover more rapidly than cortical bone. For this reason sites rich in trabecular bone (for example vertebral bodies and distal radius) are likely to show BMD changes more quickly than those richer in compact bone (such as some areas of the hip). Studies of the microanatomic structure of bone in biopsies have shown that both trabeculae and their normal interconnectedness are lost with increasing age and that the changes are more marked in women. Such architectural changes lead to loss of the mechanical strength of trabecular bone after the menopause. While hormone replacement may increase trabecular mass, its effect on restoring interconnectedness is less clear. This possibility has never been confirmed because of the practical difficulties, but if so, preservation of mechanical strength would best be achieved by early therapy used prophylactically.

The important clinical consequence of the loss of the mechanical strength is an increase in the incidence of fractures. The areas of main risk are the vertebrae, hip, and wrist. Loss of vertebral mechanical strength leads to crush fractures which are

often wedge shaped. Overall height is lost, and the vertebral column is angled forwards. Affected patients are unable to extend, for example, the cervical vertebrae, and in extreme cases are bent forward at the waist. Fracture of the hip typically occurs in the elderly (over 75 years) and is a multifactorial event in which bone strength is an important factor. The correlation between BMD and fracture risk is as good as that between blood pressure and stroke and better than between serum cholesterol and ischaemic heart disease. A decrease of one standard deviation in BMD at the hip is associated with a doubling of the fracture risk

The hormones secreted by the ovary are replaced either as oestrogens alone in women who have had a hysterectomy, or in combination with a progestogen given to ensure, as far as possible, endometrial safety. A large number of controlled trials has demonstrated that different formulations, regimens and combinations of oestrogens, given by different routes, reduce the rate of bone loss observed in untreated groups or in those in whom calcium was used effectively as a placebo. The effects were generally more prominent at the spine than at the hip. Some of the studies have shown changes to be dose sensitive. The effective dose of conjugated equine oestrogens given orally is generally thought to be 0.625 mg a day, that of oral oestradiol is generally 2 mg a day and that of oestradiol given transcutaneously as a patch 50 µg a day. Implants are given subcutaneously generally with a total dose of 50 mg oestradiol. Oestrogens have been given alone in a minority of studies (for example [redacted] but more often in combination with a progestogen to provide endometrial safety. The bone sparing properties of some progestogens, particularly those derived from 17 -nortestosterone, of which norethisterone is an example [redacted] can confound the investigation of the effects of oestrogens.

Evidence that oestrogen replacement is associated with reductions in fracture rates has been reported from retrospective studies [redacted] and confirmed in prospective studies [redacted]

The purposes of this expert report are to evaluate:

- a) the extent to which Oestrogel (an alcoholic formulation of 17-β oestradiol applied to, and absorbed through, the skin and approved for the treatment of menopausal symptoms) is capable of preventing or reversing the loss of bone mineral found in postmenopausal women.
- b) the evidence to support the proposed indication of prevention of osteoporosis submitted in this licence variation.
- c) to identify and assess any factors which might affect patient safety during the prolonged use of Oestrogel for protection against bone loss.

2. Clinical pharmacology

The pharmacokinetics of Oestrogel has been investigated previously. The results were submitted in applications for treatment of menopausal symptoms.

Many aspects of the pharmacodynamics of Oestrogel, particularly its effects on lipid metabolism, have been investigated previously and the results have also been submitted in previous applications. Relevant to this application are the pharmacodynamics relating to bone metabolism.

The effects of oestradiol on bone metabolism, inhibiting osteoclast mediated resorption and altering the balance of resorption and osteoblast mediated formation in favour of increased bone mineral, are well described and not in doubt. Less certain are the plasma levels required of replacement oestradiol to preserve bone density. [REDACTED] studied the relationship between plasma levels and biochemical markers of bone metabolism (calcium and hydroxyproline excretion expressed as a fraction of creatinine excretion) in seven groups of women. One group consisted of normally cycling women, while in the other six different preparations, including Oestrogel, were used as oestrogen replacement. An inverse relationship between levels of oestradiol and rates of excretion of biochemical markers was observed, confirming the known relationship between oestradiol and inhibition of bone resorption. The authors were able to conclude that oestradiol levels in serum of about 60 pg/ml (approximately 220 pmol/l) reduced the rates of release of biochemical markers of bone resorption to levels comparable with those found in women with continuing ovarian activity, and, by implication, that these were sufficient to preserve bone mineral. Some reservations are relevant to these data. First, the magnitudes of the correlation coefficients, 0.37 and 0.36, implied that only approximately 10% of the change in bone biochemistry was attributable to change in oestradiol levels. Second, the lack of benefit of oestradiol levels above 60 pg/ml suggested that the inverse relationships were not linear; an alternative possibility was that a threshold was obtained at higher replacement levels. Third, the biochemical markers of bone resorption are surrogates of structural change in bone, which is a surrogate of the likelihood of fracture.

Using different methodology, [REDACTED] and his colleagues found a positive relationship between serum oestradiol levels and bone density in patients using Oestrogel and also concluded that a level of 60 pg/ml was sufficient to maintain bone mineral. These data were derived from a subgroup of the patients reported in more detail by [REDACTED] (whose clinical trial report is summarised in section 3.1) and were based on only a limited number of patients. In spite of this, the consistency of the conclusions of Wimalawansa and of Reginster, and the larger body of evidence suggesting that hormone replacements providing early to mid-follicular oestradiol levels are bone sparing, point to the conclusion that oestradiol levels of 220 pmol/l and above can be considered effective in the prevention of the loss of bone mineral in the menopause.

3. Clinical trials of Oestrogen

3.1 Designs of clinical studies

The effectiveness of Oestrogen in prevention of postmenopausal bone loss has been investigated in six clinical trials with varying designs, durations of treatments and comparators. These are summarised in Table 1.

Table 1 Clinical studies of the effectiveness of Oestrogen on menopausal changes in bone mineral

Investigator	Oestrogen dose regimens (g of gel a day) ^a	Comparator and dose regimens	Methodology
[REDACTED]	5 g of gel for 24 of every 28 days	<i>Multifactorial design:</i> Oestrogen and calcium, 1000 mg a day Oestrogen alone Calcium alone Double placebo	Single centre study - 2 years. Double blind, parallel group, multifactorial controlled trial.
	2.5 g of gel for 21 of every 28 days.	Placebo	Single centre study - 2 years. Double blind, randomised, comparative.
	2.5 g of gel for 21 of every 28 days	Untreated control group	Single centre study - 2 years. Open, prospective controlled.
	2.5 g of gel daily	Conjugated equine estrogens, 0.625 mg a day Untreated control group	Single centre study - 3 years for Oestrogen, 2 years for other groups. Open, randomized comparative.
	5 g of gel daily.	Calcitonin, 0.1mg (20 IU) twice a week Placebo gel	Single centre study - 2 years. Symptomatic patients assigned to active Oestrogen groups. Non symptomatic patients randomised to Oestrogen and calcitonin, either, or no active treatment. Parallel group study.
	1.25 g or 2.5 g gel for 25 days of every month.	Placebo	Single centre study - 1 year (ongoing). Open, randomized comparative.

^a 5 g a day of Oestrogen provides 2.5 mg oestradiol: 2.5 g a day provides 1.25 mg oestradiol

3.1.1 [REDACTED]

The study is summarised in a clinical trial report available in this application.

Fifty seven women were randomised in a double blind, parallel group, placebo controlled, multifactorial trial. Selection criteria required an interval of six months to three years since the last menstrual period. Four treatment groups were established in which patients took one of the following:

- placebo Oestrogen
placebo calcium tablets

- Oestrogel, 5 g gel a day, containing 3 mg oestradiol for 24 of every 28 days
placebo calcium tablets
- placebo Oestrogel
Calcium Sandoz, 1000 mg a day by mouth
- Oestrogel, 5 g gel a day, containing 3 mg oestradiol for 24 of every 28 days
Calcium Sandoz, 1000 mg a day by mouth

Oestrogel was given at the higher of the two doses normally used. The starting dose used by many patients is 2.5 g of gel a day, containing 1.5 mg oestradiol. The gel was applied to the upper arm, lower abdomen or thigh.

Unopposed oestradiol was given for the first year. The code was then broken, and those patients who had been treated with active Oestrogel were given Utrogestan (a tablet for oral administration containing micronised progesterone) for days 13 to 24 of every 28 days for the next year.

The main efficacy variables were total body bone mineral, bone mineral content of the distal radius, bone mineral density of the spine and calcium absorption.

Potential reservations are that a small to moderate number of patients was randomised to four groups, with the result that the patient numbers available per group after two years ranged from nine to 14 patients. The high precision of the methods of measurement used (dual and single photon absorptiometry), and the impartial nature of bone density assessment compensate for the low numbers of patients per treatment group.

3.1.2 [REDACTED]

The trial is summarised in a clinical trial report available in this application.

Forty three women were randomised in a double blind comparison of Oestrogel or placebo gel with oral oestriol given for two years. Selection criteria included hysterectomy with or without oophorectomy, but that both serum FSH and LH should be greater than 30 mIU/ml and that oestradiol levels should be less than 25 pg/ml. These criteria ensured that all subjects were menopausal in the sense of cessation of ovarian activity and that they did not need a progestogen for endometrial safety. Oestrogens were given unopposed.

The dose of Oestrogen was 2.5 g of gel a day, providing 1.5 mg oestradiol for 21 of every 28 days for 2 years. The placebo group received 2 mg oestriol for 21 of every 28 days for 2 years.

The efficacy variables were bone mineral density of the lumbar spine, urinary hydroxyproline excretion (an index of bone resorption) and plasma oestradiol and oestrone levels.

The numbers of patients available for assessment after two years treatment were 19 actively treated and 20 in the placebo group.

3.1.3 [REDACTED]

The trial results are given in full in a clinical trial report available in this application.

Seventy patients, with intervals of six to 72 months between the menopause and study entry, were randomised to open treatment with Oestrogel or to no therapy. The dose of Oestrogen was 2.5 g of gel a day, providing 1.5 mg oestradiol for 21 of every 28 days for 2 years. Those assigned to Oestrogel took natural progesterone or a progestogen from days 11 to 21 of every 28 days.

The efficacy variables were bone mineral density of the lumbar vertebrae, plasma osteocalcin levels and fasting urinary calcium excretion.

Thirty three and 25 patients were available for assessment after two years.

3.1.4 [REDACTED]

The results of the trial are given in a publication.

Sixty eight patients were randomised in an open comparison of Oestrogel, conjugated equine estrogens (CEE), or no treatment. The major entry criterion was hysterectomy with bilateral oophorectomy and that no previous treatment had been given which would have affected bone or mineral metabolism.

Patients were treated with 2.5 g of gel, containing 1.5 mg oestradiol daily for three years, or 0.625 mg CEE daily for two years. Untreated patients were followed up for two years. At the end of the treatment or follow up intervals 20 patients were available for assessment in the Oestrogen group, 17 in the CEE group, and 16 in the untreated group.

The trial of Palacios therefore provides data on the effects of an active comparator, taken by mouth, as well as assessments from untreated controls. The division of a moderate study population into three groups limits the numbers available for each.

3.1.5 [REDACTED]

The results of the trial are given in a clinical trial report available in this application.

Sixty women were either assigned to Oestrogel, or randomised to one of the following groups:

- placebo
- human calcitonin, 0.1 mg (or 20 IU), twice a week
- Oestrogel, 5 g gel, containing 3 mg oestradiol, daily
- calcitonin and Oestrogel

Patients assigned to Oestrogel also took 300 mg Utrogestan (micronised progesterone) a day for 12 of every 28 days for endometrial safety.

Treatment was continued for two years. The major selection criterion was postmenopausal healthy women, either with or without symptoms.

The efficacy criteria were bone mineral density of the lumbar vertebrae and plasma oestradiol levels.

Oestrogel was therefore compared with placebo and with a peptide, given by injection, known to have active effects on bone metabolism. Because calcitonin lacked oestrogenic properties, 19 patients complaining of menopausal symptoms were necessarily assigned either to Oestrogel or Oestrogel and calcitonin. Thus almost one third of the patient population were not randomised to the full range of treatment groups, and those who took active Oestrogel were a selected population.

3.1.6

The results of the trial are given in a publication.

Sixty one patients were randomised to one of the following groups:

- Oestrogel, 1.25 g of gel, containing 0.75 mg oestradiol
- Oestrogel, 2.5 g of gel, containing 1.5 mg oestradiol
- placebo gel

All regimens were applied daily for 25 days of every month. At the time of reporting the patients had been treated for one year. The main selection criteria were women no more than five years after the menopause and who had not been treated with hormonal therapy. Some women had had a surgical menopause and others a premature menopause.

Main efficacy variables were bone mineral density of the lumbar spine by QCT, and serum levels of oestradiol, oestrone, FSH, LH and testosterone.

3.2 Scope of efficacy data

The effects of Oestrogel on bone mineral were compared mainly with those of placebo or no treatment. All six studies had groups with either placebo or no treatment. Only two trials included patients treated with compounds known positively to affect bone metabolism (conjugated equine estrogens and calcitonin). One further trial included calcium supplementation, the effects of which are much less clear. Patients taking diets with adequate calcium intakes, which would include the great majority of women agreeing to take oestrogen replacement as a prophylactic against loss of bone mineral, are generally thought not to benefit from further supplements.

In general the numbers of patients in the treatment groups were small. The largest number available for assessment after one year of therapy in any group in any study was 33. The high degree of precision with which bone density is measured, using dual photon or dual X-ray absorptiometry or quantitative computed tomography, and the generally impartial nature of the assessment itself help to compensate for the small numbers of patients in each group.

4. Demography in the clinical studies

The ages and intervals between the menopause and study entry in the six clinical trials are shown in Table 2.

Table 2 **Ages at entry and intervals between the menopause and trial entry in the clinical studies**

Investigator	Oestrogen groups age (years) at entry and interval since menopause	Control groups age (years) at entry and interval since menopause
	<i>Oestrogen only</i> Age 51.0 ± 2.6 Menopause 15.7 ± 8.8 mths	<i>Calcium only</i> Age 50.9 ± 2.1 Menopause 18.7 ± 9.4 mths ^a
	<i>Oestrogen and calcium</i> Age 49.3 ± 2.7 Menopause 14.1 ± 11.3 mths	<i>Placebo</i> Age 50.0 ± 1.6 Menopause 19.9 ± 9.5 mths ^a
	Age 53.0 ± 1.0 yrs Menopause 7.1 ± 2.0 yrs	Age 53.4 ± 1.5 Menopause 8.4 ± 1.6 yrs ^a
	Age mean 51.4 Menopause mean 2.8 yrs	<i>Untreated control</i> Age mean 53.9 Menopause mean 2.7 yrs ^a
	Age 47.1 ± 2.2 Menopause 13.2 ± 6.9 mths	<i>Conjugated estrogens</i> Age 48.9 ± 4.3 Menopause 9.6 ± 7.3 mths ^a
	<i>Oestrogen only</i> Age 52.3 ± 4.9 ^b Menopause range 11 - 72 mths ^c	<i>Calcitonin only</i> Age 57.5 ± 4.4 ^b Menopause range 36 - 108 mths ^c
	<i>Oestrogen and calcitonin</i> Age 53.2 ± 5.5 yrs ^b Menopause range 24 - 96 mths ^c	<i>Placebo</i> Age 56.7 ± 3.8 ^b Menopause range 59 - 104 mths ^c
	Av. age 48.9 - 51.3 Menopause duration < 5 years	Av. age 49.1 yrs ^a

- ^a no statistically significant difference between groups
- ^b subjects in the two active Oestrogen groups were significantly younger than those who did not receive Oestrogen.
- ^c a trend towards shorter intervals between the menopause and study entry approached statistical significance ($p = 0.08$). A comparison of intervals between menopause and study entry for all patients showed a marked difference between symptomatic and asymptomatic subjects ($p = 0.02$).

5. Results - efficacy

5.1 Bone density changes in clinical studies

Changes in bone density in patients treated with Oestrogel and in the control groups are summarised in Table 3.

Table 3 Changes in bone mineral density after one and two years treatment in Oestrogel and control groups

Investigator	Bone Mineral Density	% Change after 1 year	% Change after 2 years
[REDACTED]	<i>TBBMC</i>		
	Oestrogel	+0.4 ± 1.0%	-0.9 ± 1.0%
	Control	-6.3 ± 0.7% ^a	-8.0 ± 1.0% ^a
	<i>BMC proximal radius</i>		
	Oestrogel	+1.2 ± 0.5%	-0.1 ± 0.5%
	Control	-4.3 ± 0.6% ^a	-8.3 ± 1.9% ^b
	<i>BMC spine L2-L4</i>		
	Oestrogel	+6.6 ± 2.2%	+4.1 ± 2.6%
	Control	-3.0 ± 1.6% ^a	-4.2 ± 2.4% ^a
	<i>BMD spine L1-L4</i>		
	Oestrogel	+1.22 ± 0.49%	% change per year values given.
	Control	-1.18 ± 0.41% ^a	
	<i>BMD Total Hip</i>		
	Oestrogel	-0.31 ± 0.42%	
	Control	-1.30 ± 0.27% ^c	
	<i>BMD spine L2-L4</i>		
	Oestrogel	+3.52 ± 0.7%	+4.8 ± 0.9%
	Control	-2.7 ± 0.75%	-4.3% ± 0.75% ^c
	<i>BMD spine</i>		
	Oestrogel	+1.7 ± 3.9%	+5.6 ± 2.9%
	Control	-6.6 ± 3.5%	-9.1 ± 3.4% ^a
	<i>BMD spine</i>		
	Oestrogel	-0.4 ± 4.4%	-3.9 ± 4.9%
	Control	-5.5 ± 2.0%	-10.2 ± 2.6% ^b
	<i>BMD spine (mg/cc)</i>		
	1.25 g gel	)No significant change	Not applicable (Study in progress)
	2.5 g gel		
	Control patients after surgical menopause	-8.7% (P < 0.05)	
	Other controls	No significant change	

Notes:

- 1/ [REDACTED] - comparisons are given between both Oestrogel treated groups and both placebo groups (with or without calcium)
^a = P < 0.001, ^b = p < 0.01
- 2/ [REDACTED] - comparisons are given between Oestrogel treated and control groups
^a = P < 0.001, ^b = p < 0.01 ^c = P < 0.05
- 3/ [REDACTED] - all changes in BMD from baseline in each treatment group were statistically significant - p < 0.005.

Three studies showed marked differences in the responses to placebo and Oestrogen. [REDACTED] reported decreases in bone density after two years of placebo which ranged from 4.2% to 9.1% of baseline values. Increases in bone density in the spine in those treated with active Oestrogen ranged from 4.1% to 5.6%. All of these changes were highly statistically significant (Table 3).

[REDACTED] presented bone density data as changes per year expressed as a percentage of baseline values, and found a significant difference between the bone loss of the placebo group and the gain in those who received active treatment.

The results of [REDACTED] showed, unusually, decreases in bone density of the spine in both the placebo and active Oestrogen treated groups. Patients assigned to placebo showed greater losses than those treated with Oestrogen, and the differences were significant ($p < 0.01$). In absolute terms the differences between the groups were comparable to those reported by [REDACTED] and only slightly smaller than those of [REDACTED]. The reasons for the difference in patterns are difficult to identify. [REDACTED] patients were not randomised in the rigorous sense because symptomatic patients were assigned active treatment, and the shortfall in the control group was made up by asymptomatic women. This led to an imbalance in which patients in the Oestrogen group were younger on average than controls. The dose regimen used by [REDACTED], 5 g gel every day for two years, was the highest exposure of all the studies. Evidence emerged of incomplete compliance with calcitonin, given by twice weekly injections, raising the possibility that compliance with Oestrogen may also have been incomplete. Median serum oestradiol levels were 440 pmol/L after one year and 270 pmol/L after two years, although the levels in both years appear sufficient to prevent actual loss of bone in the majority of patients. One possible explanation is a downward drift in the computed tomography used to assess bone density over the two years of observation. In spite of the unusual pattern of results, a reasonable conclusion from [REDACTED] trial is that Oestrogen protected actively treated patients by limiting the amount of bone density lost after two years treatment.

Assessment of total bone mineral, bone content in the proximal radius [REDACTED] and bone density of the hip [REDACTED] showed results which were similar in direction and magnitude to those reported for the lumbar spine.

The report of the trial by Heung-Tat Ng, which appears to be an interim communication, is difficult to interpret. Changes in bone mineral are not presented quantitatively, but merely summarised as showing "no significant change" in any of the three treatment groups. The only exception to this was the calculation of a loss of bone density of 8.7% in a subgroup of the controls who had previously undergone oophorectomy. Assessment of the results of this study will not be possible until the trial is complete, and the data presented quantitatively and in more detail.

Taken together, the results of these trials show that Oestrogen is effective in preventing the loss of bone mineral in the lumbar spine otherwise associated with menopausal reductions in oestradiol levels. None of the studies provided a direct comparison of 2.5 and 5 g a day. The results of the two studies in which patients were treated with 5 g Oestrogen a day appeared comparable with the results of the three studies in which the dose was 2.5 g a day.

5.2 Other therapies and changes in bone mineral

Other oestrogen preparations include patches for transdermal replacement and oral oestrogens. Both of these are effective at preventing and reversing the loss of bone mineral linked to cessation of ovarian oestradiol secretion at the menopause.

██████████ compared continuous transdermal 17 beta-oestradiol 0.05 mg/day, to which 0.25 mg/day of norethisterone acetate was added for 14 days of each 28-day cycle, with oral continuous conjugated equine oestrogens, 0.625 mg/day, to which 0.15 mg/day dl-norgestrel was added for 12 days of each 28-day cycle in 66 early postmenopausal women treated for three years. Thirty matched, untreated individuals acted as controls. Both active treatments led to highly significant increases of bone density in the spine and proximal femur compared to the controls, who lost 4% and 5% of bone mineral at these sites respectively. No difference was observed between the responses of the groups assigned to active treatment.

██████████ treated 104 osteoporotic late postmenopausal women with continuous combined hormone replacement therapy (5 mg medroxyprogesterone acetate daily and either 0.625 mg oral conjugated oestrogens for 50 micrograms transdermal oestradiol daily) for an average of one year. Nineteen healthy individuals matched for menopausal age and weight acted as controls. After one year bone density increased by 7.1% in the spine and by 2.9% at the femoral neck but tended to decline in the control group. Similar changes were noted in a smaller number of patients who continued treatment for a second year.

Similar results have been reported by ██████████ in patients treated with transdermal oestradiol or conjugated equine estrogens, and by ██████████ using micronized 17 beta-oestradiol continuously with dydrogesterone.

The results of these studies, showing increases in bone mineral at sites of predominantly trabecular bone and losses in the control groups, are entirely consistent with those observed after treatment with Oestrogel, particularly in the trials of ██████████

Alternative therapies for prevention of postmenopausal bone loss include other oestrogen replacement formulations, bisphosphonates, calcitonin, fluoride and calcium supplements.

Bisphosphonates such as etidronate have been used successfully in the treatment of established osteoporosis ██████████ for their inhibitory effect on osteoclast activity. So far they have not been used widely in the prophylaxis of postmenopausal loss of bone mineral, partly because their lack of effect on menopausal symptoms is seen as a disadvantage, especially in the perimenopause. Similarly fluoride preparations have no impact on the frequency or intensity of menopausal symptoms. Beneficial effects on bone metabolism have been reported, but some forms are associated with skeletal toxicity. Further studies are needed to evaluate the usefulness of fluoride in the prevention of fractures ██████████

██████████ The peptide calcitonin is given either by injection or as a nasal spray. Evidence of a beneficial effect on bone density in postmenopausal women has been published ██████████ but the findings are not universal ██████████ Calcium itself needs to be given in adequate amounts both while the skeleton is developing to maturity and in postmenopausal women as deficiency limits bone formation. Calcium supplementation is not, however, seen as

an alternative to hormone replacement at and after the menopause as a means of compensating for increased osteoclastic activity.

5.3 Conclusions from efficacy data and dose recommendations

The five trials for which detailed results are available have shown consistent responses in patients treated with Oestrogel in spite of differences in design, dose regimens, methods of assessment and comparators. No evidence has emerged that the higher dose of 5 g of gel a day provides a greater effect on bone mineral than the more commonly used 2.5 g a day.

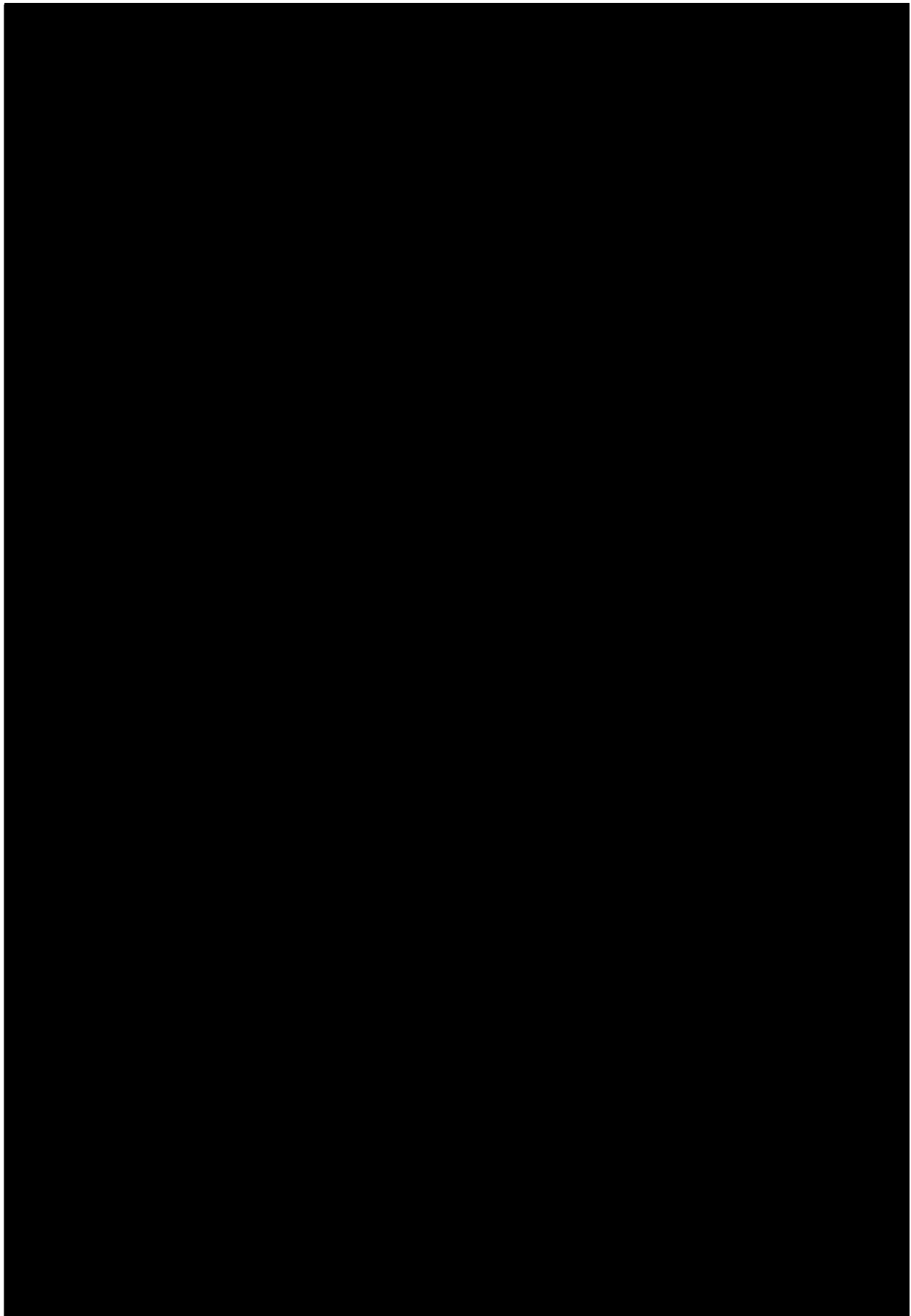
A pragmatic treatment scheme would therefore favour the use of 2.5 g of Oestrogel a day as a starting dose, which will generally provide oestradiol levels in the early to mid-follicular range. On the evidence available, oestradiol levels of 220 pmol/l or greater prevent loss of bone mineral. Serum oestradiol levels should be checked when necessary, for example if menopausal symptoms persist, or in patients known to be at particular risk of osteoporosis. When oestradiol levels are found to be less than 220 pmol/l, the method of gel application should be reviewed to ensure that the area of application is sufficient; the dose of Oestrogel should be increased to 5 g a day for patients in whom low oestradiol levels persist in spite of adequate application technique.

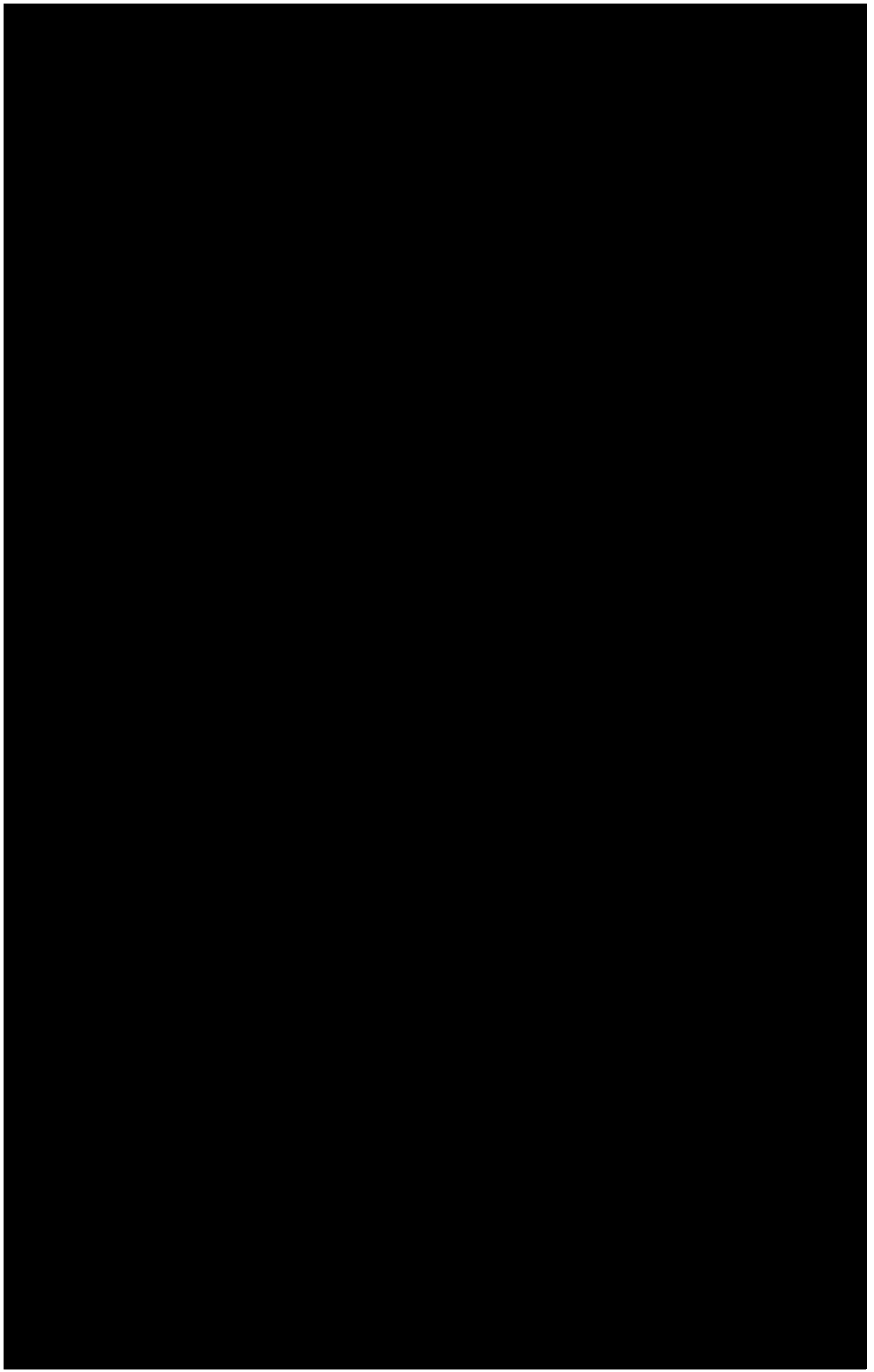
The data available do not make possible an assessment of whether combination with a progestogen for endometrial safety could affect changes in bone mineral. In general, derivatives of nortestosterone, such as norethisterone and levonorgestrel, have a positive effect on bone mineral by virtue of their anabolic properties. Derivatives of 17 hydroxyprogesterone, such as medroxyprogesterone acetate, are generally considered to be neutral in terms of bone metabolism. The most likely conclusion is therefore that combination with a progestogen for endometrial safety will at least not diminish the beneficial effects of Oestrogel on bone mineral.

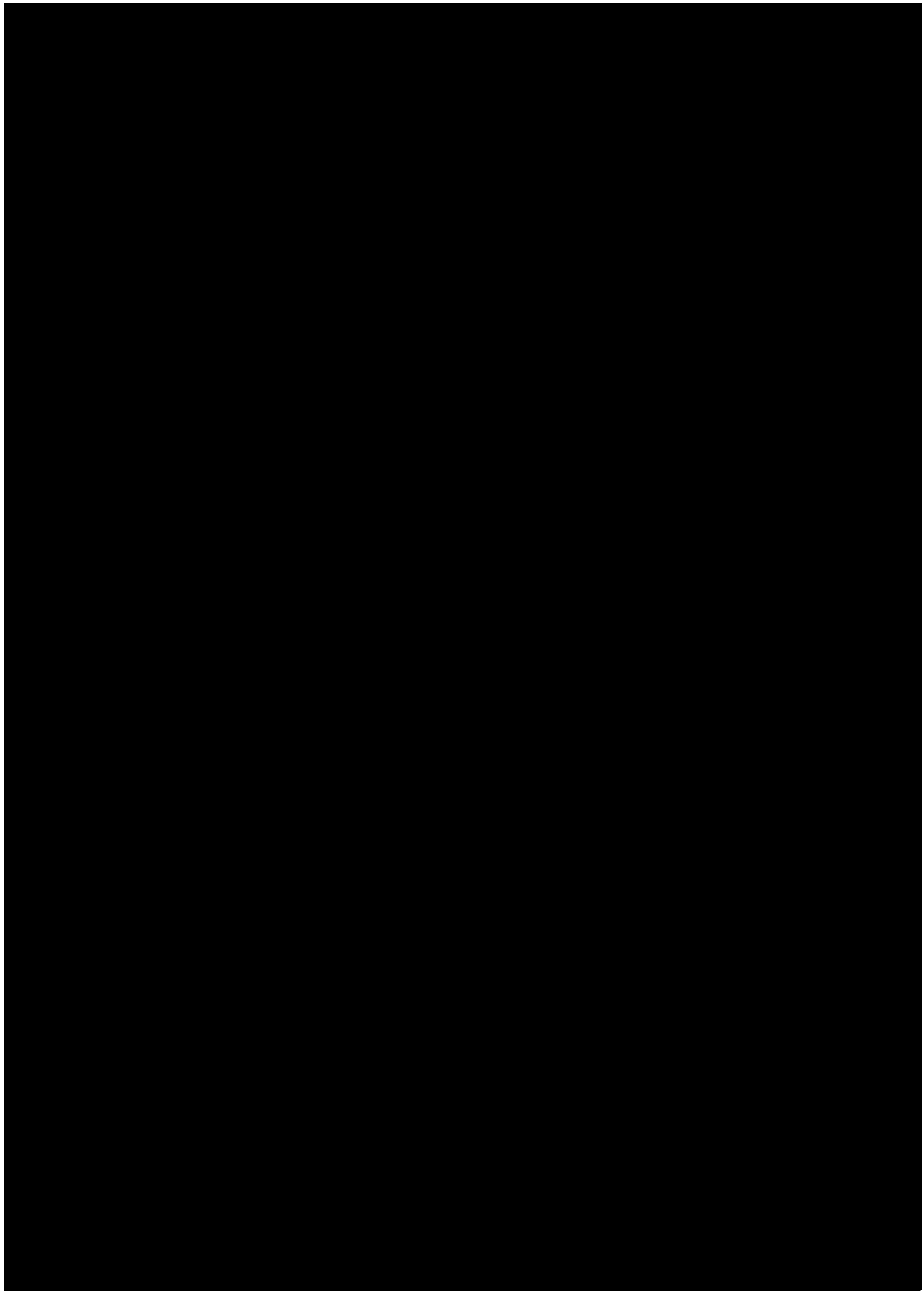
Although comparative data were limited, the changes in bone density after Oestrogel were quantitatively similar to those obtained with other oestrogen preparations and to the non-steroidal compounds used to protect against loss of mineral.

No clinical trials have been conducted to confirm that the preservation of bone mineral conferred by treatment with Oestrogel leads to a reduction in fracture rate. Evidence that replacement of oestrogens reduces fracture rates derives from retrospective [REDACTED] and prospective studies [REDACTED]. The active constituent of Oestrogel, 17- β oestradiol, is the primary oestrogen secreted by the ovary in the reproductive years. As the mechanisms which link the inhibitory properties of oestradiol on bone resorption, preservation of bone mineral, mechanical strength of bone and fracture rates are now largely understood, the ethics of a clinical trial designed to compare fracture rates in a placebo controlled study of Oestrogel would be difficult to justify.

6. Results - safety

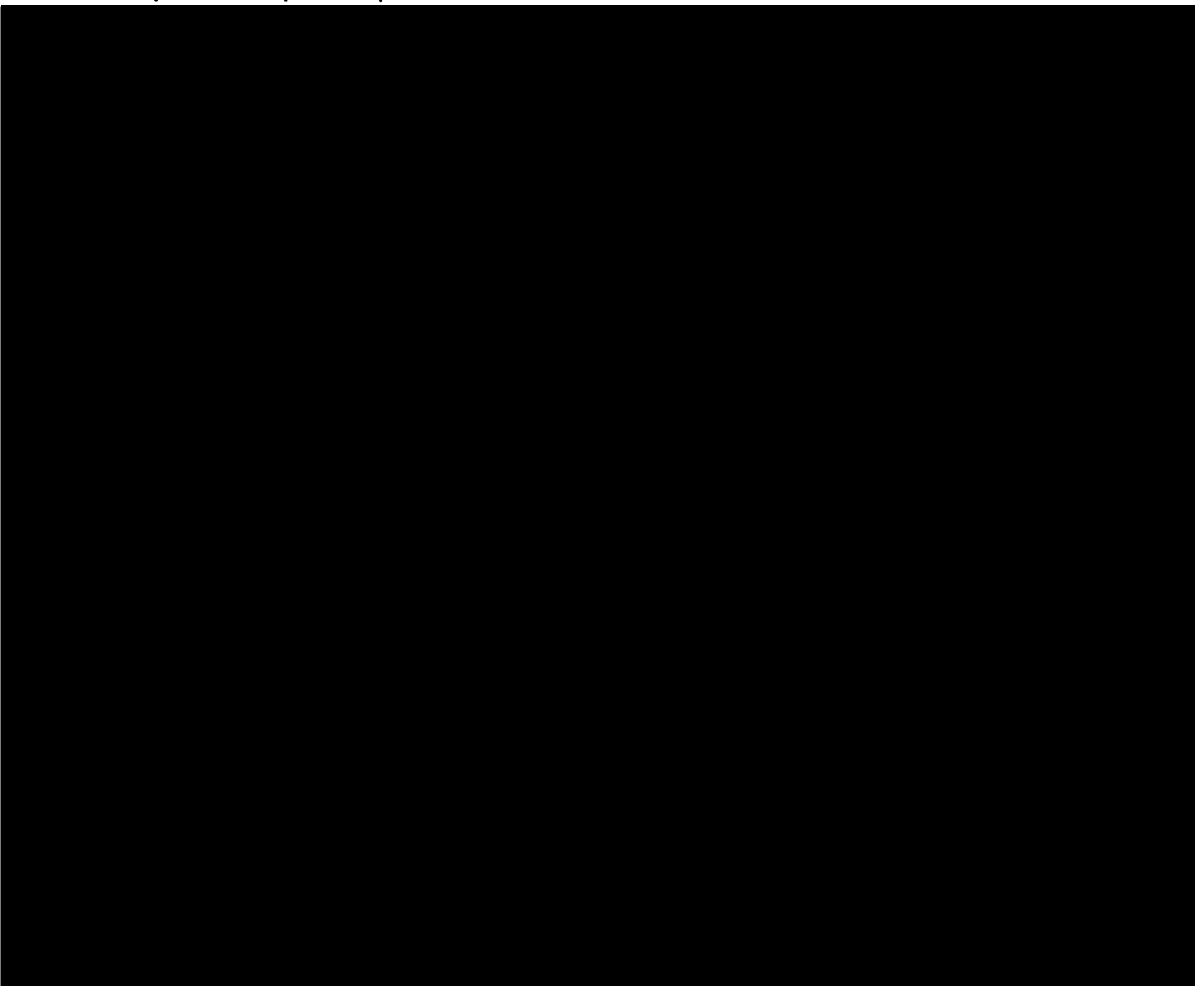






8. Benefit-risk assessment

The benefits of Oestrogel are:

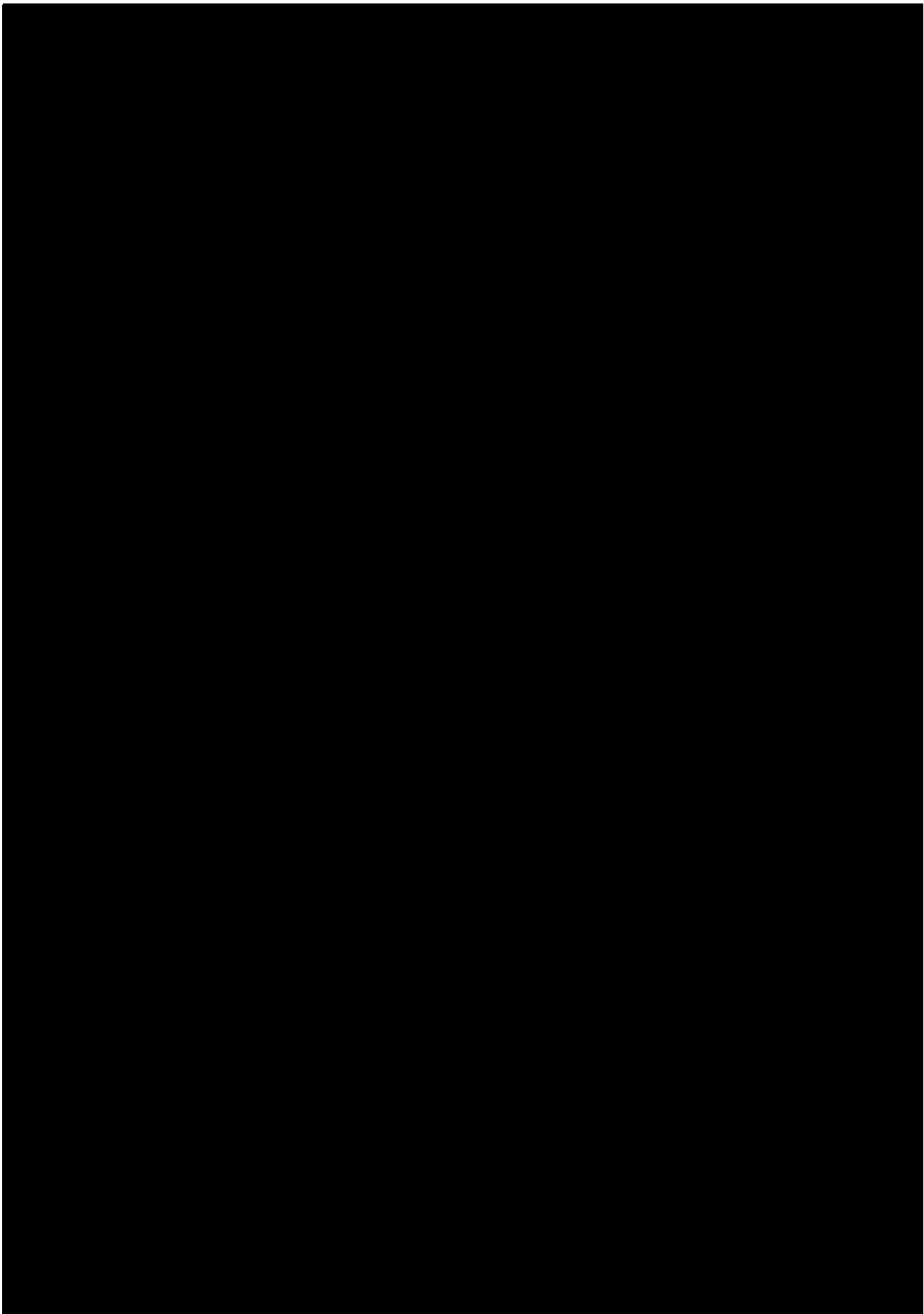
- replacement of 17- β oestradiol using the percutaneous route and achieving serum oestradiol levels within the early to mid-follicular range. Saturation of skin and subcutaneous reservoirs avoids marked diurnal variation in serum oestradiol levels.
 - relief of menopausal symptoms.
 - preservation of bone mineral demonstrated for intervals of up to three years in clinical trials, while untreated controls have shown the losses anticipated in postmenopausal patients.
- 

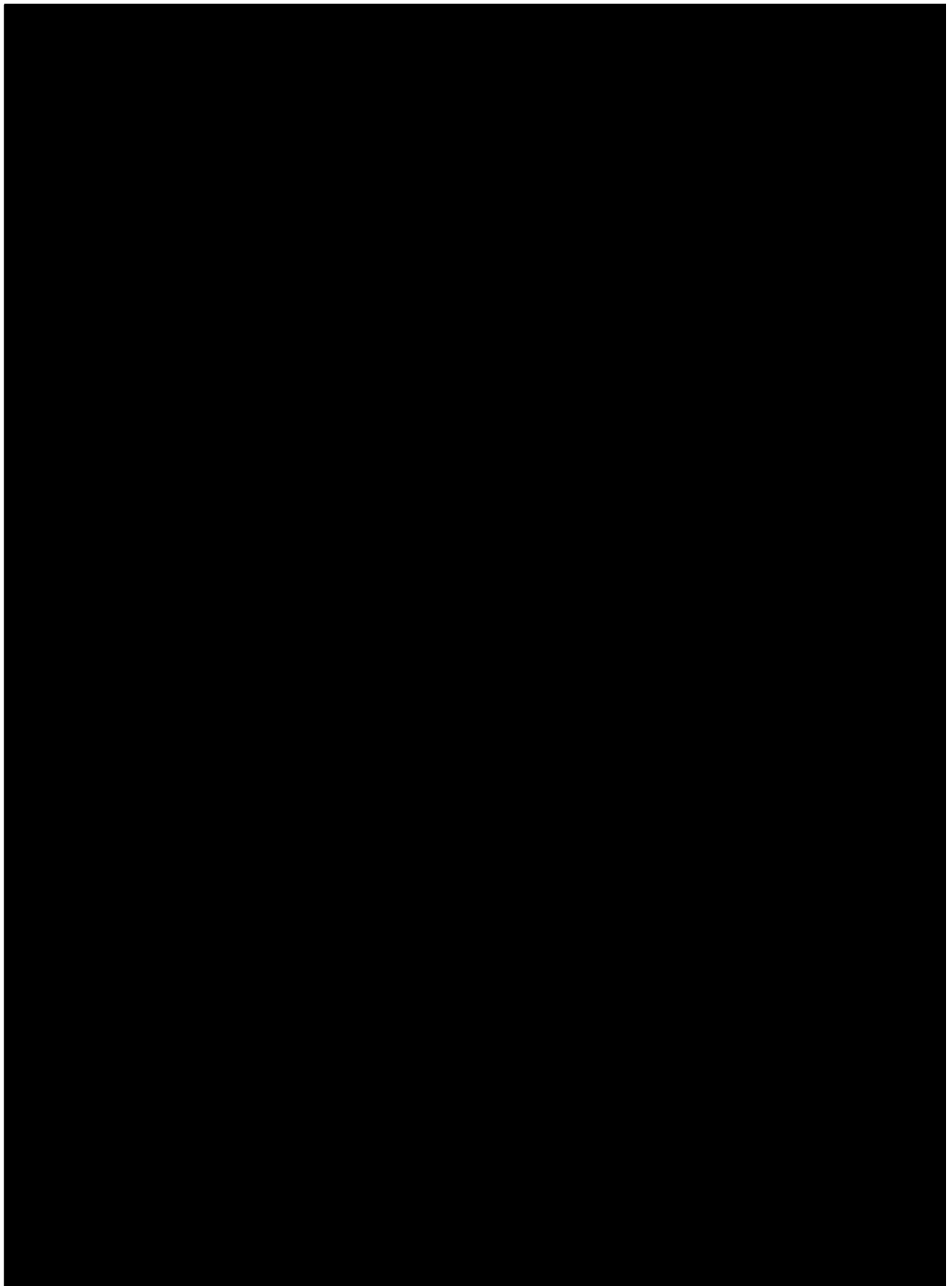
9. Conclusions

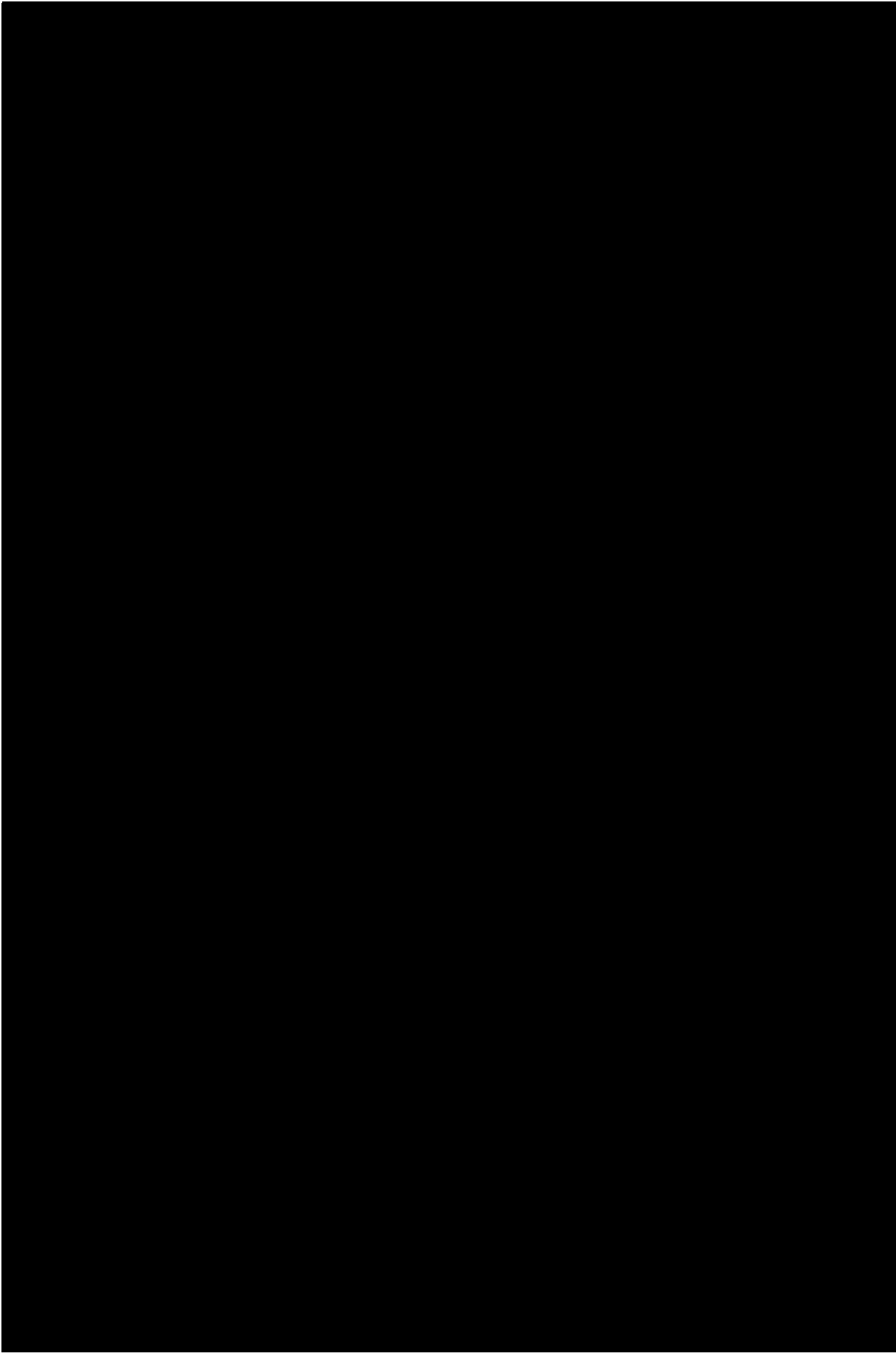
After examining in detail the documentation provided and by reviewing the published literature, I have reached the following conclusions:

- 1/ The causal association linking reductions in ovarian oestrogen secretion, decreased serum oestradiol levels, reductions in bone mineral and increases in the risk of bone fracture is well established.
- 2/ Oestrogel has been investigated in six clinical trials, of which five have provided useful data on its efficacy in preventing the loss of bone mineral characteristic in patients after the menopause. Two dose regimens, 2.5 g of gel (1.5 mg oestradiol) a day, and 5 g of gel (3 mg oestradiol) a day have been investigated. Both regimens provided bone mineral densities which ranged from approximately 4% to 9% higher than those observed in patients in the control groups after two years of treatment. No indication of a dose response relationship was found, but this may have been due to the designs of the trials. None of the five studies for which detailed results are available compared different dose regimens of Oestrogel within the same trial.
- 3/ Review of the published literature confirmed that the Oestrogel associated changes in bone mineral were consistent with those found with either transdermal oestradiol preparations or oral oestrogens. Other therapies, such as bisphosphonates and calcitonin have similar protective effects on bone, but do not provide relief of postmenopausal symptoms.
- 4/ These results support the use of Oestrogel, 2.5 g or 5 g of gel a day, for prevention of postmenopausal osteoporosis in women at risk of developing fractures.
- 5/ Women with intact uteri should receive a standard dose of a progestogen to minimise the risk of endometrial pathology. No evidence indicates that the concurrent use of a progestogen may decrease the protective effect of Oestrogel on bone mineral.
- 6/ The numbers of patients who withdrew from the studies because of adverse events was unremarkable given the prolonged treatment intervals. The symptoms reported as adverse events were not unexpected from the nature of the preparation.
- 7/ Oestrogen preparations are known to be associated with small increases in the incidences of venous thromboembolism and, after treatment in excess of five to ten years, of breast cancer. There is no indication that the effects of Oestrogel in these respects would be any more or less potent than other oestrogen formulations.
- 8/ The treatment interval for protection against postmenopausal loss of bone mineral remains a clinical decision based on the individual circumstances of the woman, and her perception of the risks and benefits.







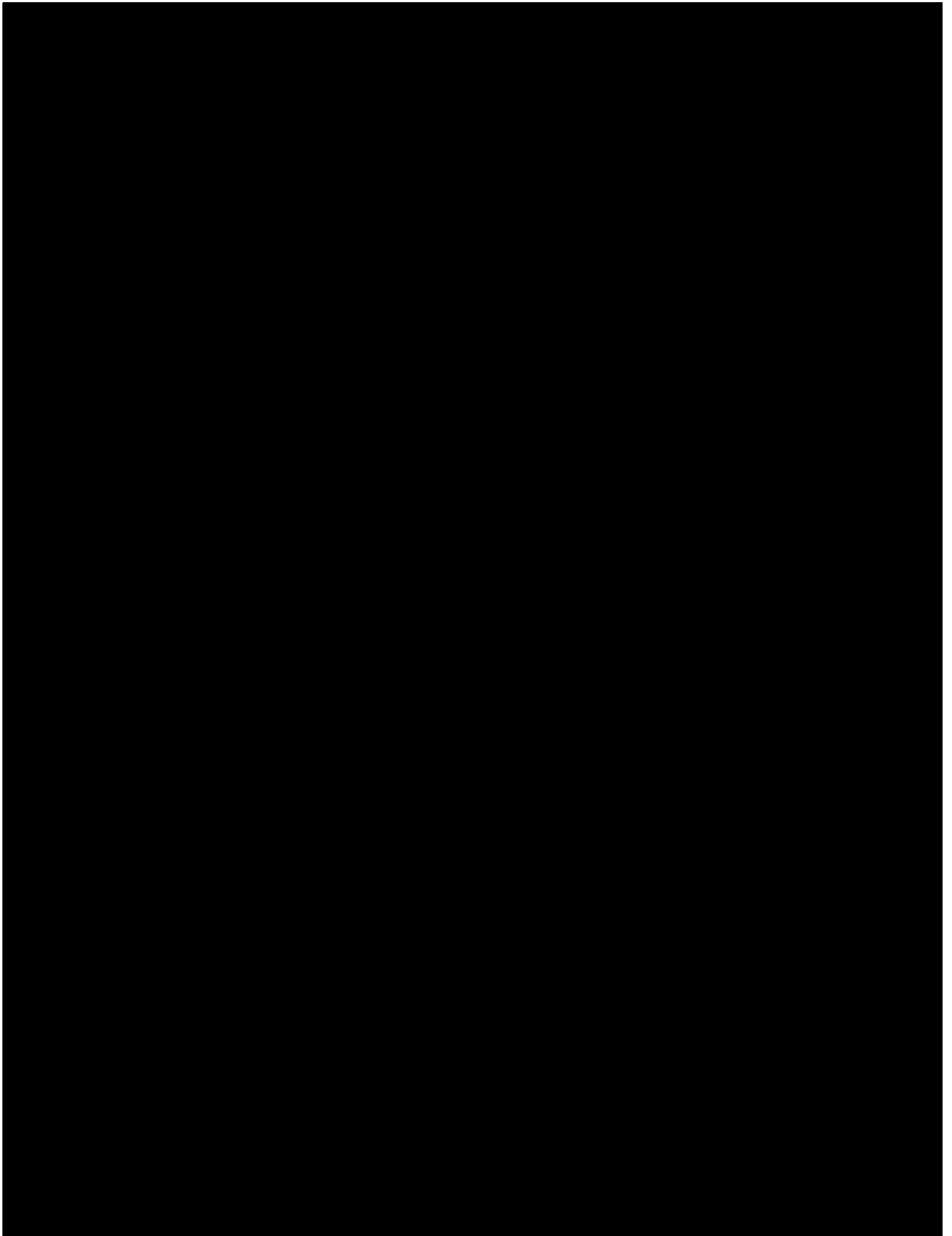


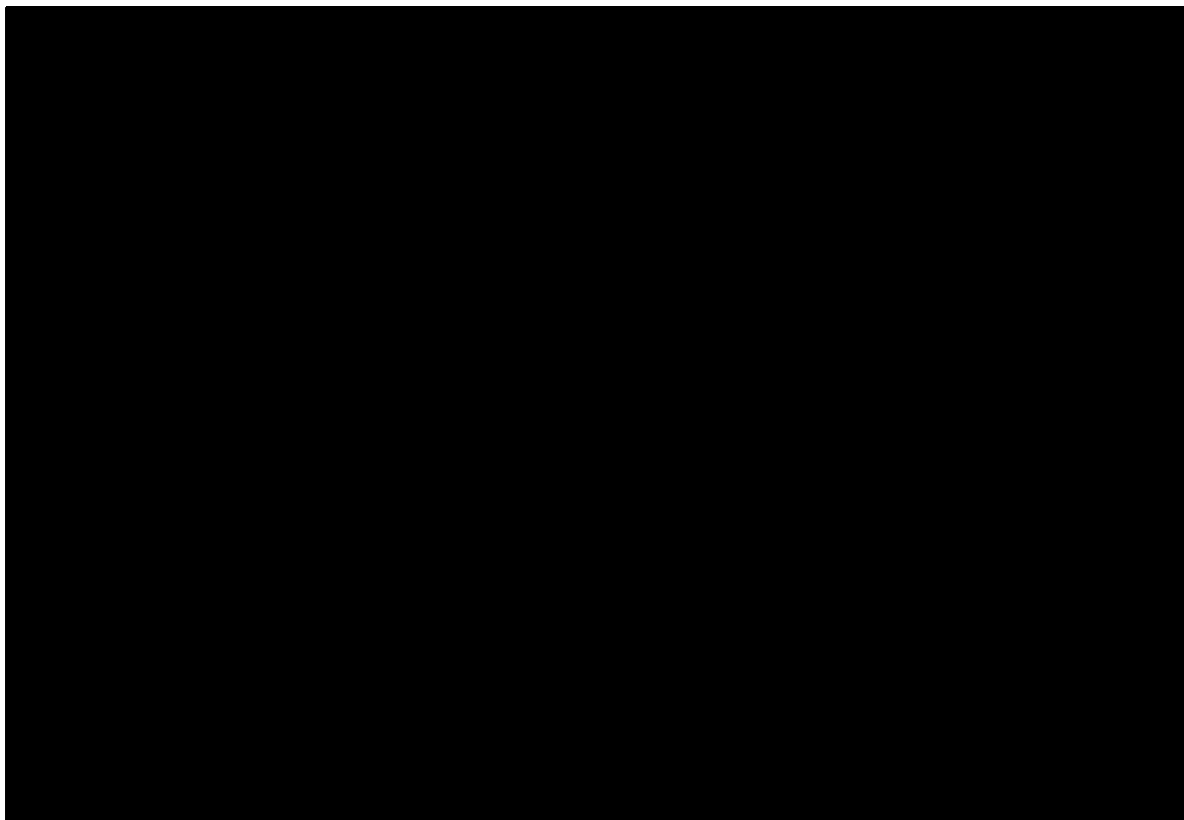


[REDACTED]

[REDACTED]

[REDACTED]





PART IC

SUMMARY OF CLINICAL TRIALS TABLES

Finished product: Oestrogen Active ingredient(s): Oestradiol					SUMMARY OF CLINICAL TRIALS referring to Part IV of the dossier			(For National Authority Use Only)	
Ref. Volume Page Vol 2 1-34	Study - investigator - coordinating center - center(s) - Report n°	Design Open single centre prospective controlled	Number of subjects with age and sex 70 F 40-60 yrs	Diagnosis + criteria for inclusion Post-menopausal women with menopause 6-72 months previously and not using HRT	Duration of treatment 2 years	Test product Dosage regimen Route of Administration Oestrogen 2.5 g (1.5 mg oestradiol) daily for 21/28 days. Applied on arms or lower abdomen. Natural progesterone or a progestogen given from day 11-21 of cycle.	Criteria for evaluation Bone mineral density (BMD) Plasma osteocalcin Fasting urinary calcium	Results (efficacy) At 24 months: BMD Oestrogen significantly higher than control ($p < 0.05$). Plasma osteocalcin no significant difference from initial levels. 2.5 g Oestrogen daily in cyclical regimen with 10 days progestogen effective in preventing bone loss.	Adverse Reactions Well tolerated. No skin reactions. 1 - menorrhagia at 12 months. 7 - venous insufficiency 1 - mastodynia

Finished product: Oestrogel					SUMMARY OF CLINICAL TRIALS referring to Part IV of the dossier			(For National Authority Use Only)		
Active ingredient(s): Oestradiol					Diagnosis + criteria for inclusion	Duration of treatment	Test product Dosage regimen Route of Administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Ref. Volume Page	Study - investigator - coordinating center - center(s) - Report n°	Design	Number of subjects with age and sex		Healthy post- menopausal women with or without symptoms	2 years	Oestrogel 5 g (3 mg oestradiol) daily + oral progesterone 300 mg for 12/28 days (intact uteri) or Human calcitonin 0.1 mg (20 iu) s.c. twice weekly or Placebo – inactive percutaneous gel	Vertebral bone mineral density (VBMD) Plasma oestradiol levels	Oestrogel: Effect on bone loss significant at yr 1 (p = 0.005) and yr 2 (p = 0.005). Plasma oestradiol levels 245–475 pmol/l. Calcitonin not effective due to likely failure in patient compliance.	No adverse events reported.
Vol 2 35–51		Randomised Controlled Prospective	60 F 38–65 yrs							

SUMMARY OF CLINICAL TRIALS referring to Part IV of the dossier				(For National Authority Use Only)								
Finished product: Oestrogel Active ingredient(s): Oestradiol				Study - investigator - coordinating center - center(s) - Report n°	Design	Number of subjects with age and sex	Diagnosis + criteria for inclusion	Duration of treatment	Test product Dosage regimen Route of Administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Vol 3 52-223				Single centre, double-blind parallel group placebo controlled	57 F 45 – 54 yrs	Healthy post-menopausal women with menopause 6 m – 3 yrs previously	2 years	Oestrogel 5 g (3 mg oestradiol) daily from days 1 – 24 of 28 days cycle. Applied on upper arm, lower abdomen or thigh. Utrogestan 100 mg on days 13 – 24 in 2nd study year for those receiving Oestrogel. Oral administration. Calcium Sandoz 1000 mg/day, oral administration	Total body bone mineral (TBBM) Bone mineral content (BMC) BMC - spine Calcium absorption (Ca Abs). Vit D metabolites	Oestrogel with or without calcium was relatively effective in the prophylaxis of osteoporosis in early menopausal women.	26 events reported by 21 subjects. Most common were gastrointestinal events – 10 subjects. 7 subjects – premature withdrawal.	

[REDACTED]

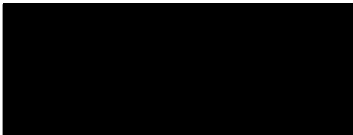
Finished product: Oestrogen

Active ingredient(s): Oestradiol

SUMMARY OF CLINICAL TRIALS referring to Part IV of the dossier				(For National Authority Use Only)									
Finished product: Oestrogen Active ingredient(s): Oestradiol				Ref. Volume Page	Study - investigator - coordinating center - center(s) - Report no.	Design	Number of subjects with age and sex	Diagnosis + criteria for inclusion	Duration of treatment	Test product Dosage regimen Route of Administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
				Vol 5 502- 723		Double blind randomised comparative single centre	43 F 40-65 yrs	Post-menopausal women, with or without ovariectomy. FSH + LH ≥ 30 mIU/ml. Oestradiol ≤ 25 pg/ml.	2 years	Oestrogen 2.5 g (1.5 mg oestradiol) daily for 21/28 days. Applied on shoulders, arms, forearms. or Placebo gel 2.5 g/day for 21/28 days + 1 oestradiol tablet 2 mg p.o for 21/28 days.	Bone mineral density (BMD) Oestradiol Oestrone plasma levels every 3 mths between day 5 + 20 of cycle.	<u>BMD Lumbar spine</u> Oestrogen: +1.22% ± 0.49% per year (p < 0.05) Placebo: -1.18% ± 0.41% (p < 0.01) <u>BMD Total Hip</u> Oestrogen: -0.3% ± 0.42% Placebo: -1.30% ± 0.27% (p < 0.001) Mean plasma hormone levels correlated with bone mass density.	No cutaneous reactions. Slight breast tenderness.

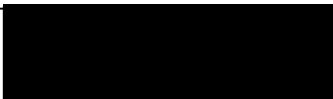
Finished product: Oestrogen Active ingredient(s): Oestradiol					SUMMARY OF CLINICAL TRIALS referring to Part IV of the dossier			(For National Authority Use Only)	
Ref. Volume Page	Study - investigator - coordinating center - center(s) - Report n°	Design	Number of subjects with age and sex	Diagnosis + criteria for inclusion	Duration of treatment	Test product Dosage regimen Route of Administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Vol 6 729- 734		Randomized Open Comparative	68 F Average age 48 yrs	Post-menopausal women who had not received HRT or treatment for bone or mineral metabolism following surgical menopause	Oestrogen: 3 years Conjugated Oestrogen: 2 years	Oestrogen 2.5 g (1.5 mg oestradiol) daily. Applied on arms. or Conjugated oestrogens 0.625 mg/day orally	Bone mineral density (BMD) Plasma oestradiol and oestrone levels	At 24 months: BMD Oestrogen = $+4.7 \pm 3.2\%$ BMD Oestrogen = $+4.3 \pm 9.2\%$ Untreated = $-9.1 \pm 3.4\%$ 2.5 g Oestrogen daily prevented bone loss and was comparable to conjugated oestrogens.	None stated.

SUMMARY OF CLINICAL TRIALS referring to Part IV of the dossier				(For National Authority Use Only)					
Finished product: Oestrogen									
Active ingredient(s): Oestradiol									
Ref. Volume Page	Study - investigator - coordinating center - center(s) - Report n°	Design	Number of subjects with age and sex	Diagnosis + criteria for inclusion	Duration of treatment	Test product Dosage regimen Route of Administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Vol 6 735- 740		Open Randomised Comparative	61 F	Post menopausal women with duration < 5 years and not received prior hormonal therapy	1 year at time of publication	Oestrogen 1.25 g (0.75 mg oestradiol) and 2.5 g (1.5 mg oestradiol) daily from day 1- 25 each month. Applied on the arms in the evening. or Placebo gel 1.25 g or 2.5 g daily day 1-25 each month. Applied on the arms in the evening.	Serum concs of estrone E1, estradiol E2, FSH, LH Testosterone. Bone mineral density (BMD).	Peak E2 levels seen at 6 hrs post admin. (557 pg/ml). Decrease in E1 in controls and increase in E1 in treatment groups was significant. Significant BMD loss only seen in surgical menopausal women. No losses seen in treatment groups.	None reported.



PART IC

INDIVIDUAL SUMMARY TABLES



Title of the study : Effect of transdermal administration of Oestradiol on postmenopausal vertebral bone loss

Company : Hoechst Marion Russel Ltd		Individual Study Table referring to Part IV of the Dossier		(For National Authority Use Only)																																																																										
Finished Product : Oestrogel		Volume : 2																																																																												
Active Ingredient : Oestradiol		Page : 1-34																																																																												
SUMMARY — CONCLUSIONS :																																																																														
Efficacy results	Vertebral bone density values are shown in the table below																																																																													
<table><tr><th rowspan="3">Group</th><th colspan="4">Bone Mineral Density</th></tr><tr><th>Initial</th><th colspan="3">% Change</th></tr><tr><th>g/cm²</th><th>1 year</th><th>2 years</th><th>Between 1-2 years</th></tr><tr><td colspan="6"><u>Oestrogel</u></td></tr><tr><td>n</td><td>33</td><td>32</td><td>33</td><td>33</td><td></td></tr><tr><td>Mean</td><td>0.937</td><td>+3.52</td><td>+4.8</td><td>+1.3</td><td></td></tr><tr><td>SD</td><td>0.097</td><td>0.7</td><td>0.9</td><td>0.7</td><td></td></tr><tr><td>SEM</td><td>0.017</td><td><0.001</td><td><0.001</td><td>0.09</td><td></td></tr><tr><td colspan="6"><u>Control</u></td></tr><tr><td>n</td><td>25</td><td>24</td><td>25</td><td>25</td><td></td></tr><tr><td>Mean</td><td>0.975</td><td>-2.7</td><td>-4.3</td><td>-1.3</td><td></td></tr><tr><td>SD</td><td>0.042</td><td>0.75</td><td>0.75</td><td>0.5</td><td></td></tr><tr><td>SEM</td><td>0.008</td><td><0.005</td><td><0.001</td><td><0.05</td><td></td></tr></table>						Group	Bone Mineral Density				Initial	% Change			g/cm ²	1 year	2 years	Between 1-2 years	<u>Oestrogel</u>						n	33	32	33	33		Mean	0.937	+3.52	+4.8	+1.3		SD	0.097	0.7	0.9	0.7		SEM	0.017	<0.001	<0.001	0.09		<u>Control</u>						n	25	24	25	25		Mean	0.975	-2.7	-4.3	-1.3		SD	0.042	0.75	0.75	0.5		SEM	0.008	<0.005	<0.001	<0.05	
Group	Bone Mineral Density																																																																													
	Initial	% Change																																																																												
	g/cm ²	1 year	2 years	Between 1-2 years																																																																										
<u>Oestrogel</u>																																																																														
n	33	32	33	33																																																																										
Mean	0.937	+3.52	+4.8	+1.3																																																																										
SD	0.097	0.7	0.9	0.7																																																																										
SEM	0.017	<0.001	<0.001	0.09																																																																										
<u>Control</u>																																																																														
n	25	24	25	25																																																																										
Mean	0.975	-2.7	-4.3	-1.3																																																																										
SD	0.042	0.75	0.75	0.5																																																																										
SEM	0.008	<0.005	<0.001	<0.05																																																																										
In the Oestrogel group, change in vertebral density expressed as a percentage of initial values or in g/cm² differed significantly between 0 and 12 months of treatment (p<0.001). Mean vertebral bone density at 6 months and at 12 months of treatment was higher than at the beginning of treatment. In the control group, change in vertebral bone density at 1 year expressed as a percentage of the initial value and in g/cm² differed significantly from 0 (p<0.005 and p=0.002). Mean vertebral bone density at 1 year was significantly lower than the initial value. At 2 years, mean vertebral BMD in the Oestrogel group was significantly higher than in the control group (p<0.05). In the Oestrogel group there was a significant increase in vertebral BMD after 18 months and after 24 months of treatment compared with initial values, irrespective of whether this increase was expressed as a percentage of initial values (p<0.001) or in g/cm² (p<0.001). In contrast, vertebral bone density was significantly reduced in the control group at the end of the 2-year study period (p<0.001). In the control group, change in vertebral bone density was statistically significant between the first and second years of follow-up (p<0.05). BMD was significantly lower in this group than at the end of the first year (p<0.05). In the Oestrogel group, change in vertebral BMD did not differ significantly from 0 between the first and second years of follow-up. Vertebral bone density after 18 and 24 months was slightly higher than at 12 months, but this was not significant. Plasma osteocalcin showed a slight, non-significant decrease at 1 year, and at 2 years mean values did not differ significantly from initial values. Urinary calcium was significantly lower after 1 year compared with the value at the start of the study (p<0.01) and at 2 years the ratio of urinary calcium to urinary creatinine was significantly lower compared with initial values (p<0.01). Mean plasma oestradiol concentration was significantly higher after 6 months of treatment than at inclusion. Mean values were between 50 and 65 pg/ml.																																																																														
Safety Results	Oestrogel was well tolerated, and no local skin reactions were reported. A single episode of menorrhagia was reported by one patient receiving Oestrogel, after 12 months of treatment (Oestrogel and Duphaston). Seven patients reported functional symptoms of 'venous insufficiency'. Of the 7 cases of withdrawal in the Oestrogel group, one case was associated with mastodynia.																																																																													
Conclusion	The results demonstrate that Oestrogel administration at a dose of 2.5 g daily in a cyclical regimen with 10 days of progestogen is effective in preventing postmenopausal bone loss.																																																																													

[Redacted]

Title of the study : Effect of percutaneous oestradiol on bone mineral density in early postmenopausal women

[Redacted]

[Redacted]

Finished Product :Oestrogel Active Ingredient :Oestradiol		Individual Study Table referring to Part IV of the Dossier	(For National Authority Use Only)																									
		Volume : 2 Page : 35-51																										
SUMMARY — CONCLUSIONS : Efficacy Results Subjects in the two Oestrogel groups were significantly younger than those in the non-Oestrogel groups. VBMD at baseline showed a trend towards lower values in the placebo and calcitonin only groups, consistent with the younger ages and trend towards shorter intervals since menopause of the Oestrogel treated subjects. Bone mineral density values are shown in the table below:																												
Vertebral bone density mg/cc Year 1																												
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The effect of Oestrogel in preventing bone loss was statistically significant at both year 1 (p = 0.005) and year 2 (p = 0.005). Median levels of plasma oestradiol in patients who received Oestrogel ranged from 245 to 475 pmol/l. Wide ranges of levels were also found in the two non-Oestrogel groups. Calcitonin was not effective in this study at preventing bone loss, due most likely to a failure of many of the patients to inject the product with the recommended frequency.																												
Safety Results	No adverse events were reported																											
Conclusion	Oestrogel was shown to be an effective means of preventing early postmenopausal bone loss.																											

[Redacted]

Title of the study : Percutaneous Estradiol as Prophylaxis of Osteoporosis in Early Postmenopausal Women

[Redacted]

SUMMARY — CONCLUSIONS :

Efficacy Results

All subjects completing 12 months of the study were accepted for efficacy analysis. No 'intent to treat' analysis was done.

TBBM

Group	Initial	TBBM % Change		
		1 year	2 years	Between 1-2 years
Placebo				
n	11	11	11	11
Mean	2957.2	-6.3	-8.0	-1.7
Sem	108.3	0.7	1.0	0.8
Calcium				
n	14	14	14	14
Mean	3053.8	-3.3	-5.2	-2.0
SEM	92.0	1.3	1.4	0.7
Oestrogen				
n	11	11	11	11
mean	3148.4	0.4	-0.9	-1.8
SEM	160.7	1.0	1.0	0.8
Oestrogen + Calcium				
n	9	9	9	9
mean	3158.3	1.4	1.7	0.4
SEM	199.8	1.0	0.9	0.8

BMC Proximal Radius

Group	Initial	BMC Proximal Radius % Change		
		1 Year	2 years	Between 1-2 years
Placebo				
n	11	11	11	11
mean	36.0	-4.3	-8.3	-4.1
SEM	1.8	0.6	1.9	0.9
Calcium				
n	14	14	14	14
mean	36.8	-2.5	-4.3	-1.8
SEM	1.8	0.4	0.9	0.6
Oestrogen				
n	11	11	11	11
mean	37.7	1.2	-0.1	-1.3
SEM	1.7	0.5	0.5	0.5
Oestrogen + Calcium				
n	9	9	9	9
mean	39.2	0.0	-0.5	-0.4
SEM	1.2	0.2	0.4	0.4

BMC Spine

Group	Initial	BMC Spine		
		% Change		
		1 year	2 years	Between 1-2 years
Placebo				
n	11	11	11	11
mean	2957.2	-3.0	-4.2	-0.9
SEM	108.8	1.6	2.4	3.4
Calcium				
n	14	14	14	14
mean	3053.8	-2.3	-4.8	-2.5
SEM	92.0	1.5	1.6	1.3
Oestrogen				
n	11	11	11	11
Mean	3148.4	6.6	4.1	-2.2
SEM	160.7	2.2	2.6	2.3
Oestrogen + Calcium				
n	9	9	9	9
mean	3158.3	4.5	3.8	-0.4
SEM	199.8	3.6	2.8	1.2

Calcium Absorption

Group	Initial	CaAbs		
		% Change		
		1 year	2 years	Between 1-2 years
Placebo				
n	11	11	11	11
mean	23.9	17.8	18.7	2.8
SEM	2.2	—	—	7.1
Calcium				
n	14	14	14	14
mean	26.7	-12.0	-8.1	11.8
SEM	2.6	—	—	8.8
Oestrogen				
n	11	11	11	11
mean	25.4	8.4	13.2	5.9
SEM	2.8	—	—	7.6
Oestrogen + Calcium				
n	9	9	9	9
mean	23.3	0.3	-5.2	-3.0
SEM	2.2	—	—	10.1

There were statistically significant differences between treatments at one year with respect to TBBM and BMC spine as well as a significant Oestrogen effect for both parameters. Both the placebo and Calcium groups experienced decreases from baseline values while the Oestrogen and Oestrogen + calcium groups either had no change or a slight increase in values. The treatment differences with respect to Ca Abs were nearly significant ($p = 0.0554$). The Calcium and Oestrogen + calcium groups had decreases from baseline values while the two groups without calcium (placebo and Oestrogen) had increases from baseline values.

Statistically significant differences at two years with respect to TBBM and BMC spine were identical to those seen at one year. The two non Oestrogen groups had further decreases from baseline in TBBM and BMC spine values. The Oestrogen group had a slight decrease from baseline in TBBM values and an increase from baseline in BMC spine values. The Oestrogen + calcium group had small increases from baseline in both TBBM and BMC spine values. The treatment differences were not statistically significant for Ca Abs.

The percent change from one year to two years for TBBM, BMC spine and Ca Abs were not statistically significant.

BMC had statistically significant differences between treatments with respect to percent change from baseline at each for the eight visits. The two non Oestrogen groups had decreases from baseline while the two Oestrogen groups had small median percent changes over the two years. In the presence of Oestrogen, there was little difference from baseline with or without calcium. Without Oestrogen, however, the lack of calcium (placebo group) led to larger decreases from baseline than were seen with Calcium. The differences between treatments at two years compared to one year were statistically significant. The Oestrogen groups had smaller decreases from the first year than the two groups without Oestrogen. Calcium led to smaller decreases than were seen without calcium. Within treatment comparisons with respect to percent change from baseline in BMC were statistically significant at every visit in both placebo and Calcium groups with both groups showing decreases from baseline.

The treatment differences with respect to percent change from baseline at one year in the Vitamin D metabolites, 25 OHD and 24,25 (OH)₂D₃ were statistically significant as were the calcium effects. Both the Calcium and Oestrogen + calcium groups had increases over baseline values while the other two groups had large decreases from baseline values. At two years, the pattern changed with all four groups having a decrease from baseline values with the largest decreases seen in the two Oestrogen groups. The differences between groups were statistically significant with respect to 24,25 (OH)₂D₃. Treatment differences with respect to 1,25 (OH)₂D₃ were not statistically significant at any time point.

Safety Results:

The adverse experiences reported were mild and few. A total of 26 adverse events were reported by 21 subjects.

Treatment	N	No. (%) with Adverse Experience
Placebo	13	6 (42.8)
Calcium	15	8 (53.3)
Oestrogen	15	3 (20)
Oest + calc	14	4 (28.5)

The most commonly reported events was gastrointestinal complaints, probably due to the calcium supplementation. Of the 10 subjects with gastrointestinal complaints, 2 were in the placebo group 5 in calcium group, 1 in Oestrogen and 2 in Oestrogen and calcium. Seven subjects withdrew from the study prematurely.

CONCLUSIONS:

This study, conducted over a two year time span, showed that Oestrogen with or without the presence of calcium was relatively effective in the prophylaxis of osteoporosis in early postmenopausal women.

[Redacted]

Title of the study :	Study of the preventive effect on post menopausal bone loss of estradiol by percutaneous route at a dose of 1.5 mg/day.
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[Redacted]

SUMMARY — CONCLUSIONS :

Efficacy Results

Significant increases ($p < 0.001$) in Oestradiol and Oestriol mean plasma values were seen in the Oestrogel group compared to those receiving placebo:-

	Oestrogel Group	Placebo Group	p
Oestradiol (pg/ml)	85.8 ± 15.8	17.8 ± 6.0	<0.001
AUC oestradiol	1777.7 ± 350.8	401.6 ± 137.3	<0.001
Oestrone (pg/ml)	84.6 ± 11.1	10.6 ± 3.5	<0.001
AUC oestrone	1818.1 ± 242.8	236.4 ± 80.3	<0.001
E_1/E_2	0.99	0.60	NS

The fasting urinary hydroxyproline/creatinine ratio was not modified in the Oestrogel group, but a significant increase was seen in the placebo group:-

	Oestrogel Group	Placebo Group	p
Urinary			
Hydroxyproline/creatinine $\mu\text{g}/\text{mg}$	30.5 ± 1.5	39.5 ± 2.1	<0.001
AUC urinary Hydroxy/creat.	704.6 ± 31.8	901.0 ± 51.3	<0.001

In the Oestrogel group the mean percent change in BMD of lumbar spine L1-L4 was $+1.22\% \pm 0.49\%$ per year ($p < 0.05$). The mean change in the placebo group was $-1.18\% \pm 0.41\%$ per year ($p < 0.01$). The difference between the two groups was significant at all points between 6 months and two years ($p < 0.001$).

The mean change in BMD of total hip was $-0.3\% \pm 0.42\%$ per year in the Oestrogel group and $-1.30\% \pm 0.27\%$ per year in the placebo group ($p < 0.001$). There was a significant difference ($p < 0.05$) between the two groups.

A significant correlation was observed between the mean plasma oestradiol and oestriol levels and the change in bone mass density.

Safety Results

Treatment with Oestrogel was well tolerated; no local cutaneous reactions were reported. Slight breast tenderness at the beginning of Oestrogel treatment was the only reported side effect.

Conclusions

Oestrogel 2.5 g daily for 21 days a month resulted in bone mass density changes similar to those previously observed with this and other oestrogens.

[Redacted]

Title of the study : Effects of percutaneous oestradiol versus oral oestrogens on bone density.

[Redacted]

		Individual Study Table referring to Part IV of the Dossier	(For National Authority Use Only)
Finished Product : Oestrogel		Volume : 6	
Active Ingredient : Oestradiol		Page : 729-734	
SUMMARY — CONCLUSIONS :			
Efficacy Results	BMD results expressed in grams of hydroxyapatite per cm ² were as follows:-		
	BMD	Percutaneous Group (n = 20)	Oral group (n = 17) Untreated group (n = 16)
	Baseline	0.769 ± 0.056	0.786 ± 0.08 0.838 ± 0.065
	12 months	0.781 ± 0.055	0.799 ± 0.063 0.782 ± 0.061
	24 months	0.811 ± 0.053	0.816 ± 0.092 0.761 ± 0.064
	36 months	0.804 ± 0.072	— —
In the Oestrogel group, the bone density gain was 1.7% ± 3.9% after 12 months, 5.6% ± 2.9% (p <0.001) after 24 months and 4.7 ± 3.2% (p <0.01) after 36 months in relation to initial values. In the oral oestrogen group the gains were 3.5% ± 13.0% after 12 months and 4.3% ± 9.2% (p <0.001) after 24 months. The untreated group showed a BMD loss of 6.6% ± 3.5% (p <0.001) after 12 months, and 9.1% ± 3.4% (p <0.001) after 24 months. There was no statistically significant difference between the percutaneous and oral oestrogen groups. Both treated groups showed significant differences at 12 and 24 months when compared with the control group.			
Safety Results	None stated.		
Conclusion	2.5 g Oestrogel daily prevented postmenopausal bone loss and was comparable in this respect to 0.625 mg conjugated oestrogens daily.		

Title of the study : Estradiol Administered in a Percutaneous Gel for the Prevention of Postmenopausal Bone Loss.

Estradiol levels of 24 post menopausal women after administration of Oestrogel

Time (hr)	Estradiol (mean, pg/ml)
0*	<25.00
2	234.00
4	484.00
6	557.00
8	323.60
12	80.40
16	41.60
20	<25.00

Lumbar spine BMD measured on each group before and after ERT indicated no significant changes. Four women in Group 3 (placebo) who had a surgical menopause and did not have ERT showed a rate of bone loss of 8.7% per year ($p < 0.05$). Women in Group 3 who were either in natural menopause (14) or in premature menopause (3) did not show any changes. No other significant decreases were noted in the remaining 13 women with surgical menopause who received ERT

The results of the study indicate that: (1) loss of BMD in the control group was observed significantly only in surgical menopausal women and no significant loss of BMD was observed in women receiving ERT treatments; (2) decrease of E1 in control group and increase of E1 in the treatment groups were both significant.

Safety Results

No adverse events recorded.

Conclusions

Percutaneous ERT may be used in the prevention of postmenopausal bone loss, particularly in surgical menopausal women and the increased E1 may play a beneficial role in inhibiting loss of bone mass and relieving menopausal syndrome. A longer period of follow-up is required to show differences between different dosages of Oestrogel.

[Redacted]

Title of the study :	Use of plasma 17 β -estradiol as a guideline for parenteral administration of estrogen for the prevention and treatment of osteoporosis.
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[Redacted]

Study 2

Both Oestrogel-treated groups stopped their rate of bone loss. The control group maintained a rate of loss of 3.8%/year. The rate of bone loss of the two treated groups was significantly lower than the untreated group ($p < 0.01$). Changes observed between the two treated groups were not significantly different. Application of 2.5 mg gel/day gave a plasma level of 75 ± 7.4 pg/ml E2 and 5.0 g gel/day gave a plasma level of 110 ± 10.3 pg/ml E2.

Safety Results

No adverse events recorded.

Conclusions

In the majority of post menopausal women when compliance and application techniques are correct, the maximum effect of estrogen on the bone is achieved with the application of 2.5 g gel/day. Doubling of the dose did not appear to produce a parallel increase in bone mass.