RCTS INCLUDING THE GENERAL METHODOLOGY & THE CONTENT OF A CLINICAL PROTOCOL

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EVIDENCE BASED MEDICINE

Objective: To base medical practice on:

- Objectivity
- exercise of critical thinking

Prerequisites: rational and experimental control of any allegation.

Exclusion of:

- intuitive strategies
- enthusiastic convictions
- pathophysiological reasoning only
- experts recommendations (From eminence-based to evidence-based)

DRUG DEVELOPMENT

Succession of steps required to ensure:

- Pharmaceutical grade
- Safety
- Efficacy

PRE-CLINICAL STUDIES:

- Pharmaceutical Development
- Animal studies

Clinical studies

PHARMACEUTICAL DEVELOPMENT

- Initial assessment of the drug market.
- Development planning (and different phases).
- Seeking for funding.
- Filing of patent.
- First manufacturing steps (chemical synthesis, biotechnology, extraction techniques).
- First stages of drug development (oral, injection, topical ...).
- Industrial synthesis or manufacturing steps.
- Pharmaceutical quality control checks (manufacturing conditions, conservation, control)

ANIMAL STUDIES

- Efficacy:
  - Pharmacodynamic Studies
  - Pharmacokinetic Studies
- Safety:
- Acute Toxicity Studies.
- Toxicity studies with repeated administration.
- Reproduction-Teratogenesis.
- Mutagenesis Studies.
- Carcinogenesis Studies.
- Local Toxicity Study.

EFFICACY

Animal

Pharmacodynamic Studies

- They seek to define
  - the therapeutic effect (effective dose, type and duration of the effect on the isolated organ or in different animal species).
  - Its mechanism (mediator, receptor ...).
  - Side effects.
  - The doses causing the major effect and side effects (therapeutic window)

EFFICACY

Animal

Pharmacokinetic Studies

- They seek to define
  - the conditions of absorption, distribution and elimination of the product.
  - The metabolism in the respective species.
- It implies some adjustments using assay techniques

TOXICITY

Animal

- Acute toxicity: Toxic doses in animals and organs suffering from this toxicity
- Lethal Dose 50 (LD50): dose at which 50% of animals are killed.
- Lethal dose 0 (DL0): maximum tolerated dose without death.
- Lethal dose 100 (LD100): minimum dose for which all animals died.
- Conditions (convulsion or adynamism, total death or prolonged coma ...) and if possible cause of death.

TOXICITY

Animal

- Toxicity of repeated dose: subacute and chronic toxicity
- Determine in animal
  - tolerated doses for long periods.
  - organs or functions affected by toxicity.
- The duration of the study depends on the expected duration required in humans.

TOXICITY

Animal

- Reproduction studies
- Fertility with administration to cohorts of male and female animals before mating.
- Embryogenesis with administration to cohorts of pregnant females.
- Perinatality with administration in late pregnancy or during lactation.
- The studies should be carried out if possible on a species having the same drug metabolism tested in men.

TOXICITY

Animal

Mutagenesis Studies

- Investigate modifications of the genetic material induced by the drug.
- Potential risk for future generations.
- Potential cancer risk to the current generation.

TOXICITY

Animal

Carcinogenesis Studies

- Systematic identification of tumors in animals receiving the product during most of their lives.
- Evidence of exposure of animals to a drug should be given by measurements of plasma drug concentration.

TOXICITY

Animal

Local Toxicity Studies

- According to way the drug is used, local tolerance studies: skin, eye, nasal …
- Possibly, studying toxi-allergy, photo-toxicity ....

HUMAN STUDIES

After toxicological, pharmacological, pharmacokinetic, pharmaceutical and market studies

If it is possible to expect:

- A therapeutic effect
- A safe utilization
- A profitable commercial development

HUMAN STUDIES

Phase I : study of the first administration in humans

Phase II : study of pharmacological efficacy

Phase III : study of therapeutic efficacy

Phase IV : after marketing authorization.

PHASE I : FIRST ADMINISTRATION IN HUMANS

Determines the tolerance in humans

- Dose causing the first expected pharmacological effects
- Dose causing the first side effects.

PHASE II : PHARMACOLOGICAL EFFICACY

Determines

- the conditions of efficacy
- therapeutic modalities.

Includes human pharmacology studies: effective dose, route of administration, effect-dose relationship, …

At the end of Phase II, the optimal prescription requirements (dose, mode of administration, duration), symptoms reflecting increasing therapeutic effect and symptoms revealing side effects must be precisely defined.

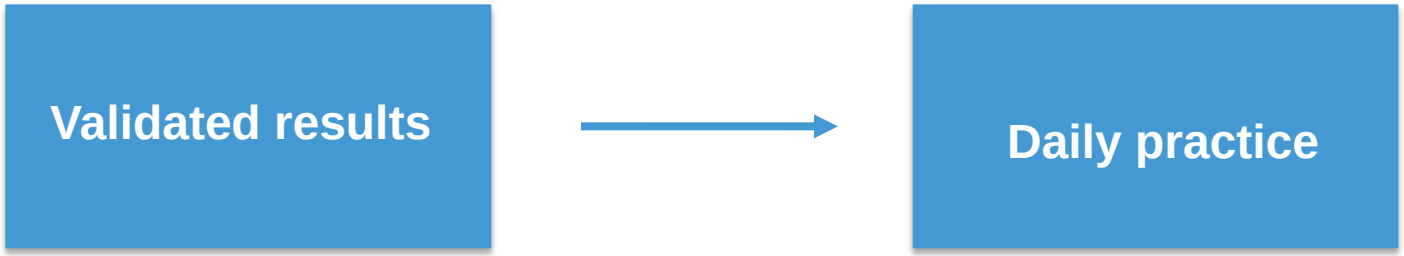
PHASE III : THERAPEUTIC EFFICACY

- Determines efficacy in different indications claimed and asesses tolerance.
- Performed on a homogeneous patients cohort according to the methodological principles of the therapeutic trial.
- Search for a difference between the NCE and the control group: statistically significant and clinically meaningful.

PHASE IV : AFTER MARKETING AUTHORIZATION

- Study of efficacy and safety under normal conditions of prescription.

- Detection of rare side effects that can not be detected within the limited framework of phase II / III studies.



Supremacy of facts on opinions

THERAPEUTIC TRIALS METHODOLOGY

Principles

- Comparison,
- Significance,
- Causality.

THE COMPARISON

Evaluation of the value of a therapy in comparison with:

- A previous situation
- No treatment
- Another treatment

Importance of the witness group:

- untreated
- Placebo
- standard of care

CAUSALITY

- Groups must be strictly similar except for the treatments.
- At the beginning: Importance of randomization
- During the trial: Importance of blind procedures

RANDOMIZATION

- The draw is the only way to assign treatments to the subjects to have comparable groups for all known and unknown parameters. The randomized allocation of treatments is a point of no return. So it's important to check in advance that the patient is definitely eligible for the trial. The draw takes place as late as possible just before the treatment initiation. It is usually prepared in advance and allows the allocation of the treatment to the patient as they enter the trial.

BLIND PROCEDURES

- Whenever possible, the exact nature of the assigned treatment must remain unknown to the patient and/or to the physician, preferably both. Unblinding during the trial is justified only if knowledge of the treatment received is mandatory for patient care. It must therefore be pre-planned. It is only when the trial is completed that unblinding of treatments for all subjects will occur.

THE MEANING

- Accountability of the difference highlighted judgment of statistical significance ($p < 0.05$).

POWER CALCULATION

- It should be stated with the elements used for the calculation: the variability of the primary outcome , the expected relevant clinical difference, and the accepted risk of error (false negative or false positive). This number gives an order of magnitude; it can be reassessed in the light of preliminary data from a pilot study. On a practical level, it must be achieved within the shortest time. It is an essential but often limiting factor, it confirms that the trial was appropriately designed

SECTIONS OF THE PROTOCOL

- Objectives of the Study
- Definition of Disease
- Selection of Patients
- Definition of Treatments
- Randomization
- Blinded methods
- Outcomes measures
- Power calculation
- Monitoring of the trial
- Data management and analysis

OBJECTIVES OF A TRIAL

Demonstrate the efficacy and safety of a new treatment, its superiority over standard of care, in patients with a specific disease whose evolution is considered on a specified outcome.

DEFINITION OF THE DISEASE

It must be based on few, specific, simple, unambiguous, objective (if possible), easy and fast to assess outcomes

SELECTION OF PATIENTS

Recruitment generally homogenous; patients must be able to accept and follow the trial constraints. In addition, they must be prepared to receive anyone of the investigated treatments: this is called the "ambivalence clause". The exclusion criteria including particular aspects of the disease and patients or treatment characteristics should be clearly indentified.

DEFINITION OF TREATMENTS

- For each treatment : dose, rythm, conditions and duration of administration.
- The procedures to assess compliance should be specified, while respecting the blinded nature of the trial.
- The risk of intake of unexpected treatments has to be considered as well as the way to manage them.

OUTCOMES MEASURES FOR EFFICACY

- They should be clear, accurate, objective, validated and related to the clinical situation

- Their measurement must be easy, specific, reproducible, standardized and similarly conducted regardless of the treatment received.

OUTCOMES MEASURES

They should be:

- relevant (addressing the issues)
- clinically relevant
- available in all subjects
- not too difficult to collect
- measurable with accuracy and precision
- sensitive (to detect small differences)
- consensual.

Always prefer a primary endpoint (power calculation) compared to secondary criteria (supportive).

SURROGATE ENDPOINTS

- Changes correlated with the primary endpoint (predictive value) in the untreated population
- Changes correlated with the primary endpoint (predictive value) in the treated population
- Quantitative assessment of the changes in primary outcome derived from changes in the surrogate outcome.

DATA ANALYSIS

Must be pre-planned and described: parameters to analyze and tests to be used must be specified.

DATA ANALYSIS

- Description of the population
- Description of protocol violations
- Wrong inclusions
- Treatment non compliance or persistence
- Loss to follow-up
- Data management:
  - no post-hoc analysis
  - no subgroup analysis

LOST TO FOLLOW-UP: INTENTION TO TREAT ANALYSIS (ITT)

They should be taken into account in the analysis since the causes of premature withdrawal are rarely independent of the treatment received:

- Maximum bias (worst-case scenario)
- Report of the last observation (LOCF)
- Modeling
- Interpolation or AUC
- Survival curve (for the duration of follow-up)

INFORMED CONSENT

THE CONSENT

- Medical contract between the Investigator and the Patient
- Principle of self-determination
- Contract confirming the willingness to partake in the trial (both sides)

PARTICIPATION IN A TRIAL IS BASED ON THREE CONDITIONS:

- Voluntary, free, unconstrained
- Comprehensive and understandable information
- Consent given by someone having the capacity to do so

THE REQUEST FOR INFORMED CONSENT MUST INCLUDE:

- the purpose of the test and objectives of research
- the side effects and possible risks
- The methodology
- the practical conduct of the trial
- the possibility to withdraw at any time
- the possibility of refusing to participate in the trial without prejudice

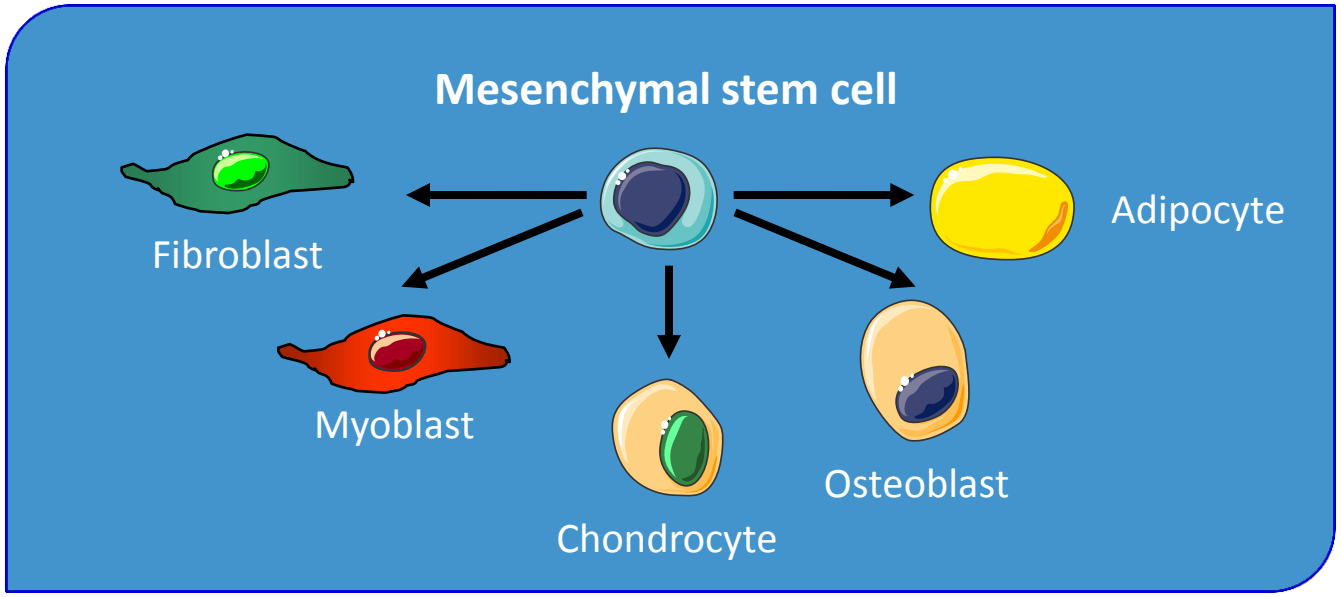
MONITORING THE TRIAL

It must be precise and detailed. Data will be collected on a standardized case report form (CRF) which should contain only the mandatory and relevant information. It is appropriate that a single person (CRA) is specifically responsible for monitoring the conduct of a trial.

RATIONALE OF STRONTIUM RANELATE IN OSTEOARTHRITIS

STRONTIUM RANELATE – RATIONALE IN OA

- Osteoblasts and chondrocytes share the same embryological origin from the mesenchymal tissue.

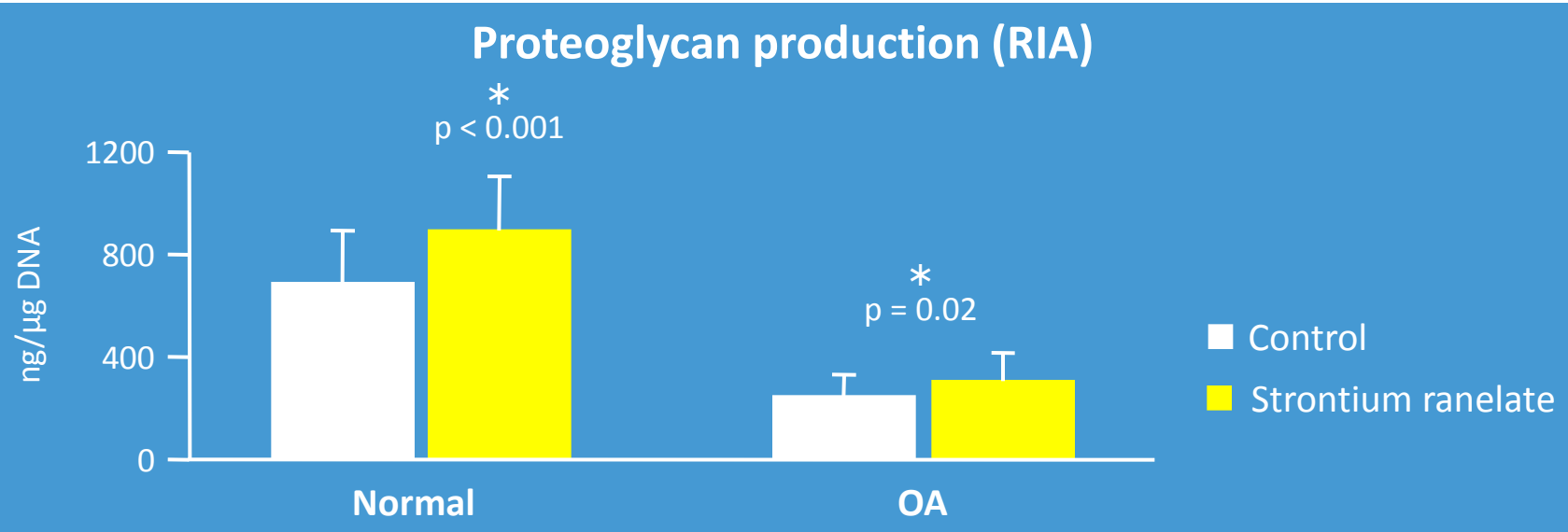


- Strontium ranelate could act through the calcium-sensing receptor expressed by chondrocytes (matrix synthesis stimulation).

We hypothesised that a drug efficient on osteoblasts can have positive effects on chondrocytes

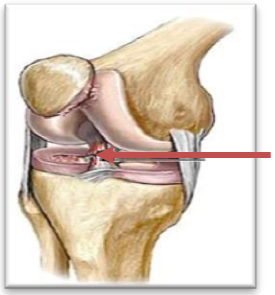
STRONTIUM RANELATE – RATIONALE IN OA IN VITRO RESULTS

- In normal and OA human chondrocytes cultures, Strontium ranelate (10^{-3} M) demonstrated a potential structure modifying effect:
  - Increases type II collagen synthesis
  - Increases high molecular weight proteoglycan synthesis
  - Enhance IGF1-stimulated proteoglycan synthesis



* Henrotin et al. *JBMR* 2001;16: 299-308

STRONTIUM RANELATE – RATIONALE IN OA IN VIVO RESULTS



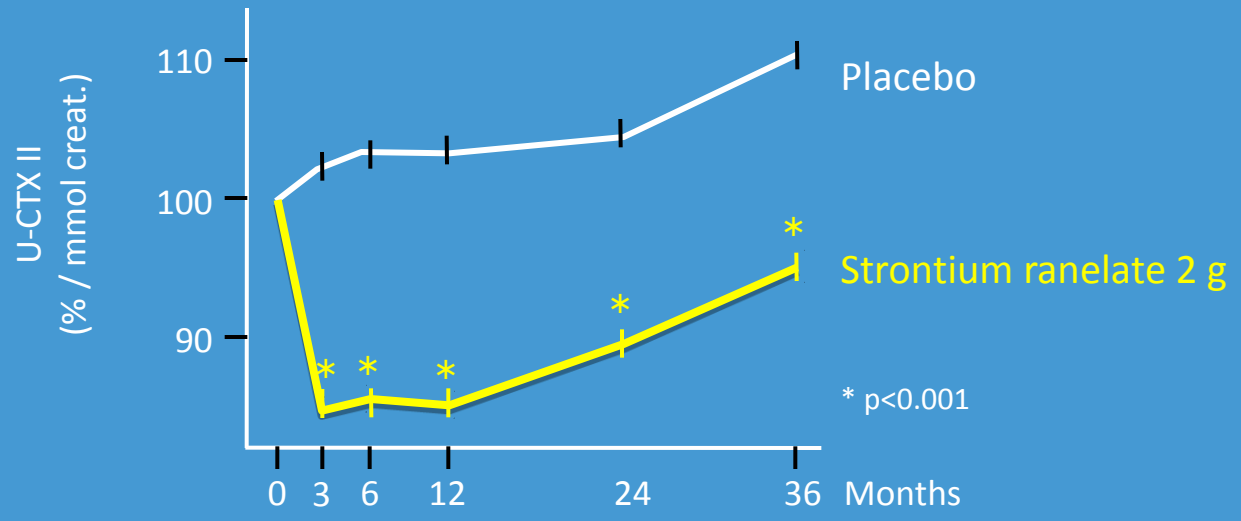
Treatment initiation

- Positive effect of Strontium Ranelate on:
  - Macroscopic lesions of femoral condyles and tibial plateaus
  - Subchondral bone thickness
  - COLLAGEN

These effects are associated with a decrease in subchondral bone sclerosis.

REDUCTION OF URINARY CTX II IN POST MENOPAUSAL WOMEN

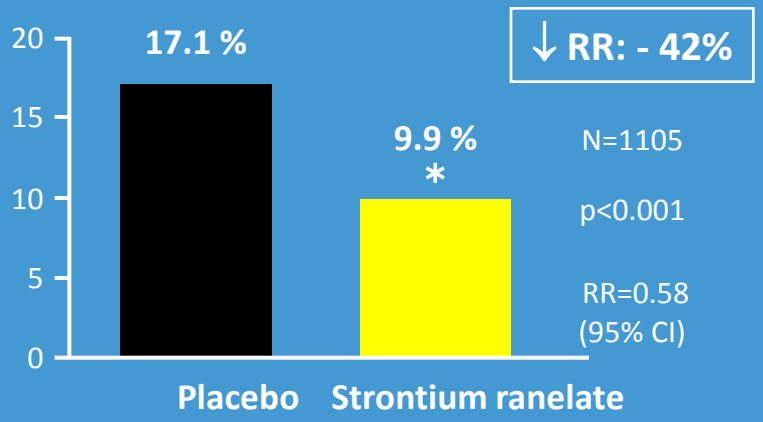
- Postmenopausal women phase I study
  - After 6 and 12 weeks of treatment with strontium ranelate 2 g/day a significant decrease (around 40%) on the urinary CTX II levels compared to baseline was observed in 36 healthy volunteers.
- TROPOS phase III study
  - In 2,617 patients treated for 3 years with strontium ranelate 2 g/d or placebo* a 15-20% urinary CTX II decrease was observed in the strontium ranelate group compared to placebo.



* Alexandersen et al. *Bone* 2007 (40:219-222)

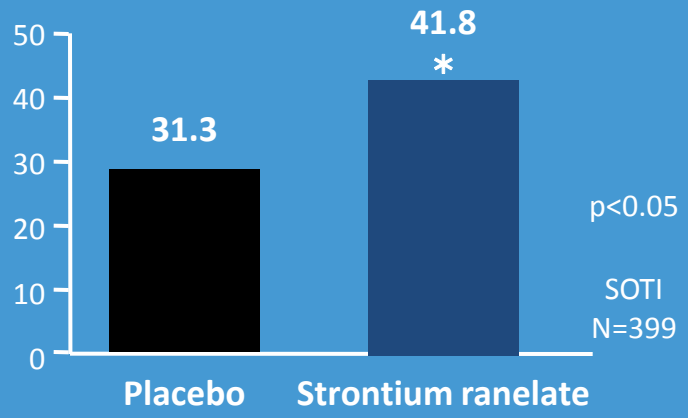
EFFECTS OF STRONTIUM RANELATE ON SPINAL OSTEOARTHRITIS

Percentage of patients with progression of the overall score after 3 years



Strontium ranelate reduced spine OA radiological progression

Proportion of patients with improvement in back pain (increase of at least one point on the Likert scale) after 3 years



Strontium ranelate reduced back pain in patients with spine OA

Bruyère O. et al, *Ann Rheum Dis.* 2008; 67(3):335-339

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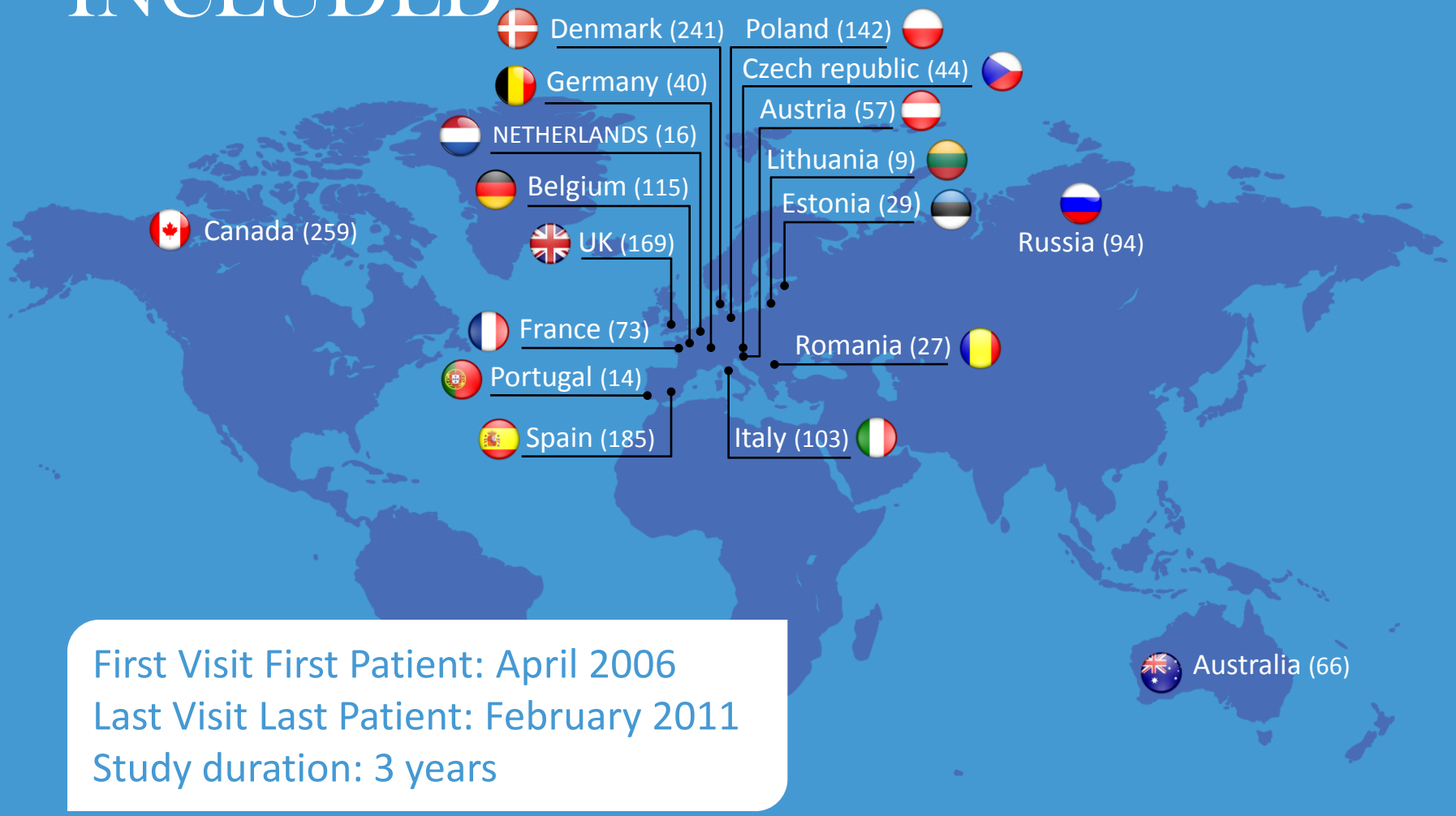
CL3-12911-018 STUDY PROTOCOL

WORLDWIDE STUDY 98 CENTRES, 18 COUNTRIES - 1,683 PATIENTS INCLUDED



First Visit First Patient: April 2006
Last Visit Last Patient: February 2011
Study duration: 3 years

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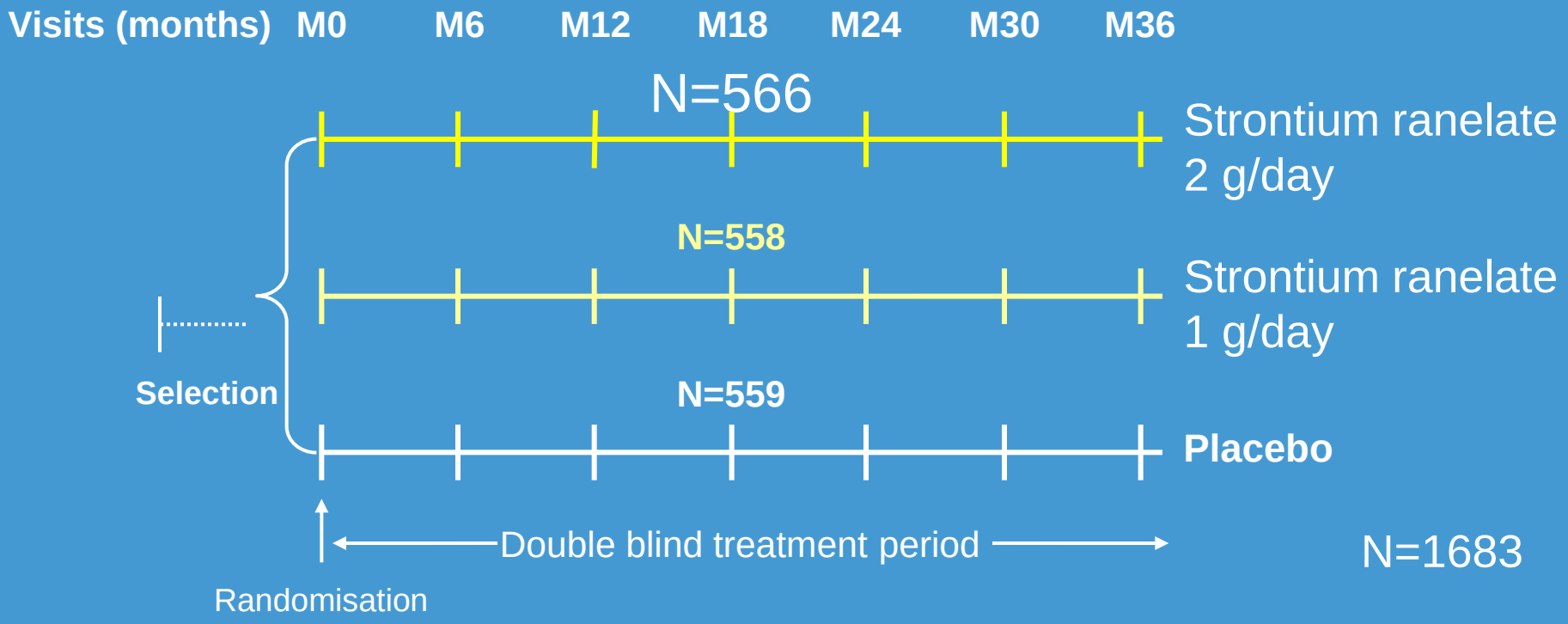
OSTEOARTHRITIS STUDY DESIGN

Objective: Efficacy and safety of two doses of strontium ranelate (1 g and 2 g per day) versus placebo in reducing radiological progression of knee osteoarthritis over 3 years



Design: International (18 countries, 98 centres), double-blind, placebo-controlled, randomised 3-year study

MAIN INCLUSION CRITERIA

- Caucasian males or females
- Aged 50 years or over
- Ambulatory (able to walk unassisted)
- Primary knee osteoarthritis based on Clinical criteria of the American College of Rheumatology (Altman et al, 1986)
  - Knee pain on most days of the previous month (1/2 days)
  - Intensity of at least 40 mm on a VAS
  - At least 3 of the followings: age >50 years, stiffness <30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth.

RADIOLOGICAL INCLUSION CRITERIA

Kellgren and Lawrence grade II or III

Predominant osteoarthritis of the medial compartment of the knee

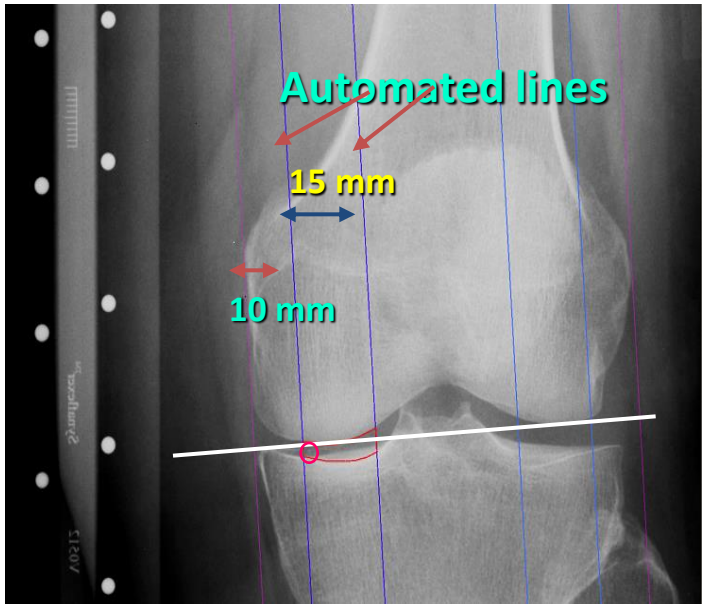
Joint space with between 2.5 mm and 5 mm

MAIN EXCLUSION CRITERIA

- Predominant osteoarthritis of the lateral compartment of the knee
- Knee prosthesis (or planned within 1 year)
- Previous surgical operation of the knee
- Secondary osteoarthritis of the knee
- Medical history of venous thrombolic events (VTE) or patients at high risk of VTE
- Progressive major illnesses
- Previous treatments likely to have an action on cartilage and bone metabolism
  - BPs <1 year prior to selection
  - Diacerein, chondroitin sulphate, glucosamine (all forms, ≥1500 mg/day), avocado/soybean <3 months prior to selection
  - Treatment with anti MMPs inhibitory properties
  - Glucocortcoids (oral, inhalated >1500 µg/day; or intra-articular <3 months prior to selection)

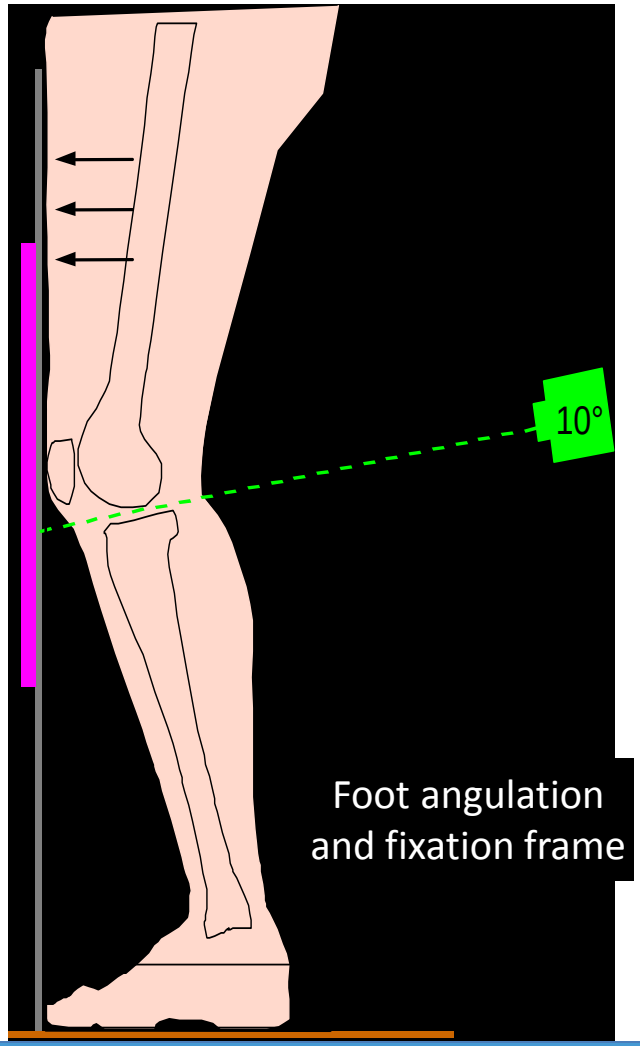
PRIMARY ENDPOINT FOR STRUCTURE MODIFYING TREATMENT

- Radiological Joint Space Narrowing (JSN) of the medial tibio-femoral compartment of the target joint
- Central reading in Pr. R. Chapurlat center (Lyon, France)
- Semi-automated validated method*
- Second independent reading Pr. JY Reginster (Liège, Belgium, same method)



* Gensburger D, Arlot M, Sornay-Rendu E, Roux JP, Delmas P., *Arthritis Rheum*. 2009; 61(3):336-343

KNEE X-RAY ACQUISITION AND READING METHOD



Validated method: radiographs obtained in fixed flexion postero-anterior view using a positioning frame (Synaflexer®). Beam angle was fixed: 10°

Each knee X-ray was read with knowledge of the time sequence, using a validated semi-automated device*

All X-Rays were blinded to treatment assignment and patient identity

KNEE X-RAY ACQUISITION QUALITY CONTROL AND ELIGIBILITY

- All radiological centers were initially certified by a central facility (Synarc)

- Eligibility was checked by Synarcby confirming:
  - Kellgren-Lawrence score II and III
  - Joint space between 2.5 and 5 mm
  - No presence of predominant osteoarthritis of the lateral compartment

- All radiological centers were trained at the study initiation and once every year by specialized personnel (detailed manuals with instruction on the acquisition method were also provided)

MAIN PLANNED SECONDARY END POINTS

- Radiological progressions: JSN ≥0.5 mm over 3 years*
- Radioclinical progressions: JSN ≥0.5 mm and no clinical improvement (≤20 % WOMAC pain subscore) over 3 years**
- Pain and function assessment: algo-functionnal questionnaire WOMAC, VAS.
- In subsets: MRI imaging of the knee, subchondral bone CT scan

* Bruyere et al, *Ann Rheum Dis* 2005 ** Abadie et al, *Osteoarthritis and cartilage* 2004

No relevant between-group differences in demographic and disease characteristics - Population consistent with selection criteria and ostoarthritis population

	Strontium ranelate 1 g (N=445)	Strontium ranelate 2 g (N=454)	Placebo (N=472)
Age in years	62.3 (7.0)	63.1 (7.3)	62.8 (7.3)
Gender (%)			
Female	69	69	69
Male	31	32	31
Disease duration in years	7 (6)	6 (6)	6 (6)
BMI (Kg/m^2)	30 (5)	30 (5)	30 (5)
KL II (%)	60	60	63
KL III (%)	40	40	37
Mean JSW (mm)	3.45 ± 0.86	3.53 ± 0.80	3.51 ± 0.82
Mean VAS/100 (mm)	52 ± 22	56 ± 22	54 ± 23
WOMAC /300 (mm)			
Global score/100	130 ± 61	136 ± 63	128 ± 62
Pain subscore/100	42 ± 21	45 ± 22	42 ± 22
Stiffness subscore/100	46 ± 25	48 ± 25	45 ± 25
Physical function subscore/100	42 ± 21	44 ± 23	41 ± 22

Mean compliance was 93% and mean (median) treatment duration was 30 months (36 months)

STUDY WITHDRAWALS

The study withdrawal rate was of 42%

	Strontium ranelate 1 g	Strontium ranelate 2 g	Placebo	ALL
Included and randomised	558	566	559	1683
Withdrawn, N (%)	245 (43.9%)	238 (42.0%)	220 (39.4%)	703 (41.8)
Due to non-medical reason	151 (27.1%)	135 (23.9%)	147 (26.3%)	433 (25.7)
Due to adverse event	75 (13.4%)	84 (14.8%)	58 (10.4%)	217 (12.9)
Due to lack of efficacy	10 (1.8%)	9 (1.6%)	9 (1.6%)	28 (1.7)
Due to protocol deviation	9 (1.6%)	10 (1.8%)	6 (1.1%)	25 (1.5)
Lost to follow-up, N (%)	1 (0.2%)	2 (0.4%)	3 (0.5%)	6 (0.4)

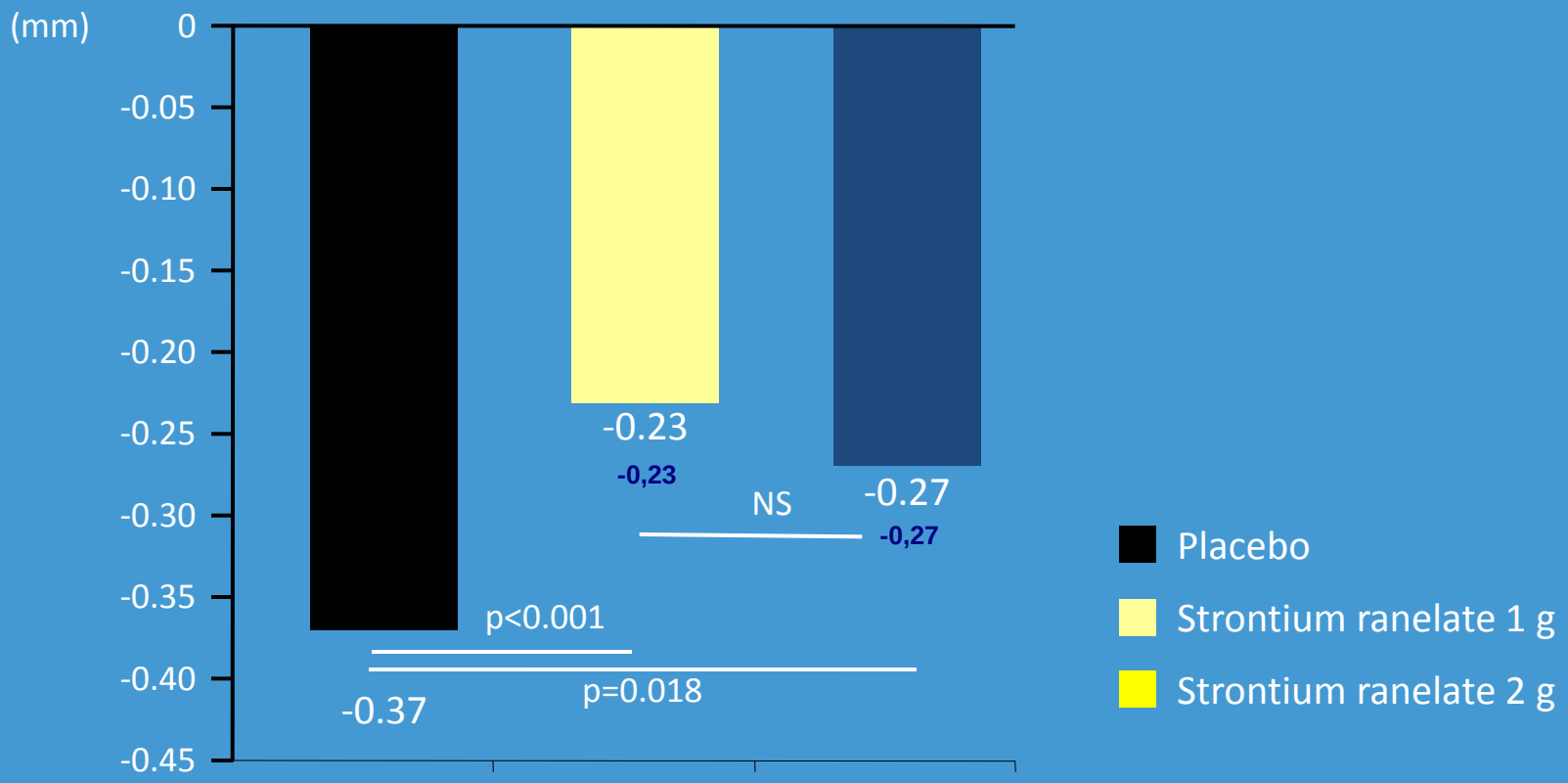
WITHDRAWAL RATE COMPARISON WITH MAIN COMPETITORS

Study	Duration (years)	Population (patients)	WD rate (%)	Annual rate (%) *
Glucosamine Sulphate Pavelka & al, October 2002	3	202	40	13.3
Glucosamine sulphate Reginster & al, January 2001	3	212	34	11.3
Chondroitins Sulphate Michel & al, 2005	2	300	27	13,5
Chondroitins Sulphate STOPP study, Kahan et al 2009,	2	622	32	16
Risedronate KOSTAR study. Bingham & al,	2	2,483	24	12
Doxycycline Brandt et al, July 2005	2,5	431	29	16.1
Glucosamine and/or chondroitine sulphate GAIT study. Sawitzke & al, October 2008	2	572	30	15
Strontium Ranelate CL3-12911-018 study	3	1,683	42	14

* Assuming that withdrawal is linear

PRIMARY END POINT: JOINT SPACE NARROWING

Significantly lower JSN in both strontium ranelate groups compared to placebo



Strontium ranelate 1 g - placebo = 0,14 (0.04) - 95%CI [0.05; 0.23]

Strontium ranelate 2 g - placebo = 0,10 (0.04) - 95%CI [0.02; 0.19]

ITT = 1371

Sensitivity and RS analyses confirm the robustness of the main analysis

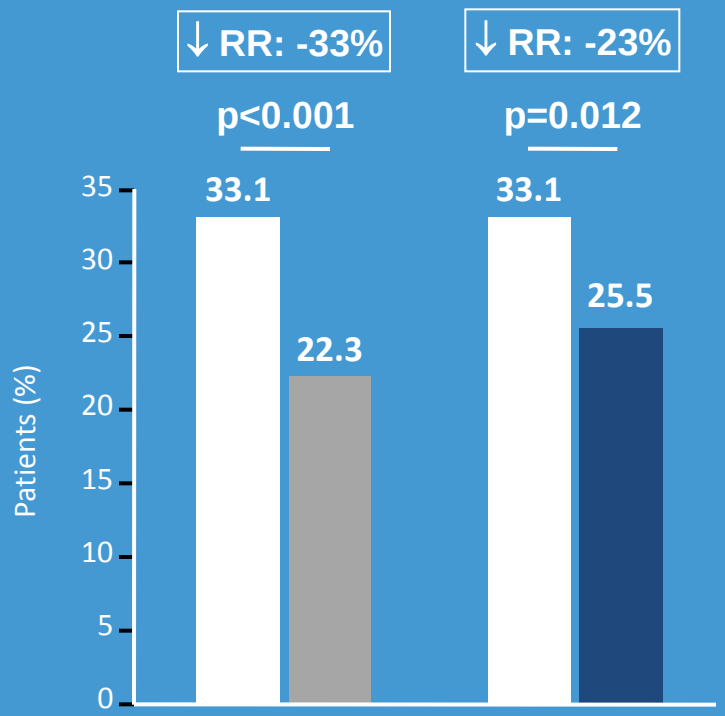
		Strontium ranelate 1g (N=445)	Strontium ranelate 2g (N=454)	Placebo (N=472)
Change END-baseline	Mean (SD)	-0.23 (0.56)	-0.27 (0.63)	-0.37 (0.59)
Mixed model for repeated measurments (MMRM)	E (SE) p-value IC 95%	0.14 (0.05) 0.004 [0.05; 0.24]	0.10 (0.05) 0.043 [0.00; 0.20]	
Multiple imputation (Markov Chin Monte Carlo)	E (SE) p-value IC 95%	0.14 (0.05) 0.003 [0.04; 0.24]	0.10 (0.05) 0.044 [0.00; 0.20]	
Pattern mixture model	E (SE) p-value IC 95%	0.13 (0.04) 0.001 [0.05; 0.22]	0.11 (0.04) 0.008 [0.03; 0.20]	
Randomised Set analysis	N	558	566	559
	E (SE) p-value IC 95%	0.11 (0.03) 0.001 [0.04; 0.18]	0.08 (0.03) 0.027 [0.007; 0.15]	

ITT = 1371

SECONDARY END POINT: PROGRESSORS

Less radiological and radioclinical progressors in both strontium ranelate group compared to placebo

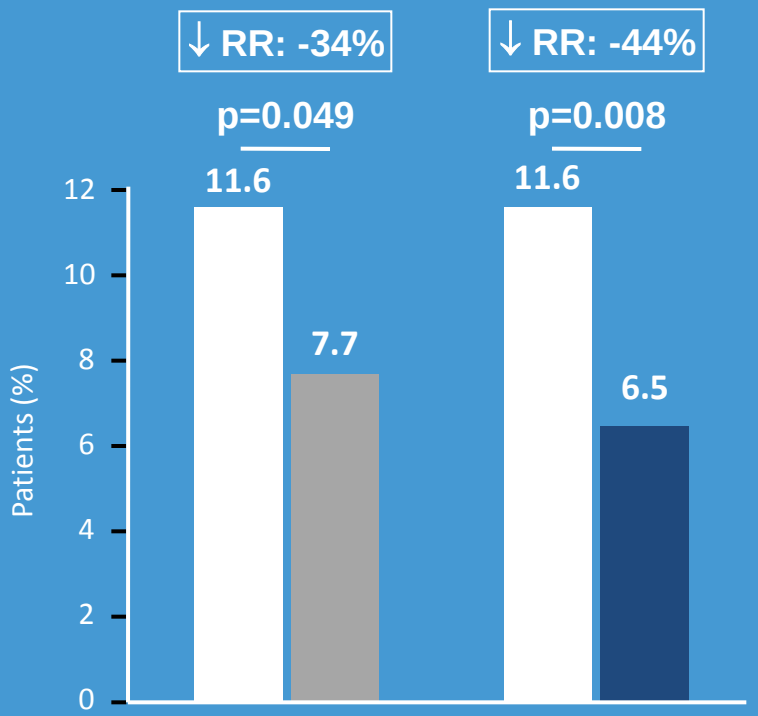
Radiological cartilage loss ≥0,5 mm*



Strontium ranelate 1 g - placebo = -10.8 (2.9)%
Strontium ranelate 2 g - placebo = -7.5 (3.0)%

NNT strontium ranelate 1 g - Placebo = 10
NNT strontium ranelate 2 g - Placebo = 14

Radiological cartilage loss ≥0,5 mm No WOMAC improvement (≤20 %)**



Strontium ranelate 1 g - placebo = -3.9 (2.0)%
Strontium ranelate 2 g - placebo = -5.1 (1.9)%

NNT Strontium ranelate 1 g - Placebo = 26
NNT Strontium ranelate 2 g - Placebo = 20

* Bruyere et al, *Ann Rheum Dis* 2005 - ** Abadie et al, *Osteoarthritis and cartilage* 2004

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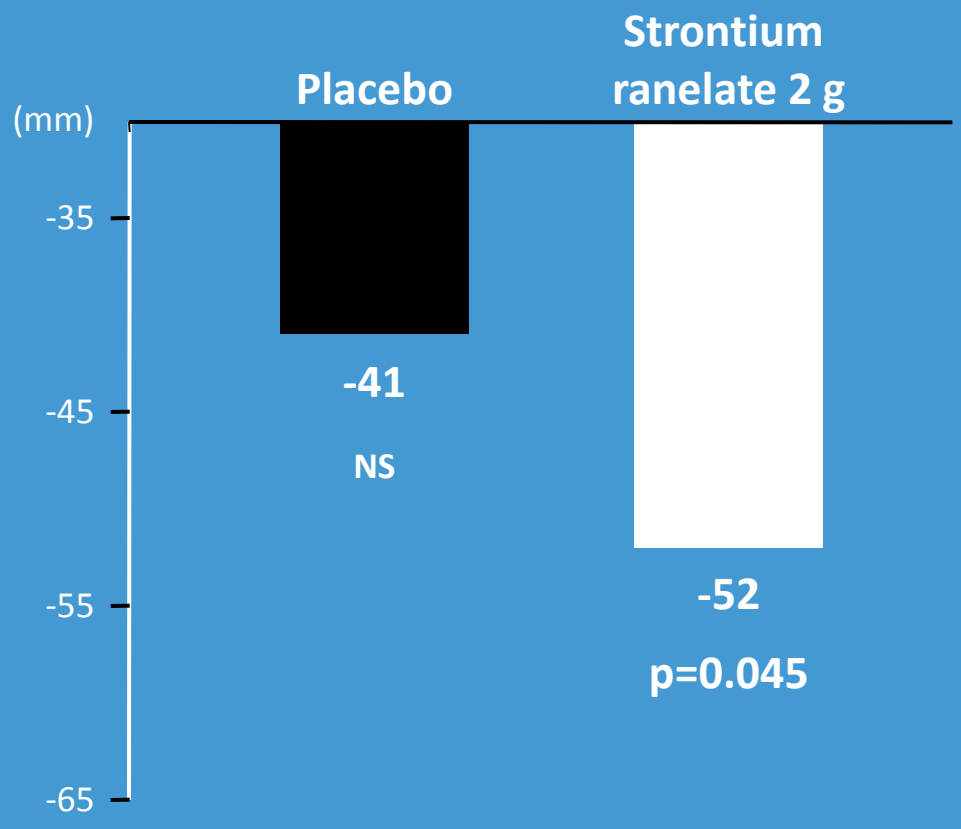
SECONDARY END POINT: EFFECTS ON SYMPTOMS ASSESSED ON WOMAC

Improvement of total WOMAC for strontium ranelate 2 g compared to placebo



Strontium ranelate 2 g - placebo = -8.0 (4.0) mm

ITT N=1371

CLINICAL RELEVANCE OF WOMAC CHANGES

- The Minimally Perceptible Clinical Improvement (MPCI) published threshold (Ehrich et al, 2000)*.
- The MPCI allowed to identify the number of patients with a relevant improvement in the WOMAC. The MPCI can be calculated for all WOMAC subscores.
- The Minimal Clinical Important Improvement (MCII) published threshold (Tubach et al, 2005)**.
- This MCII value can be considered as a treatment target from a patient's perspective and represents patients with a substantial improvement.
- It is recommended as a secondary criterion by the CHMP for development of symptom-modifying drugs in OA. It can be calculated for the WOMAC physical function subscore and the VAS.

* Ehrich et al. *J Rheumatol.* 2000; 27:2635-41 - ** Tubach et al. *Ann Rheum Dis* 2005; 64: 29-33

CLINICAL RELEVANCE OF WOMAC CHANGES

	Strontium ranelate 1 g (N=445)	Strontium ranelate 2 g (N=454)	Placebo (N=472)
MPCI Pain subscore Patients above MPCI threshold, n (%) Difference relative to placebo, (%) [95% CI] P-value	 256 (58.9) 3.9 [-2.6; 10.4] 0.239	 289 (65.5) 10.6 [4.2; 16.9] 0.001	 255 (55)
MPCI Physical function subscore Patients above MPCI threshold, n (%) Difference relative to placebo, (%) [95% CI] P-value	 235 (53.8) 4.6 [-1.9; 11.2] 0.164	 257 (57.9) 8.7 [2.3; 15.2] 0.008	 229 (49.1)
MPCI Stiffness subscore Patients above MPCI threshold, n (%) Difference relative to placebo, (%) [95% CI] P-value	 255 (57.7) 4.9 [-1.5; 11.4] 0.136	 270 (60.1) 7.4 [0.9; 13.8] 0.025	 247 (52.8)
MCII Physical function subscore Patients above MPCI threshold, n (%) Difference relative to placebo, (%) [95% CI] P-value	 237 (54.2) 4.7 [-1.9; 11.2] 0.161	 257 (57.9) 8.3 [1.9; 14.8] 0.012	 231 (49.6)

A greater number of patients in the strontium ranelate groups reached the MPCI and MCII thresholds than in the placebo group

SAFETY

MAIN EMERGENT SERIOUS ADVERSE EVENTS BY SOC

N (%)	Strontium ranelate 1 g (N=548)	Strontium ranelate 2 g (N=564)	Placebo (N=556)	Significance (2 g versus placebo)
Musculoskeletal and connective tissue disorders	18 (3.3)	28 (5.0)	23 (4.1)	NS
Cardiac disorders	9 (1.6)	15 (2.7)	6 (1.1)	NS
Neoplasm benign, malignant and unspecified	16 (2.9)	14 (2.5)	15 (2.7)	NS
Infections and infestations	6 (1.1)	13 (2.3)	7 (1.3)	NS
Injury, poisoning and procedural complications	9 (1.6)	8 (1.4)	10 (1.8)	NS
Nervous system disorders	7 (1.3)	8 (1.4)	9 (1.6)	NS
Vascular disorders	12 (2.2)	6 (1.1)	3 (0.5)	NS
Gastrointestinal disorders	10 (1.8)	6 (1.1)	12 (2.2)	NS

CLINICAL TRIALS WITH PARTICULAR DESIGN

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International Osteoporosis Foundation

PRAGMATIC TRIAL

- Such trial is not intended to demonstrate the intrinsic efficacy of a treatment , but to help physicians to choose the "best" treatment for a given type of patients, in an accurate indication .

- It is a complex ratio between advantages and disadvantages of a particular medication in a specific environment

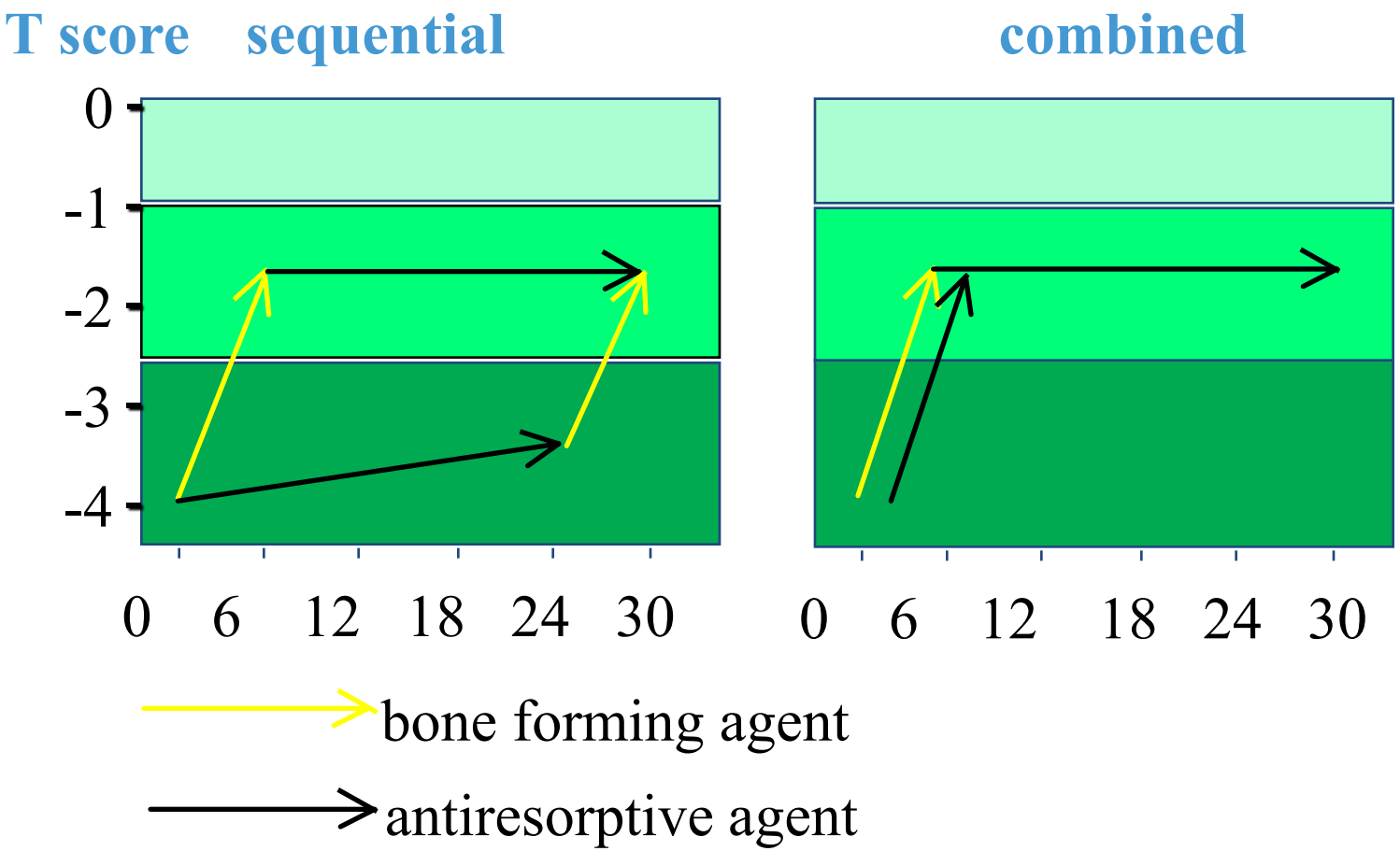
Explanatory trial

- Parity of context (elimination of confounders)

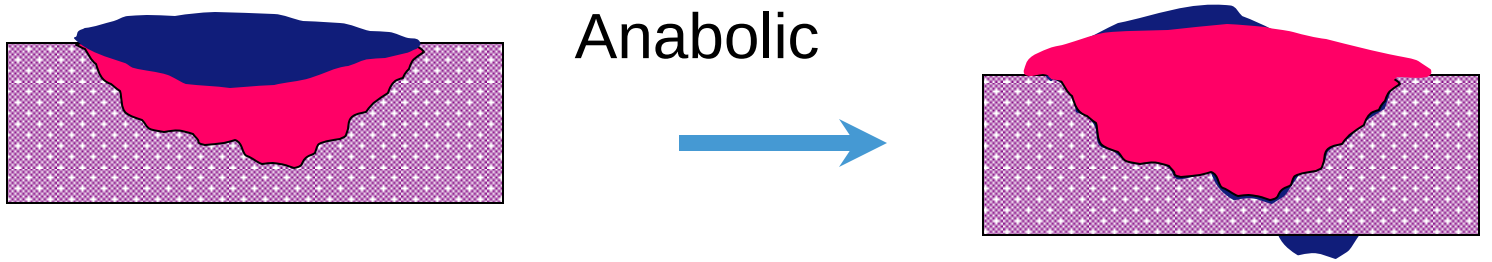
Pragmatic trial

- Integration of context (maximal approach to real-life clinical situations)

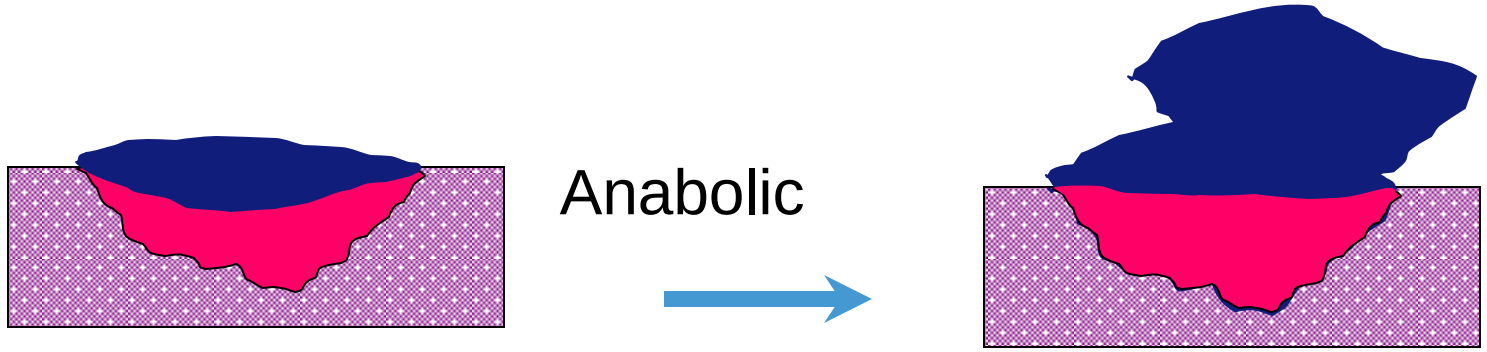
Treatment of osteoporosis : perspectives



Potential Effect of Previous Antiresorptive on Anabolic Response

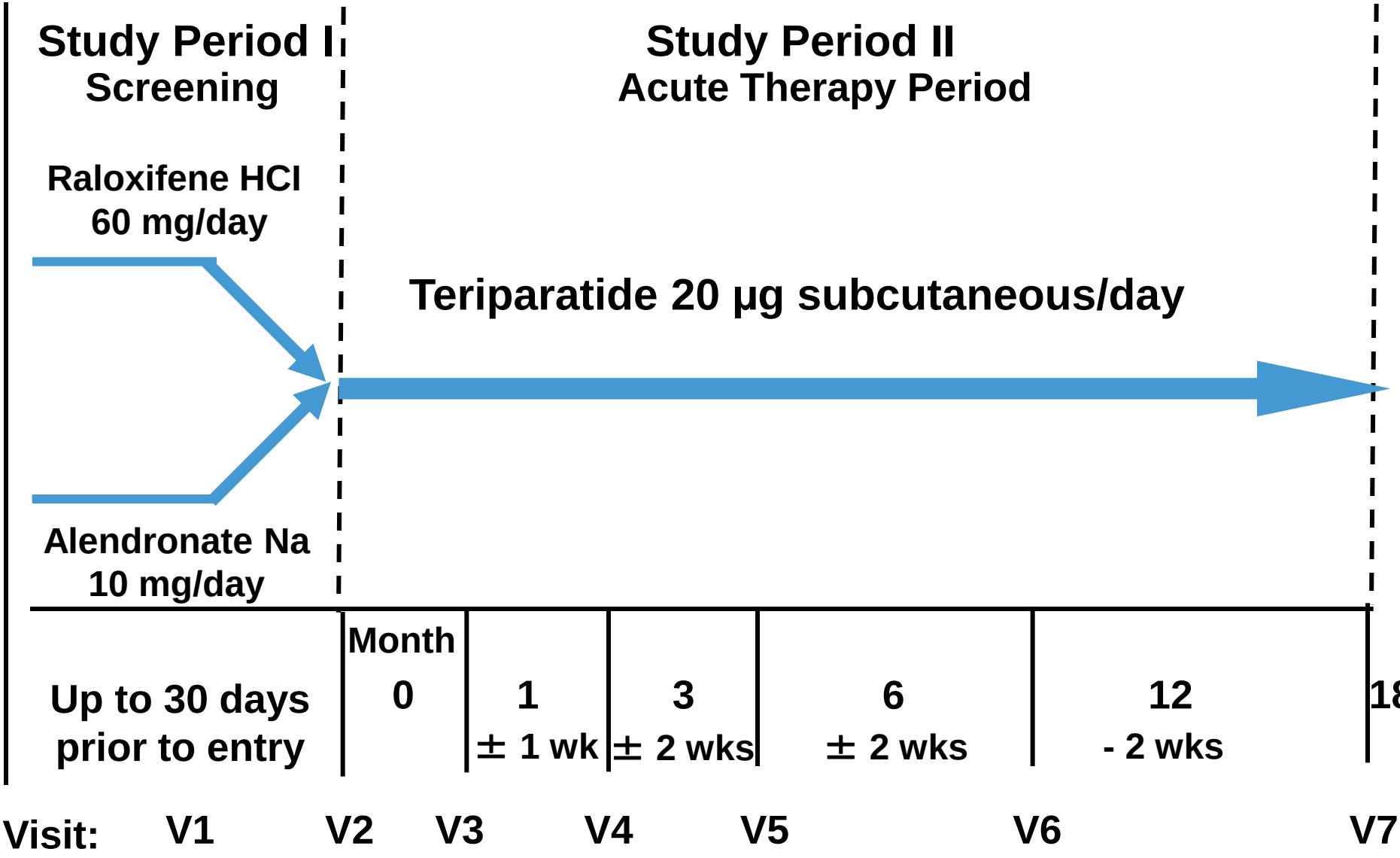


+ Antiresorptive



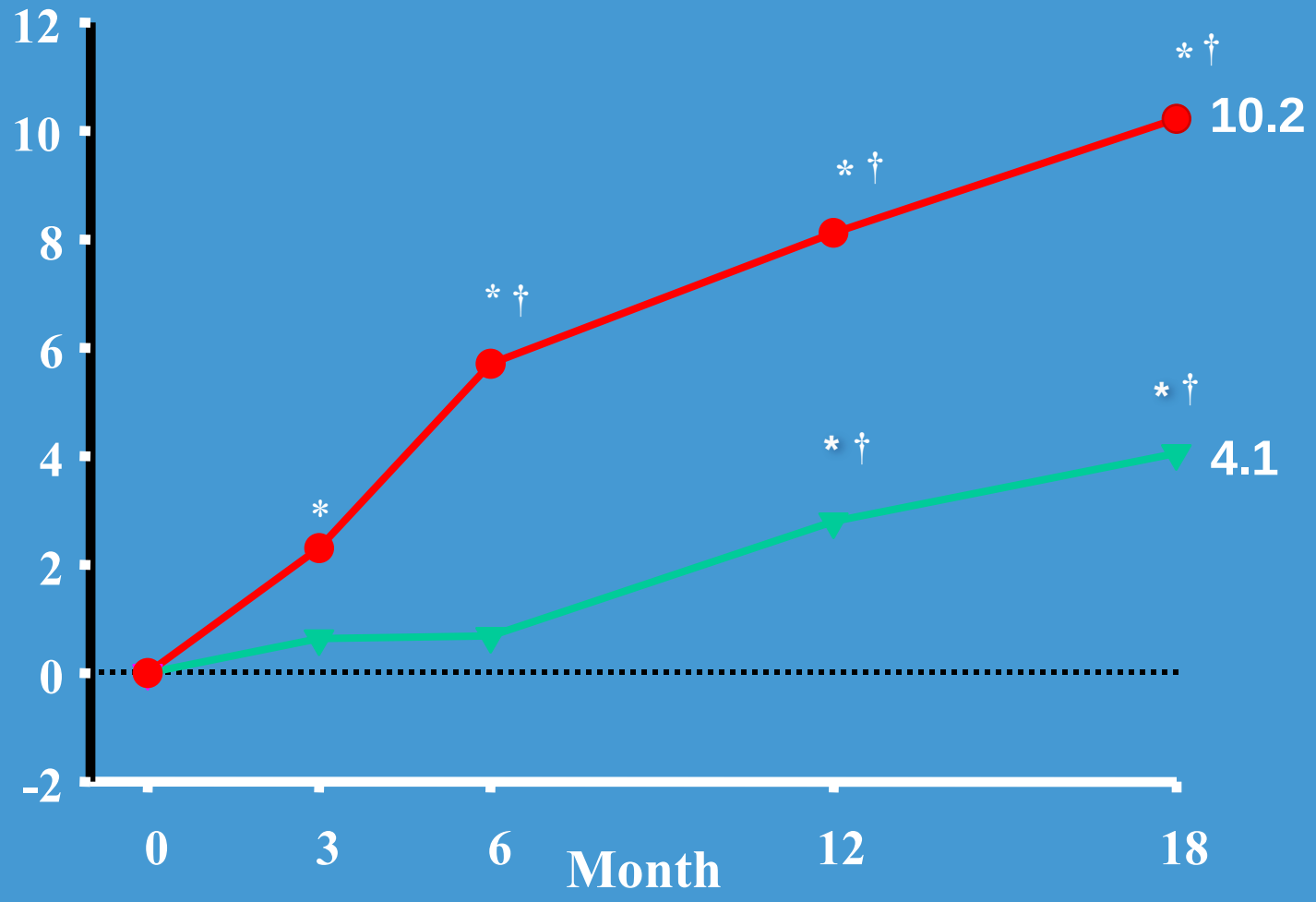
+++ Antiresorptive

AAA: STUDY DESIGN



Change in BMD on Teriparatide Treatment

Lumbar Spine



Raloxifene-TPTD

* P<0.05 from baseline

CROSS-OVER STUDY

The subject is taken as its own control.

- He receives both treatments :
  - Topical treatments are administered simultaneously at different locations.
  - The treatments are prescribed in two successive periods

CROSS-OVER STUDY

Interesting

for the clinician : expression as a preference

for the statistician : lowest intra-individual variability compared to the inter –individual one.

- But methodological problems :
  - Chronic and stable disease only
  - Duration of treatment period
  - Return to baseline (washout)
  - Interference between treatments if simultaneous

CROSS-OVER STUDY

Main Evaluation Criteria :% of Responders

	Treatment A	Treatment B
First period	80 %	60%
Second period	55 %	35 %

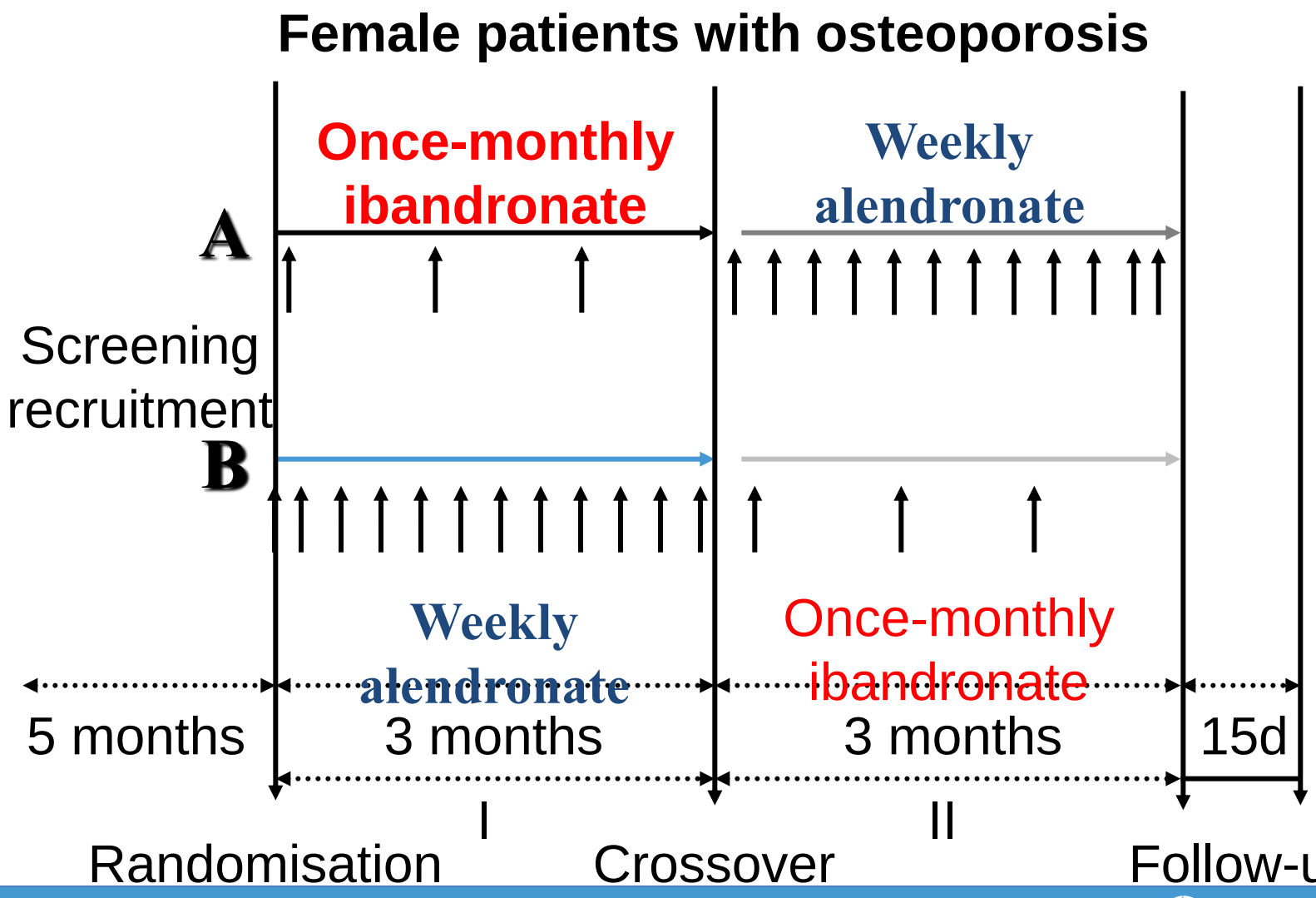
Effect " Treatment Sequence"

	Treatment A	Treatment B
First period	80 %	60%
Second period	70 %	85 %

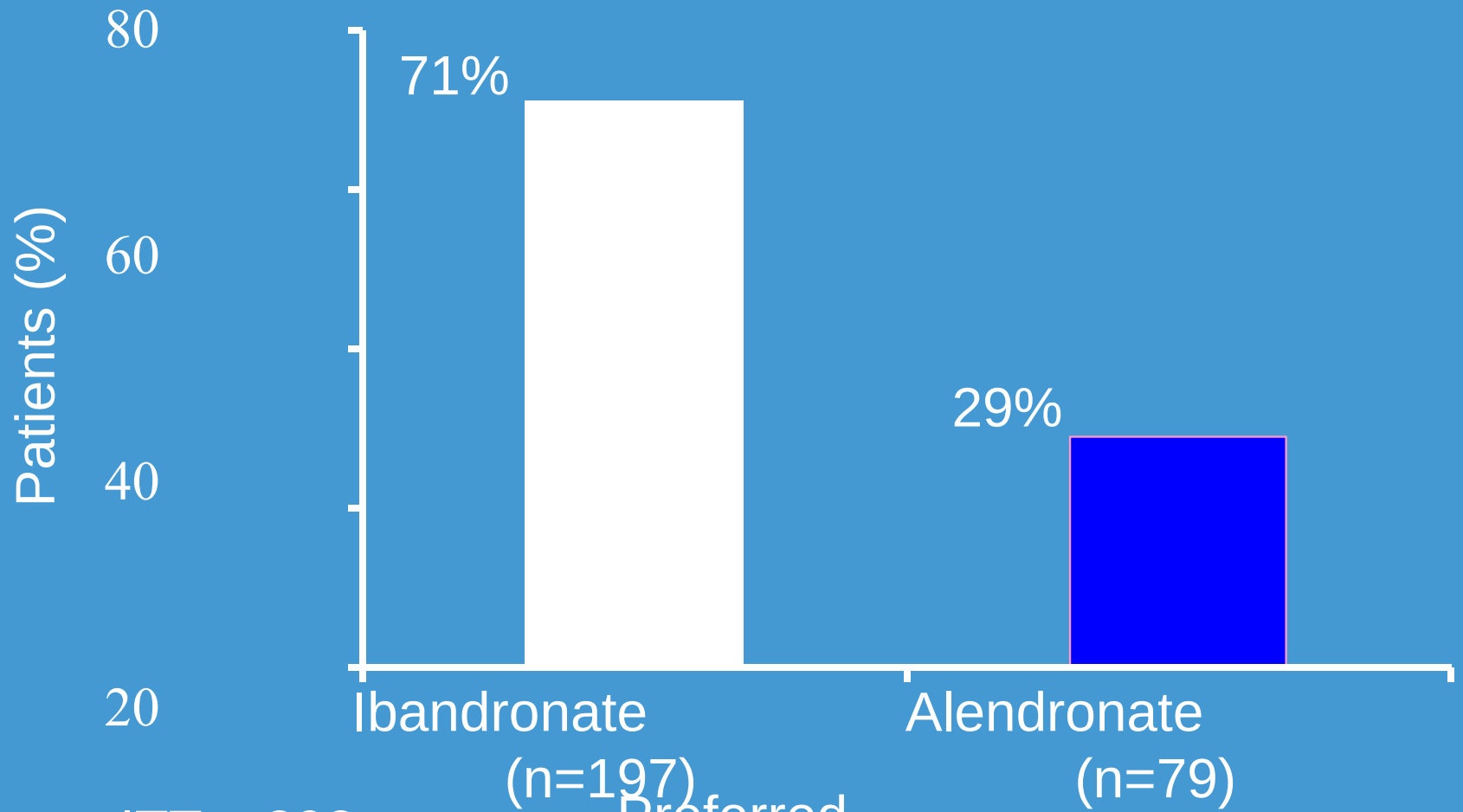
Effect "Treatment x Sequence"

DOES PATIENT PREFERENCE INFLUENCE THERAPEUTIC ADHERENCE?

Preference for once-monthly versus weekly oral dosing evaluated in BALTO I



The majority of patients* prefer monthly ibandronate over weekly alendronate



mITT = 298

*Patients expressing a preference

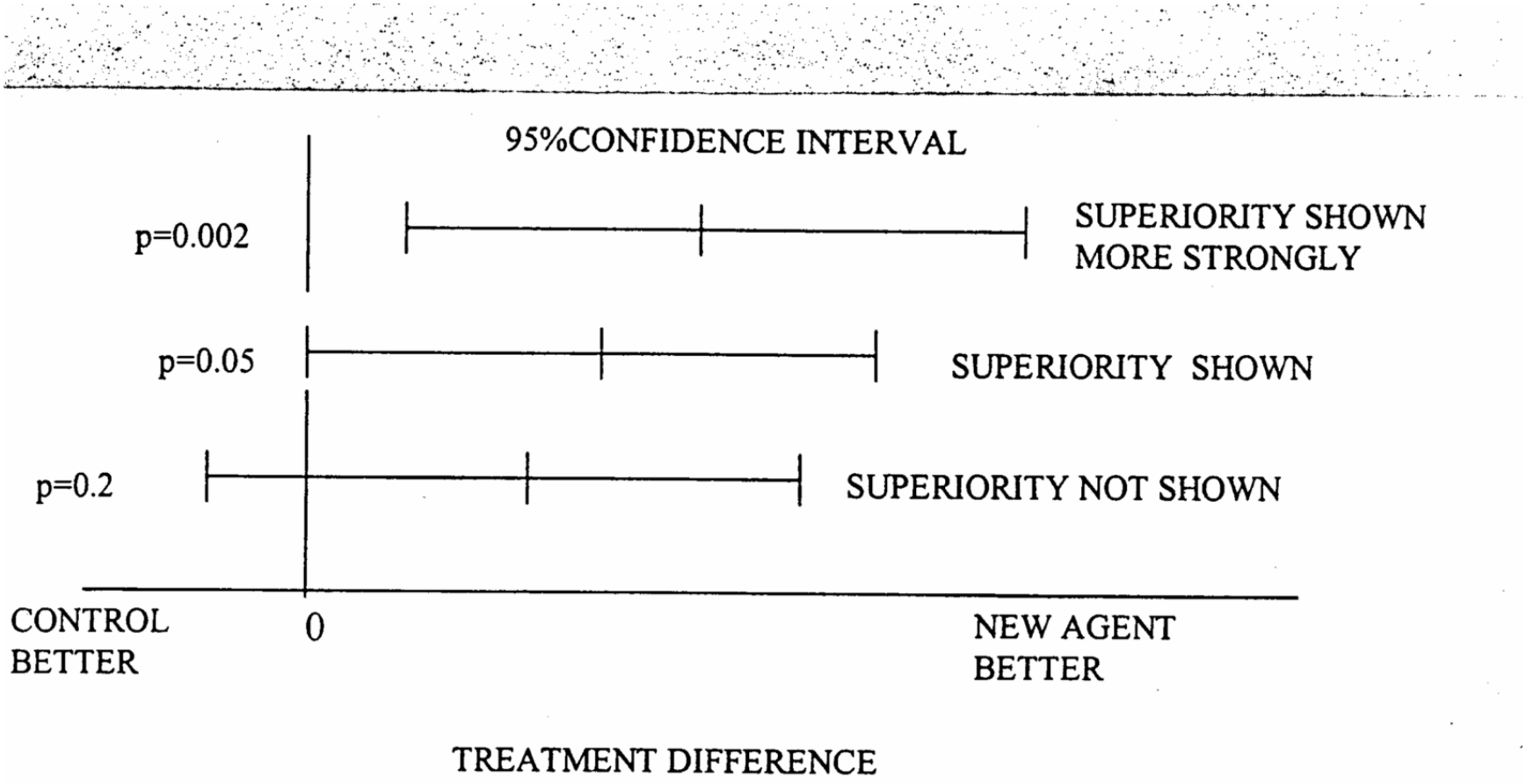
Data on file

EQUIVALENCE TRIAL

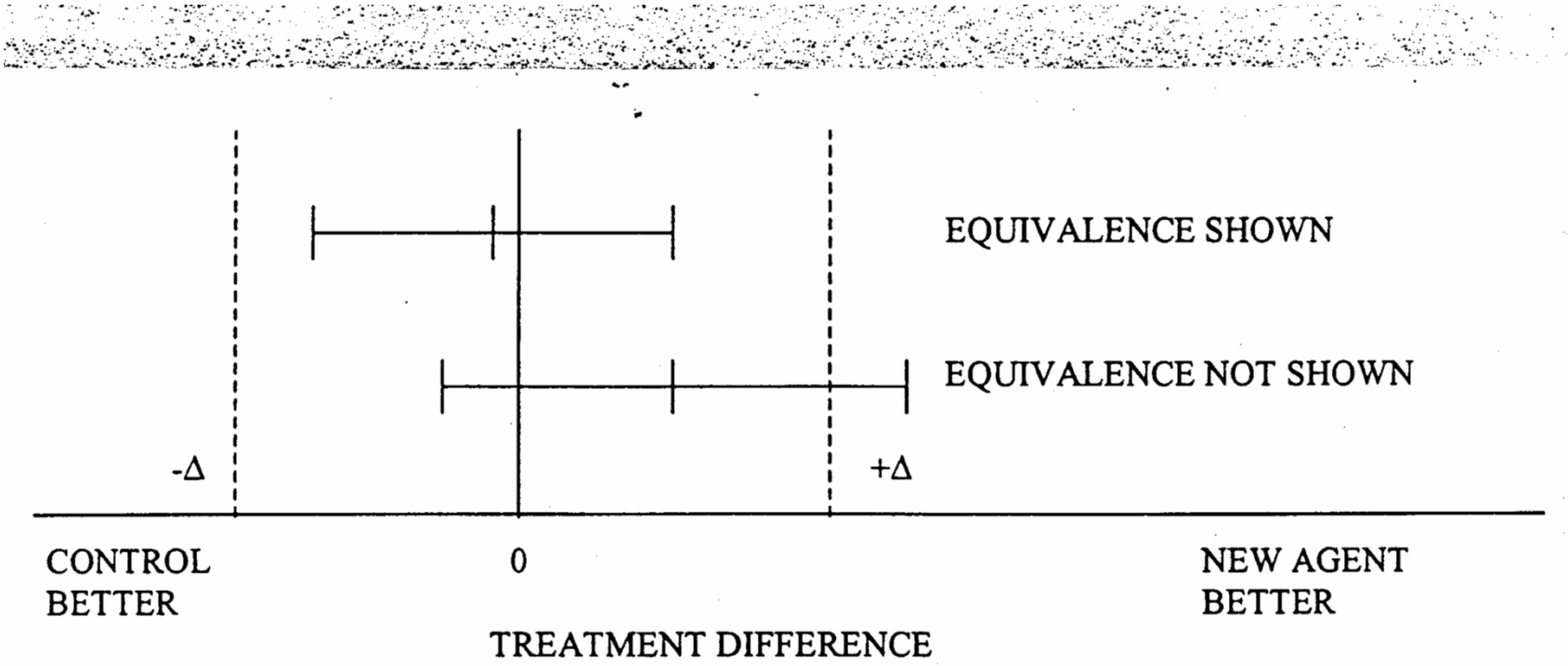
Demonstration of similar efficacy of a treatment compared to a control (reference) treatment

- Real equivalence trials
- Non-inferiority trials

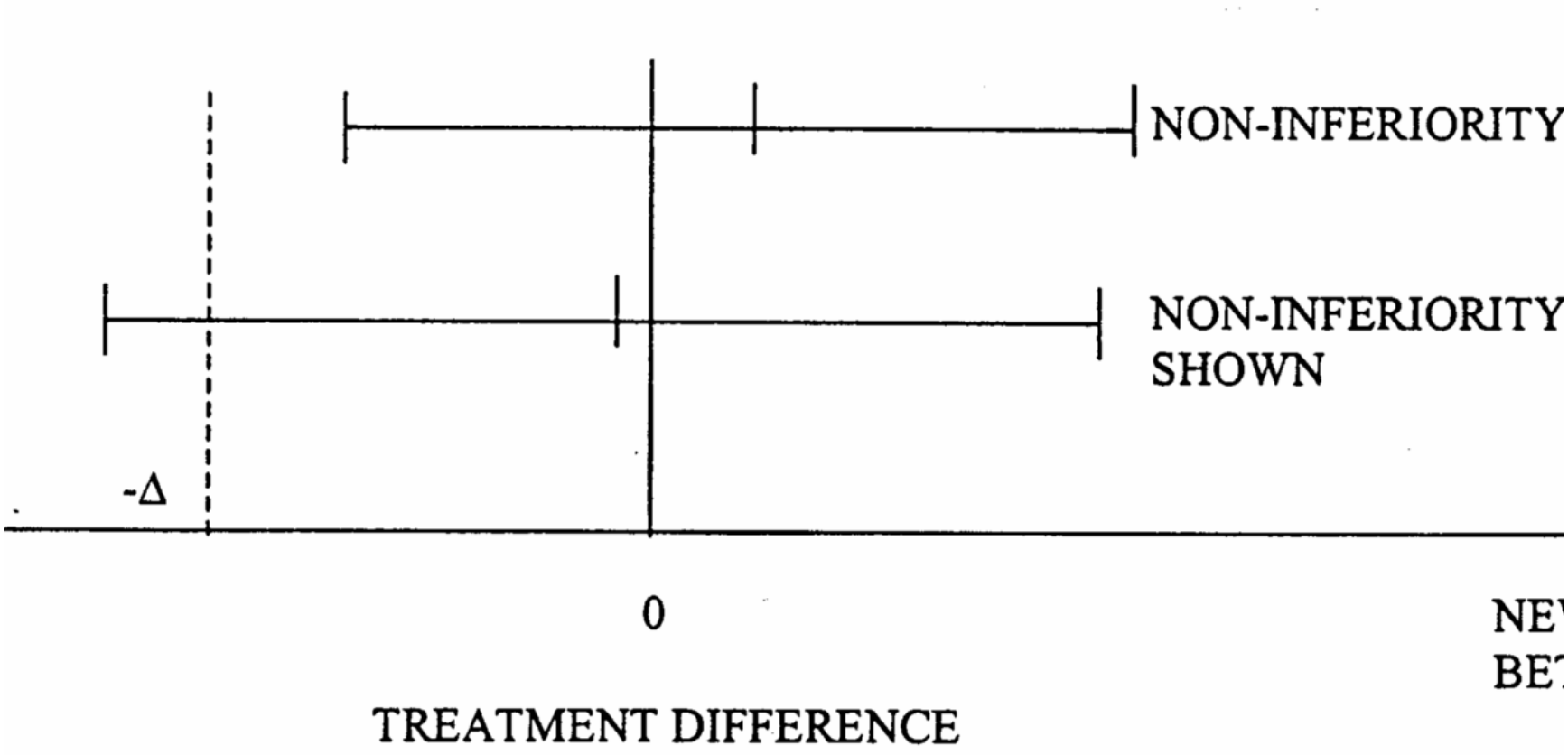
RELATIONSHIP BETWEEN SIGNIFICANCE TESTS AND CONFIDENCE INTERVALS



CONFIDENCE INTERVAL APPROACH TO ANALYSIS OF EQUIVALENCE TRIAL



CONFIDENCE INTERVAL APPROACH TO ANALYSIS OF NON-INFERIORITY TRIAL



EQUIVALENCE TRIAL : METHODOLOGY

- Objective (non-inferiority , equivalence ...) defined before the trial
- No transformation of a failure of a superiority demonstration
- Prior quantification of the effect of the reference treatment
- Choice of end-pointsfor assessment of efficacy
- Choice of the equivalence margin with respect to the superiority margin
- Use of a placebo for external validation

EQUIVALENCE TEST : BENCHMARK TREATMENT

- Benchmark treatment registered
- Trial conditions identical to those which led to the registration (dose, route, population)
- Comparable efficacy
- Minimized protocol violations

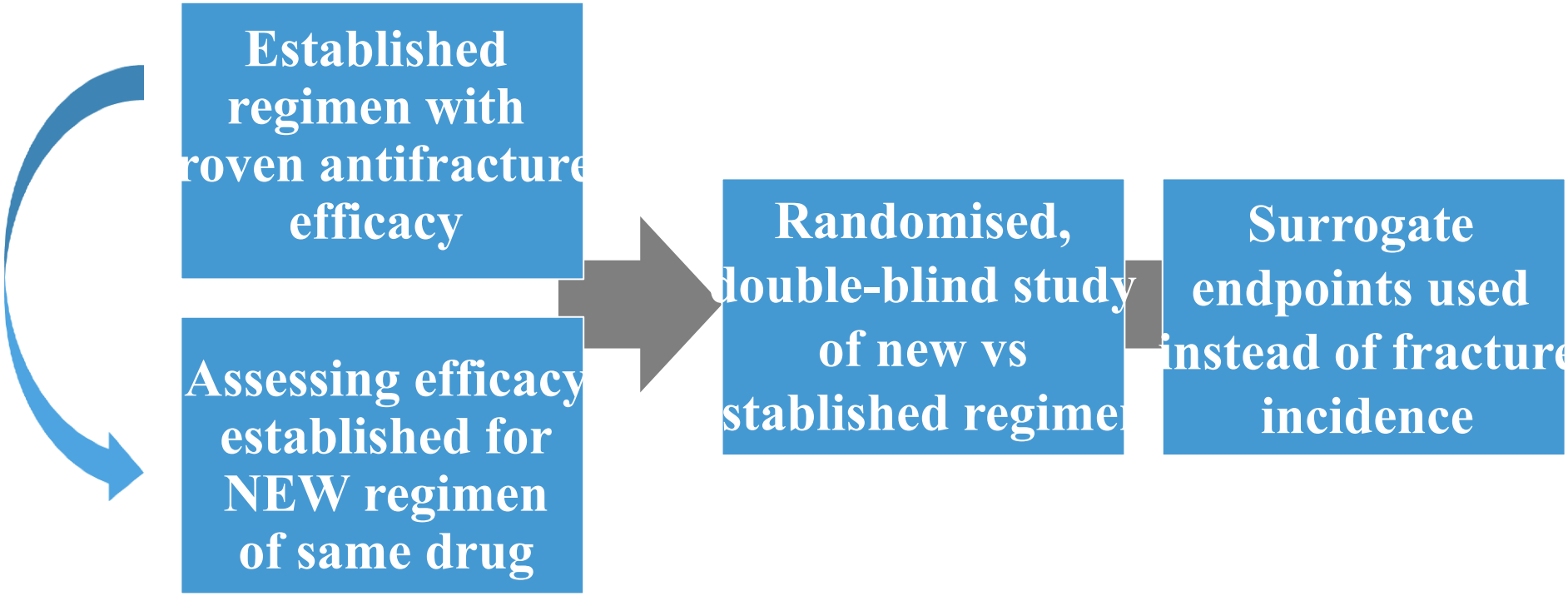
NON- INFERIORITY TRIAL

Criterion: % responders Margin: 20%

Expected effect of reference treatment : 60%

	New treatment	Reference treatment
Non-inferiority	55 %	62 %
Inferiority	40 %	58 %
Non-assessable	35 %	35 %

THE BRIDGING CONCEPT



Weekly, monthly and IV quarterly injection regimens were licensed based

BMD = bone mineral density; IV = intravenous
Ibandronato i.v. 3mg trimestral no está comercializado en España

endpoints

TWO-YEAR EFFICACY AND TOLERABILITY OF ONCE-MONTHLY ORAL IBANDRONATE IN POSTMENOPAUSAL OSTEOPOROSIS: THE MOBILE* STUDY

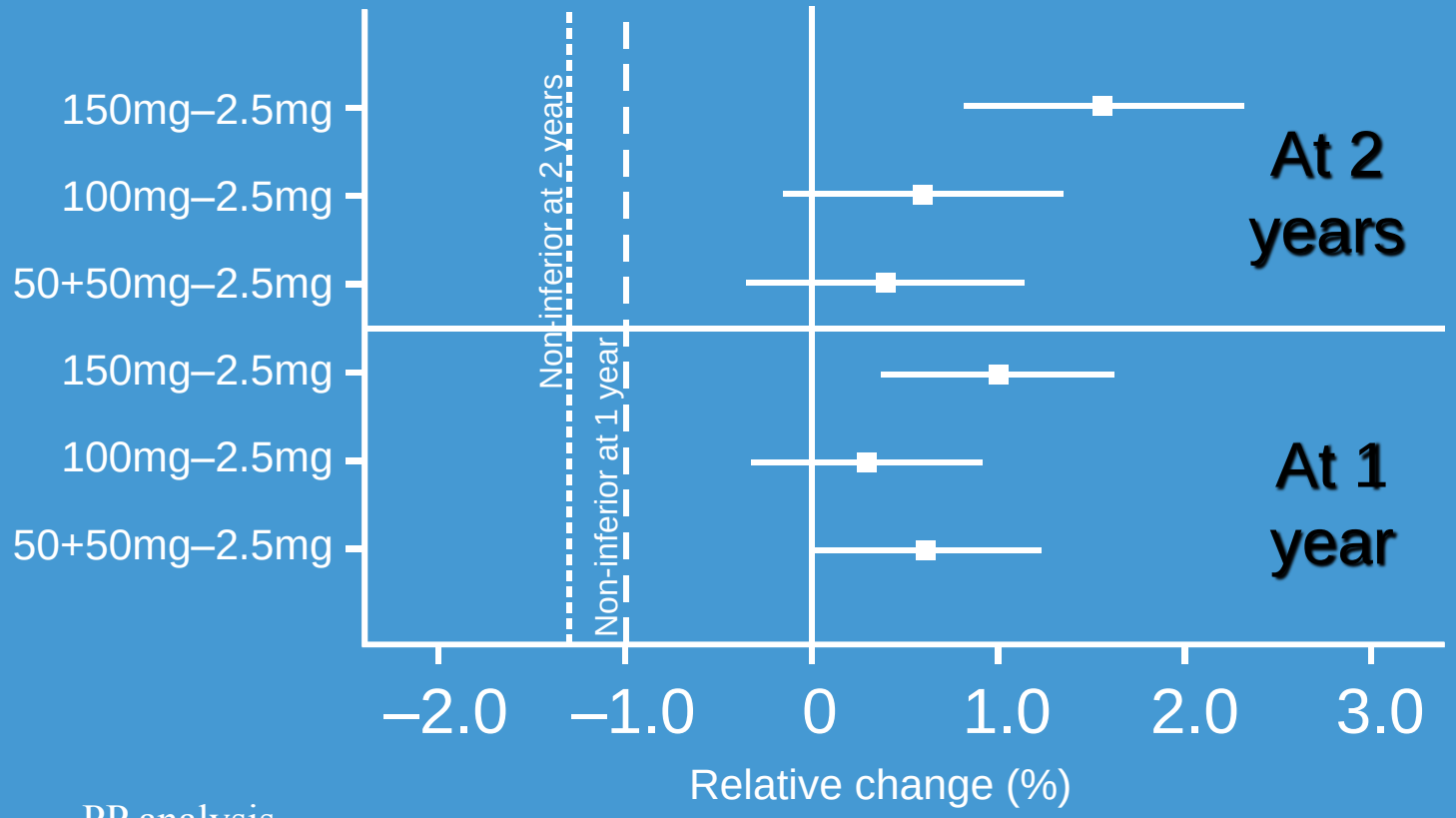
*Monthly Oral iBandronate in LadiEs

STUDY DESIGN

- Randomised, double-blind, phase III, non-inferiority study
- 4x treatment groups
  - 2.5mg daily ibandronate
  - 100mg once-monthly ibandronate (2x50mg, single doses, consecutive days)
  - 100mg once-monthly ibandronate (2x50mg, single day)
  - 150mg once-monthly ibandronate (3x50mg, single day)
- All participants received daily calcium (500mg) and vitamin D (400IU)

Miller PD, et al. J Bone Miner Res. Published online March 15, 2005; doi: 10.1359/JBMR.050313

Once-monthly oral ibandronate is non-inferior to daily for increase in lumbar spine BMD



PP analysis