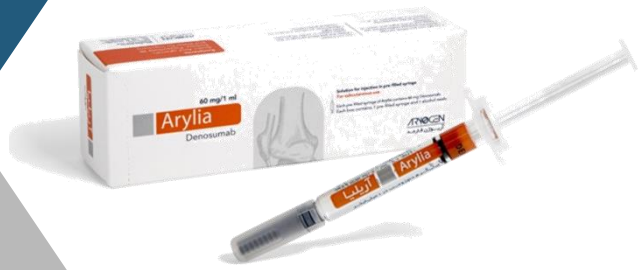
Arylia
Phase III Clinical Trial



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Arylia
Denosumab
Pre-filled Syringe, 60 mg/1 mL

Outlines

1. Design and Method
2. Results (Efficacy and Safety)
3. Conclusion

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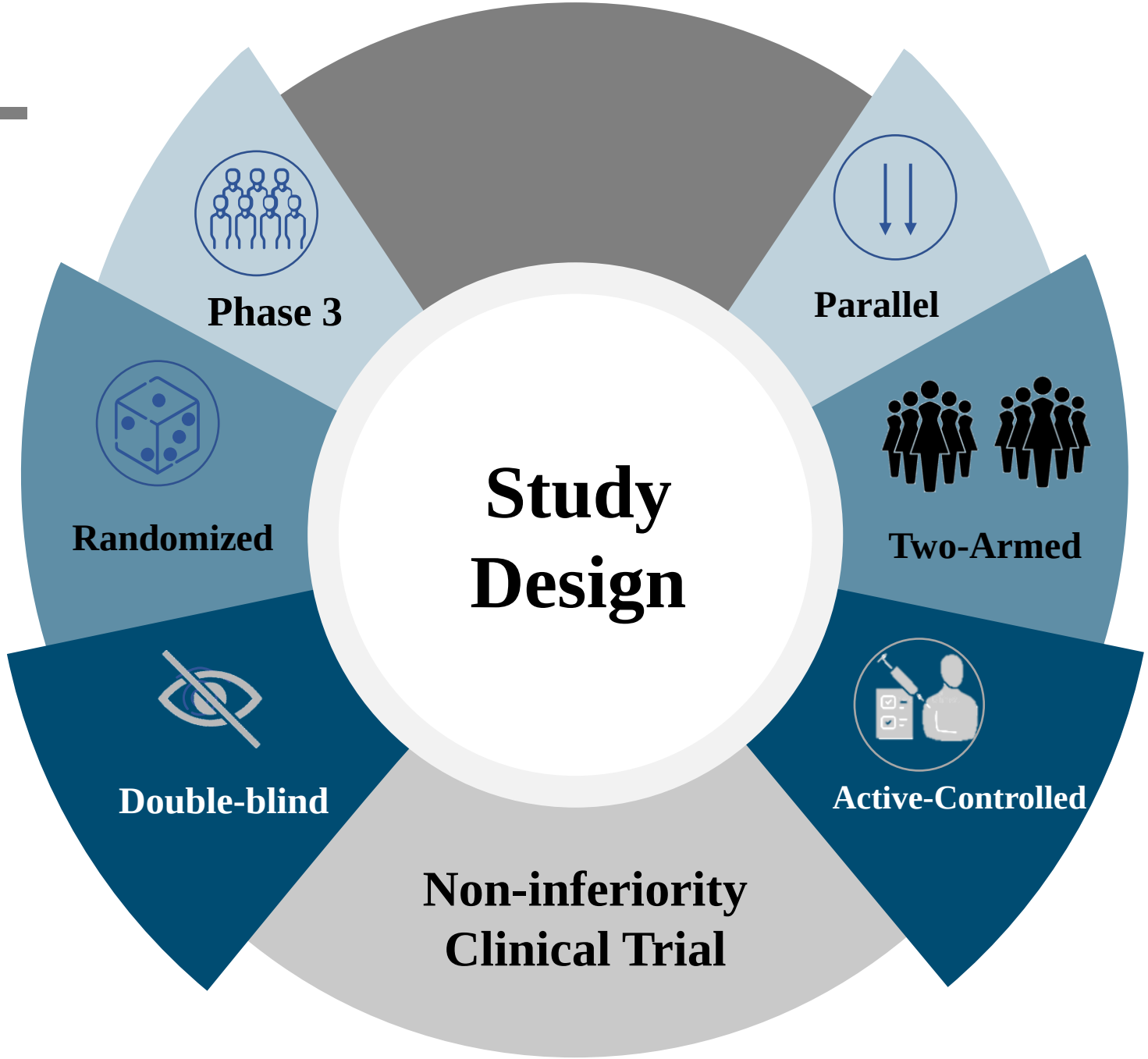
Design and Method

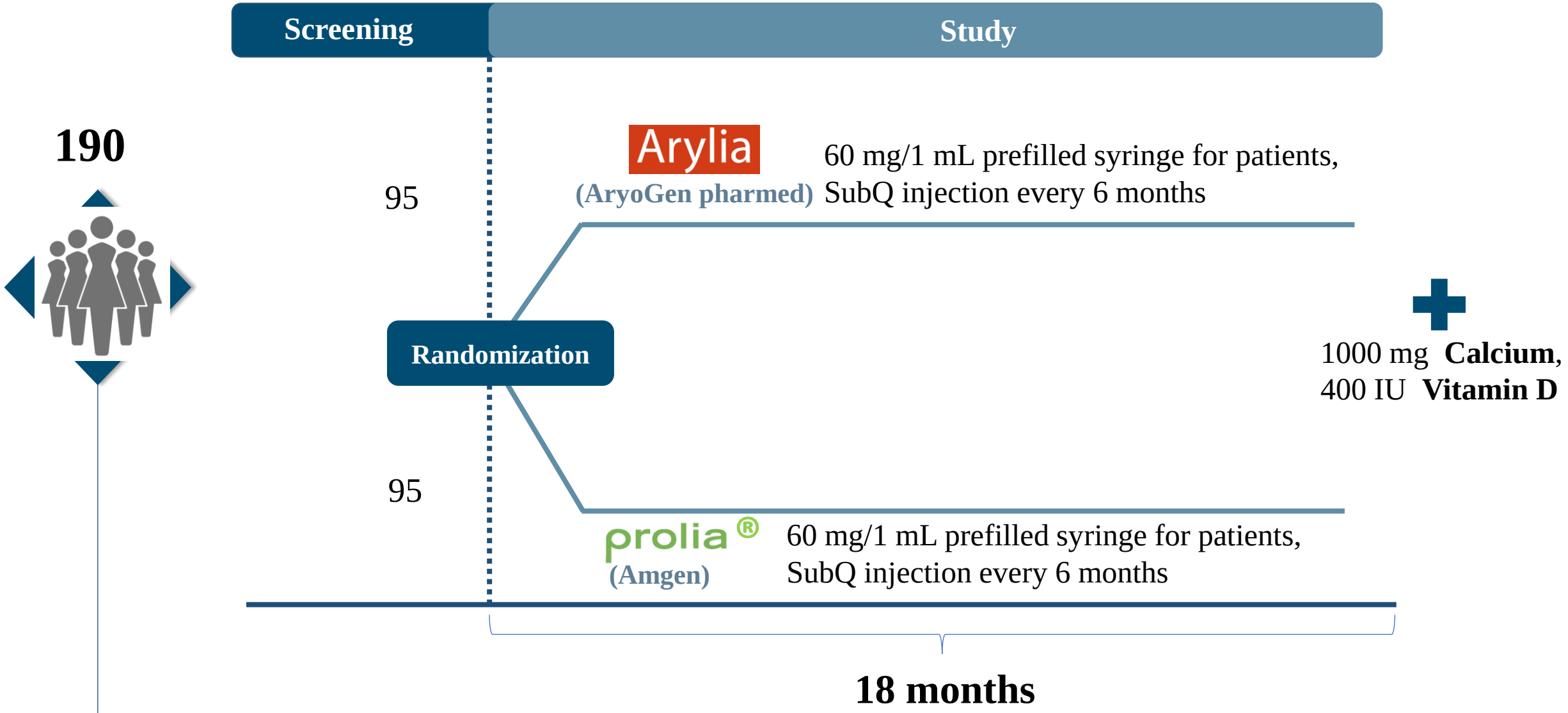
Study Design



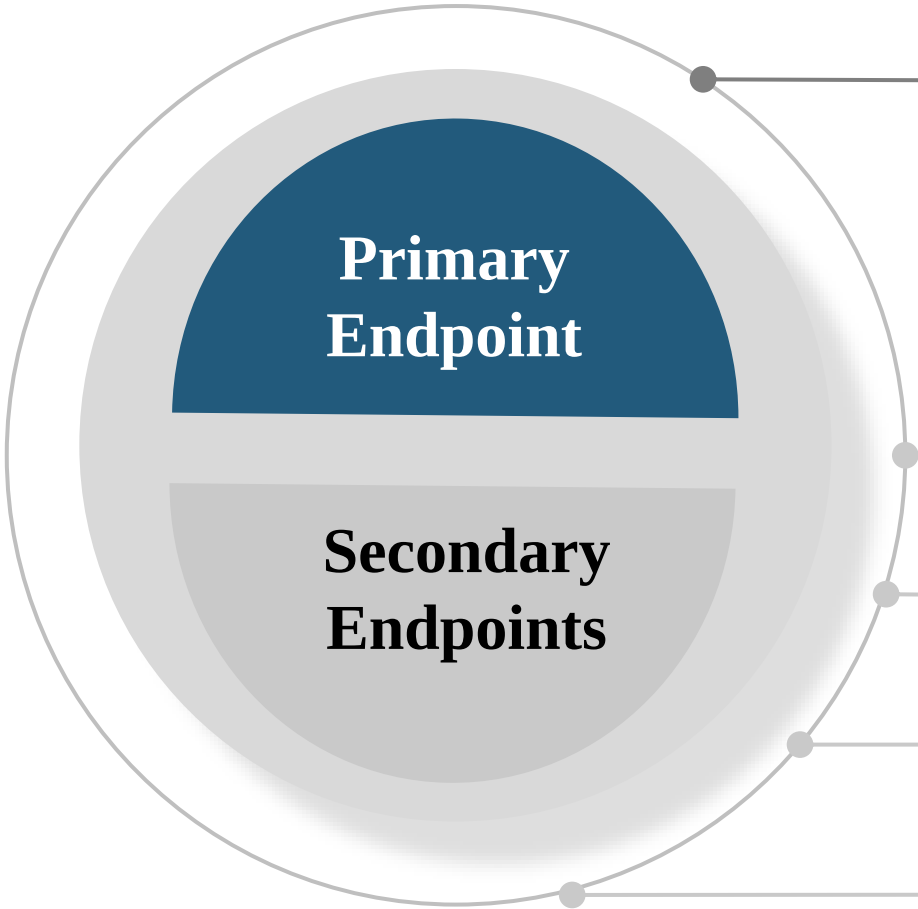
Study Centers

✓ A total of **190 patients** from **12 centers** in Iran were included:

Intervention



Study Endpoints



BMD Changes at month 18 in:

Lumbar Spine (L1-L4)
Hip and Femoral Neck

Incidence of new vertebral fractures

Trend of bone turnover biomarkers

Adverse events

Immunogenicity

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Inclusion Criteria

1

Postmenopausal **women**

2

Aged between **45 up to 75 years old**

3

Lumbar spine (L1-L4), hip or femoral neck:

- 4 ≤ T-score ≤ -2.5

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Exclusion Criteria

Conditions that affect the Safety and efficacy of drugs were excluded, e.g.:

Safety:

- ⊗ Malignancy
- ⊗ ONJ risk factors
- ⊗ Severe and active infections

Efficacy:

- ⊗ Use of parenteral bisphosphonates in the last 12 months
- ⊗ Use of oral bisphosphonates in the last 3 months
- ⊗ Use of corticosteroids (>5 mg/prednisone daily or equivalent for ≥ 3 months
- ⊗ 25 hydroxy vitamin D level < 20 ng/mL
- ⊗ Impossible to measure BMD
- ⊗ Unable to take 1000 mg elemental calcium (as a supplement)

Exclusion Criteria

- **Not complying with 18 months follow-up**
- **Hypersensitivity to denosumab or any other component of the formulation**
- **Malabsorption syndrome**
- **History of thyroid or parathyroid surgery and intestinal resection, which has caused malabsorption**
- **Patients with CKD stage 4 or 5 (GFR< 30 cc/min)**
- **25 hydroxy vitamin D level < 20 ng/mL**
- **Pre-existing untreated hypocalcemia (adjusted serum calcium < 8 mg/dL)**
- **Untreated hypo/hypercalciuria**
- **ONJ risk factors**
- **Malignancy**
- **Severe and active infections**
- **Bed rest patients**

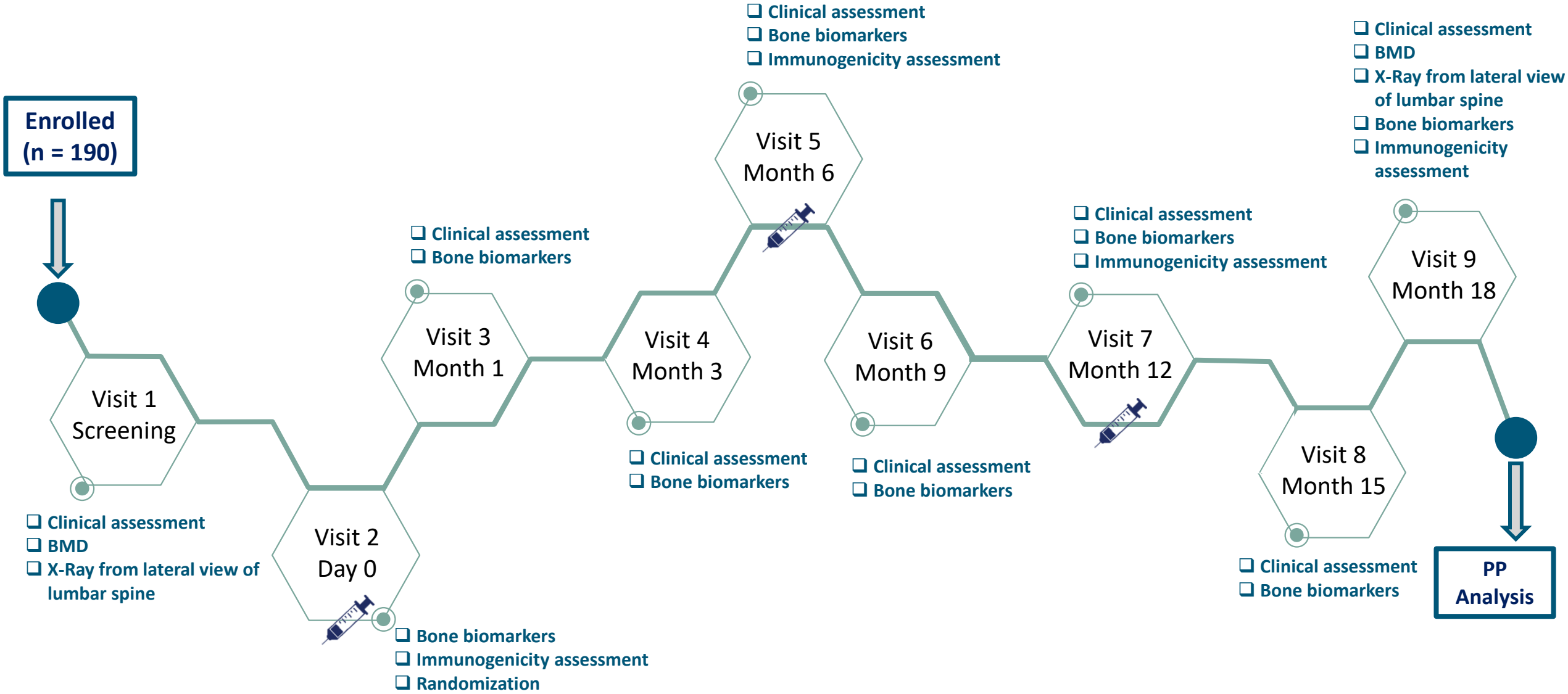
Exclusion Criteria

- **Unable to take 1000 mg elemental calcium (as a supplement)**
- **Impossible to measure BMD**
- **Conditions that affect bone turnover (e.g., hypo/hyperparathyroidism, RA, Hypocalcemia)**
- **One severe or more than two moderate vertebral fractures**
- **Use of parenteral bisphosphonates within the last 12 months**
- **Use of oral bisphosphonates in the last 3 months**
- **History of severe skeletal pain with bisphosphonates**
- **Use of parathyroid hormone or its derivatives, systemic hormone replacement therapy, selective estrogen receptor modulator, calcitonin, or calcitriol in the 6 weeks before study enrollment**
- **Use of corticosteroids (>5 mg/prednisone daily or equivalent for ≥ 3 months) in the past 3 months or more**
- **Use of heparin (more than 20,000 international units/day for 6 months and longer) in the last 6 months and more**
- **Possible to receive corticosteroids (>5 mg prednisolone daily for ≥ 3 months) or heparin (more than 20,000 IU/d for 6 months and longer) during the study period because of chronic diseases such as allergy, asthma, and coagulation disorders.**

Withdrawal Criteria

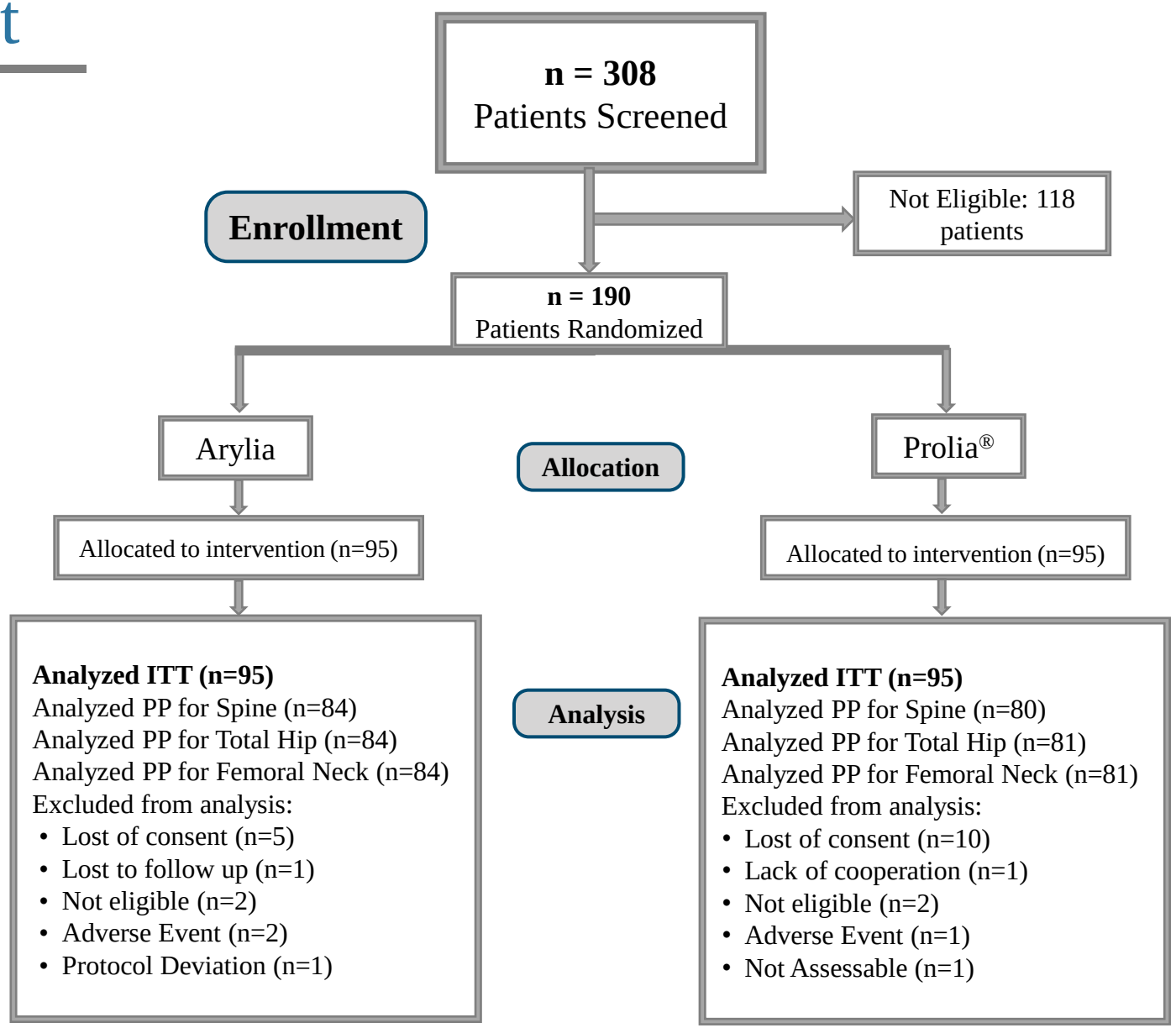
- **Withdrawal of consent by the patient**
- **Non-compliance**
- **Based on the opinion of an investigator due to adverse events**
- **Lost to follow-up**
- **Treatment changes or use of prohibited drugs in the protocol**

Study Timeline

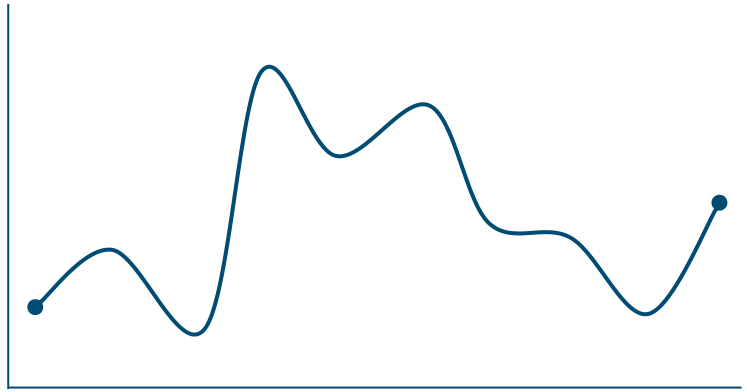


Adverse events were reported in all study time points

Study Consort



Efficacy Results



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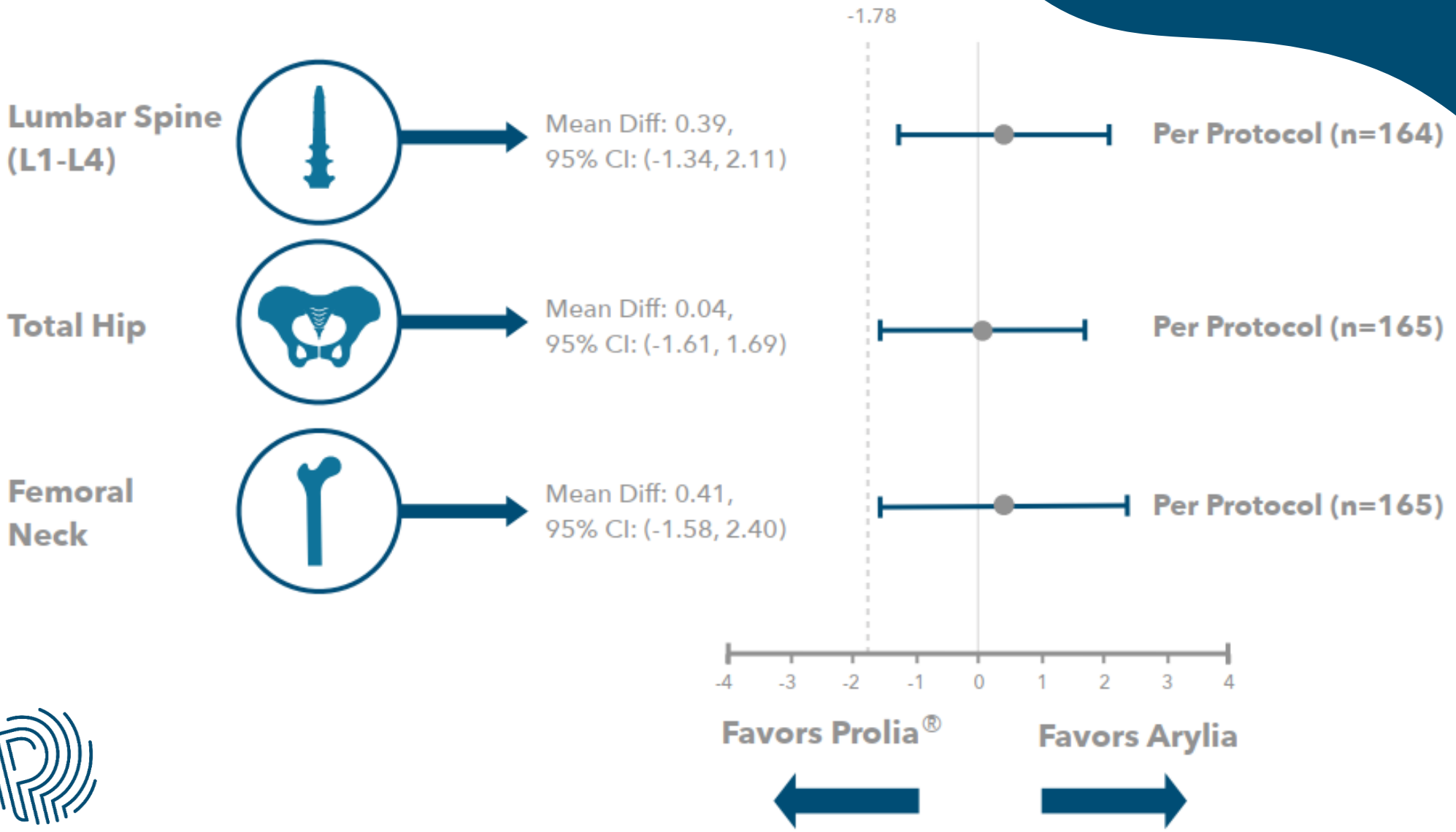
Non-Inferiority at:



Forest plot for BMD improvement (Per Protocol)

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BMD Changes

From baseline to month 18
Comparison between two groups (per protocol)

Site	BMD percent change Arylia		BMD percent change Prolia®		*p*-value
	Mean	SD	Mean	SD	
Spine	5.91	5.58	5.52	5.59	0.66
Total hip	2.32	5.24	2.28	5.52	0.96
Femoral neck	1.91	6.32	1.50	6.62	0.68

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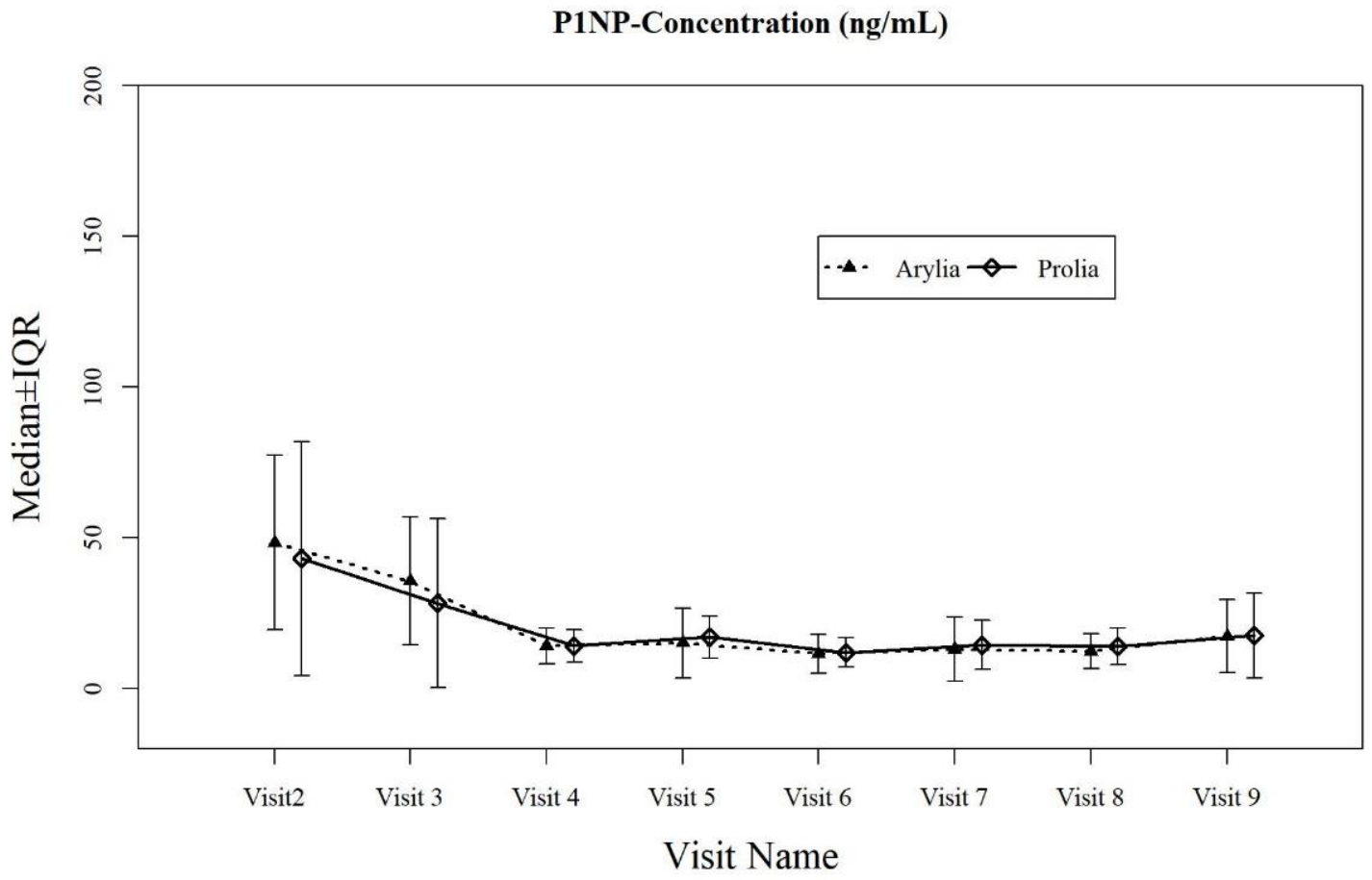
Trend of P1NP



Trend of Bone biomarkers (P1NP) during time

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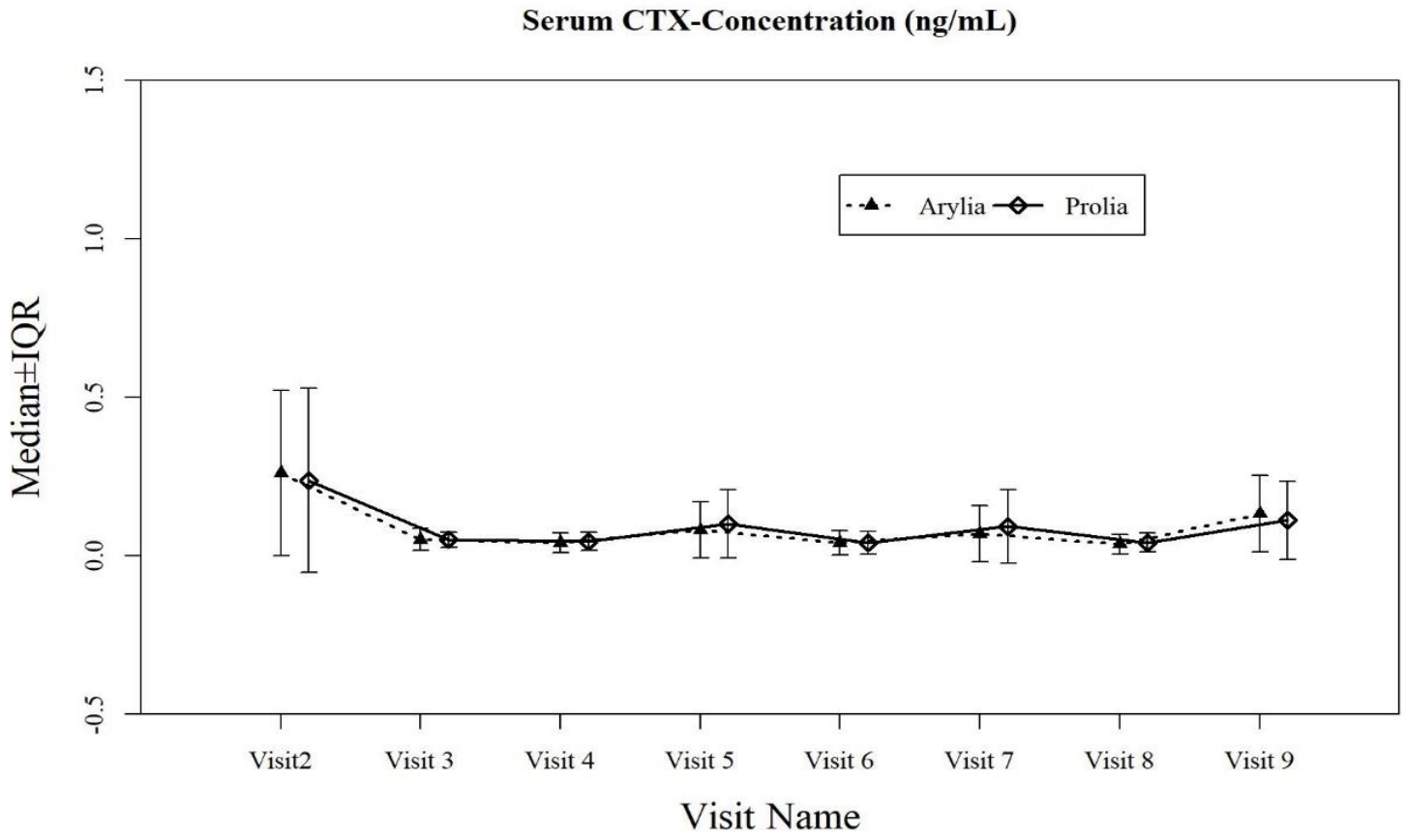
Trend of Serum CTX



Trend of Bone biomarkers (Serum CTX) during time

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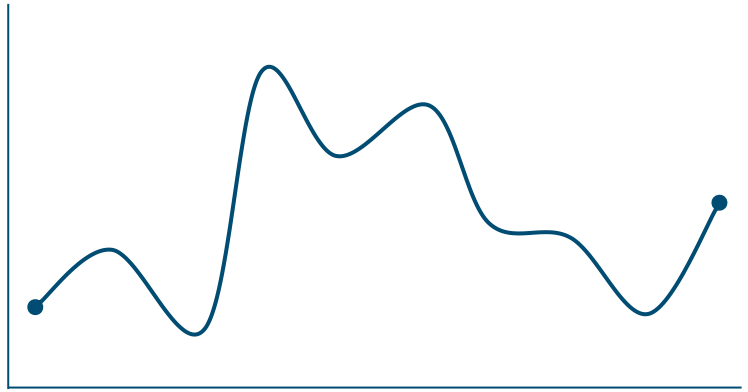
Safety Results



Most Common Adverse Events (AEs)

System Organ Class	Preferred Term	Arylia (n=95) n (%)	Prolia® (n=95) n (%)
Metabolism and nutrition disorders	Hypocalcaemia	16 (16.84)	11 (11.58)
	Hypertriglyceridaemia	3 (3.16)	2 (2.11)
Musculoskeletal and connective tissue disorders	Back pain	2 (2.11)	4 (4.21)
	Arthralgia	3 (3.16)	1 (1.05)
Vascular disorders	Hypertension	7 (7.37)	3 (3.16)

No statistically significant **difference in most common AEs** between two groups.

Casual Relationship

Casual Relationship	Arylia (n=95) n (%)	Prolia® (n=95) n (%)
At least Possibly Related AEs	۲۲ (۲۳/۱۶)	۲۴ (۲۵/۲۶)
At least Possibly Related SAEs	۰ (۰)	۰ (۰)

No relationship between serious adverse events and drugs

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SAEs (Resulted in hospitalization)

PT	Causality	Group
Arteriosclerosis	Unlikely	Prolia®
Bunion operation	Unlikely	Prolia®
Cystocele/ Rectocele	Unlikely	Arylia
Diverticulitis	Unlikely	Arylia
Incisional hernia	Unlikely	Arylia
Intraductal proliferative breast lesion	Unlikely	Prolia®
Knee arthroplasty	Unlikely	Prolia®
Osteoarthritis	Unlikely	Arylia
Papillary cystadenoma lymphomatosum	Unlikely	Prolia®
Sinusitis	Unlikely	Prolia®
Transient ischaemic attack	Unlikely	Arylia
Wrist fracture	Unlikely	Arylia

All of the above-mentioned SAEs were unrelated to the drug and mostly depended on the patient's underlying conditions.

Adverse Events

Grade 3:

No statistically **significant difference** between two groups

p-value=0.42

Grade 4 and 5:

Not occurred

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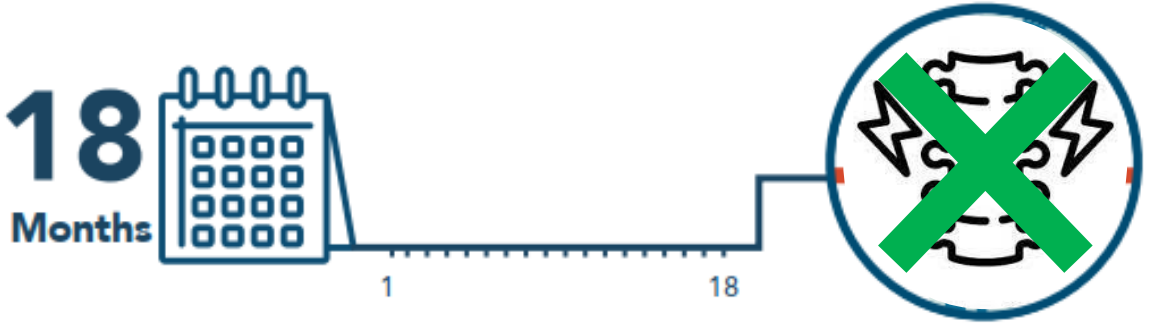
No new vertebral fractures during 18 months



Immunogenicity

Only one patient had serum anti-body against Denosumab.

No statistically significant **difference** between two groups.

Arylia was proved to be **Non-Inferior** to the **reference product** in terms of **efficacy.**

prolia® (denosumab) injection

Arylia
Denosumab

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Article

- ✓ Phase III Clinical Trial
- ✓ Arthritis Research & Therapy
- ✓ Impact Factor: 5.156

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Arthritis Research & Therapy

RESEARCH Open Access

Efficacy and safety of the biosimilar denosumab candidate (Arylia) compared to the reference product (Prolia®) in postmenopausal osteoporosis: a phase III, randomized, two-armed, double-blind, parallel, active-controlled, and noninferiority clinical trial

Ahmadreza Jamshidi[1], Mahdi Vojdanian[2], Mohsen Soroush[3], Mahmoud Akbarian[2], Mehrdad Aghaei[4], Asghar Hajiabbasi[5], Zahra Mirfeizi[6], Alireza Khabbazi[7], Gholamhosein Alishiri[8], Anousheh Haghighi[9], Ahmad Salimzadeh[10], Hadi Karimzadeh[11], Fatemeh Shirani[12], Mohammad Reza Hatef Fard[13], MohammadAli Nazarinia[14], Soosan Soroosh[15], Nassim Anjidani[16] and Farhad Gharibdoost[2*]

Abstract

Background/objective: Osteoporosis is a global health concern with an increasing prevalence worldwide. Denosumab is an antiresoptive agent that has been demonstrated to be effective and safe in osteoporotic patients. This study aimed to compare the efficacy and safety of the biosimilar denosumab candidate (Arylia) to the originator product (Prolia®) in postmenopausal osteoporotic patients.

Methods: In this randomized, double-blind, active-controlled, noninferiority trial, postmenopausal osteoporotic patients received 60 mg of subcutaneous Arylia or Prolia® at months 0, 6, and 12 and were followed up for 18 months. The primary endpoint was the noninferiority of the biosimilar product to the reference product in the percentage change of bone mineral density (BMD) in 18 months at the lumbar spine (L_1-L_4), total hip, and femoral neck. The secondary endpoints were safety assessment, the incidence of new vertebral fractures, and the trend of bone turnover markers (BTMs).

Results: A total of 190 patients were randomized to receive either biosimilar ($n = 95$) or reference ($n = 95$) denosumab. In the per-protocol (PP) analysis, the lower limits of the 95% two-sided confidence intervals of the difference between Arylia and Prolia® in increasing BMD were greater than the predetermined noninferiority margin of − 1.78 at the lumbar spine, total hip, and femoral neck sites (mean differences [95% CIs] of 0.39 [− 1.34 to 2.11], 0.04 [− 1.61 to 1.69], and 0.41 [− 1.58 to 2.40], respectively). The two products were also comparable in terms of safety, new vertebral fractures, and trend of BTMs.

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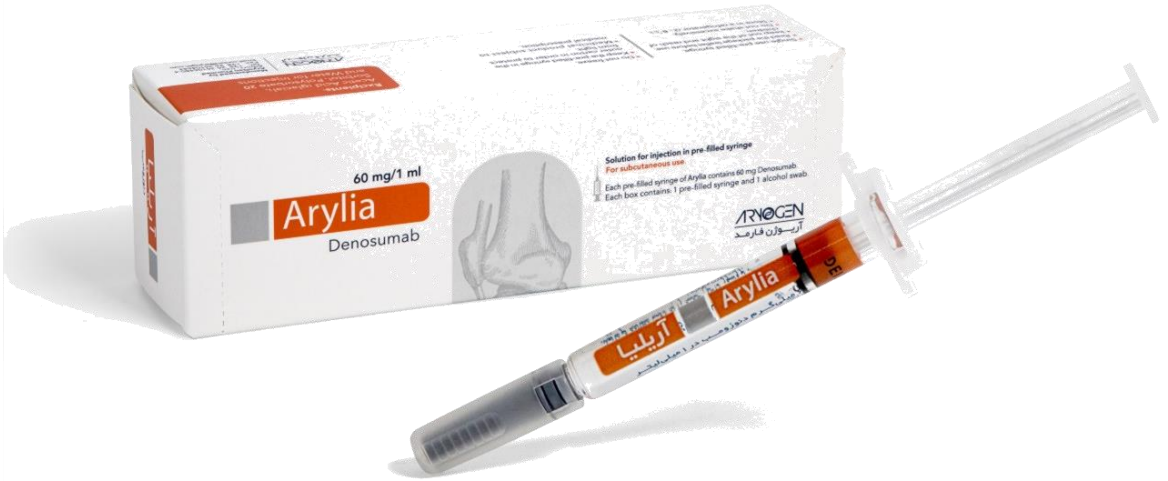
Thanks
for Your Attention



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Arylia
Denosumab
Pre-filled Syringe, 60 mg/1 mL

ARYOGEN

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