Palovarotene for the Treatment of Patients with Fibrodysplasia Ossificans Progressiva (FOP)

Ipsen

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

June 28, 2023

Introduction

Howard Mayer, MD

Executive Vice President,
Head of Research and Development

Ipsen

Fibrodysplasia Ossificans Progressiva (FOP) is Ultra-Rare, Severely Disabling Disease

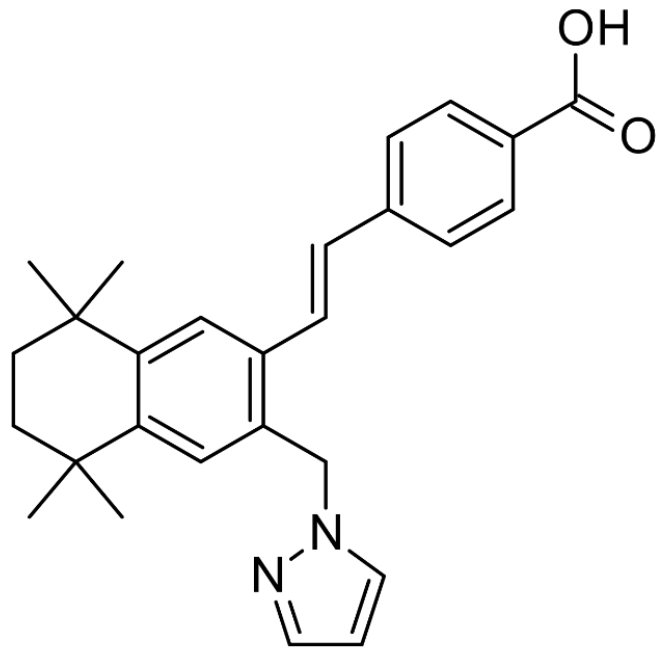
- Patients form heterotopic ossification (HO)
  - Bone in soft tissue where bone normally does not exist
  - HO is key pathophysiologic process leading to disease progression and morbidity
- Genetic disease starting in early childhood[1]

1. Pignolo, Hsiao, 2021

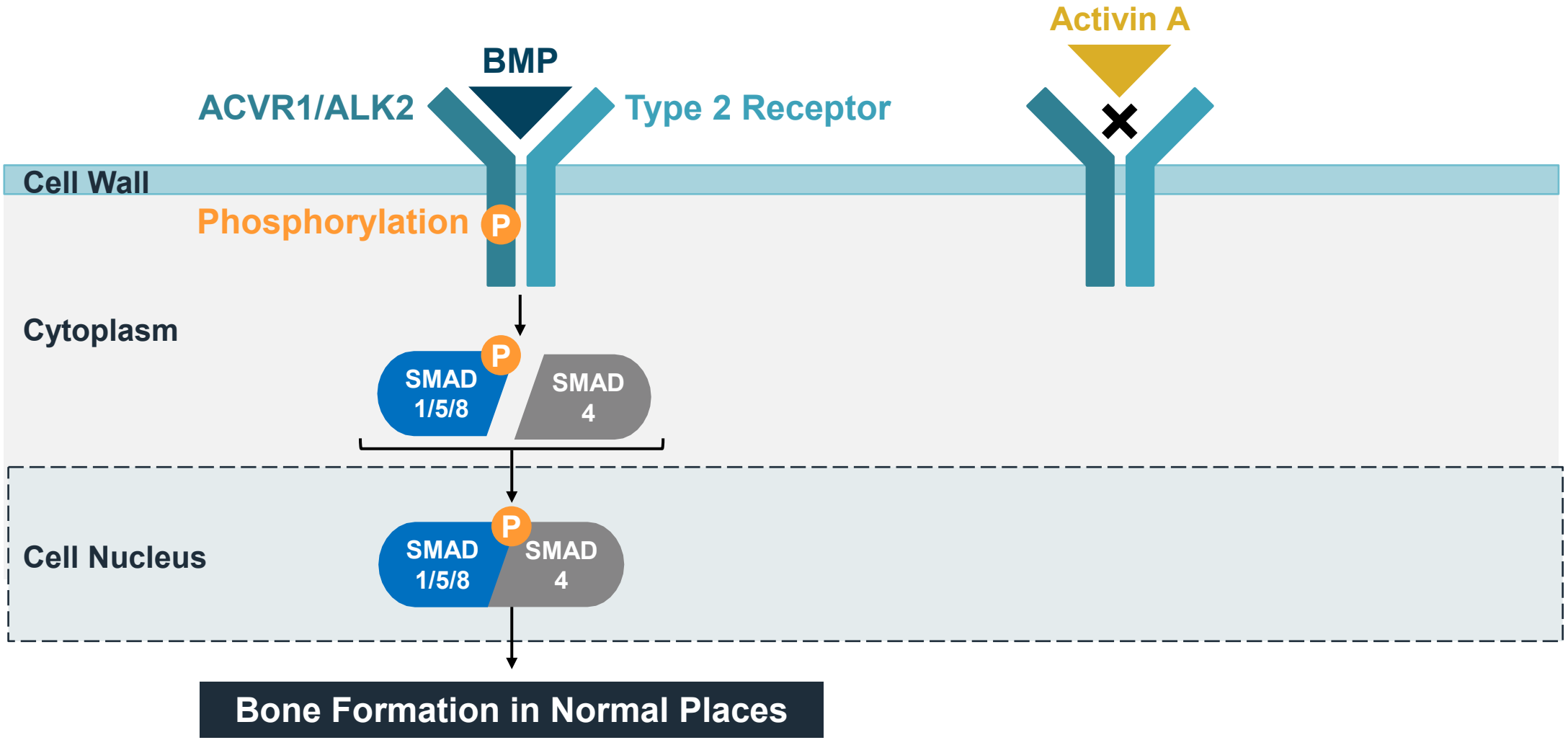
Palovarotene has Potential to be First Disease-Modifying Therapeutic to Treat FOP

- Orally bioavailable retinoic acid receptor gamma (RARγ) selective agonist
- Reduces new HO volume, a hallmark of FOP progression

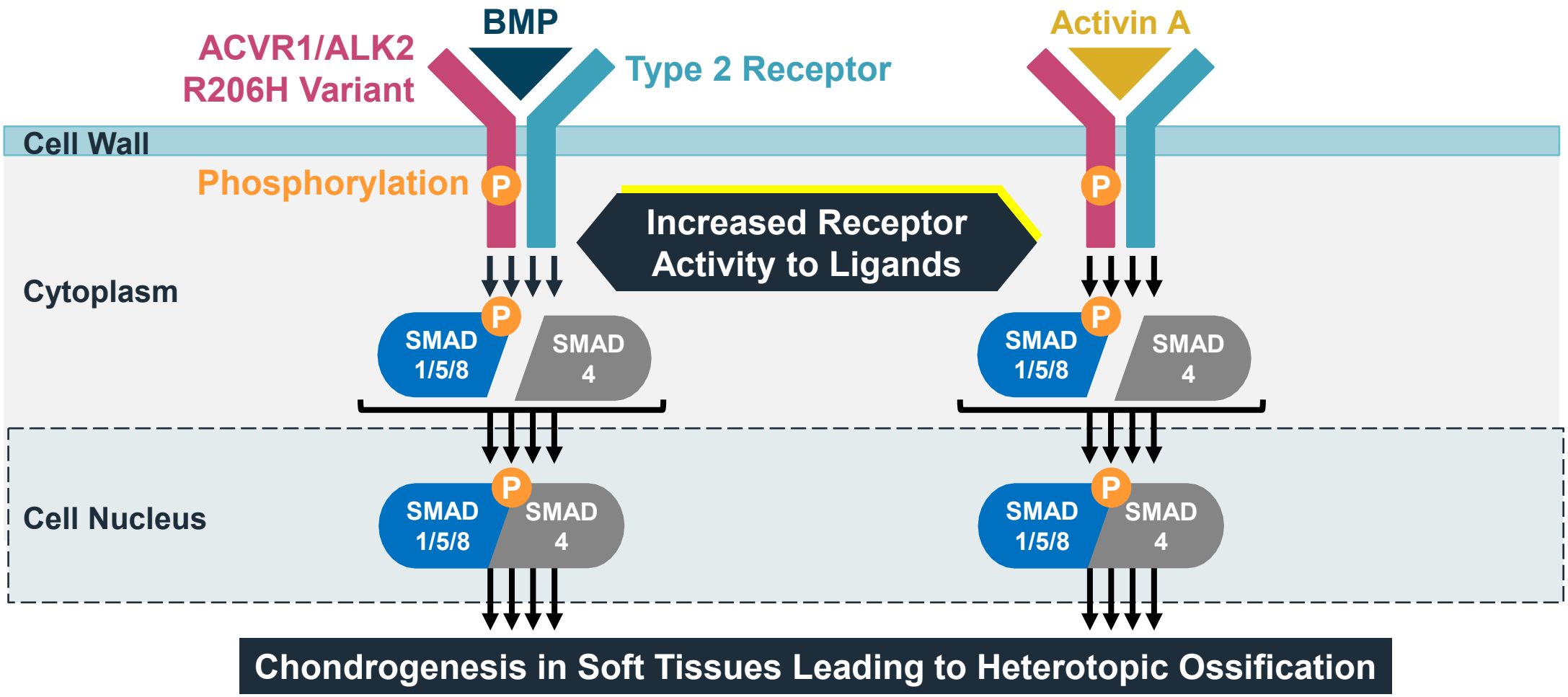
Palovarotene Structure



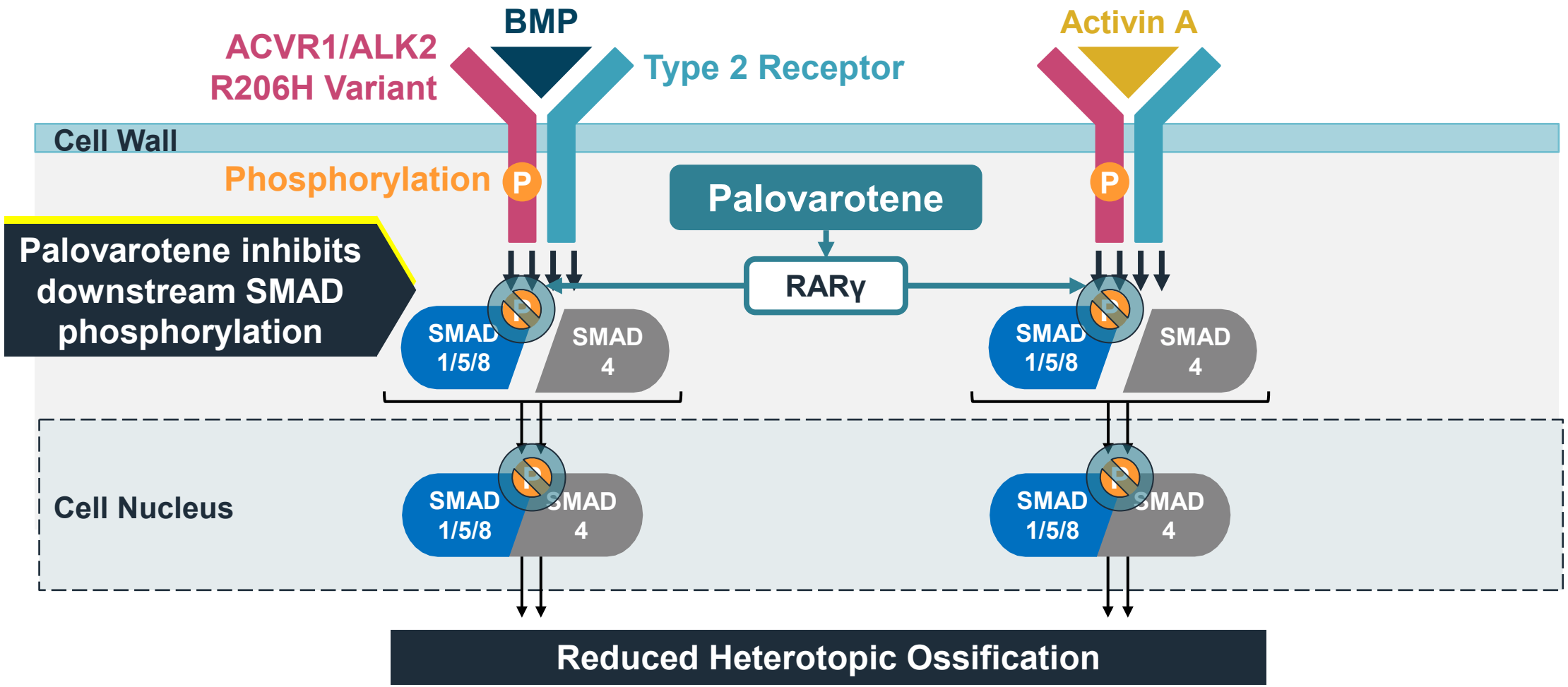
In Normal Cell Signaling Bone Morphogenetic Proteins (BMPs) Regulate Bone Formation



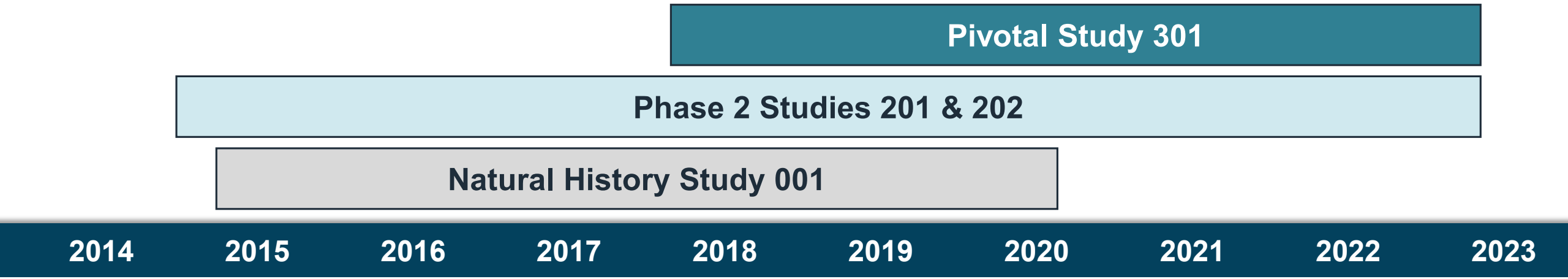
FOP Results in Hyperactive BMP Signaling by Altering ACVR1/ALK2 Response to Ligands



Palovarotene Inhibits Chondrogenesis Through Regulation of BMP Signaling



Palovarotene Clinical Development Program Enrolled ~25% of Known FOP Population



- 2014 limited information existed on outcomes in FOP
- Orphan drug, breakthrough therapy, and rare pediatric disease designations
- Partial clinical hold by FDA due to risk of premature physeal closure (PPC) in December of 2019

Proposed Target Population
Females ≥ 8 and Males ≥ 10 Years of Age

- Based on benefit-risk assessment considering risk of PPC, skeletal maturity, and risk of developing HO
- Development of HO and associated physical impairment can occur in patients starting at birth
  - Irreversible and cumulative[1]
- Early intervention critical to preserving patient function
- Efficacy and safety data support positive benefit-risk
- Risk management activities will inform and guide physicians, patients, and caregivers on safe use of palovarotene

1. Pignolo, 2019

Palovarotene Proposed Indication

The prevention of heterotopic ossification (HO) in adults and children (aged 8 years and above for females and 10 years and above for males) with fibrodysplasia ossificans progressiva (FOP)

Palovarotene Proposed Oral Dosing Regimen

Chronic Regimen

5 mg once-daily

Chronic dosing stopped during flare-up regimen

Flare-up Regimen (12 Weeks)

20 mg once-daily (4 weeks)

followed by

10 mg once-daily (8 weeks)

4-week extensions if symptoms persist

Palovarotene to be administered with food (swallowed whole or sprinkled on food)
Weight-adjusted dosing

Palovarotene: Positive Benefit-Risk Profile in Target Population

Unmet Need

- Ultra-rare, genetic condition
- Causes severe deformity and disability starting in early childhood
- Associated with complete immobilization and early mortality
- No approved treatment options for FOP

Efficacy

- Palovarotene-treated patients achieved 54% reduction in mean annualized new HO
- Modifies underlying cause of disease progression and disability in patients with FOP

Safety

- Well-characterized safety profile
- Proposed risk management activities will inform and guide patients and physicians on the safe use of palovarotene

Target population: females ≥ 8 and males ≥ 10 years of age

Agenda

Unmet Need	**Matthew Brown, MBBS, MD, FRACP, FAA** Professor of Medicine, King's College London Chief Scientific Officer, Genomics England
Efficacy	**Rose Marino, MD** Vice President, Clinical Development Rare Disease Ipsen
Safety and Risk Management Activities	**Jennifer Schranz, MD** Senior Vice President, Global Head of Rare Disease Ipsen
Clinical Perspective	**Edward Hsiao, MD, PhD** Professor of Medicine, Division of Endocrinology and Metabolism University of California, San Francisco
Moderator for Q&A	**Drew Sansone, MS** Vice President, Regulatory and Quality, North America Ipsen

Additional Experts

Andrew Strahs, PhD
Head of Global Biometry, R&D - Clinical Development Operations
Ipsen

Julien Ogier, PhD
Vice President, Clinical Pharmacology - Pharmacometrics
Ipsen

Unmet Medical Need in FOP

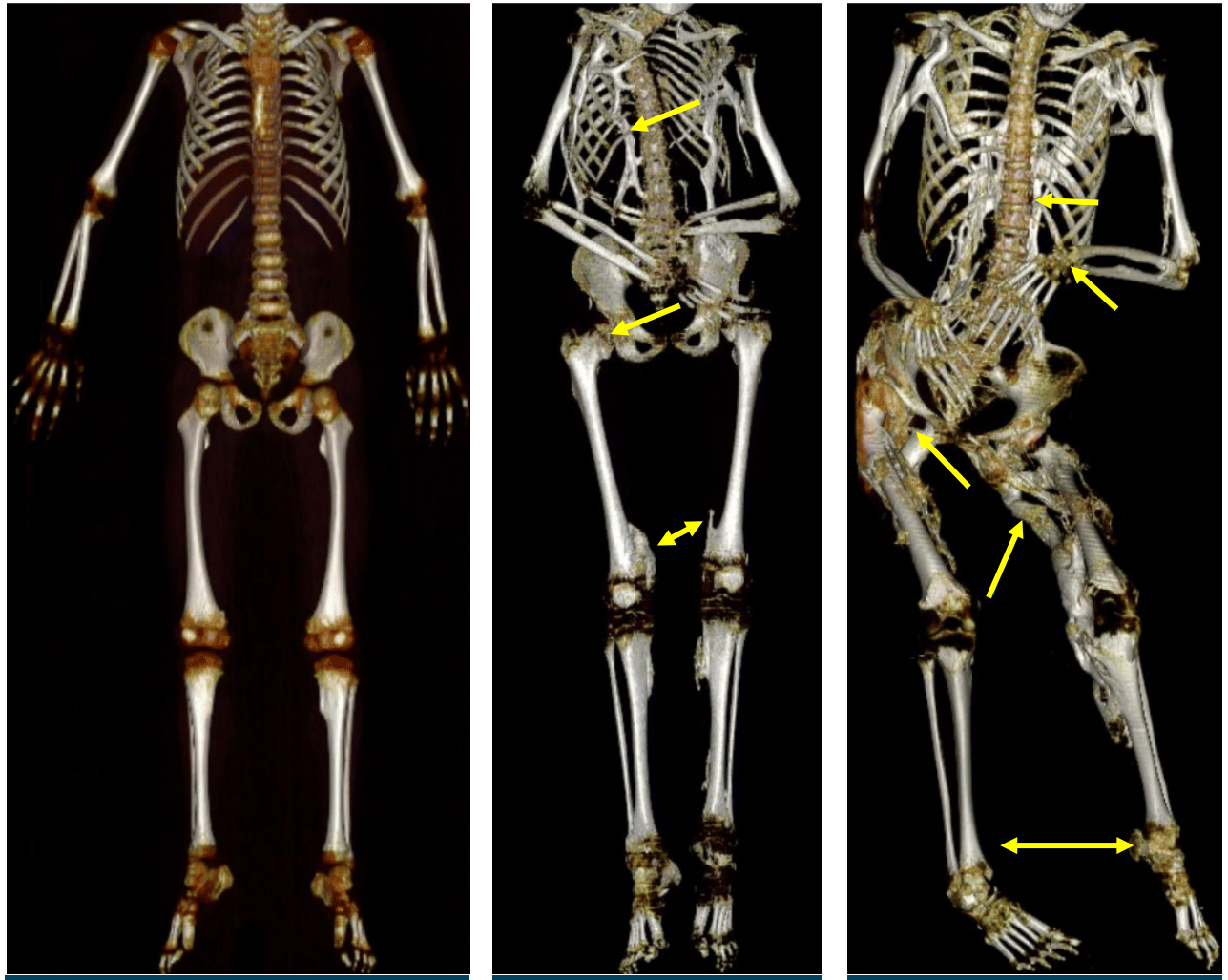
Matthew Brown, MBBS, MD, FRACP, FAA

Professor of Medicine, King's College London

Chief Scientific Officer, Genomics England

FOP is a Genetic Condition that Affects Injury Response and Repair Mechanisms

- FOP disrupts normal muscle repair and regeneration
- Patients form heterotopic ossification or extra-skeletal bone in muscles and soft tissue
- FOP is ultra-rare disease
  - ~1 / 1.14 million[1]
  - < 400 patients in US



4 yrs old
No measurable HO

10 yrs old
HO=188,690 mm^3

31 yrs old
HO=1,515,484 mm^3

Images from Pignolo, 2019

1. Pignolo, 2021

Flare-Ups are Common in FOP; Patients Experience Approximately 2 Flare-Ups Per Year

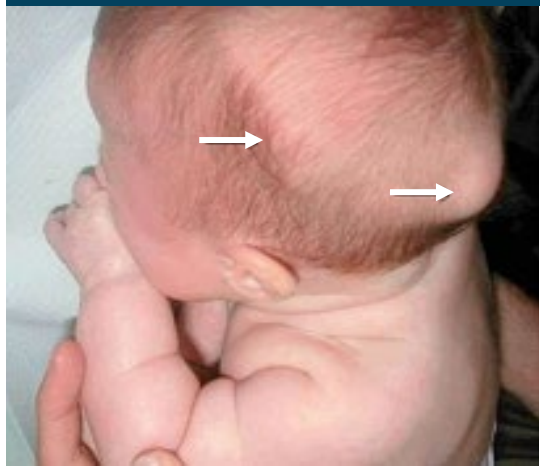
- Characterized by pain, swelling, and signs of inflammation
- Usually occur in response to blunt muscle trauma, surgery, or viral illness
- ~50% occur spontaneously, without any known cause
- No predictors of patients at higher risk of developing new HO as result of injury or event or due to spontaneous flare-up

Pignolo, 2016

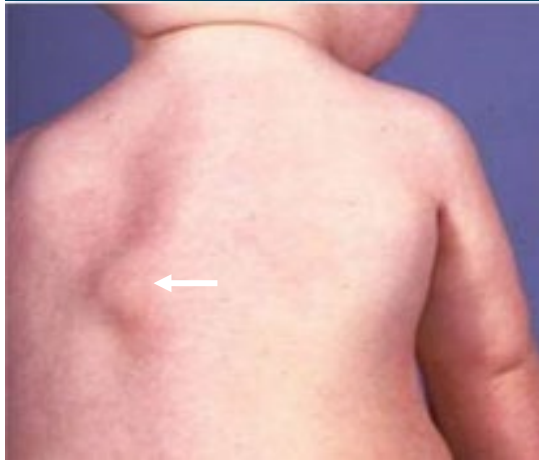
Heterotopic Ossification Accumulates Throughout Body Over Time

- Forms as segments, sheets, or ribbons of extra bone[1]
- Restricts patient's ability to function[1,2]
- HO formation results in significant and irreversible morbidity[1,2]

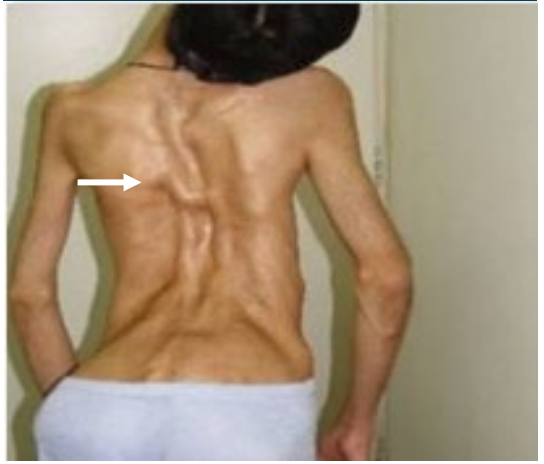
Nodule on scalp



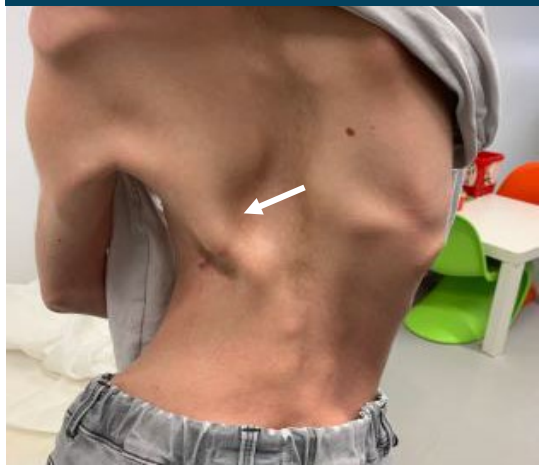
Nodule on back



Ribbons

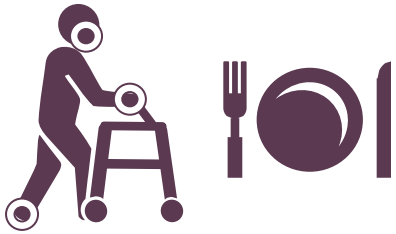


Deformity



1. Kaplan, 2022; 2. Hsiao, 2019; Images (1-3) from Kitterman, 2012, Image (4) Provided by Dr. Genevieve Baujat

Five Stages of FOP Highlight Clinical Burden and Disease Progression



1 Early / Mild

- HO formation in neck, back, and upper limbs
- No or minimal assistance

2 Moderate

- + Chest and lower limbs
- Limited chest expansion
- Some assistance
- Ability to walk, may use wheelchair

3 Late / Severe

- + Jaw
- No chest expansion; rigid chest wall
- Assistance needed for most activities
- Require assistive device / wheelchair to walk
- **Median 13 assistive devices required by 15 years old[1]**

4 Profound

- + Wrists and ankles
- Most joints ankylosed
- Symptomatic TIS* (pulmonary hypertension, heart failure)
- Dependent for all activities of daily living
- **Wheelchair bound ~25 years old**

5 End-Stage

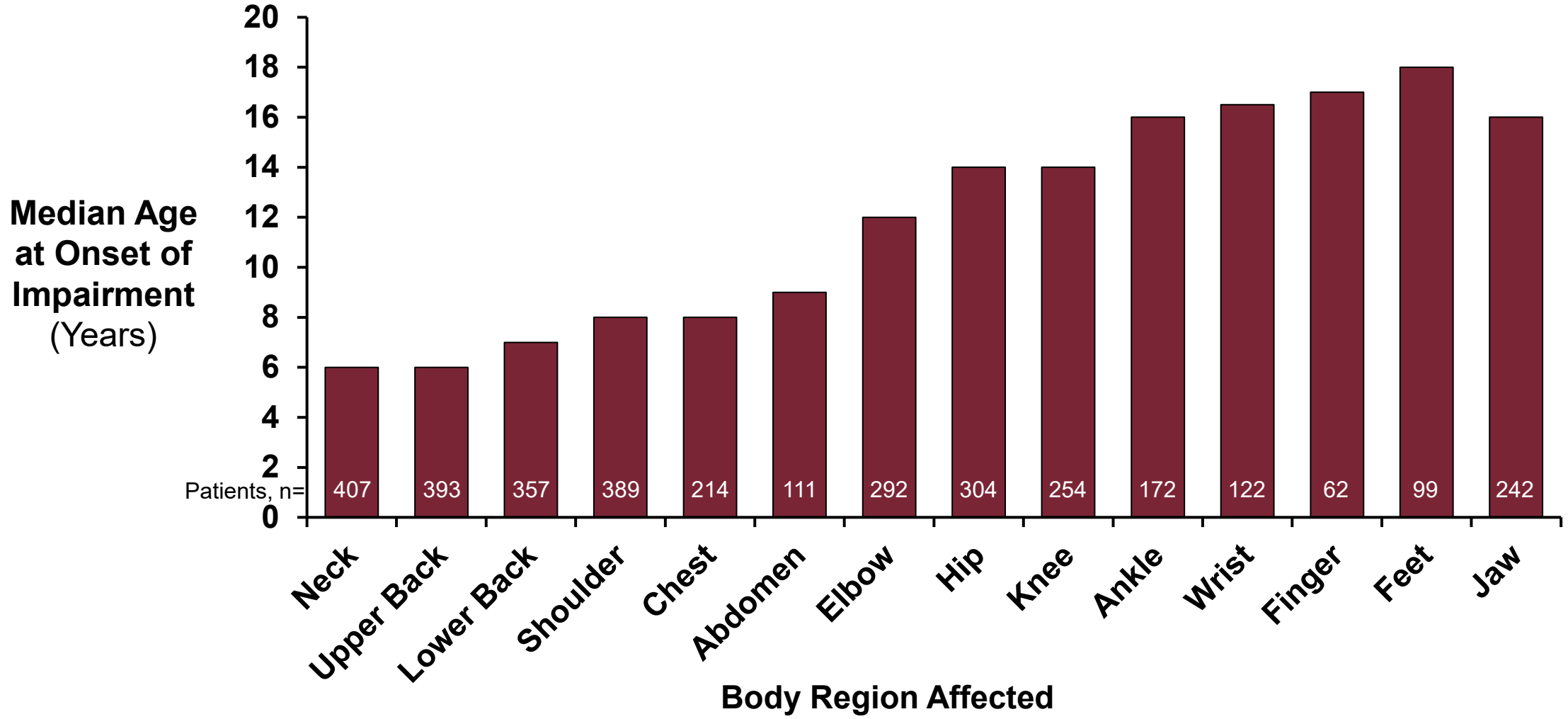
- All joints
- Symptomatic TIS*
- Dependent for all activities of daily living
- Mostly bed-bound
- Recurrent respiratory infections including pneumonia
- **Life expectancy ~56 years old**

Pignolo and Kaplan, 2018

*TIS = thoracic insufficiency syndrome

1. Pignolo, 2020

Onset of Physical Impairment Begins in Childhood; Linked to Affected Body Regions



N=500; Pignolo, 2016

No FDA Approved Treatments for FOP

- Surgery not recommended, precipitates new HO formation
- High-dose corticosteroids used for flare-ups in limited locations[1]
  - Known risks of long-term chronic administration
  - No data that corticosteroids reduce HO or mitigate disease progression
- Multidisciplinary management is often our best chance of slowing progressive decline

1. Kaplan, 2022

Patients with FOP Need Treatments that Slow Formation of HO and Alter Trajectory of Disease

- No effective or FDA approved medical treatments for FOP
- Multiple clinical consequences of HO accumulation
- Patients will inevitably lose significant function and require full-time caregiver assistance to survive

Any Reduction in New HO is a Clinically Meaningful Outcome for Patients

Efficacy

Rose Marino, MD

Vice President, Clinical Development Rare Disease

Ipsen

Phase 2 Studies Inform Dose Selection in Study 301

- Patients assessed at time of flare-up demonstrated HO formation starts before clinical symptoms present
  - Supported utility of chronic daily treatment
- Multiple flare-up dosing regimens and durations evaluated
  - Higher flare-up dosage over longer duration maximally inhibits HO formation

Phase 2 studies informed chronic / flare-up treatment regimen is optimal approach to reduce HO formation

Natural History Study Guided Selection of Endpoints for Interventional Trial

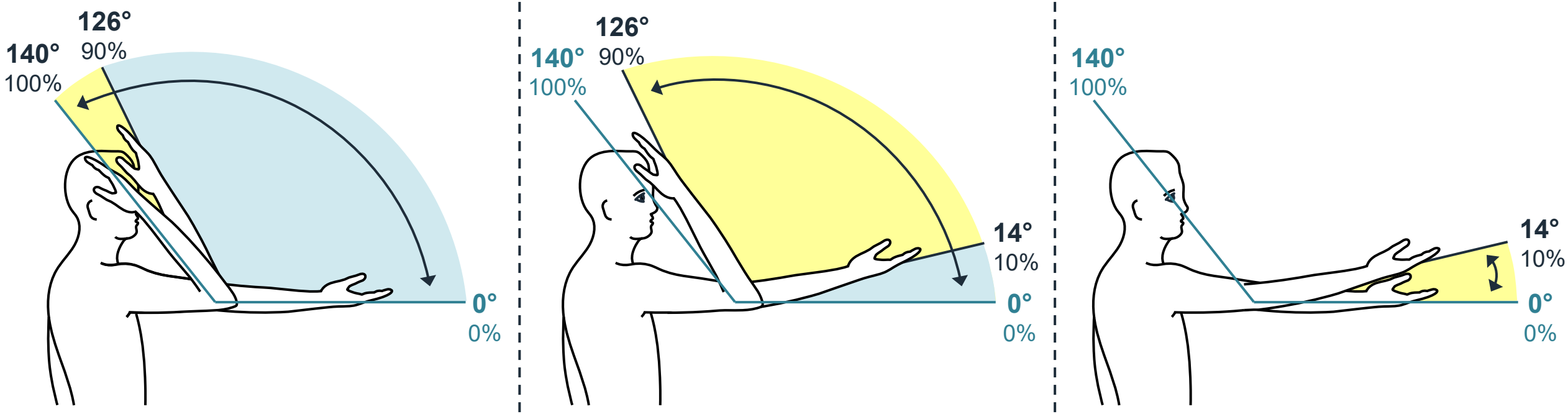
- 3-year study enrolled ~14% (N=114) of known patients with FOP globally
- Evaluated FOP disease progression and patient characteristics

Key learnings from NHS

1. Available functional endpoints not suitable to demonstrate disease progression over course of interventional trial
2. HO reduction is objective measure that can reliably demonstrate disease progression in FOP

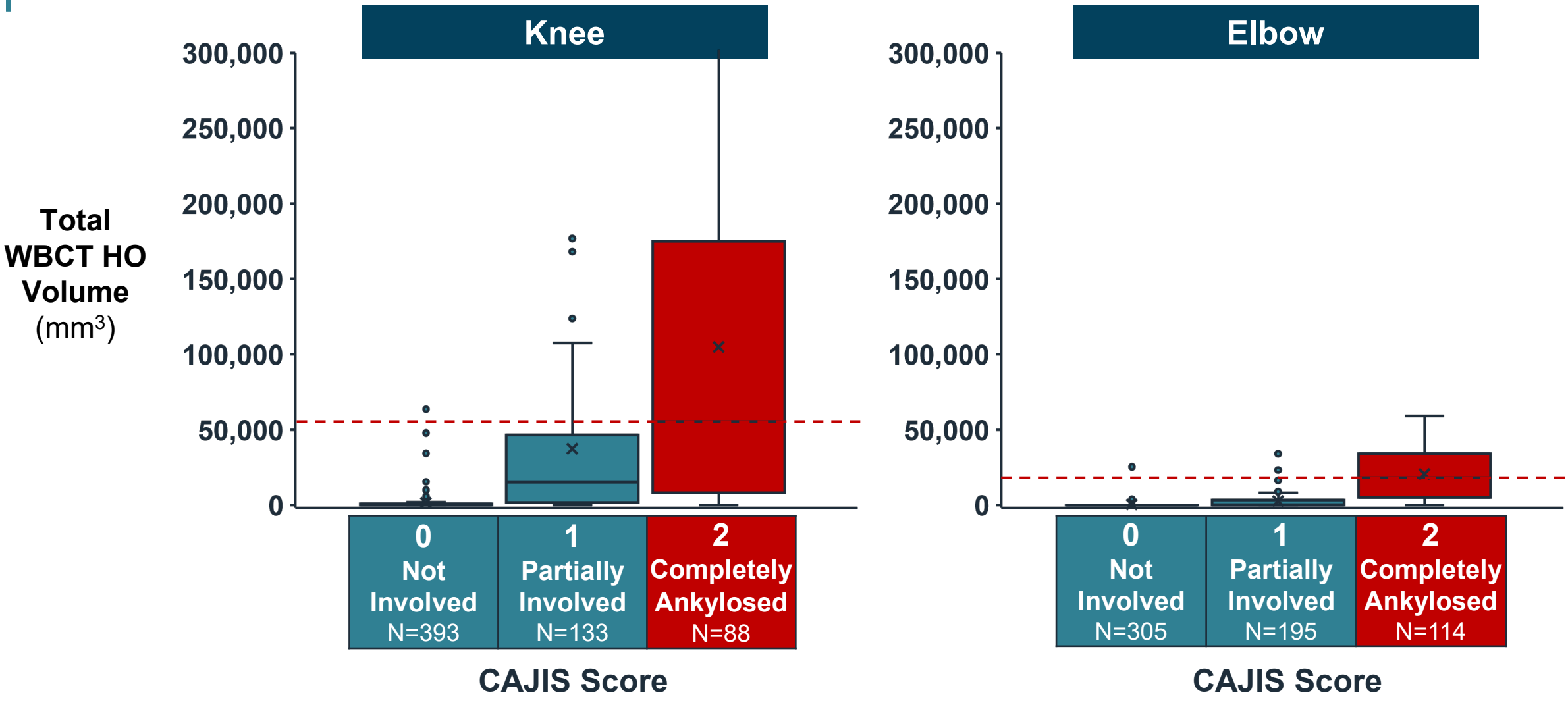
CAJIS Useful to Assess Disease Status Rather than Progression in a Clinical Trial

CAJIS = 0	CAJIS = 1	CAJIS = 2
Range of Motion = 90 - 100%	Range of Motion = 10 - 90%	Range of Motion = 0 - 10%



CAJIS = Cumulative Analogue Joint Involvement Scale

NHS Showed Higher HO Volume Associated with Worse Function Within Specific Body Regions



All Visits Combined; x = mean; - - - HO volume resulting in complete joint ankylosis, median (mm^3)

Historical Perspective (2016-2017): Phase 3 Clinical Trial Design Considerations

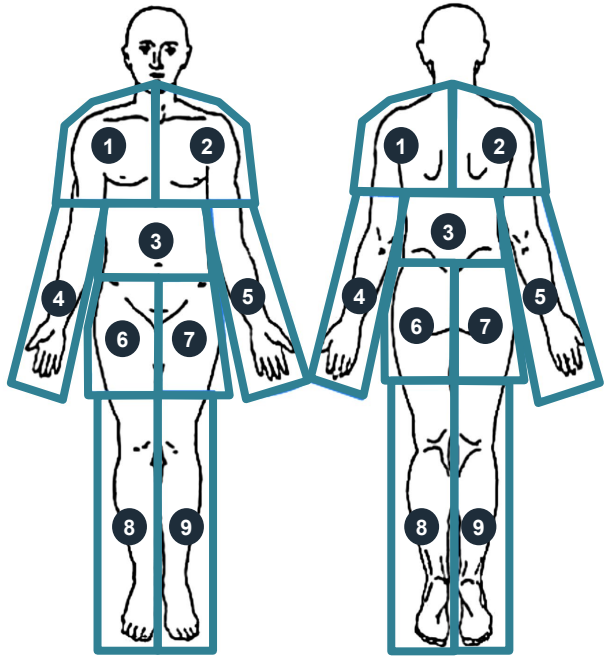
- Study 301 design informed by emerging information from NHS
  - Size, scope and duration of randomized controlled trial considered
  - NHS already ongoing and actively collecting data
  - Patient reported outcomes lack sensitivity to demonstrate meaningful change over short-term
  - HO is an objective endpoint which allowed for alternative trial designs to be considered

NHS selected as external control group for Study 301

Key Characteristics Support NHS as Control Group for Study 301

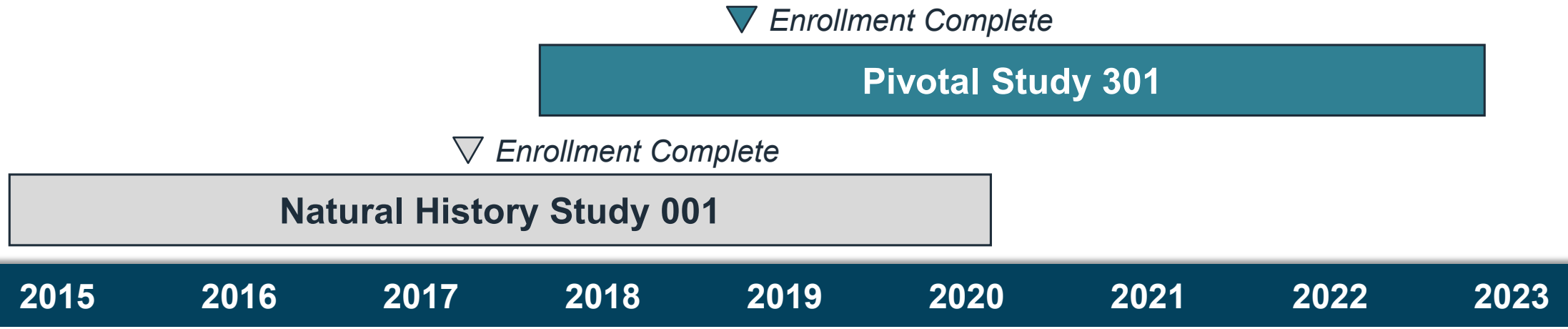
Blinded and Objective WBCT Read Process for HO

- All whole-body HO measurements performed by 2 independent radiologists with adjudication by 3rd reader
  - Blinded to study, treatment, and post-baseline timepoints
  - Followed detailed imaging charter to assess HO in each of 9 anatomical regions



1. Right shoulder, chest, upper back, neck
2. Left shoulder, chest, upper back, neck
3. Mid torso
4. Right arm
5. Left arm
6. Right hip
7. Left hip
8. Right lower leg
9. Left lower leg

NHS and Study 301 Were Conducted Concurrently and Same Clinical Sites Participated



- Enrollment of NHS complete before Study 301 began
- Standard of care and background therapy in FOP unchanged
  - Symptomatic treatment was permitted in both studies
  - Concomitant medications do not affect primary outcome

Study 301 and NHS: Baseline Demographics and Disease Characteristics

	Palovarotene N = 99	Untreated N = 111
Age, mean (SD)	**15.1** (10)	**17.5** (10)
< 8 / 10	20%	21%
≥ 8 / 10 - < 14	34%	19%
≥ 14	46%	60%
Male	**54%**	**54%**
Total WBCT HO Volume, mean	**269,461**	**308,252**
Total regions with HO, mean	**6.2**	**6.4**
CAJIS total score, mean	**10.0**	**11.8**
FOP-PFQ worst score over time, mean	**44.3**	**47.0**

- Sensitivity analyses show differences in baseline characteristics do not impact efficacy

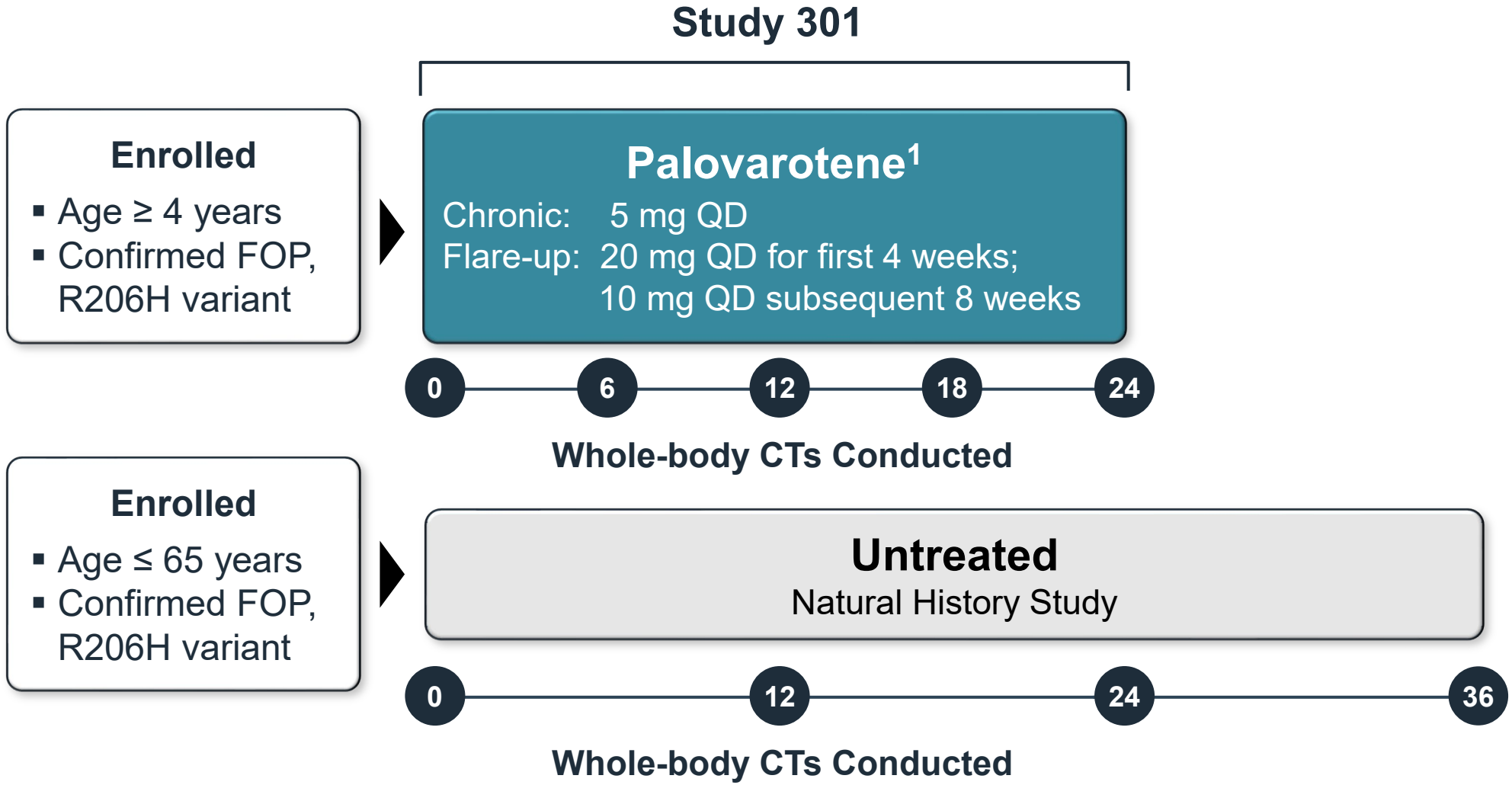
Principal safety population
CAJIS = Cumulative Analogue Joint Involvement Scale; FOP-PFQ = FOP-Physical Function Questionnaire

Natural History Study is Valid Comparator for Pivotal Study 301

- Primary outcome of annualized new HO volume
  - Objective measure
  - Assessed in a blinded fashion using the same read charter
  - Scans interspersed and read concurrently
- Studies ran concurrently
  - Same clinical sites participated
  - Standard of care and background therapy unchanged
- Similar enrollment populations
- Results adjusted for baseline potential prognostic factors

Study 301

Study 301: Phase 3 Open-Label Study in FOP Compared to Natural History Study (NHS)



1. Dosing was weight-adjusted in patients with < 90% skeletal maturity on hand/wrist radiography

Study 301: Primary Endpoint

- **Primary Endpoint:** annualized change in new HO volume
  - HO formation is key characteristic of FOP progression
  - Provides objective assessment of HO formation

Study 301: Additional Efficacy Endpoints

Secondary Endpoints

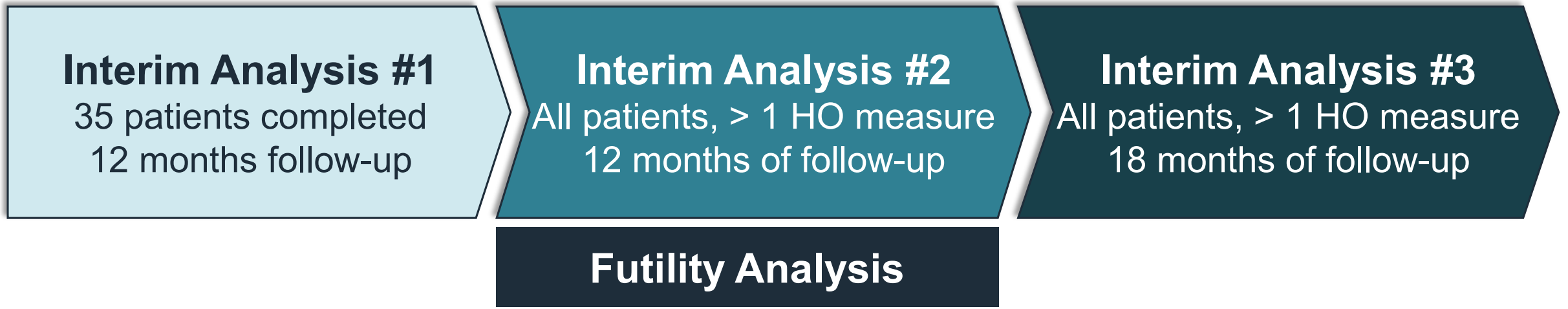
- Patients (%) with any new HO at Month 12
- Body regions with new HO at Month 12
- Patients (%) reporting flare-ups at Month 12
- Flare-up rate per patient-year exposure

Exploratory Endpoints

- Functional assessments
  - CAJIS
  - FOP-PFQ
  - PROMIS

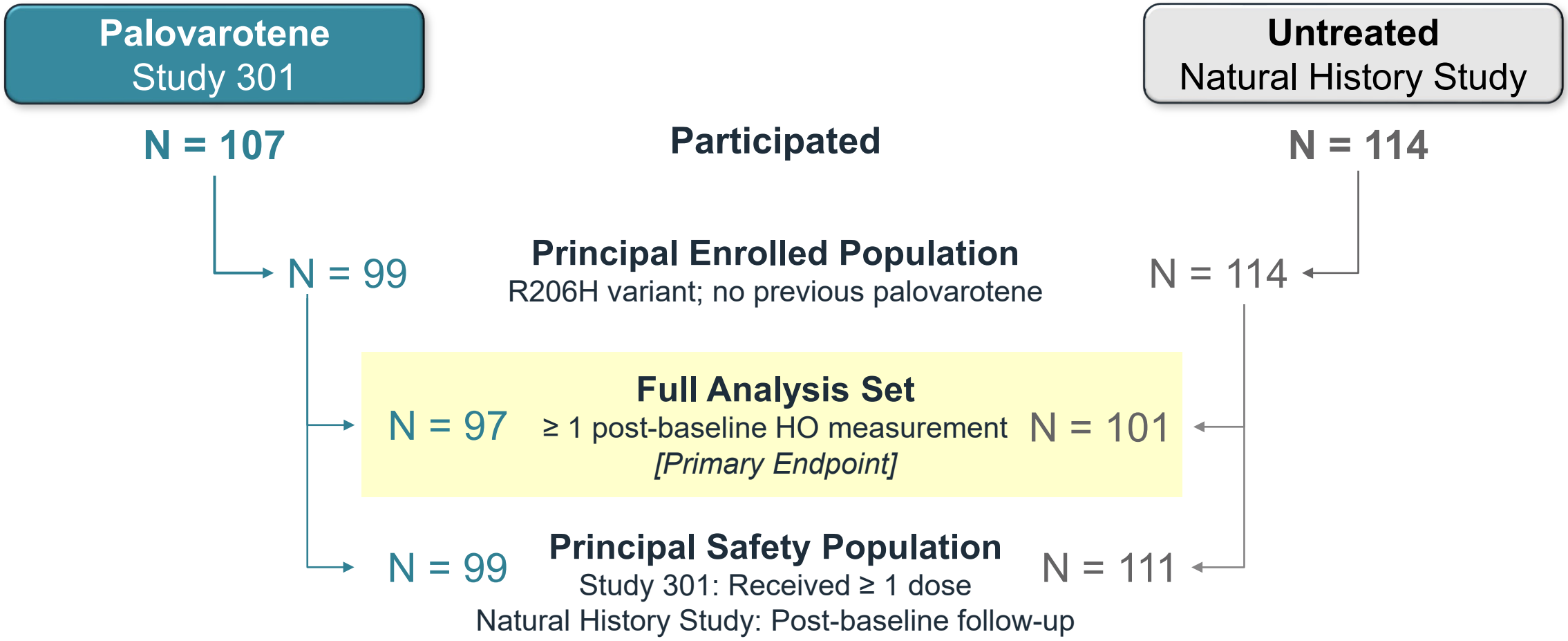
CAJIS = Cumulative Analogue Joint Involvement Scale
FOP-PFQ = FOP-Physical Function Questionnaire
PROMIS = Patient Reported Outcomes Measurement Information System

Study 301 (Pivotal Study): Three Interim Analyses (IA) Performed



- Primary endpoint assessed at all 3 IAs (annualized change in new HO)
  - **Bayesian compound Poisson model**
    Likelihood of HO growth event and volume of growth per event
  - **Included square-root transformation of HO volume**
    Requires new HO volumes be non-negative

Study 301 and NHS: Disposition



Study 301: Second Interim Analysis (IA2)

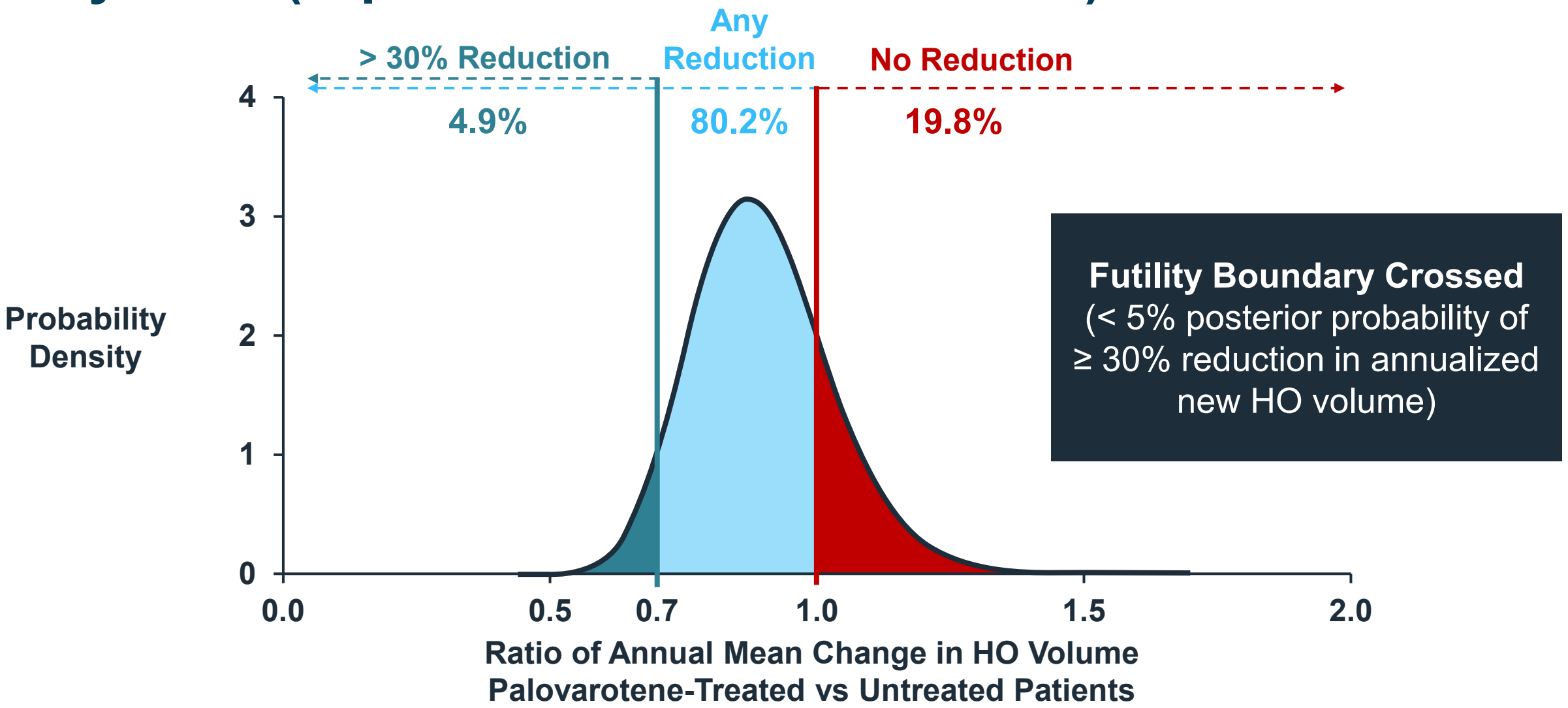
Interim Analysis #1
35 patients completed
12 months follow-up

Interim Analysis #2
All patients, > 1 HO measure
12 months of follow-up

Interim Analysis #3
All patients, > 1 HO measure
18 months of follow-up

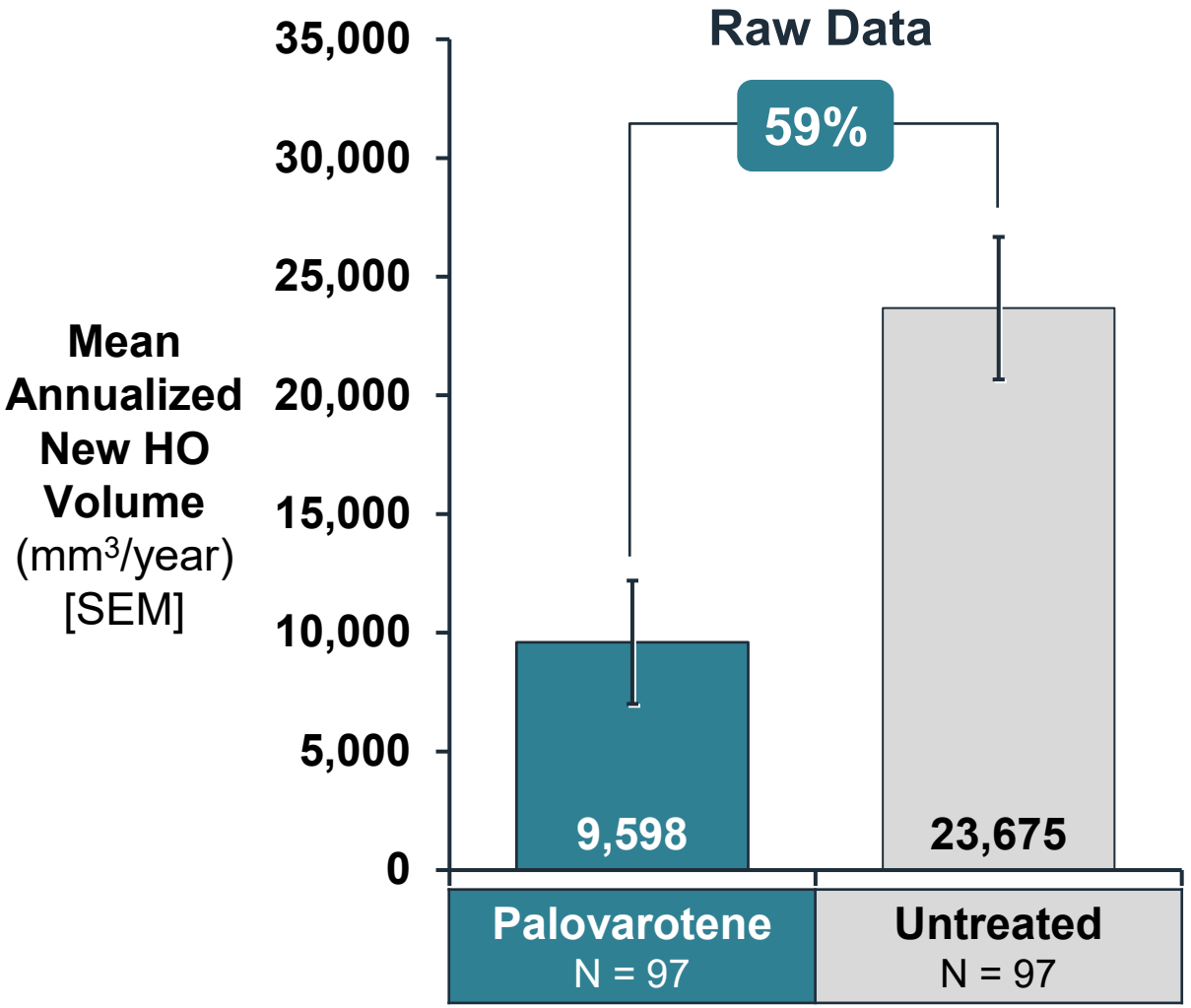
Futility Analysis

IA2 Primary: Annualized Change in New HO Using Bayesian (Square-Root Transformation)



Bayesian model (square-root transformation) in principal FAS population

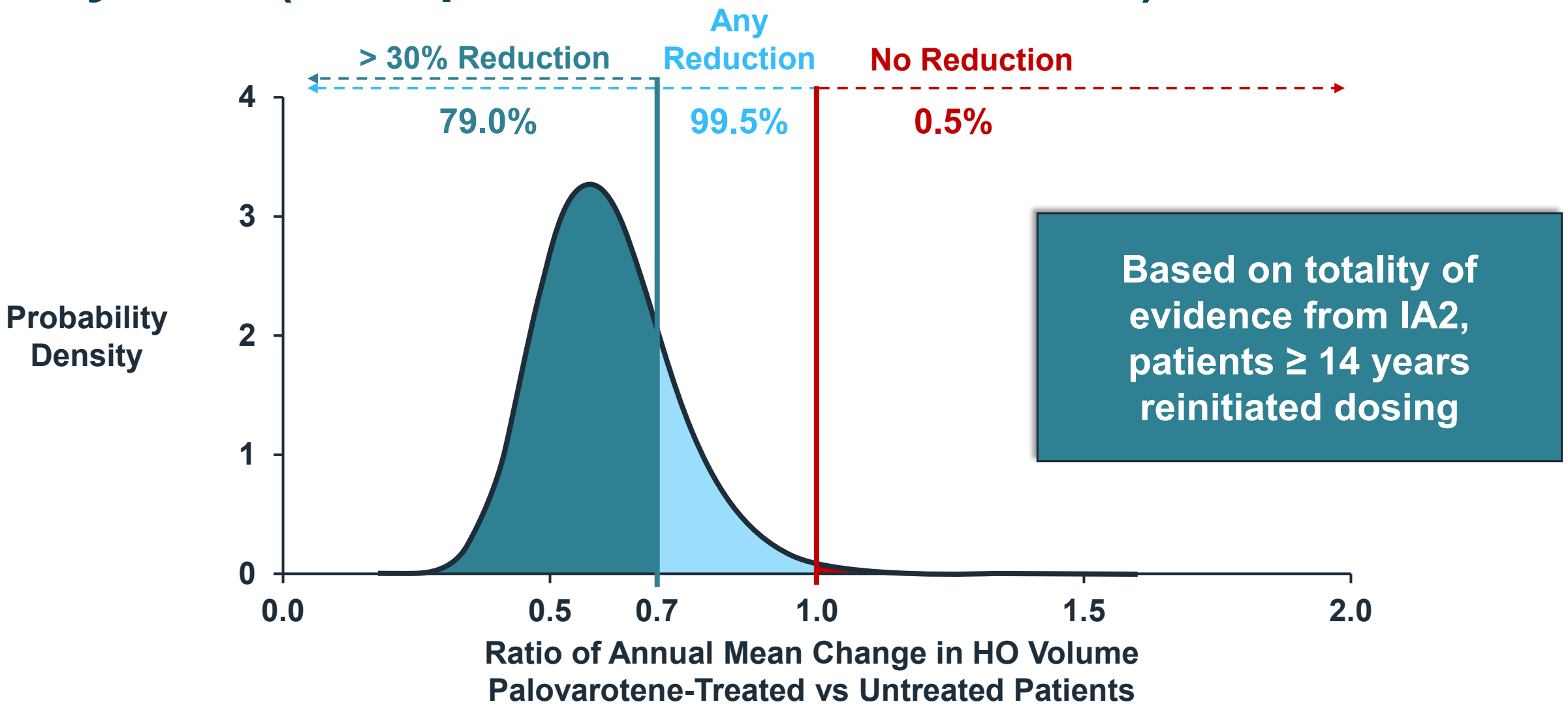
IA2: Comparison of Raw Data Showed Robust Treatment Effect



- Additional analyses showed robust treatment effect favoring palovarotene
  - Wilcoxon ranked-sum test
  - Weighted linear mixed effects model (wLME)

IA2 principal FAS population

IA2 Post-Hoc: Annualized Change in New HO Using Bayesian (No Square-Root Transformation)



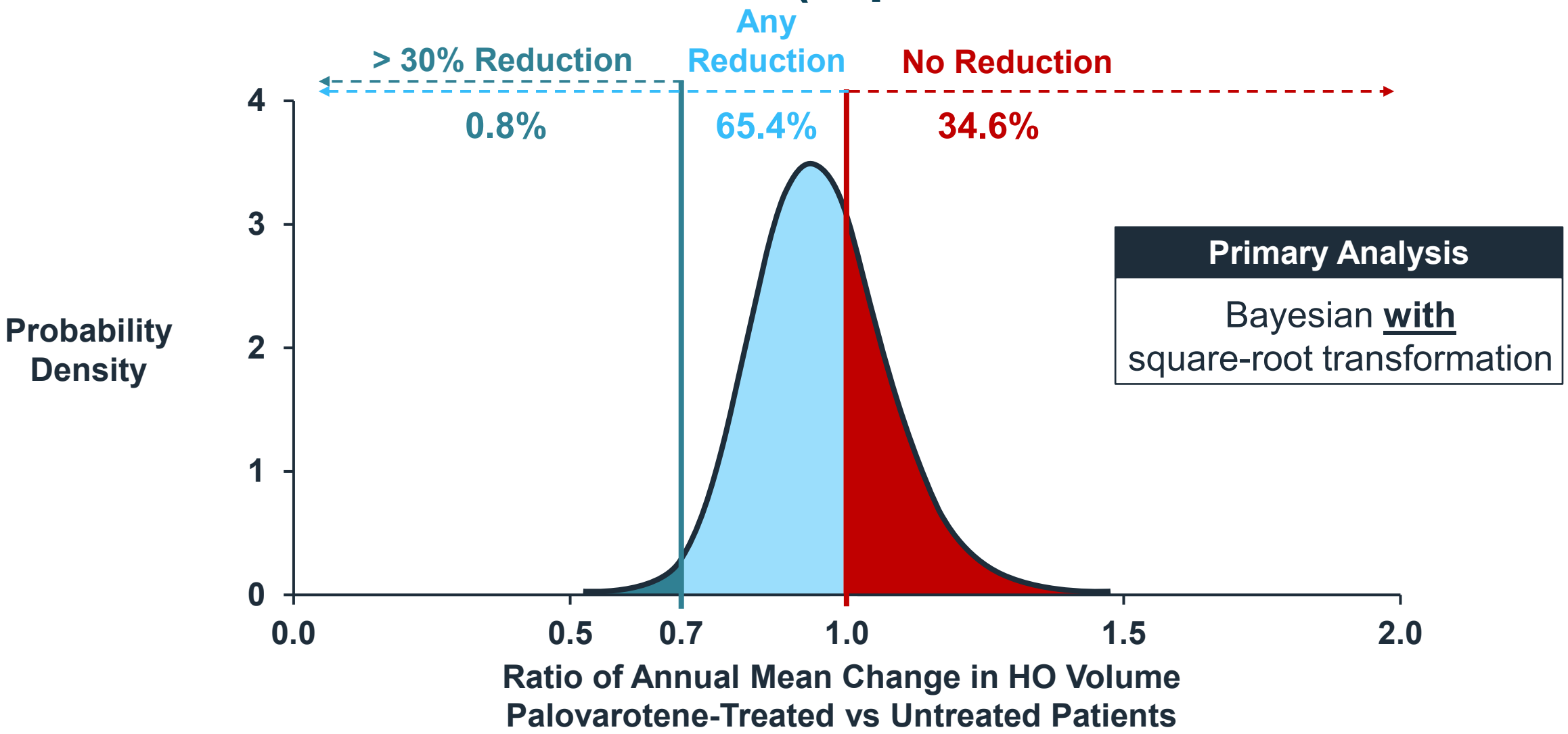
Bayesian model (no square-root transformation) in principal FAS population

Study 301: Third Interim Analysis (IA3)

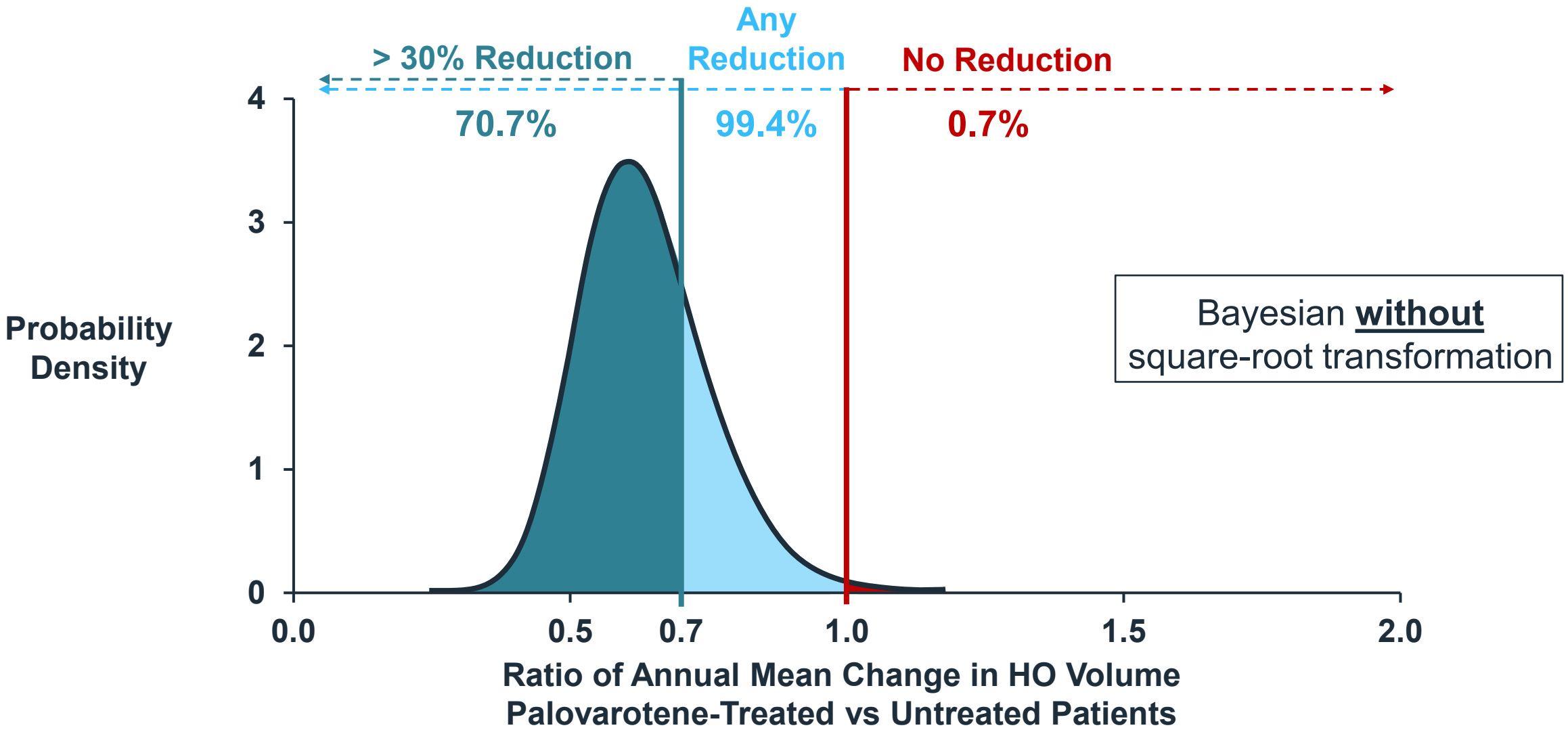
Interim Analysis #1	Interim Analysis #2	**Interim Analysis #3**
35 patients completed 12 months follow-up	All patients, > 1 HO measure 12 months of follow-up	**All patients, > 1 HO measure** **18 months of follow-up**

- Annualized change in new HO volume assessments
  - Bayesian model with square-root transformation of HO volume
  - wLME including all observed data without alteration
- Data censored due to dosing interruptions and partial clinical hold
  - December 2019: patients < 14 years stopped dosing
  - January 2020: patients ≥ 14 years dosing interrupted

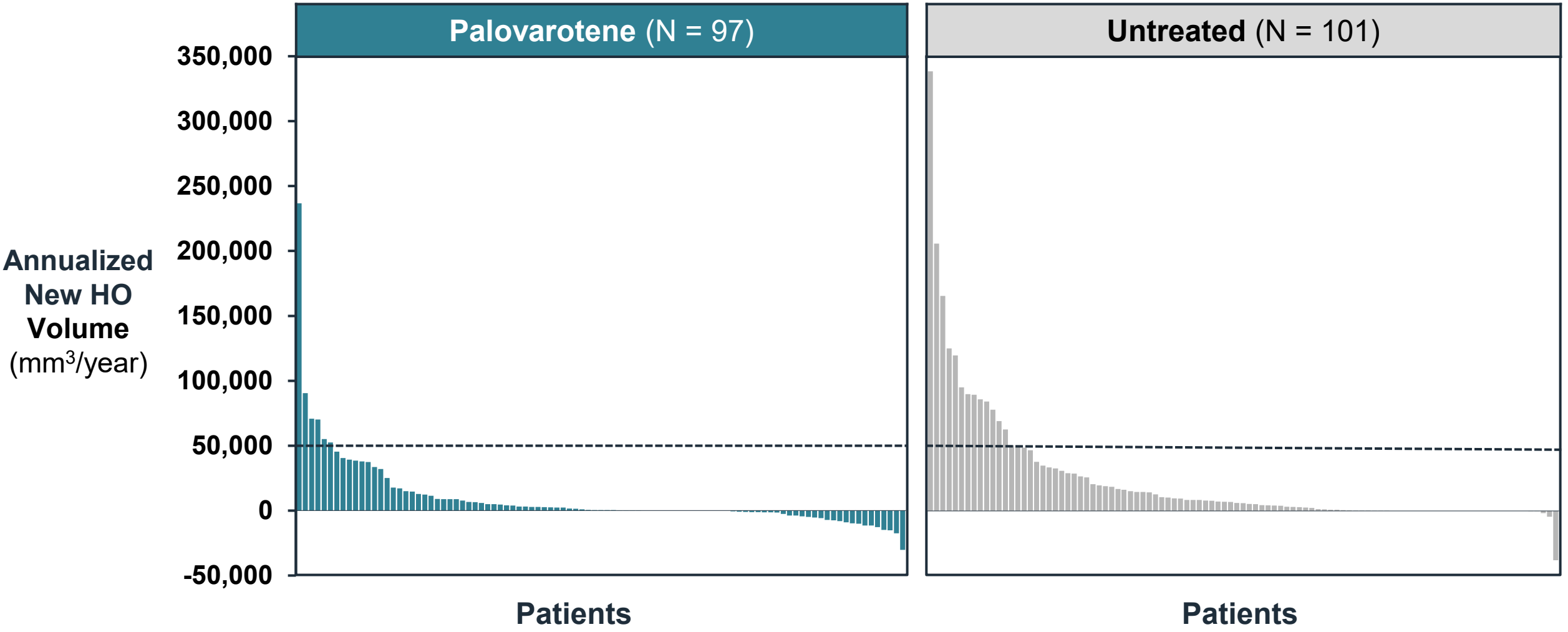
IA3: Annualized Change in New HO Using Bayesian was Consistent with IA2 Results (Square-Root Transformation)



IA3: 99.4% Probability that Palovarotene Reduces Annual Mean New HO using Bayesian (No Square-Root Transformation)

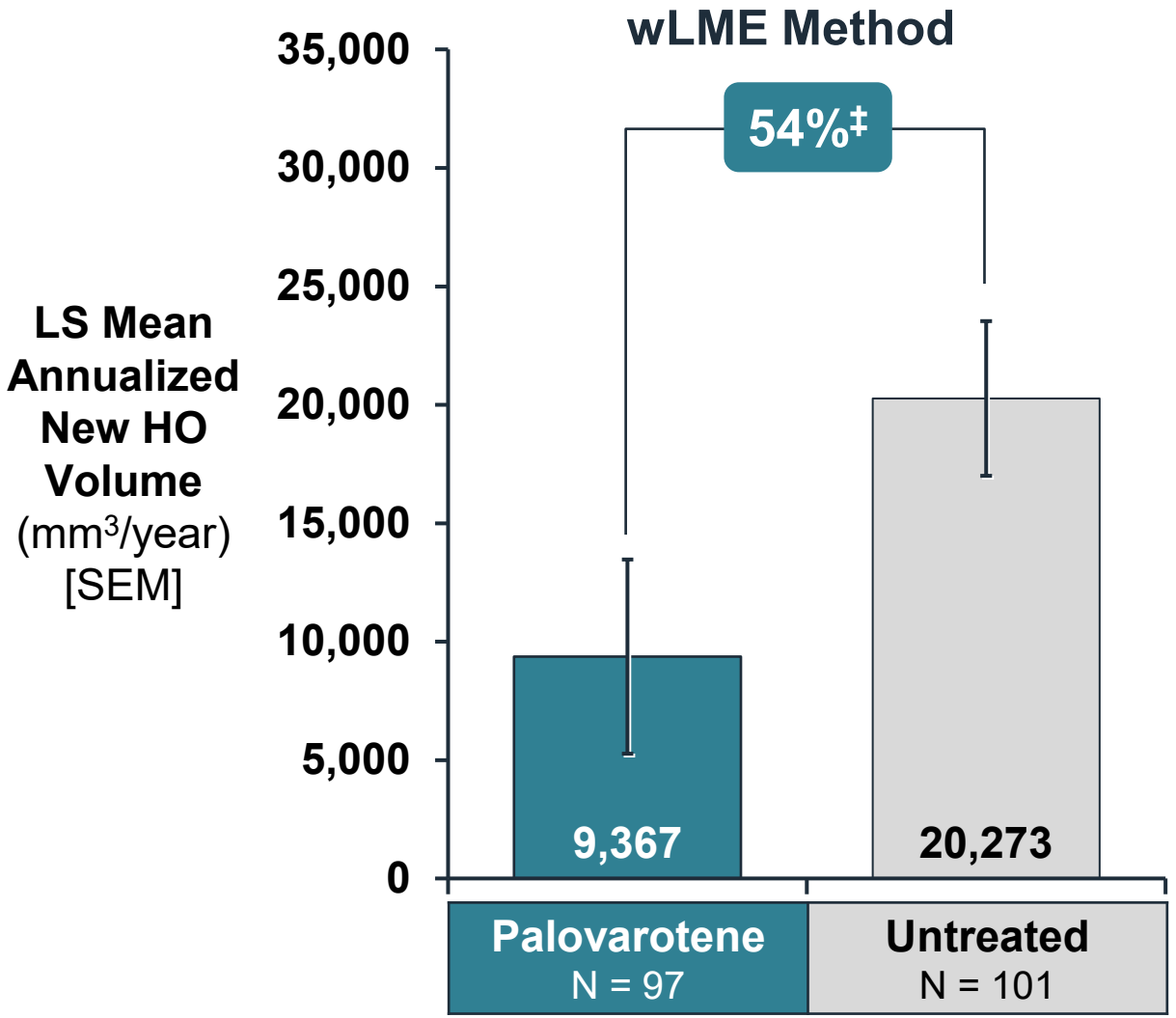


Patient Level Data Show Less Annualized New HO in Palovarotene-Treated Patients



Principal FAS population

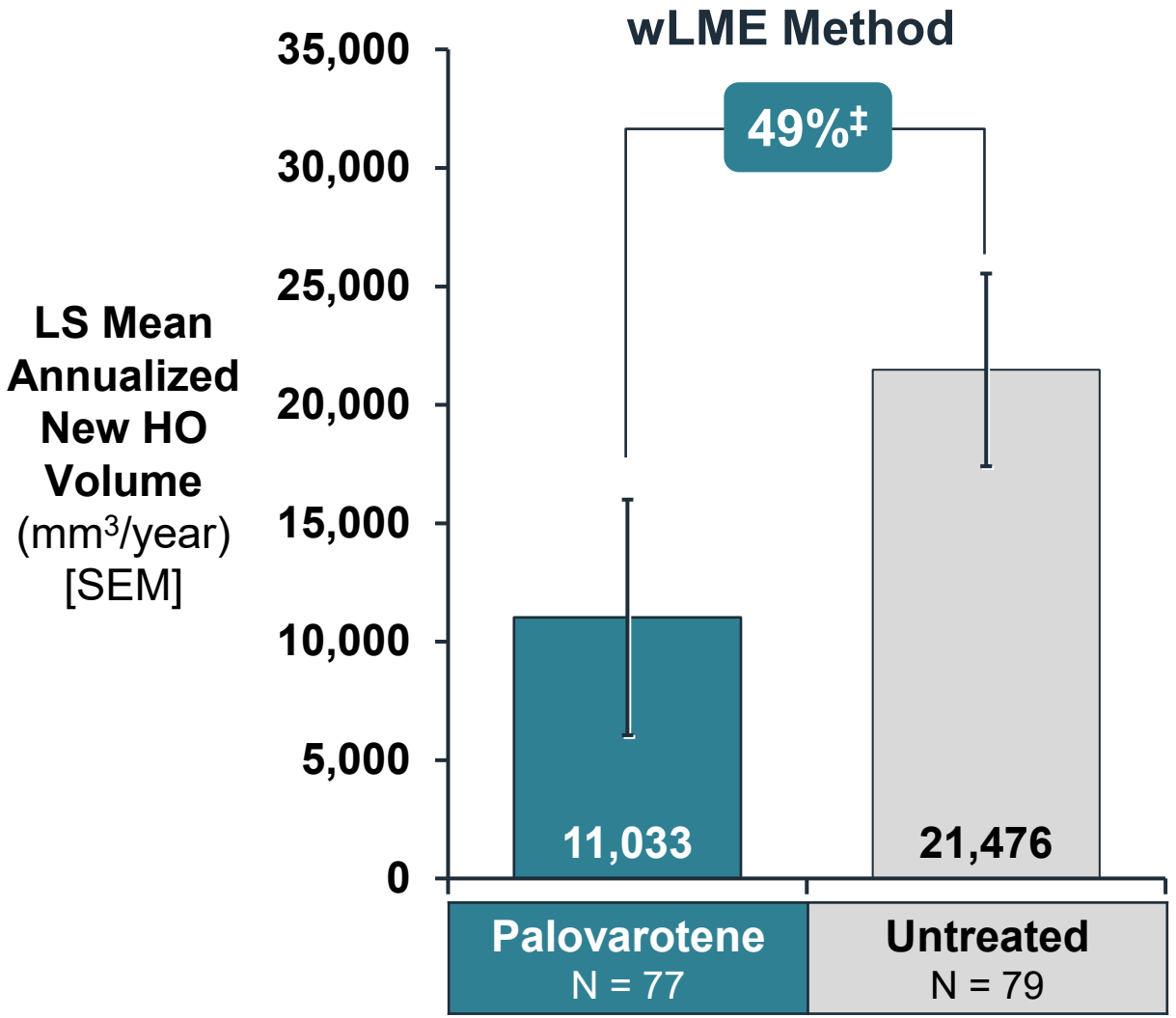
Overall Population: 54% Reduction in Annualized New HO with Palovarotene



‡ Nominal p-value = 0.0392

wLME model (no square-root transformation, all observed data without alteration); principal FAS population

Target Population: 49% Reduction in Annualized New HO with Palovarotene

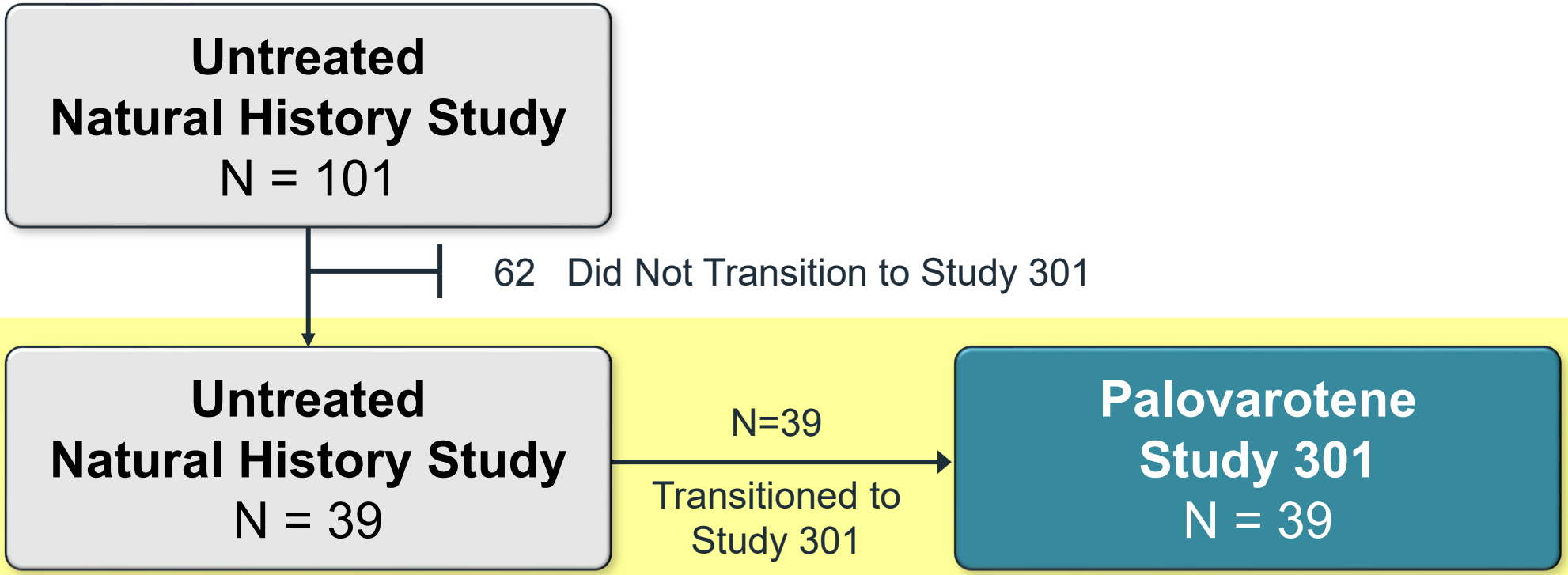


‡ Nominal p-value = 0.1124

wLME model (no square-root transformation, all observed data without alteration); principal FAS population

Sensitivity Analyses Support NHS as Valid Comparator for Study 301

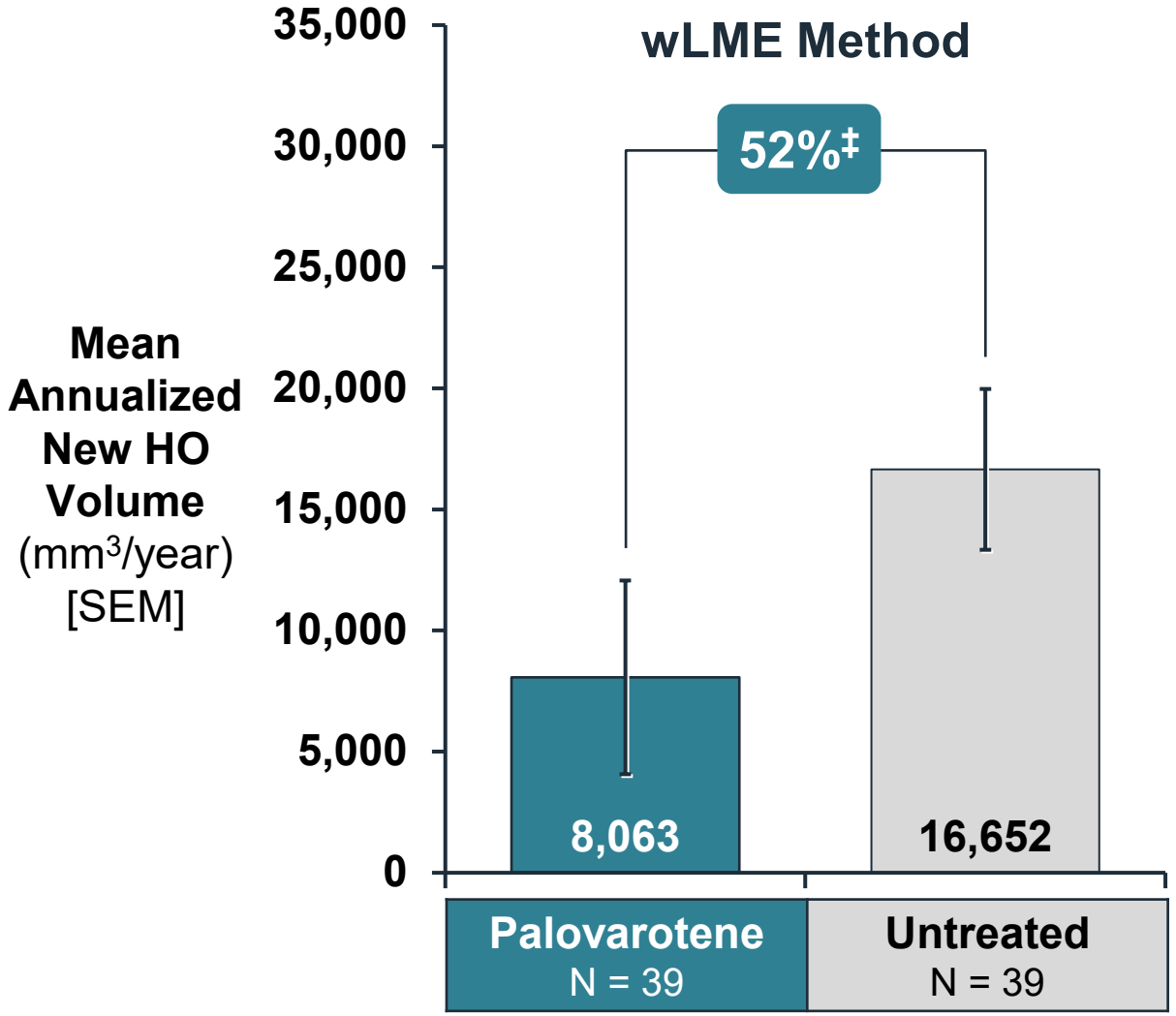
Transition Paired Analysis: 39 Patients Contribute Data to Both NHS and Study 301



- **Transition Paired Analysis**
  Assessment of patients who contributed post-baseline data to both studies

Principal FAS population

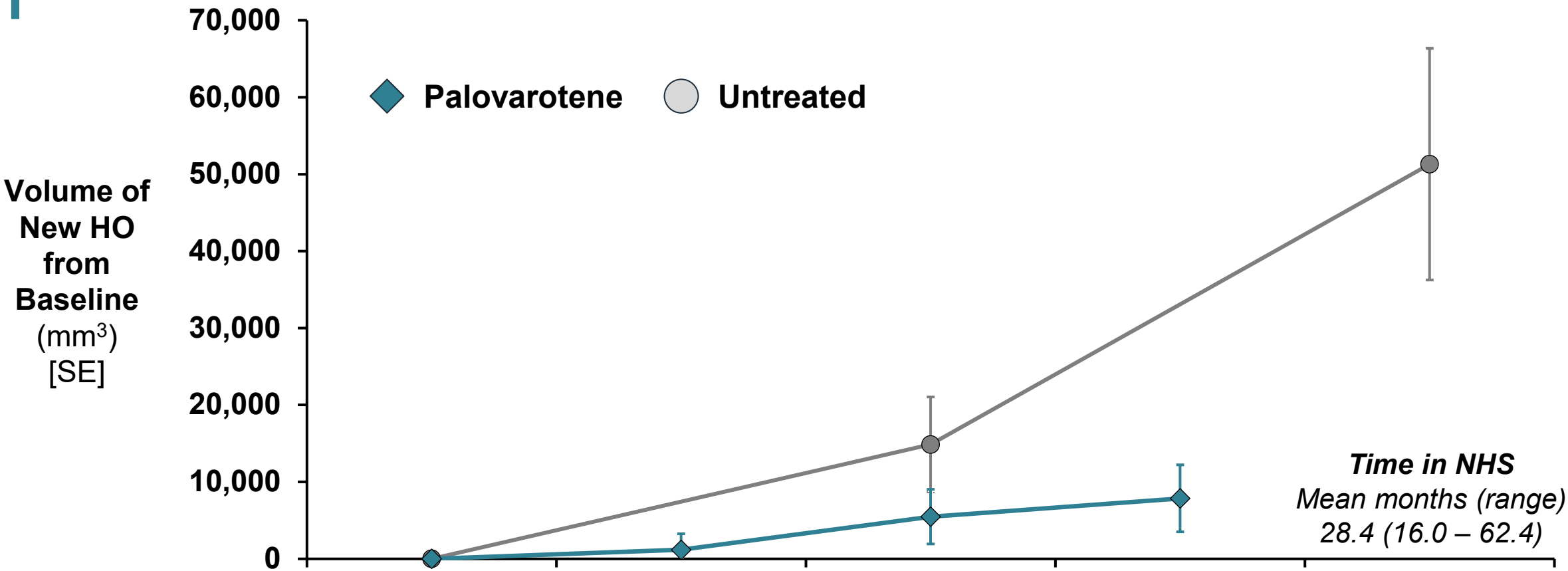
Transition Paired Analysis: Showed Consistent Efficacy with Overall Population



‡ Nominal p-value = 0.0634

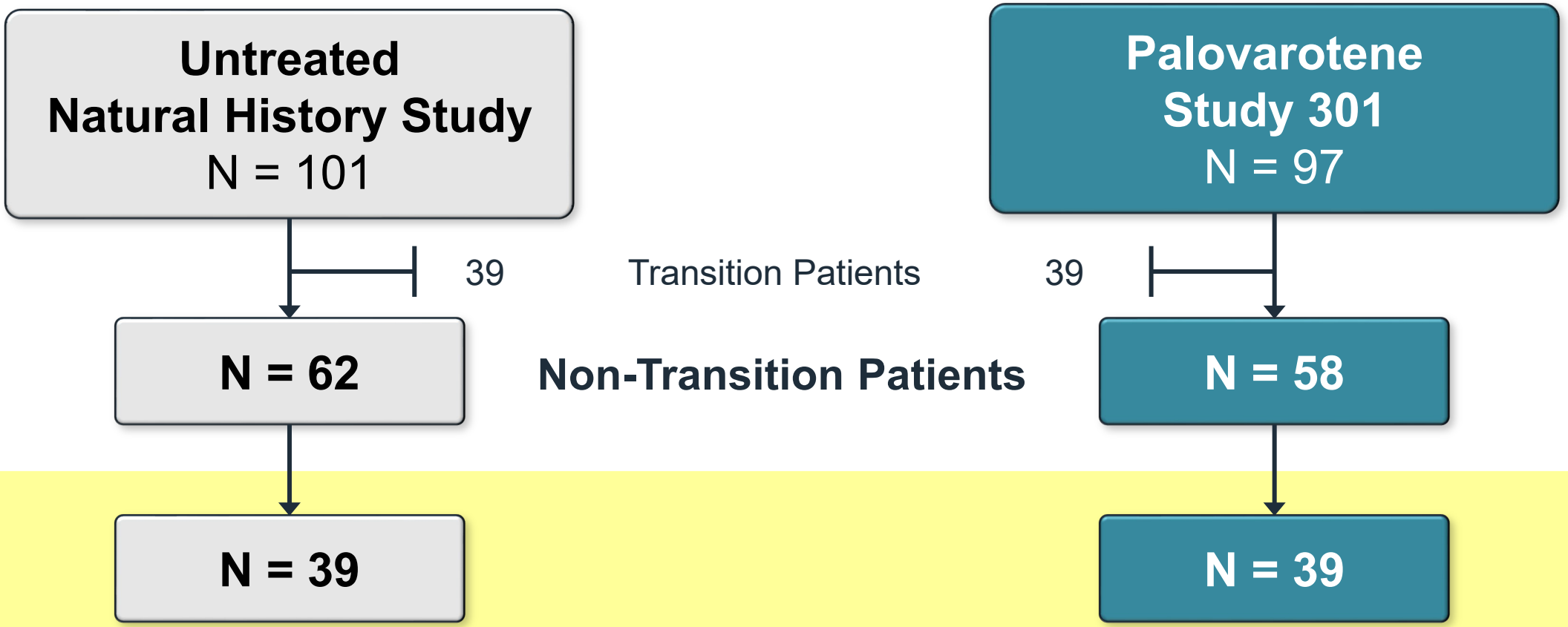
wLME model (no square-root transformation, all observed data without alteration) in principal FAS population

Transition Paired Analysis: Patients Accumulated Less New HO Over Time with Palovarotene



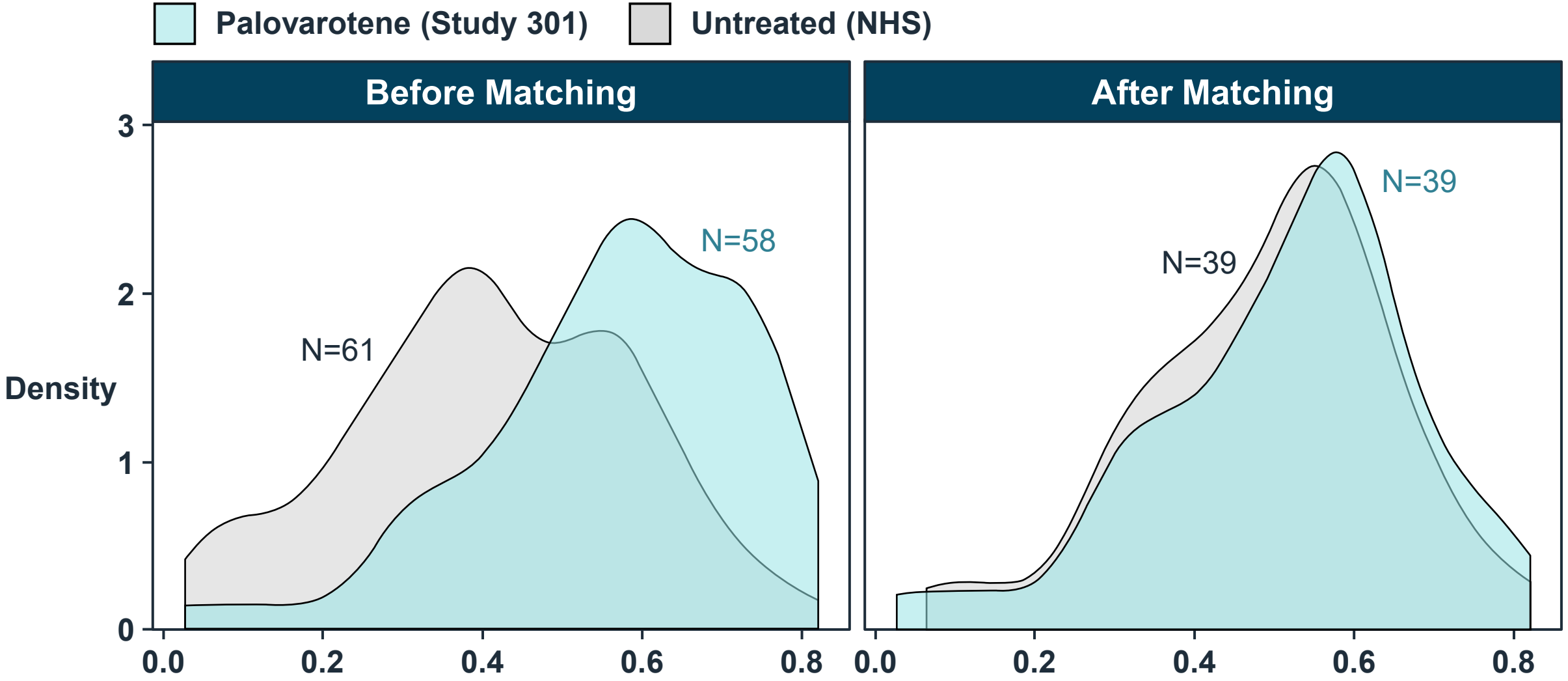
Patients (n)	Baseline	Month 6	Month 12	Month 18	Last NHS Visit / Study 301 Baseline
Untreated	39	*NA*	37	*NA*	39
Palovarotene	39	38	38	26	

Matched Pairs Analysis

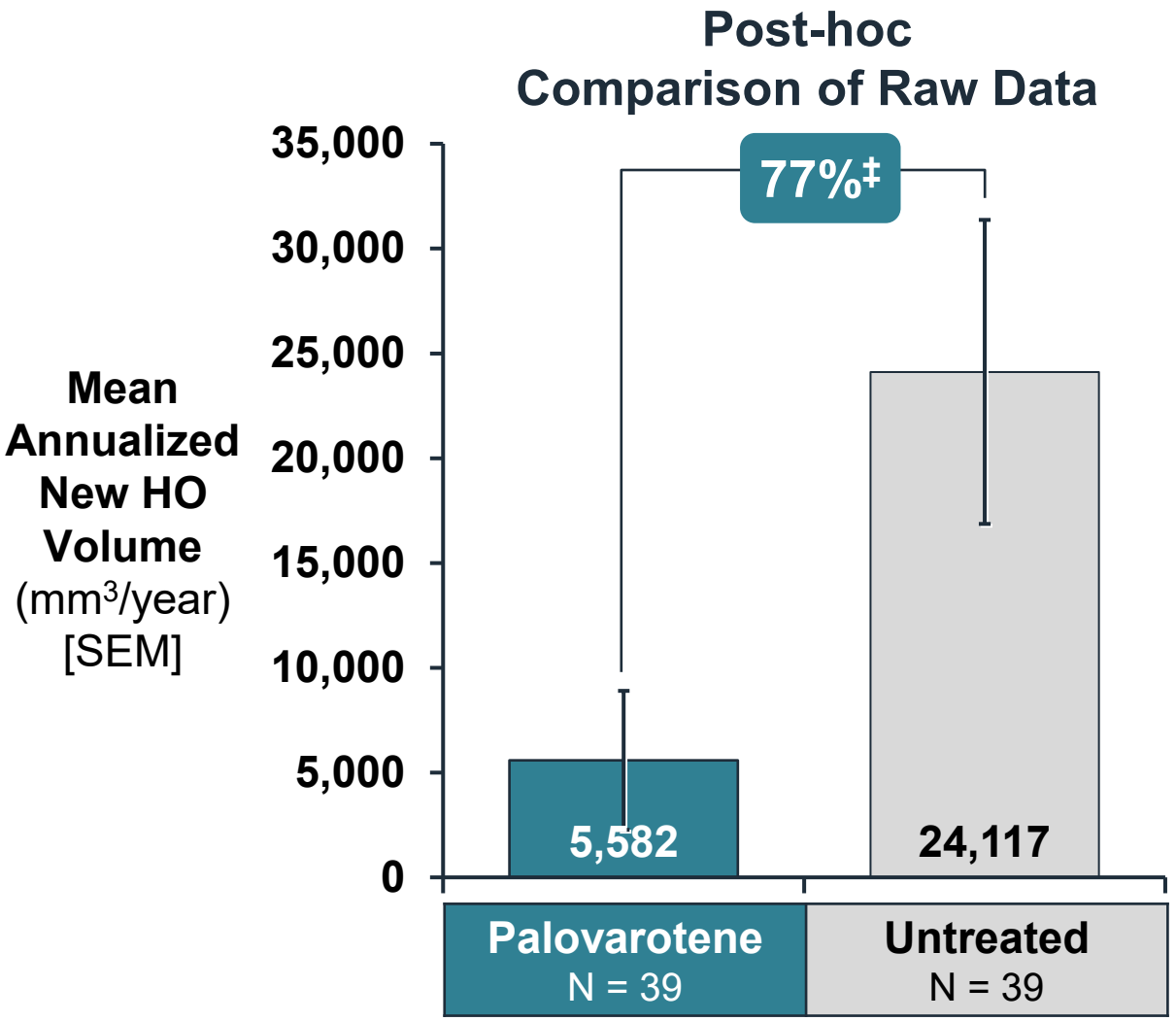


- **Matched Pairs Analysis**
  Based on distribution of propensity scores and caliper matching algorithm

Matched Pairs Analysis: Propensity Score Distribution Supports Comparability of Patients



Matched Pairs Analysis: 77% Reduction in New HO Volume in Study 301 Compared with NHS



‡Sample t-test p-value = < 0.05

Multiple Sensitivity Analyses Support NHS as Valid Comparator for Study 301

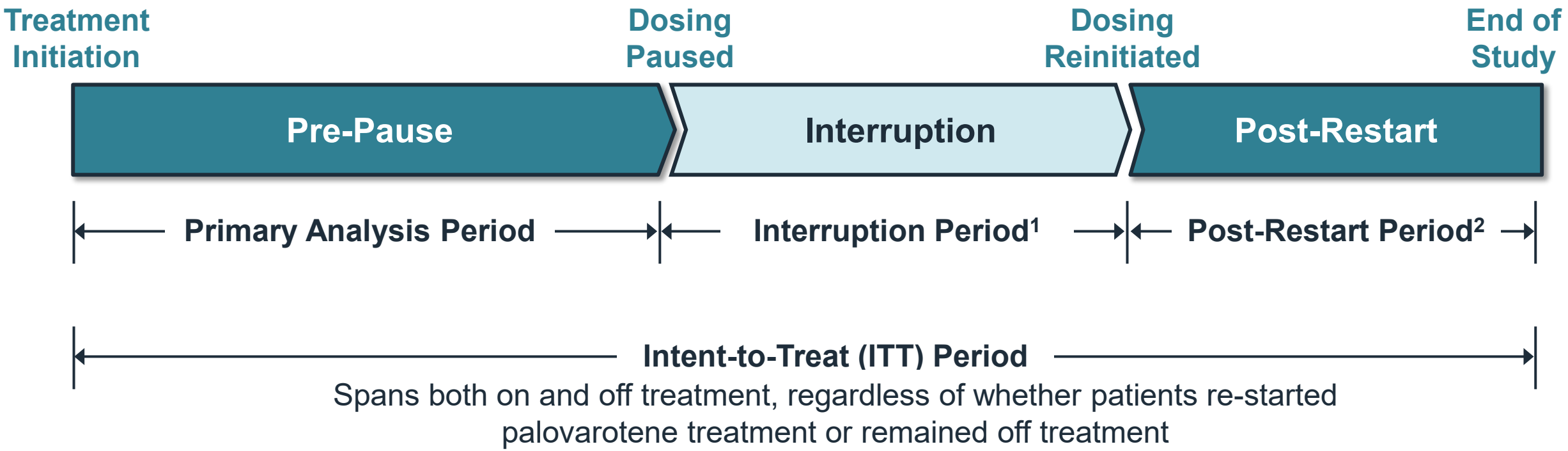
Sensitivity Analysis	Results	Nominal P-value
Primary Endpoint (wLME method)	**54% reduction**	**0.0392**
Transition Paired Analysis	**52% reduction**	**0.0634**
Matched Pairs Analysis	**77% reduction**	**< 0.05**
Analysis with Adjustment for Additional Covariates	**56% reduction**	**0.0314**
Propensity Score Analysis	**57% reduction**	**0.0264**
Propensity Weighted Analysis	**67% reduction**	**< 0.05**

Sensitivity analyses consistently demonstrate efficacy of palovarotene

Long-Term Results Support Efficacy of Palovarotene

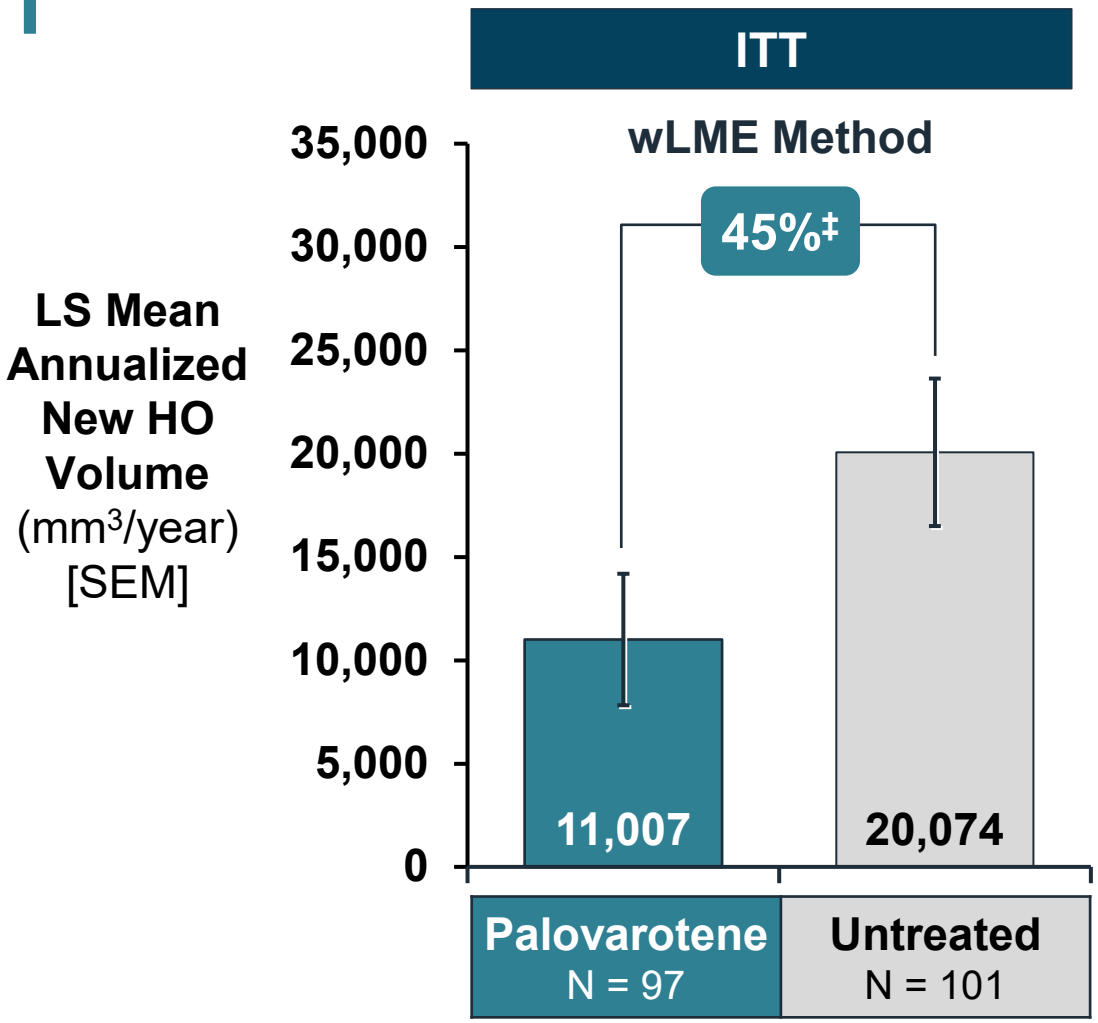
Data from Last-Patient-Last-Visit

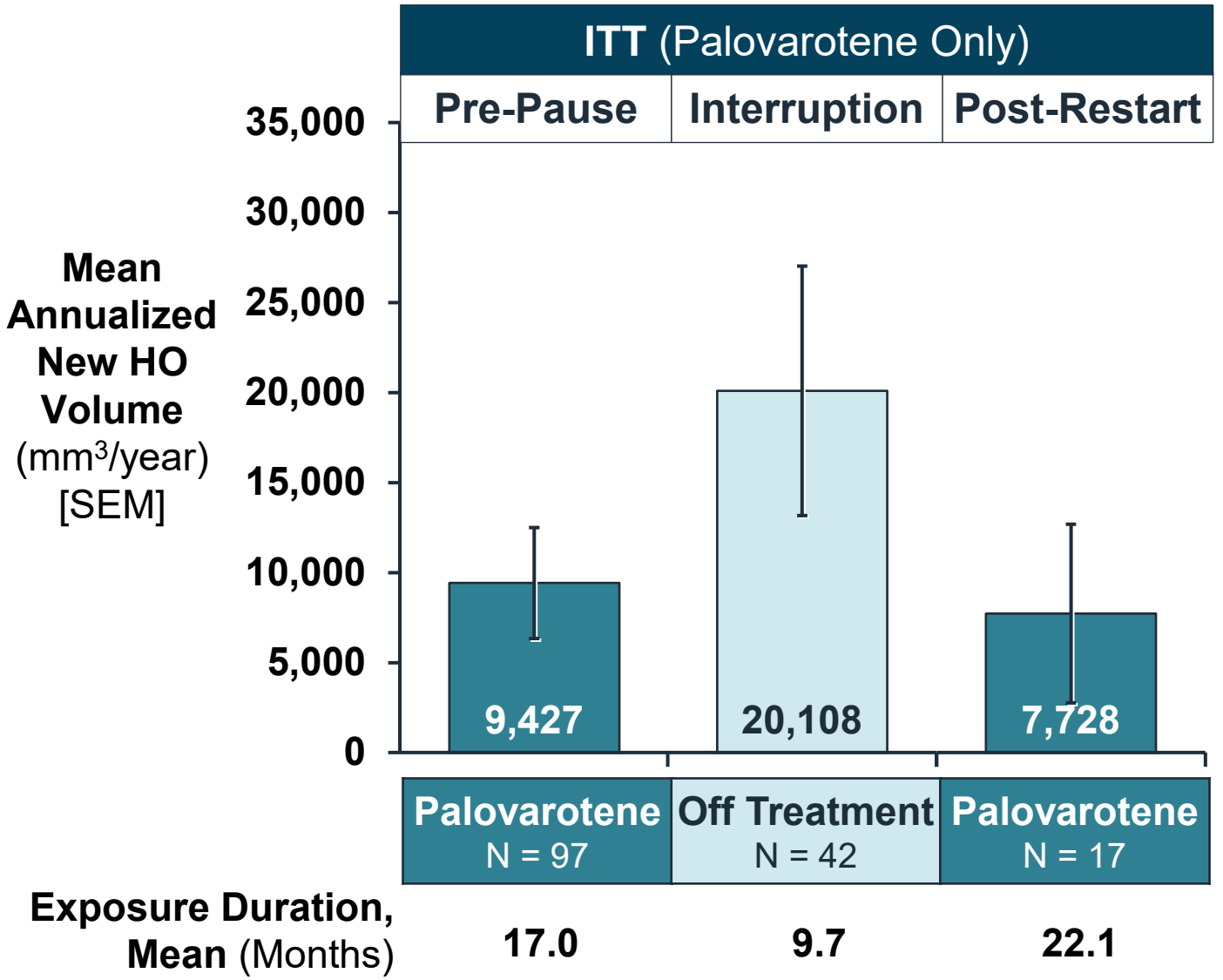
Analyses Using Entire Dataset up to Last-Patient-Last-Visit Support Longer-Term Effect of Palovarotene



1. Period from last WBCT scan before treatment interruption to the first WBCT scan after palovarotene treatment was re-started
2. Patients who restarted palovarotene treatment with 2 or more WBCT scans during this period (after re-start)

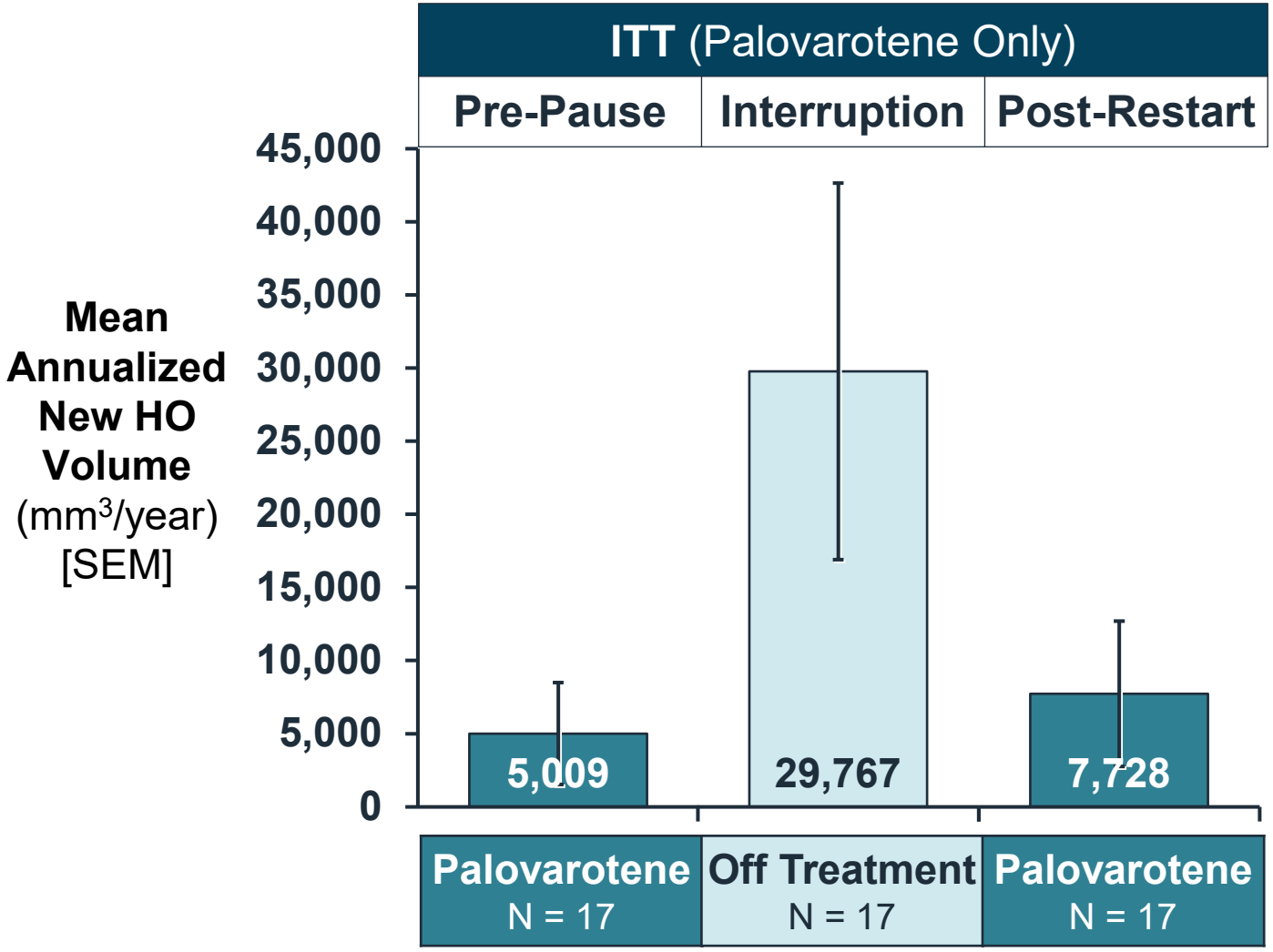
Long-Term Analyses (Study 301 and NHS) Provide Additional Evidence of Palovarotene Benefit





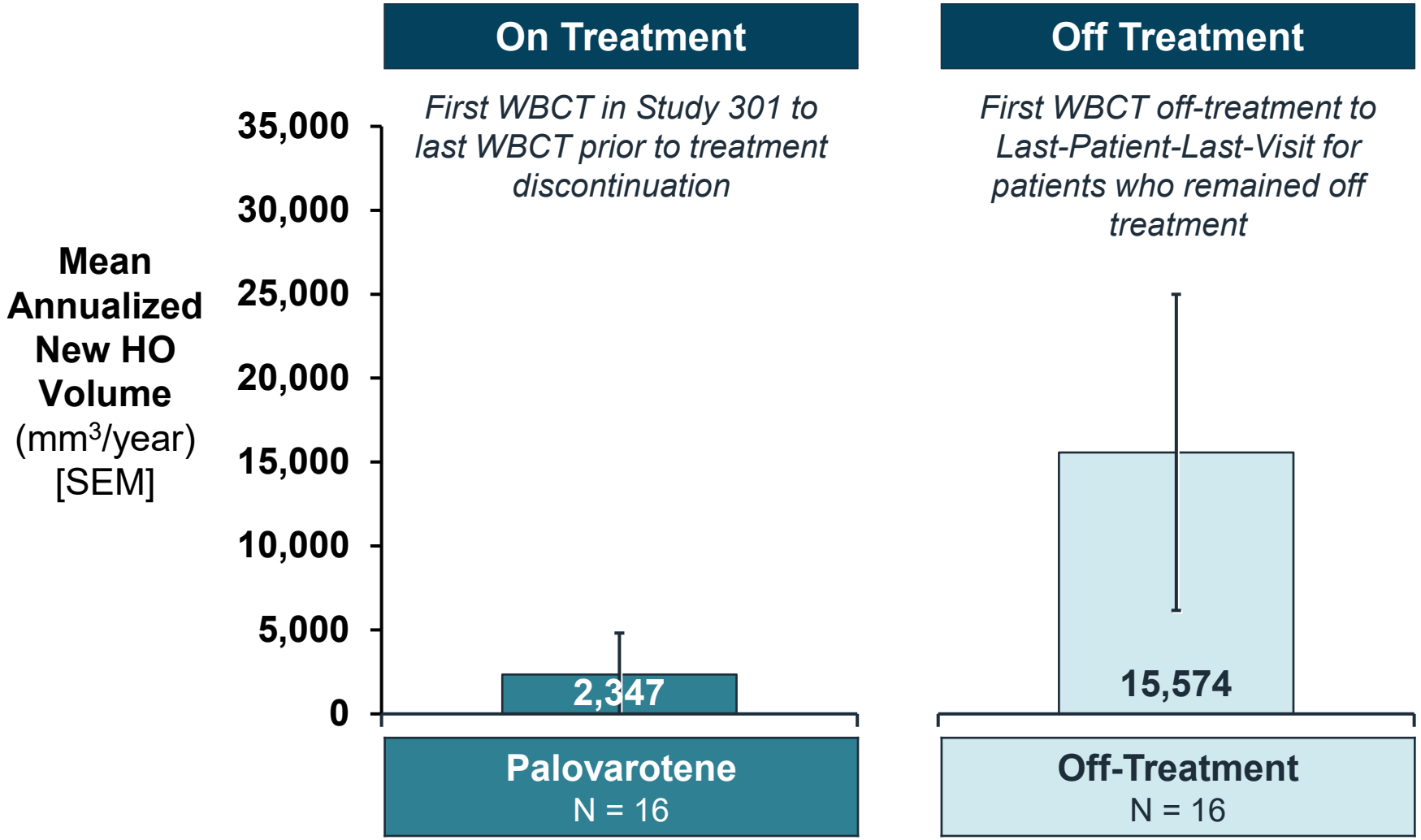
‡ Nominal p-value = 0.0659

Long-Term Analysis in 17 Patients with Data in All Periods Showed Benefit While On Treatment



Exposure Duration, Mean (Months) **20.9** **6.8** **22.1**

Annualized New HO for Patients Who Did Not Re-Start Treatment (N = 16)



Secondary and Exploratory Endpoints

Secondary: Proportion of Patients and Body Regions with New HO Similar Between Groups

	Palovarotene	Untreated
Patients with any new HO at M12, % (n/N)	**64%** (59/92)	**62%** (56/90)
Body regions with any new HO at M12, mean (SD) (N)	**1.3** (1.4) (97)	**1.5** (1.6) (101)

- Overall volume of new HO less in palovarotene-treated patients

Principal FAS population; PPY = per patient year

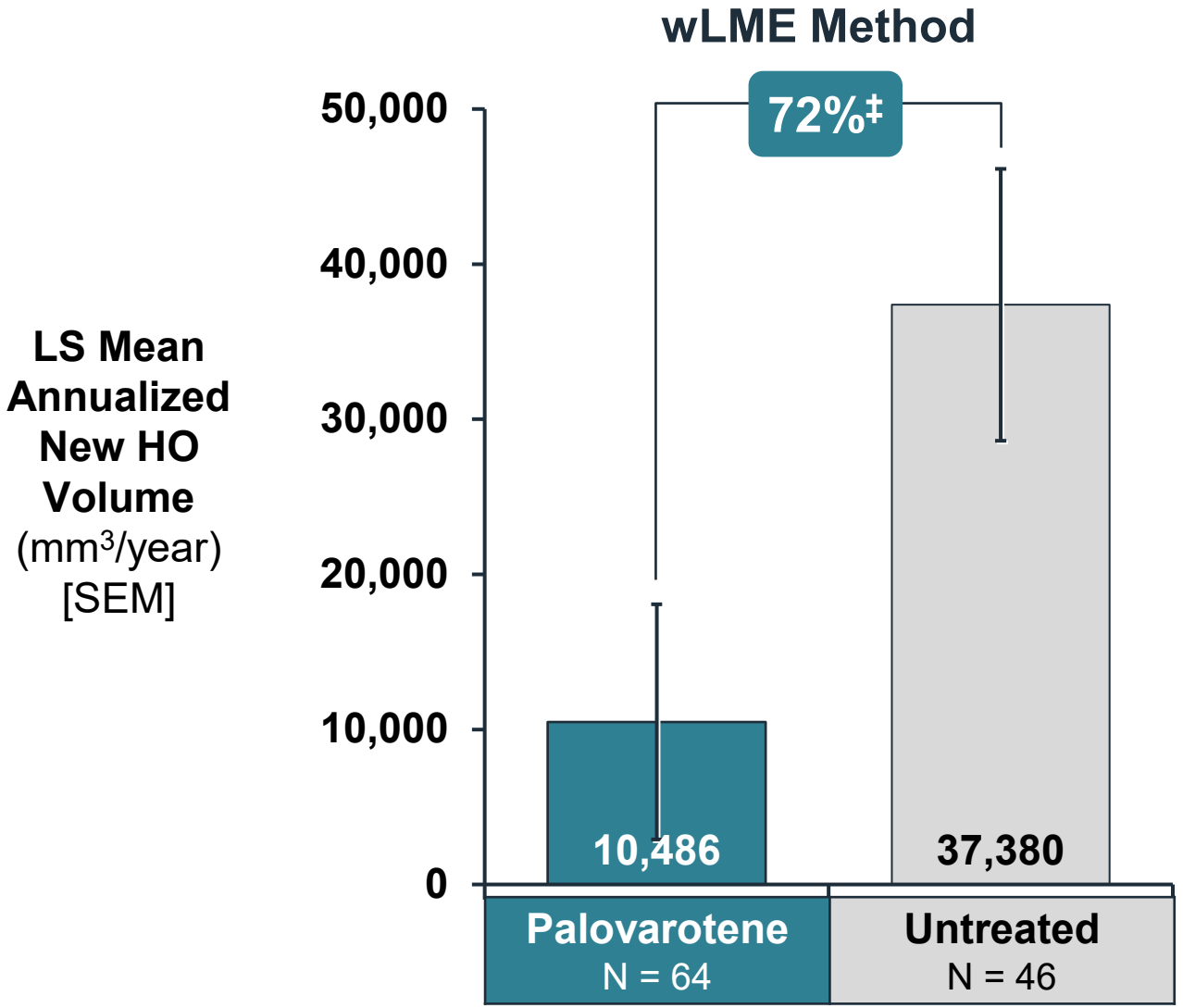
Observed Differences in Flare-up Rate in Study 301 and NHS May Be Due to Ascertainment Methods

Secondary Endpoints	Palovarotene	Untreated
Patients with ≥ 1 flare-up through M12, % (n/N)	**65%** (64/99)	**54%** (60/111)
Flare-ups PPY; rate (95% CI) (N)	**1.8** (1.6, 2.0) (99)	**0.8** (0.7, 1.0) (111)

- Patients with FOP experience average of 1.5 – 2.6 flare-ups per year[1,2]
- Possible explanations for differences in observed rate
  1. How flare-ups captured (e.g., daily diaries in Study 301)
  2. More frequent clinical contact of patients in Study 301
  3. Untreated patients less motivated to report flare-ups compared to patients who would receive treatment for a flare

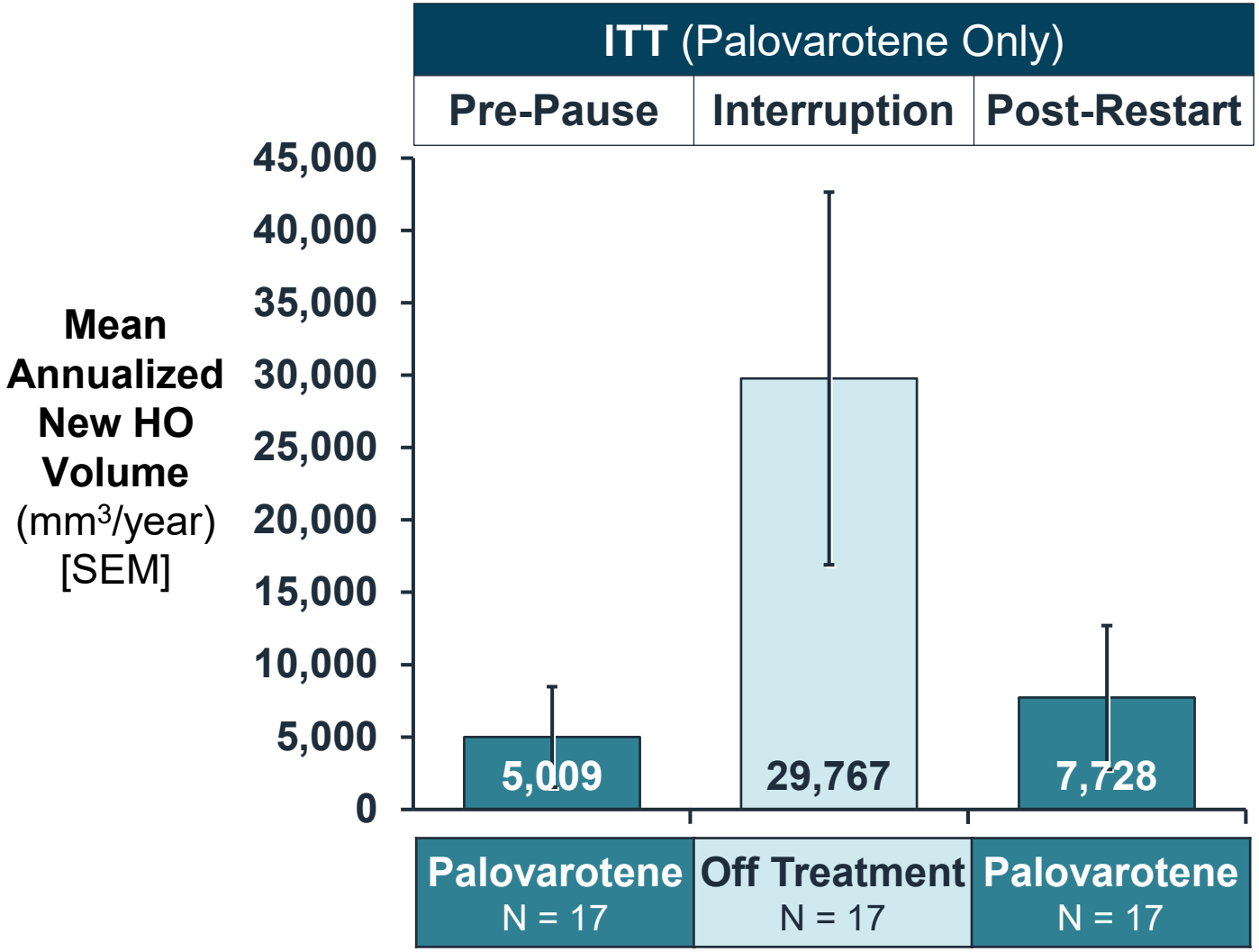
1. Pignolo, 2016; 2. Dahir et al. J Endocrine Soc 2021 (5; Suppl. 1); A251-A252
Principal safety population, PPY = per patient year

Lower Volume of Annualized New HO with Palovarotene When Looking at Patients with ≥ 1 Flare-Up at Month 12



‡Nominal p-value 0.0373

Long-Term Analyses Show Lower HO Volume When Patients are Receiving Palovarotene



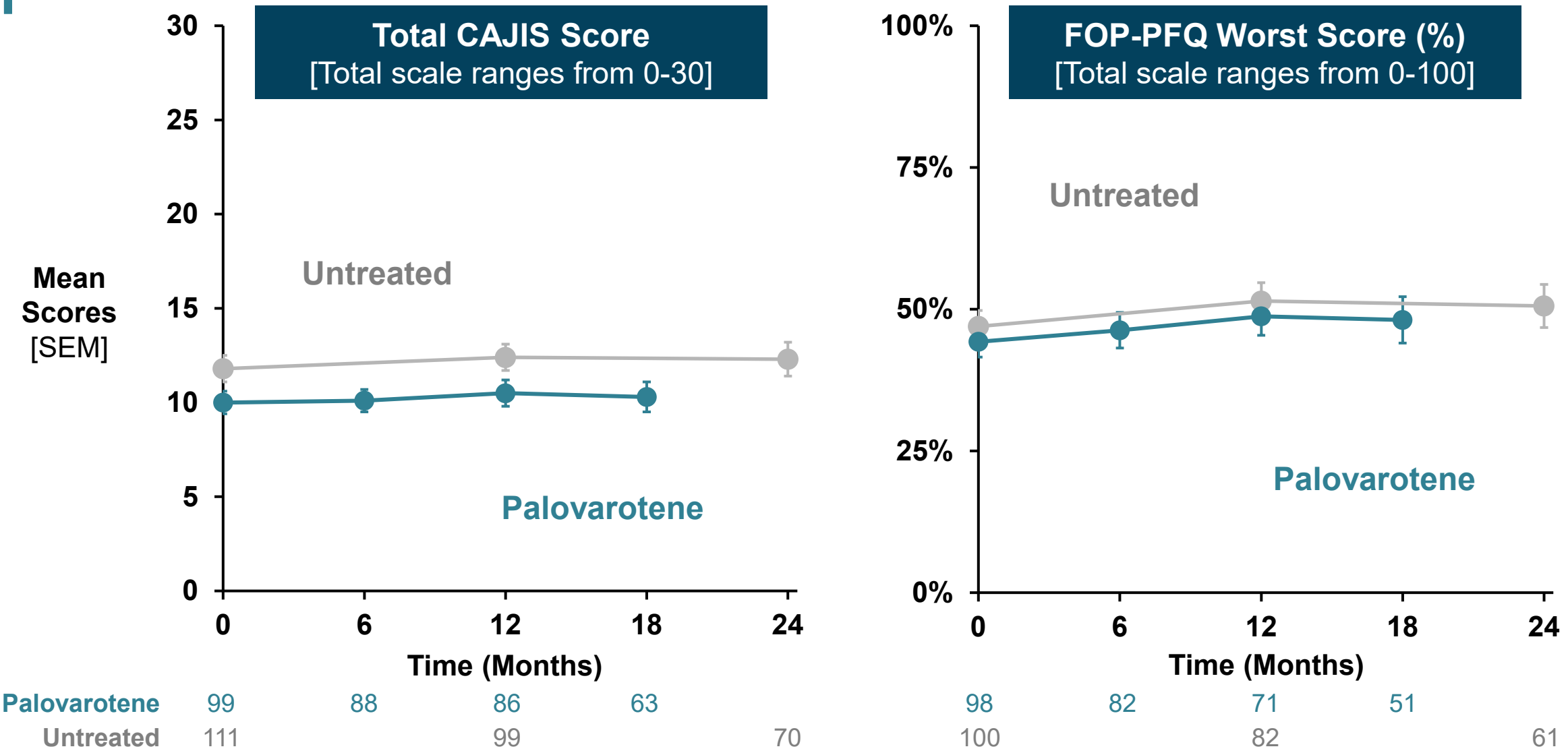
Physician and Patient Reported Outcomes Included as Exploratory Endpoints

- **CAJIS:** physician reported assessment of range of motion
- **FOP-PFQ:** disease-specific patient reported outcomes (PROs) on activities of daily living and physical performance
- **PROMIS:** age-specific general health-related PROs

- Designed to track function over lifetime of patient with FOP
- Not sufficiently sensitive to measure change over course of clinical trial

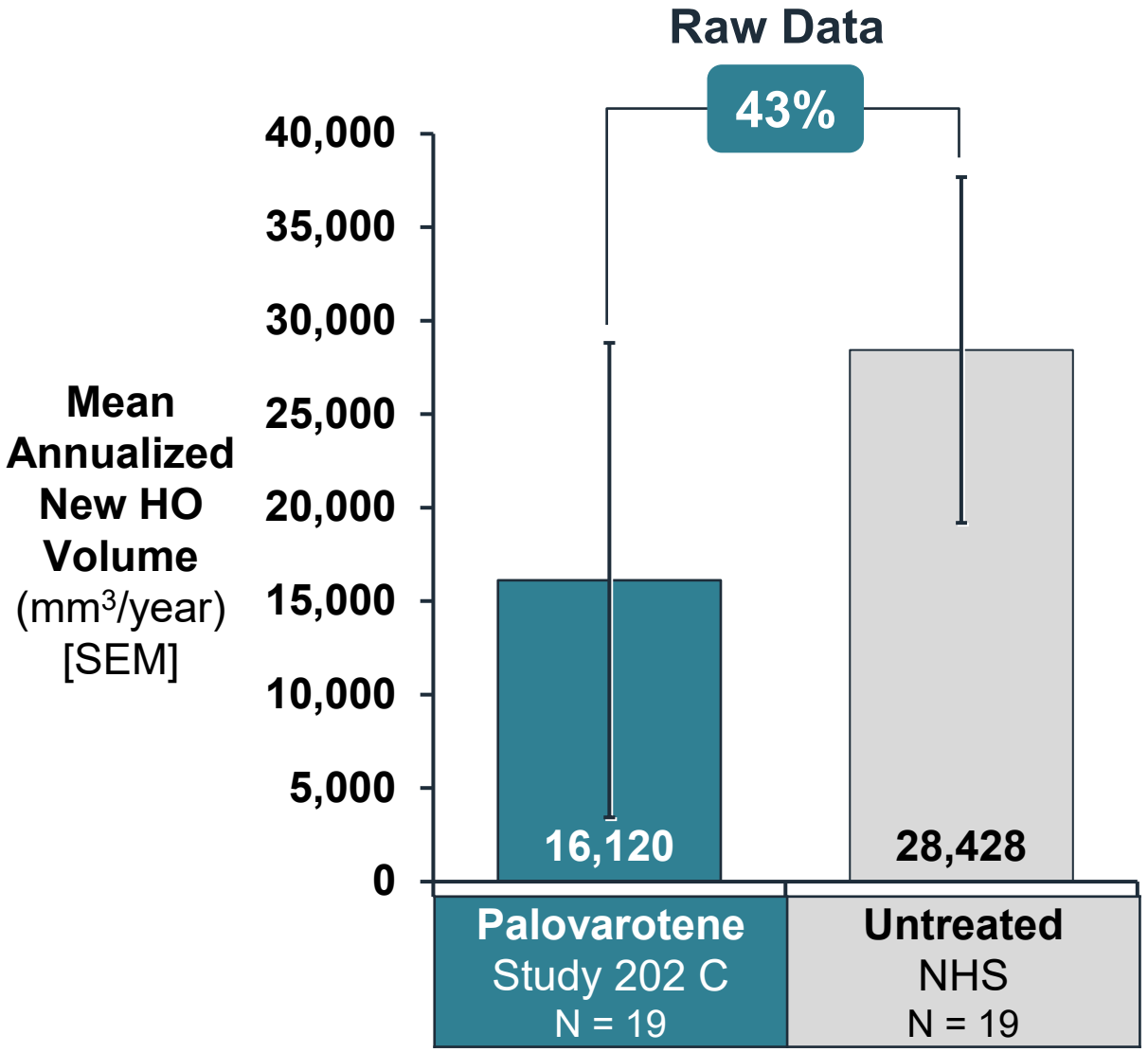
CAJIS = Cumulative Analogue Joint Involvement Scale
FOP-PFQ = FOP-Physical Function Questionnaire
PROMIS = Patient Reported Outcomes Measurement Information System

Functional Assessments Not Sensitive to Demonstrate Impact Given Study Duration



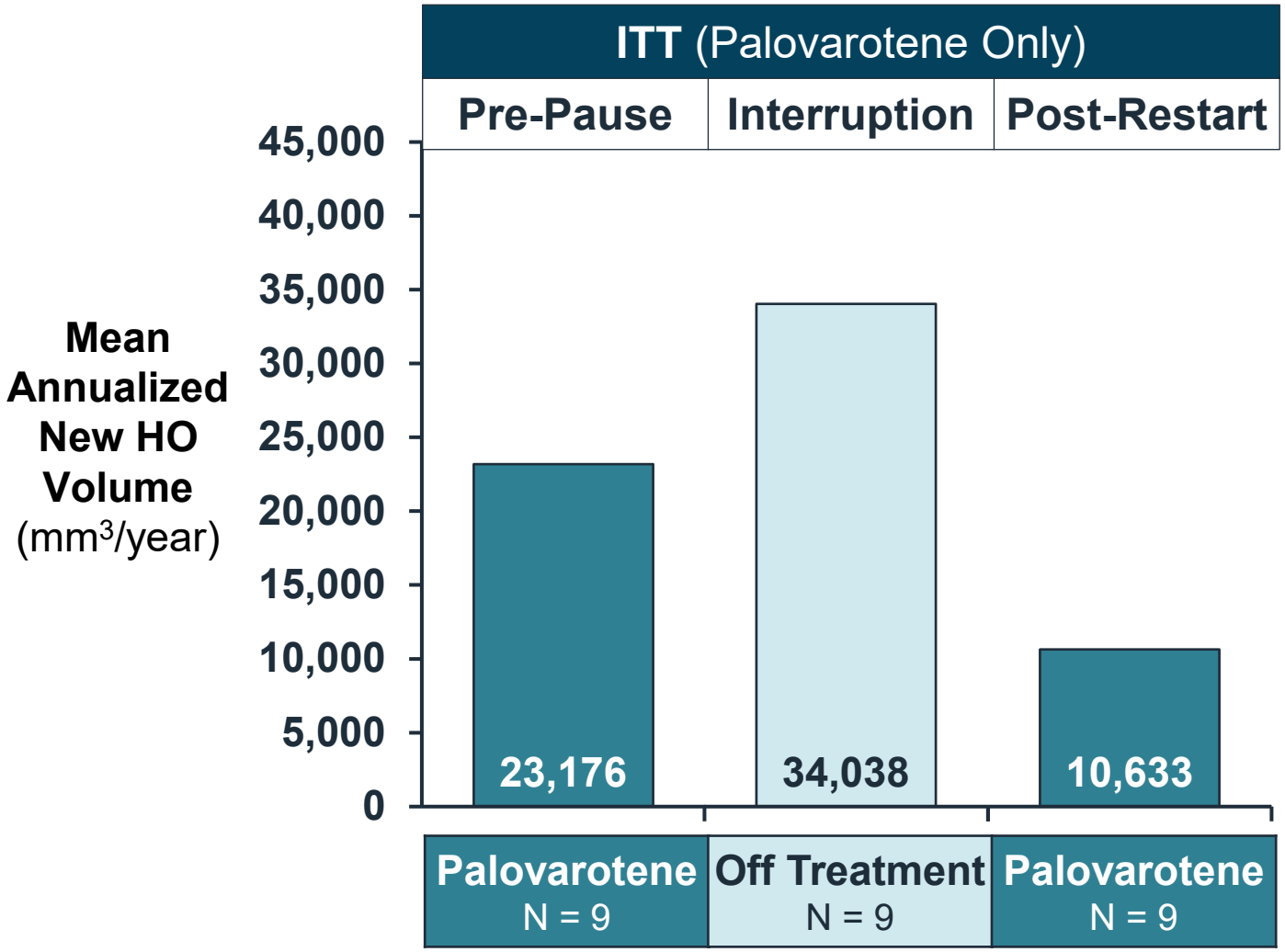
Supportive Evidence of Efficacy

Study 202C: Matched Analysis of Reduction in New HO Volume Among Palovarotene-Treated and Untreated Patients



- Study 202C only Phase 2 Study to include WBCT scans in all patients
- Matched analysis includes patients from NHS who did not cross over into Study 202
- Patients matched based on age, sex, time since last flare-up, age-adjusted HO volume, and CAJIS

Study 202C: Long-Term Data Show Lower Annualized New HO Volume While On Treatment



Palovarotene Reduces Volume of New HO

- 54% reduction in new HO (wLME)
- Sensitivity analyses show consistent benefit of palovarotene and support NHS as a valid comparator
- Volume of new HO consistently lower in palovarotene-treated patients despite lower reported flare-up rate in NHS
- Long-term analyses and data from Study 202C provide supportive evidence of palovarotene efficacy

Palovarotene modifies underlying cause of disease progression and disability in patients with FOP

Safety and Risk Management Activities

Jennifer Schranz, MD

Senior Vice President,
Global Head of Rare Disease
Ipsen

Palovarotene Safety Exposures in FOP

	Palovarotene
Total Patients with FOP	**164**
Patients ≥ 8 / 10 years (target population)	**139**
Mean exposure, years	**3.54**
Median exposure, years (range)	**3.62** (0.10, 7.00)
> 30 months in study	**78%**

- Palovarotene safety evaluated in > 300 healthy participants and > 700 patients in other indications
  - Support safety profile observed in FOP

Target population: females ≥ 8 and males ≥ 10 years of age

31 January 2022 Cutoff

Premature Physeal Closure (PPC)

Target Population: PPC Reported in 13 Palovarotene-Treated Patients

Age at Study Enrollment	Palovarotene	
	n / N	%
Total PPC Events (Age < 18)	**27 / 102**	**26%**
Age < 8/10	**14 / 25**	**56%**
Age ≥ 8/10 to < 14	**13 / 39**	**33%**
Age ≥ 14 to < 18	**0 / 38**	**0%**

- PPC events include a continuum of partial through complete closure of the growth plates

Target population: females ≥ 8 and males ≥ 10 years of age

31 January 2022 Cutoff

PPC Risk on Growth and Potential Long-Term Consequences

Growth

- Does not generally stop upon treatment initiation or PPC diagnosis
- Signs of growth disturbances (clinical height measures or radiological assessments) seen prior to identification of PPC
  - Proposed monitoring can inform ongoing risk-benefit decisions

Other Long-Term Concerns

- No femoral angular deformity
- No difference in leg length asymmetry between treated and untreated patients

General Safety

Target Population: Overall Safety Profile

	Palovarotene N = 139
AEs	100%
Mild AEs	17%
Moderate AEs	58%
Severe AEs	25%
AEs leading to dose modification	37%
AEs leading to treatment discontinuation	9%
SAEs	41%
AEs leading to death	0

Target population: females ≥ 8 and males ≥ 10 years of age

31 January 2022 Cutoff

Target Population: Mucocutaneous Events Were Most Commonly Reported AE

		Palovarotene N = 139
AEs		**100%**
Mucocutaneous	**Dry skin**	**81%**
	Lip dry	**57%**
	Alopecia	**42%**
	Pruritus	**42%**
	Erythema	**36%**
	Rash	**33%**
	Pruritis generalized	**31%**
Musculoskeletal	**Arthralgia**	**50%**
	Pain in extremity	**42%**

Events reported in > 30% of treated patients
Target population: females ≥ 8 and males ≥ 10 years of age

31 January 2022 Cutoff

Target Population: Dose Reductions Effective, Allowing Patients to Remain on Treatment

	Palovarotene N = 139
AEs leading to dose reductions	**37%**
Drug eruption	**9.4%**
Dry skin	**8.6%**
Pruritis	**5.8%**
Pruritis generalized	**5.0%**
Skin exfoliation	**4.3%**

Events reported in > 5 treated patients
Target population: females ≥ 8 and males ≥ 10 years of age

31 January 2022 Cutoff

Target Population: Few Patients Discontinued Treatment Due to an AE

	Palovarotene N = 139
AEs leading to treatment discontinuation	**8.6%**
Dry skin	1.4%
Amylase increased	0.7%
Cellulitis	0.7%
Depression	0.7%
Epiphyses premature fusion (PPC)	0.7%
Erythema	0.7%
Furuncle	0.7%
Intentional self-injury	0.7%
Lipase increased	0.7%
Localized infection	0.7%
Malnutrition	0.7%
Mobility decreased	0.7%
Myoclonus	0.7%
Hemophilus infection	0.7%

Target population: females ≥ 8 and males ≥ 10 years of age

Target Population: Most Common SAEs

	Palovarotene N = 139
SAEs	**41%**
Coronavirus infection	7.9%
Epiphyses premature fusion (PPC)	7.2%[#]
Pneumonia	2.9%
Condition aggravated (flare-up)	2.9%
Arthralgia	2.2%
Pain in extremity	2.2%
Peripheral swelling	2.2%
Cellulitis	2.2%
Exposure to communicable disease	2.2%

[#] 3 Events of PPC not included; 2 occurred post-treatment and 1 was incorrectly captured as pre-treatment event

Events reported in > 2 treated patients
Target population: females ≥ 8 and males ≥ 10 years of age

31 January 2022 Cutoff

Planned Pharmacovigilance and Educational Program

Pharmacists

- Only distributed through single specialty pharmacy
- Trained on USPI, educational program overview, and all educational materials

Potential Prescribers (HCPs)

- Receive introductory letter and educational materials
- Confirm review prior to prescribing palovarotene

Patients

- Receive overview of key risks
- Tailored educational materials specific to females, growing pediatric patients, and caregivers

10-Year Post-Approval Registry Study in Patients Treated with Palovarotene

- Protocol based with sites' personnel trained in data collection
- **Primary objective:** collect and assess real-world safety data
  - Pregnancy outcomes, PPC, and fractures
- **Secondary objectives:** measures of effectiveness and function
  - Mobility and QoL (CAJIS, FOP-PFQ, PROMIS, AADAs)
  - Number of flare-ups and outcomes of new bone growth
- Patients enrolled at clinic visits, with follow-up visits on-site or remotely (per routine clinical practice)

AADA = Aids, Assistive Devices, and Adaptations

Palovarotene has a Well-Characterized Safety Profile

- Mucocutaneous events most common
- Majority of AEs mild to moderate
- Dose reductions and supportive care were effective in managing AEs, allowing patients to remain on treatment
- PPC and teratogenicity are important risks and are communicated in boxed warning in proposed label
- Education and risk mitigation program to inform and guide on safe use of palovarotene

Clinical Perspective

Edward Hsiao, MD, PhD

Professor of Medicine

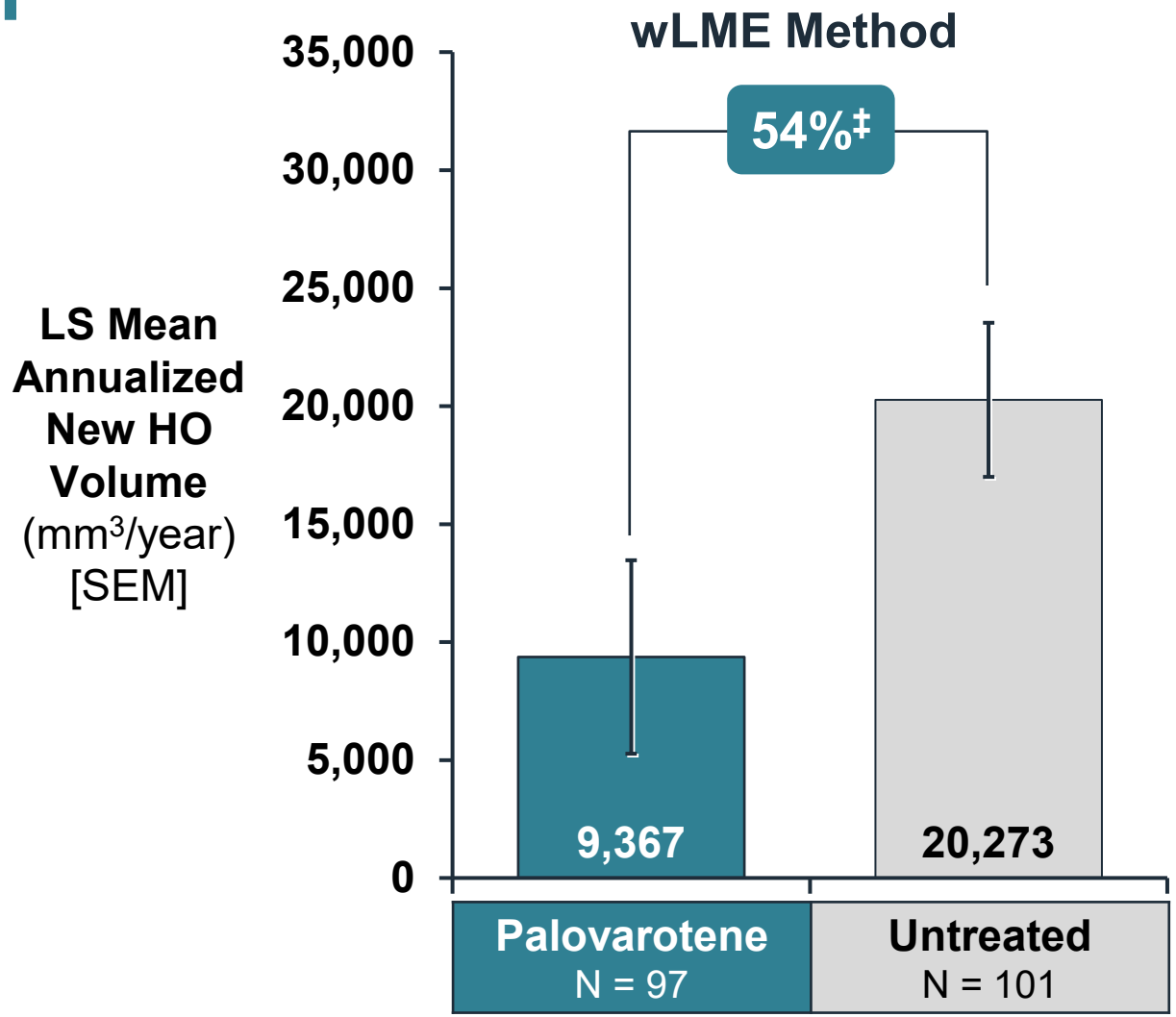
Division of Endocrinology and Metabolism

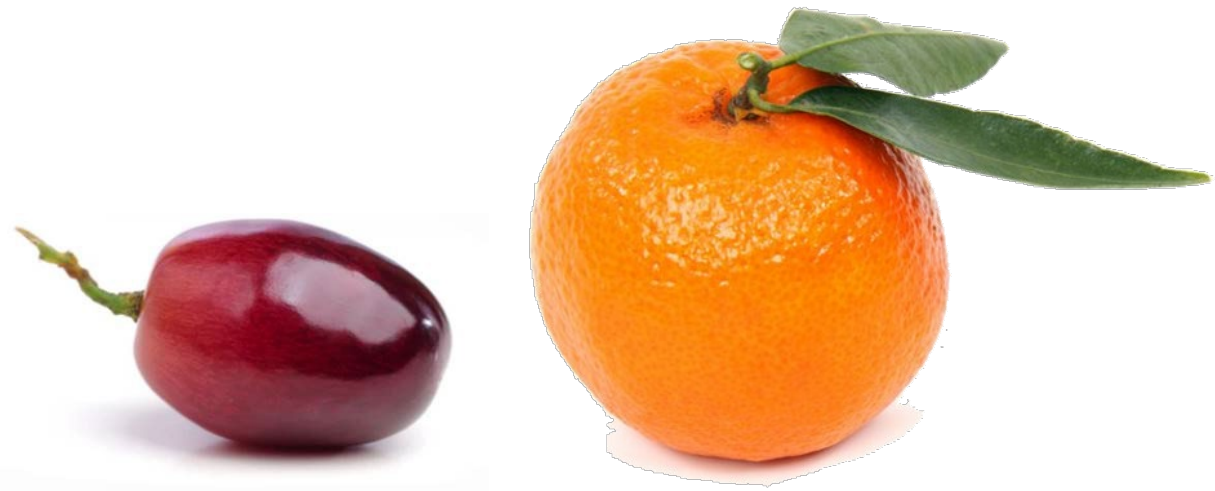
University of California, San Francisco

FOP is a Devastating Disease: Blocking New Bone = Treatment to Slow Progression

- New bone growth affects **all aspects of daily living**
  - **Mobility:** All patients eventually lose ability to do basic activities of daily living (walking, eating, toileting, etc.)
  - **QoL:** Bone can prevent patients from sitting comfortably or increase risk of skin breakdown/ulcers
- Abnormal bone formation is the fundamental cause of disability in FOP
- Bone formation is permanent
- Standard of care limited to symptomatic treatment

Reduction in New HO with Palovarotene is a Clinically Meaningful Outcome for Patients





~9,000 mm³

~20,000 mm³

Amount of new HO a patient accumulates per year

‡ Nominal p-value = 0.0392

Need to Weigh Risks of Treatment vs Benefit of Slowing New Bone Formation

- Risks of PPC clearly communicated to pediatric patients
  - Bone formation in FOP cumulative and irreversible
  - Early intervention critical to preserve function over time
- Difference in observed flare-up rate between Study 301 and NHS
  - Volume of new HO lower with palovarotene
- Mucocutaneous AEs most common
  - Manageable with supportive treatment and dose reductions
- Decision to treat based on individual benefit-risk assessment

Benefits of Palovarotene Outweigh Risks

- Palovarotene is the first therapeutic option shown to slow the trajectory of new HO accumulation
  - Reducing new bone formation is an essential strategy for slowing disease progression
- Palovarotene not for all patients with FOP
- Risks and benefits can be balanced
  - Risks must be considered for each individual patient prior to treatment initiation

Moderator for Q&A

Drew Sansone, MS

Vice President, Regulatory and Quality

North America

Ipsen

THANK YOU

Study Collaborators
Investigators
Site Personnel
Patients and Families

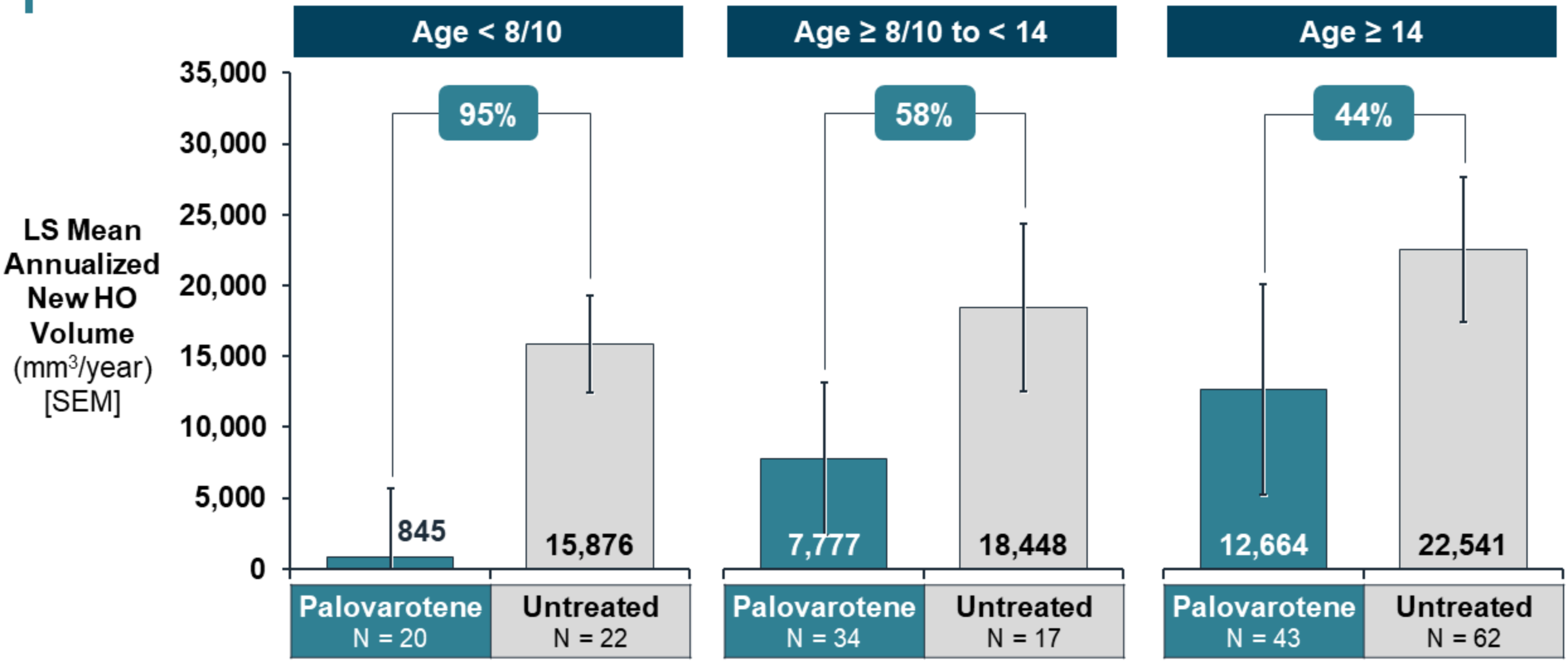
Palovarotene for the Treatment of Patients with Fibrodysplasia Ossificans Progressiva (FOP)

Ipsen

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

June 28, 2023

Reductions in Annualized New HO with Palovarotene Across Age Categories

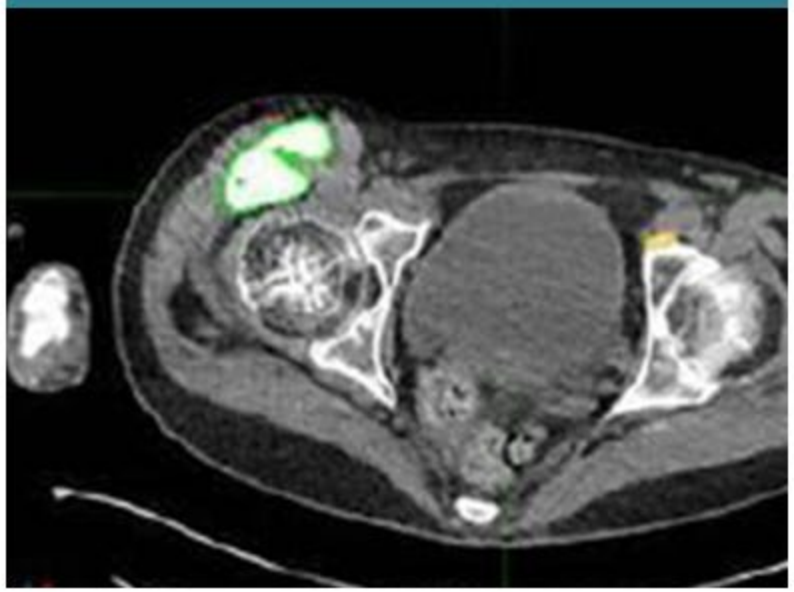
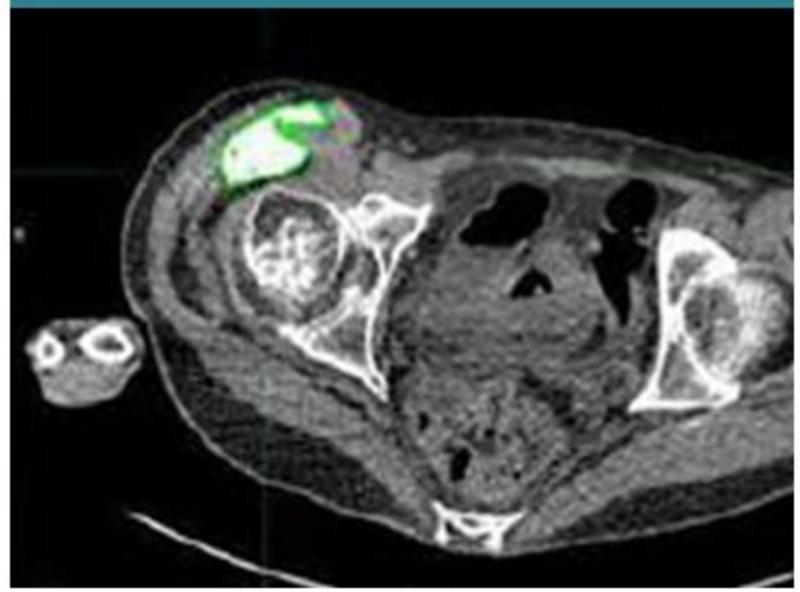
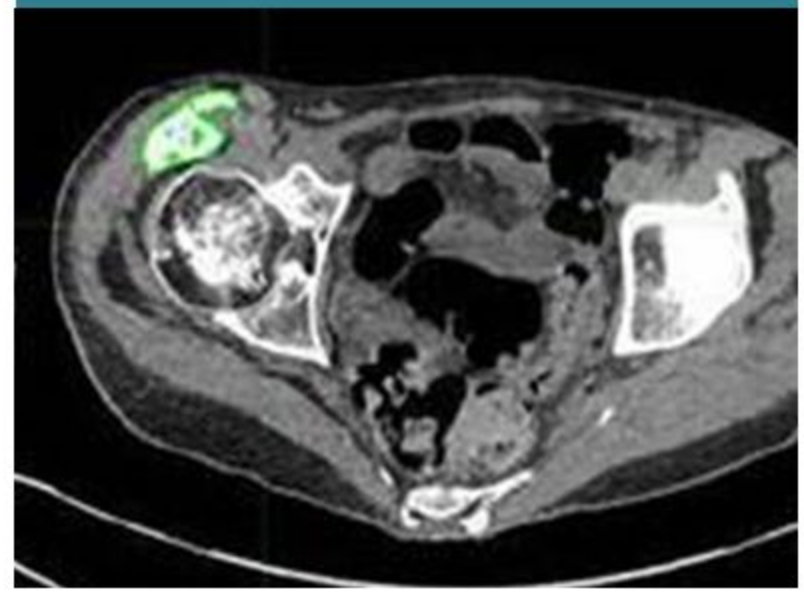


Greater Use of Systemic Glucocorticoids in NHS Compared to PVO-1A-301

- 72% NHS patients vs 65% Study 301 patients received systemic glucocorticoids[1]
- 74% NHS flare-ups vs 66% Study 301 flare-ups were treated with systemic glucocorticoids[2]
- Systemic glucocorticoids are not known to impact HO formation

1. Principal Safety Set
2. Target population

‘Negative New HO’ May be Result of Simultaneous Increase(s) and Decrease(s) in Different Lesions

Baseline	Month 12	Month 24
		
HO volume: 259,480 mm^3	**HO volume:** 224,440 mm^3 **Reduction:** 35,040 mm^3	**HO volume:** 180,350 mm^3 **Reduction:** 79,130 mm^3

Palovarotene treated patient; images from Parexel imaging database

Reduced Efficacy in Females Likely Related to Age Differences

	Annualized New HO				
	Palovarotene N = 97		Untreated N = 101		Percent Reduction (palovarotene vs untreated)
	n	mm^3	n	mm^3	
Males	51	**8,353**	56	**31,276**	**73%**
Females	46	**10,618**	45	**14,317**	**26%**

- Untreated females formed 54% less new HO compared to untreated males
- Difference may be due to an older female patient population
  - Untreated female patient mean age 18.7 years
  - Untreated male patient mean age 16.5 years
- Treated females younger than untreated females; thus more likely to form HO
  - Treated females: 13.6 years vs Untreated females 18.7 years

Assessment of Impact of Differences in WBCT Visit Schedules in Study 301 vs NHS

New HO Volume		Posterior Pr($\gamma < 1$)	Median Posterior γ (95% Credible Interval)	% Reduction	
				Square-Root Scale	Standard Scale
Square-root transformation	Collapsed over 12-month interval	0.9065	**0.84** (0.64, 1.09)	16%	36%
No square-root transformation	Collapsed over 12-month interval	0.997	**0.61** (0.42, 0.87)	-	39%