Clinical Clips in NF1-PN: Key Advances from AAN 2026

Independent Coverage from AAN 2026

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Learning Objectives

Upon completion of this activity, participants should be better able to:

- **Summarize** key emerging NF1 findings presented at AAN 2026.
- **Apply** new evidence to identify patients most likely to derive meaningful clinical benefit from current and emerging therapeutic strategies.
- **Integrate** updated data into longitudinal NF1 management decisions, including monitoring, goal reassessment, and care across life stages.

KOMET Trial: Adult Patient Experience With Selumetinib vs Placebo in NF1-PN

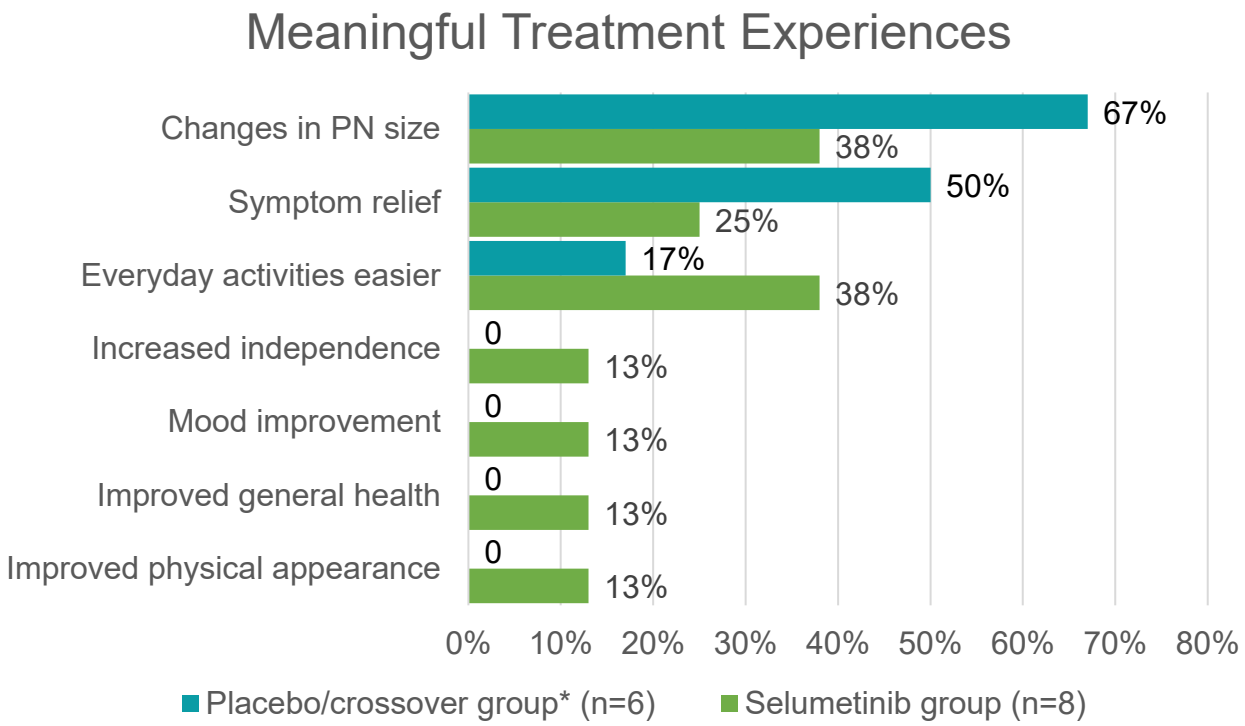
- **Mechanism:** Selective MEK1/2 inhibitor targeting RAS/MAPK pathway dysregulation in NF1
- **Study Design:** Phase 3, randomized, placebo-controlled trial in adults with symptomatic, inoperable NF1-PN, with longitudinal qualitative interview sub-study across multiple countries
- **Efficacy** (baseline: N=25, n=13 selumetinib; n=12 placebo)**:**
- High baseline burden: chronic pain (~80%), sensory symptoms, and major functional limitations impacting mobility, work, and daily activities
- **By Cycle 12:**
  - Improvements in pain, tingling, swelling, and perceived tumor size
  - Functional gains: mobility, range of motion, ability to perform daily tasks
  - Sleep and fatigue improved
- **Placebo group:** minimal change until crossover
- **Long-term (~20 months):**
  - Sustained or further improved symptom relief
  - Emerging benefits in emotional and social functioning (confidence, engagement)
- ~50% of patients reported tumor size reduction as meaningful, but symptom relief often drove perceived benefit

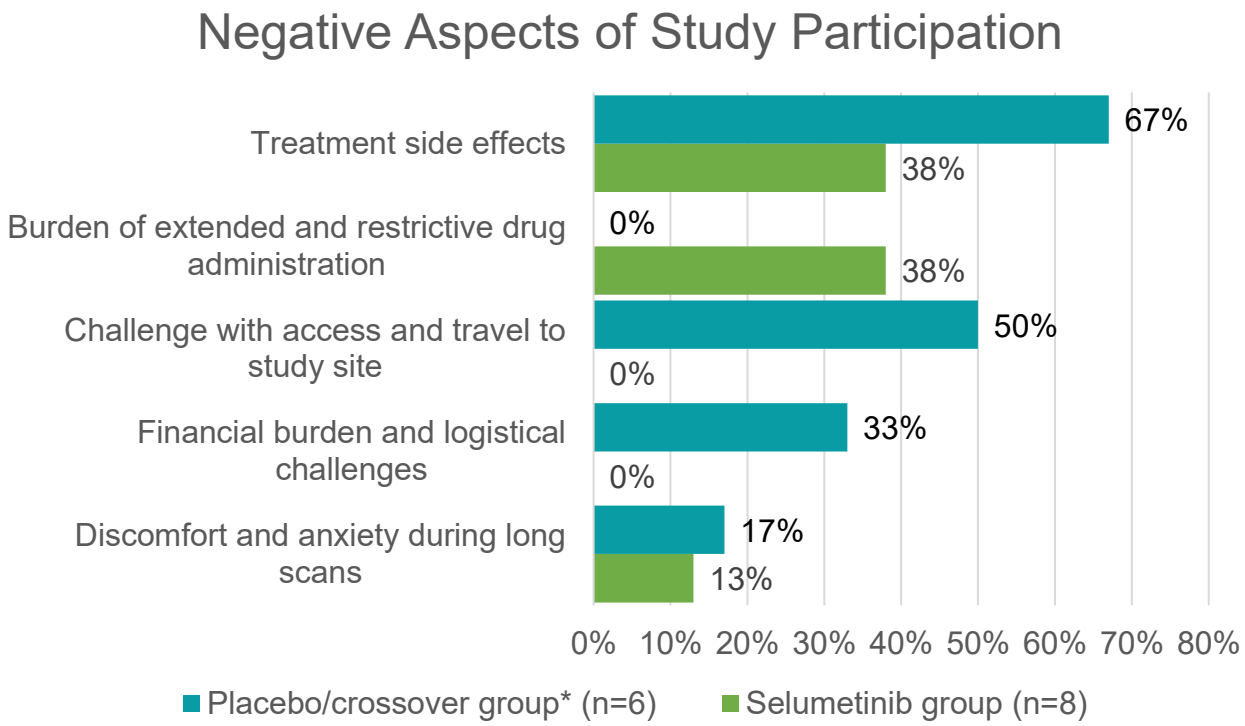
NF1, Neurofibromatosis Type 1; PN, Plexiform Neurofibromas. Adeyemi A. AAN 2026. Poster 007.

KOMET Trial: Adult Patient Experience With Selumetinib vs Placebo in NF1-PN

Half of 14 participants responded that the decrease in the size of their target PN had been meaningful at the end of Interview 3

- At the end of Interview 3, 14 participants were asked to describe any meaningful treatment experiences as well as their clinical trial experiences, both positive and negative





*Crossover to selumetinib took place at the end of Cycle 12 or earlier if there was confirmed radiological progression per ICR REINS criteria; all patients were receiving selumetinib at Interview 3. ICR, independent central review; n/N, number; NF1, Neurofibromatosis Type 1; PN, Plexiform Neurofibromas; REINS, Response Evaluation in Neurofibromatosis and Schwannomatosis.

Adeyemi A. AAN 2026. Poster 007.

KOMET Trial: Adult Patient Experience With Selumetinib vs Placebo in NF1-PN

- **Safety / Tolerability Insight (qualitative):**
- Treatment burden includes logistics, access, and long-term adherence challenges
- Reinforces need to balance clinical benefit with real-world feasibility
- **Clinical Takeaway:**
- Selumetinib provides early, durable, and patient-meaningful improvements in symptom burden and daily function, often beyond what imaging alone captures.
- **What matters for practice:**
  - Symptom and functional improvement can occur even without dramatic radiographic change
  - Patient-reported outcomes should guide treatment decisions and monitoring
  - Benefits extend into mobility, sleep, and psychosocial well-being, reinforcing a multidimensional definition of clinical benefit

NF1, Neurofibromatosis Type 1; PN, Plexiform Neurofibromas. Adeyemi A. AAN 2026. Poster 007.

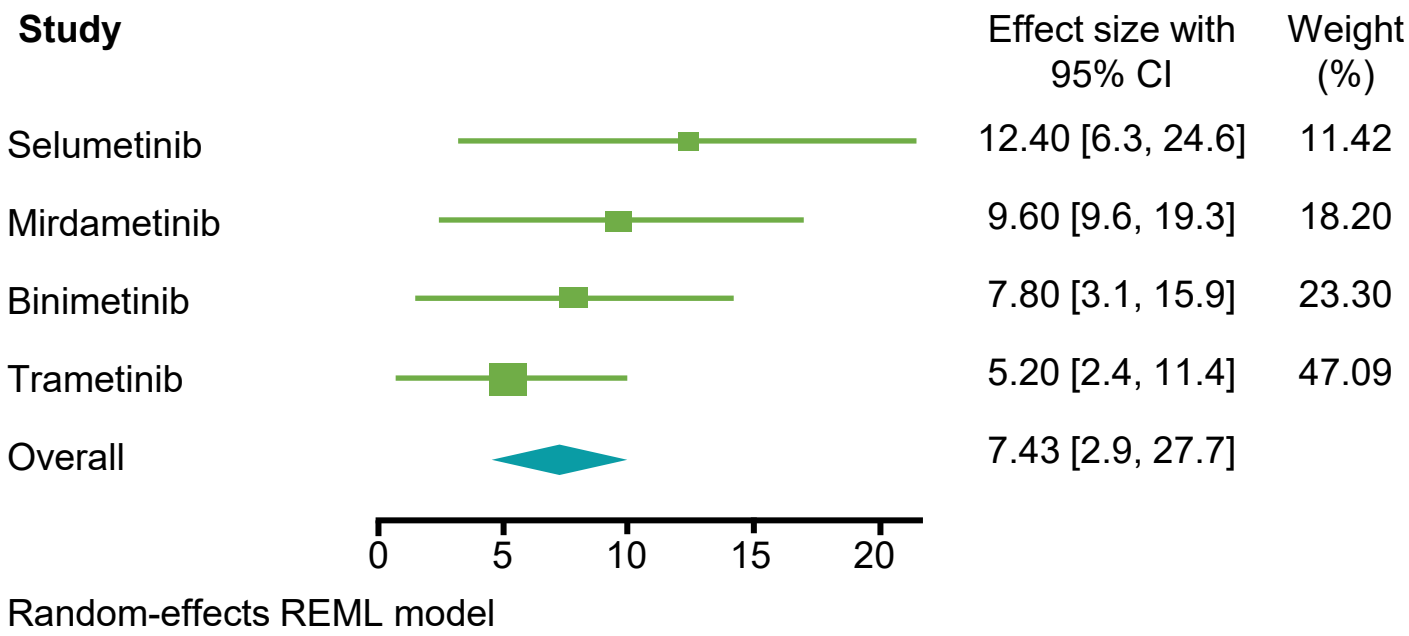
Network Meta-analysis: Comparative Efficacy of MEK Inhibitors in NF1-PN

- **Mechanism:** MEK inhibitors (selumetinib, mirdametinib, trametinib, binimetinib) target the RAS/RAF/MEK/ERK pathway driving NF1-associated tumor growth
- **Study Design:** Systematic review and Bayesian network meta-analysis of 7 trials (n=843) in pediatric and adult patients with symptomatic, inoperable NF1-PN
- **Efficacy (N=843):**
- Mean age: 12.8 ± 7.1 years (predominantly pediatric population)
- Mean follow-up: ~24.5 months
- Pooled response rates 46–71% across agents
- Primary endpoint: **≥20% tumor volume reduction (partial response)**
- Selumetinib (n=355) demonstrated highest efficacy (OR 12.4; SUCRA 0.93), followed by mirdametinib (n=254; OR 9.6; SUCRA 0.84), binimetinib (n=88; OR 7.8; SUCRA 0.69) and trametinib (n=146; OR 5.2; SUCRA 0.54)
- Mean volumetric tumor reduction: ~31% (selumetinib) and ~28% (mirdametinib)

NF1, Neurofibromatosis Type 1; PN, Plexiform Neurofibromas; OR, odds ratio; SUCRA, Surface Under the Cumulative Ranking Curve. Kakde M. AAN 2026. Poster 6-005.

Network Meta-analysis: Comparative Efficacy of MEK Inhibitors in NF1-PN

Objective Response Rate (ORR≥20% Tumor Reduction)



Drug Name	Pain Reduction (SMD)	Functional Gain (SMD)	Quality of Life (SMD)	Combined SE
Selumetinib	-0.82	0.58	0.65	0.12
Mirdametinib	-0.75	0.52	0.6	0.13
Binimetinib	-0.68	0.48	0.55	0.15
Trametinib	-0.62	0.42	0.48	0.16

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Network Meta-analysis: Comparative Efficacy of MEK Inhibitors in NF1-PN

- **Safety:**
- Common AEs: acneiform rash (41%), diarrhea (34%), elevated CPK (18%), asymptomatic LVEF decline (6%)
- <8% discontinued due to toxicity
- **Limitations:**
- Indirect comparison across trials; heterogeneity in populations, endpoints, and follow-up
- **Clinical Takeaways:**
- MEK inhibitors demonstrate consistent and clinically meaningful activity in NF1-PN, with selumetinib showing the strongest efficacy signal; however, differences are modest and should be interpreted in the context of cross-trial variability and individual patient factors
- Choice of MEK inhibitor should be guided by **patient age, tolerability, access, and long-term management considerations**, not efficacy differences alone

AE, adverse event; CPK, creatine phosphokinase; LVEF, left ventricular ejection fraction; NF1, Neurofibromatosis Type 1; PN, Plexiform Neurofibromas.
Kakde M. AAN 2026. Poster 6-005.

Retrospective Study: MEK Inhibitors in NF1-Associated High-Grade Glioma

- **Mechanism:** MEK inhibitors target RAS/MAPK pathway activation driven by NF1 loss, with established activity in low-grade gliomas and emerging exploration in high-grade disease
- **Study Design:** Single-center retrospective analysis (N=9) of NF1 patients with high-grade glioma (HGAP [n=6], GBM [n=2], high–grade glioma IDH wt [n=1]) treated with MEK inhibitors following progression
- For HGAP, the most frequent molecular alteration was ATRX mutation (N=6) followed by CDKN2A/B loss (N=2), whereas BRAF, TERT, TP53, and NOTCH3 mutations were identified in GBM.
- **Efficacy:**
  - Majority received prior radiation ± systemic therapy before MEKi
  - MEKi used post-progression (later-line setting); Mean MEKi duration: **~3.5 cycles (range 2–6)**
  - Median PFS: ~3 months (HGAP) and 2.5 months (GBM)
  - Overall survival: 21.9 months (HGAP) and 37.5 months (GBM)
  - Some patients demonstrated ongoing survival and treatment continuation
- **Safety:** 4 discontinued due to complications not attributed to MEK inhibitor therapy
- **Clinical Takeaway:** MEK inhibitors may have a potential role in NF1-associated high-grade gliomas, particularly HGAP, but responses appear limited and variable, highlighting the need for further investigation in this high-risk population

GBM, glioblastoma; HGAP, high-grade astrocytoma with pilocytic features; HGG, high-grade glioma; NF1, Neurofibromatosis Type 1; PN, Plexiform Neurofibromas; OR, odds ratio; SUCRA, Surface Under the Cumulative Ranking Curve. Yu TM-C. AAN 2026. Poster 6-007.

Retrospective Study: MEK Inhibitors in NF1-Associated High-Grade Glioma

Patient	Age/Sex	Pathology	Tumor location	Surgery	Systemic treatment	MEK inhibitor	PFS for MEKi (months)	OS for MEKi (months]	OS (months)
1	34.7 F	HGAP	Left thalamus	Biopsy only	-	Selumetinib, 7 cycles	8	9	12
2	22.0 M	HGAP	Left medical temporal	Resection	-	Miradametinib, 7-8 cycles	6	6	11
3	31.3 F	HGAP	Brain, pineal region	Resection	aTMZ 7 cycles	Selumetinib, 3 cycles	3	6.4	27.2
4	23.5 F	HGAP	Posterior medulla	Resection	Avastin	Selumetinib, 1 cycle Miradametinib, 1 cycle	3	13	14
5	50.1 M	HGAP	T spine	Resection	aTMZ 3 cycles	Selumetinib, 3 cycles	3	5	13
6	25.7 M	Glioblastoma (IDH wt)	T spine (T11-12)	Subtotal resection	aTMZ 12 cycles TMZ rechallenge Avastin 4 doses	Selumetinib, 2 cycles	2	12	36
7	51.4 F	Glioblastoma (IDH wt)	Right temporal lobe	Resection x2 LITT x1	aTMZ 12 cycles Avastin 10 doses Carboplatin x1 CCNU 4 cycles	Dabrafenib & Trametinib, 2 cycles	3	7	38
8	58.9 M	HGAP	Right cerebellum	Biopsy only x2	aTMZ 18 cycles CCNU 4 cycles Avastin 9 cycles	Selumitinib, 3 cycles	2	2.8	54
9	46.0 M	HGG (IDH wt)	Left frontal	Resection	TMZ 6 weeks Ulixertinib 16 weeks	Mirdametinib, 2 cycles	2.5	2.5	11.5

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Real-World Study: Selumetinib Impact on Pain Medication Use in Adults With NF1-PN

- **Mechanism:** Selective MEK1/2 inhibitor targeting RAS/MAPK pathway, associated with tumor reduction and symptom improvement in NF1-PN
- **Study Design:** Retrospective U.S. claims database analysis of adults (N=160) treated with selumetinib; ≥12 months pre- and post-index data, with up to 3-year follow-up
- **Efficacy:**
  - PPMU increased pre-treatment (47% → 57%), then decreased post-initiation to 48% at 1 year and 29% at 3 years (~2-fold reduction)
  - Consistent reductions across all pain medication classes (opioids, gabapentin, others)
  - Gabapentin use declined (29% → 13%); opioid use decreased (14% → 8%)
  - Each year on selumetinib associated with ~19–23% reduction in likelihood of PPMU
  - Discontinuation signal: patients who stopped selumetinib had higher PPMU at 3 years, suggesting symptom recurrence

NF1, Neurofibromatosis Type 1; PN, Plexiform Neurofibromas; PPMU, prescription pain medication utilization. Jordan JT. AAN 2026. Poster 006.

Real-World Study: Selumetinib Impact on Pain Medication Use in Adults With NF1-PN

- **Safety:** Not directly assessed; real-world analysis focused on medication utilization as a proxy for symptom burden
- **Clinical Takeaway:**
- Selumetinib is associated with durable, real-world reductions in pain medication use, reinforcing its impact on symptom burden beyond imaging.
- **What this means for practice:**
- Reduction in opioid and gabapentin use is a clinically meaningful, patient-centered outcome
- Treatment persistence matters — discontinuation may lead to symptom rebound
- Supports integrating real-world functional endpoints (medication use, daily function) alongside radiographic response when evaluating benefit

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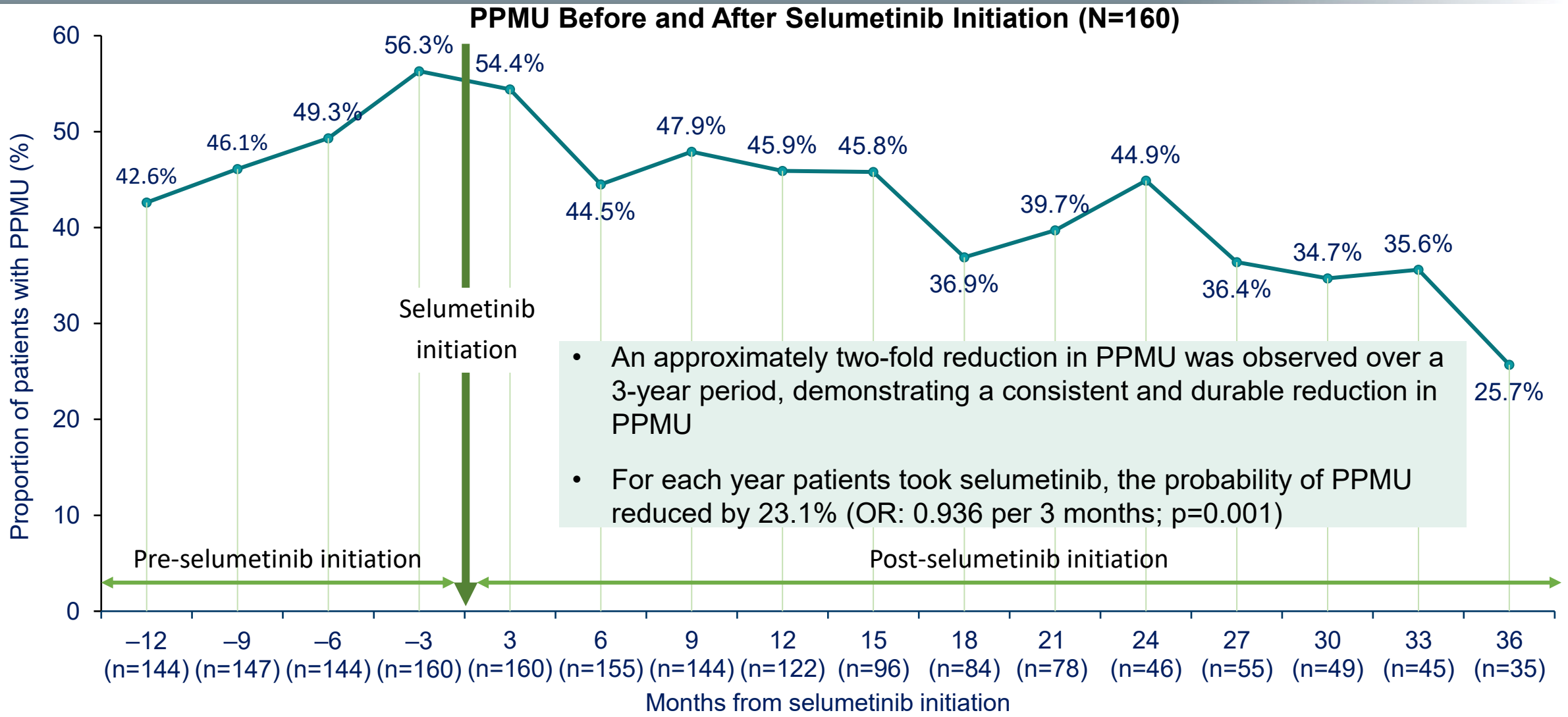
Real-World Study: Selumetinib Impact on Pain Medication Use in Adults With NF1-PN



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