***In the KOMET study, 20% of adult patients in the Koselugo group achieved ≥20% PN volume reduction (14/71; 95% CI: 11, 31) vs 5% in the placebo group (4/74; 95% CI: 2, 13) from baseline at the end of Cycle 16. DCO August 5, 2024. These responses were confirmed at a subsequent assessment within 3-6 months.[1,3]**

The importance of early referral and management of adults with symptomatic, inoperable NF1 PN

INDICATION

KOSELUGO is indicated for the treatment of adult and pediatric patients 1 year of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS associated with Koselugo include Left Ventricular Dysfunction, Ocular Toxicity, Gastrointestinal Toxicity, Skin Toxicity, Increased Creatine Phosphokinase (CPK), Increased Levels of Vitamin E and Risk of Bleeding (Koselugo Capsules), and Embryo-Fetal Toxicity.

ADVERSE REACTIONS

Common adverse reactions ≥40% in pediatric patients include vomiting, diarrhea, increased CPK, dry skin, paronychia, nausea, dermatitis acneiform, and pyrexia.

Common adverse reactions ≥40% in adult patients include rash (all), dermatitis acneiform, and diarrhea.

DRUG INTERACTIONS include strong/moderate CYP3A4 inhibitors or fluconazole and strong/moderate CYP3A4 inducers.

Please see additional Important Safety Information throughout and the full Prescribing Information for Koselugo (selumetinib).

CI=confidence interval; DCO=data cutoff; FDA=Food and Drug Administration.
All patients featured have been compensated by Alexion.

In patients with NF1, PN are prevalent and debilitating[4-6]

~1 IN 3000

people worldwide are affected by NF1, an autosomal dominant disorder. Approximately half of the cases are caused by sporadic variants in individuals with no family history.[4-6]

of patients with NF1 have PN,* benign tumors that grow along peripheral nerve sheaths.[5,6] PN are highly variable and can progress over time. They can grow anywhere in the body and have the potential to cause life-altering clinical complications that rarely resolve or improve spontaneously.[7]

NF1-related symptoms include:

Physical impact
Pain[4,7]
Visible deformities[4]
Motor dysfunction[4,7]
Airway compromise[4,7]
Vision impairment[8]
Bladder/bowel dysfunction[4]

Cognitive impact
Impaired attention[9]
Impaired executive function[9]
Learning difficulties[9]

Psychosocial impact
Anxiety[10]
Depression[10]
Social stigma[10]
Psychological stress[10]
Difficulties with peer relationships[10]

The burden of living with NF1 PN is multifaceted, limiting daily activities, impairing physical, mental, and emotional well-being, and increasing out-of-pocket costs due to work absences and attending medical appointments.[10-13]

Some internal PN are seen only on MRI
Advanced imaging plays an essential role in diagnosis and disease management.[4,14]

Early action is crucial to help navigate and manage NF1 PN[7]

*Using whole-body MRI.

MRI=magnetic resonance imaging; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas.

Surgery is the mainstay of NF1 PN management, but may not be appropriate for many patients and can be associated with challenges[4,15,16]

50% **of patients with NF1 PN have at least 1 inoperable PN due to the location or nature of the PN, such as[4,15†]:**

- Proximity to vital organs
- Poorly defined margins
- Challenging locations such as the head, neck, spine, or trunk
- Hypervascularity

†Based on an observational, cross-sectional study using a one-time survey among pediatric patients with NF1 PN (n=61) aged 8-18 years as well as caregivers of patients (n=82) aged 2-7 years with NF1 PN, from December 2020 to January 2021.[15]

In those who undergo surgery, complication risks include[15-17]:


Delayed healing


Permanent neurological deficits


Bleeding


Functional impairment


Necrosis


Nerve damage

Many patients who undergo surgical debulking can also experience PN regrowth, requiring repeat surgeries throughout life[16]

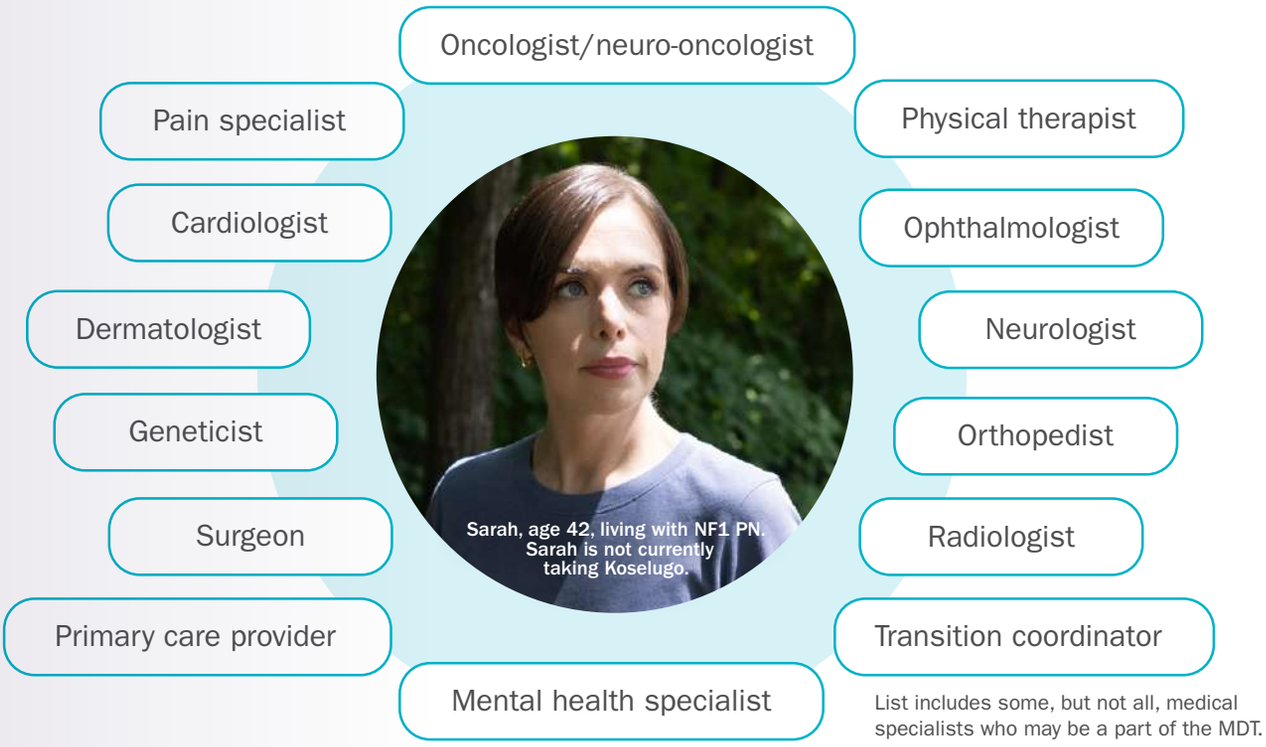
of PN can regrow following surgery, depending on the extent of excision[18,19‡]

‡Based on a retrospective review of inpatient and outpatient records of 121 patients who had 302 procedures on 168 tumors over a 20-year period at a single large pediatric referral center and a retrospective review of 96 patients who had 186 subtotal or partial resections on 130 tumors over a 10-year follow-up period at an NF center.[18,19]

NF=neurofibromatosis; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas.

A multidisciplinary team can strengthen patient care[20,21]

Timely NF1 PN management starts with you



List includes some, but not all, medical specialists who may be a part of the MDT.

Discover Koselugo (selumetinib)—an FDA-approved oral treatment option for your adult patients with symptomatic, inoperable NF1 PN[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Left Ventricular Dysfunction. Koselugo can cause cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥10% below baseline. In the pediatric safety pool, Grade 2 LVEF decrease occurred, as well as decreased LVEF of ≥20% resulting in dose interruption and dose reduction. The median time to first occurrence of LVEF decrease was approximately 12 months. In the adult population, Grade 2 LVEF decrease occurred, with decreased LVEF resulting in dose interruption. The median time to first occurrence of LVEF decrease was approximately 4 months. Assess ejection fraction by echocardiogram prior to initiating treatment, every 3 months during the first year of treatment, every 6 months thereafter, and as clinically indicated. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction. In patients who interrupt Koselugo for decreased LVEF, obtain an echocardiogram or a cardiac MRI every 3 to 6 weeks until resolution. Upon resolution of decreased LVEF, obtain an echocardiogram or a cardiac MRI every 2 to 3 months.

Ocular Toxicity. Koselugo can cause ocular toxicity, including retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED), and blurred vision. In the pediatric safety pool, blurred vision, photophobia, cataracts, ocular hypertension, and retinal tear occurred. Blurred vision resulted in dose interruption. RPED occurred in the pediatric population during treatment with Koselugo and resulted in permanent discontinuation. In the adult population, blurred vision and vitreous floaters occurred in patients receiving Koselugo. Conduct ophthalmic assessments prior to initiating Koselugo, at regular intervals during treatment, and for new or worsening visual changes. Permanently discontinue Koselugo in patients with RVO. Withhold Koselugo in patients with RPED, conduct ophthalmic assessments every 3 weeks until resolution, and resume Koselugo at a reduced dose.

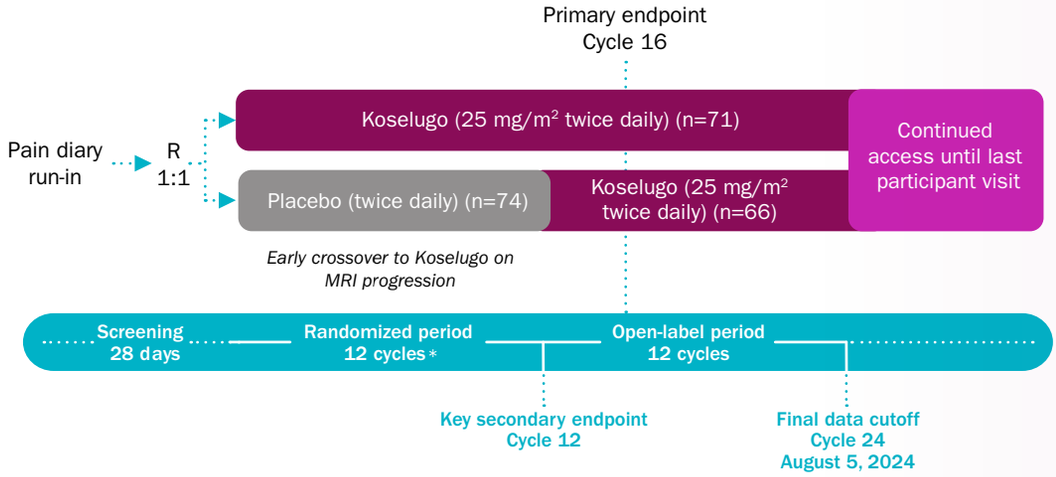
Please see additional Important Safety Information throughout and the full Prescribing Information for Koselugo (selumetinib).

FDA=Food and Drug Administration; MDT=multidisciplinary team; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas.

KOMET: the largest placebo-controlled clinical trial conducted to date in adults with symptomatic, inoperable NF1 PN[3]

KOMET was the first Phase 3, multicenter, international study with a parallel, randomized, double-blind, placebo-controlled design in adults with NF1 PN. KOMET was designed to evaluate the efficacy and safety of Koselugo in 145 adults with NF1 and symptomatic, inoperable PN.[3]

KOMET study design[3]



Primary endpoint: overall response rate by the end of Cycle 16 vs placebo[3]

Defined as the percentage of patients with complete response (disappearance of the target PN) or confirmed partial response (target PN volume decrease of ≥20% from baseline) by the end of Cycle 16, as determined by ICR per REiNS criteria[3†]

Select key secondary endpoint: change in PAINS-pNF chronic target PN pain intensity score from baseline at Cycle 12 vs placebo[3‡]

Assessed in patients with a PAINS-pNF chronic target PN pain intensity score ≥3 at baseline[3]

*A cycle is 28 days.[3]
†Response was confirmed by a consecutive 3D MRI scan within 3-6 months after the first response.[1]
‡PAINS-pNF is an NF1 PN–specific adaptation of the NRS-11 scale developed by the NCI. The PAINS-pNF scale is designed to assess both episodic and chronic pain related to NF1 PN separately. Participants rate their pain on a scale from 0 (no pain) to 10 (worst possible pain), considering pain spikes and usual chronic pain in a specific tumor location using 2 separate scales.[3]

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Toxicity. Koselugo can cause gastrointestinal toxicities, including diarrhea and colitis. In the pediatric safety pool (N=134), diarrhea occurred in 59% of patients, in addition to diarrhea resulting in permanent discontinuation and dose interruption. In the adult population (N=71), diarrhea occurred in 42% of patients who received Koselugo, in addition to diarrhea resulting in dose interruption. The median time to first onset of diarrhea was approximately 2 months in the pediatric safety pool and 1 month in the adult population. Advise patients to start an anti-diarrheal agent (eg, loperamide) and to increase fluid intake immediately after the first episode of diarrhea. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Please see additional Important Safety Information throughout and the full Prescribing Information for Koselugo (selumetinib).

3D=three-dimensional; ICR=independent central review; MRI=magnetic resonance imaging; NCI=National Cancer Institute; NF1=neurofibromatosis type 1; NRS-11=Numeric Rating Scale-11; PAINS-pNF=Pain Intensity Scale for Plexiform Neurofibromas; PN=plexiform neurofibromas; R=randomized; REiNS=Response Evaluation in Neurofibromatosis and Schwannomatosis.

Koselugo® (selumetinib)
10 mg & 25 mg capsules
5 mg & 7.5 mg oral granules

Baseline characteristics of the adults enrolled in KOMET reflect those seen in clinical practice[3,22]

Eligibility criteria in KOMET

Key inclusion criteria[3]

- ≥18 years of age with NF1 and symptomatic, inoperable PN
- A completed PAINS-pNF diary with a documented chronic target PN pain score on ≥4 of 7 days over ≥2 weeks during screening
- Stable chronic pain medication at baseline
- Naïve to MEK inhibitors

Key exclusion criteria[23]

- Confirmed or suspected malignant glioma or malignant peripheral nerve sheath tumor
- Receipt of the last dose of systemic PN target treatment within 4 weeks or 5 half-lives, whichever is longer, prior to the first dose of study intervention
- Received radiotherapy in the 6 weeks prior to the start of study intervention or any prior radiotherapy directed at the target or nontarget PN

Baseline characteristics were generally well-balanced between treatment groups[3]

PN-related morbidities present in >20% of patients included pain, motor dysfunction, and disfigurement.[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Skin Toxicity. Koselugo (selumetinib) can cause severe rashes, including dermatitis acneiform. In the pediatric safety pool (N=134), rash occurred in 68% of patients. The most frequent rashes included dermatitis acneiform (47%) and maculopapular rash (31%). Pruritus, alopecia, and eczema occurred. In the adult population (N=71), rash occurred in 85% of patients who received Koselugo. The most frequent rash included dermatitis acneiform (66%). Alopecia and pruritus occurred in patients who received Koselugo. Grade 3 rash and rash resulting in dose interruption and dose reduction occurred in both the pediatric safety pool and the adult population. Permanent discontinuation also occurred in the adult population. Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Increased Creatine Phosphokinase (CPK). Koselugo can cause increased CPK, myalgia, and rhabdomyolysis. In the pediatric safety pool (N=134), increased CPK, based on laboratory data, occurred in 73% of patients, including Grade 3 or 4. In the adult population (N=71), increased CPK, based on laboratory data, occurred in 70% of patients who received Koselugo, including Grade 3 or 4. Increased CPK resulted in dose interruption and dose reduction in both the pediatric safety pool and adult population. Increased CPK concurrent with myalgia occurred in both populations, including one patient who permanently discontinued Koselugo for myalgia in the pediatric safety pool. Obtain serum CPK prior to initiating Koselugo, periodically during treatment, and as clinically indicated. If increased CPK occurs, evaluate for rhabdomyolysis or other causes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Increased Levels of Vitamin E and Risk of Bleeding (Koselugo Capsules). Koselugo capsules contain vitamin E, which can inhibit platelet aggregation and antagonize vitamin K-dependent clotting factors. Supplemental vitamin E is not recommended if daily vitamin E intake (including the amount of vitamin E in Koselugo and supplement) will exceed the recommended or safe limits due to increased risk of bleeding. An increased risk of bleeding may occur in patients who are co-administered vitamin-K antagonists or anti-platelet antagonists with Koselugo capsules. Monitor for bleeding in these patients and increase international normalized ratio (INR) monitoring in patients taking a vitamin-K antagonist. Perform anticoagulant assessments more frequently and adjust the dose of vitamin-K antagonists or anti-platelet agents as appropriate. Koselugo oral granules do not contain vitamin E.

Please see additional Important Safety Information throughout and the full Prescribing Information for Koselugo (selumetinib).

MEK=mitogen-activated protein kinase kinase; NF1=neurofibromatosis type 1; PAINS-pNF=Pain Intensity Scale for Plexiform Neurofibromas; PN=plexiform neurofibromas.

Koselugo is the only therapy proven to deliver significant PN volume reduction vs placebo in adults with symptomatic, inoperable NF1 PN[3]

Overall response rate* by the end of Cycle 16 (primary endpoint)[1]

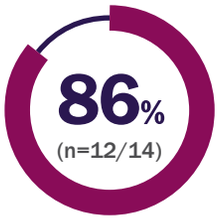
20%
(14/71) of patients on Koselugo
(95% CI: 11, 31)

≥20% PN reduction
(*P*=0.011)

5%
(4/74) of patients on placebo†
(95% CI: 2, 13)

The median time to onset of response to Koselugo was 3.7 months (range: 3.6, 11.2)[1]

Koselugo had a sustained effect on PN volume over time[3]



of Koselugo responders remained in response for ≥6 months[1]

The median duration of response was not reached for Koselugo[1†]

The duration of response for placebo was not determined[1]

*Defined as the percentage of patients with a complete response (disappearance of target PN) or confirmed partial response (≥20% reduction in PN volume from baseline confirmed at a subsequent tumor assessment within 3-6 months after first response) by the end of Cycle 16 as determined by ICR and REiNS criteria. DCO August 5, 2024.[3]

†Two out of 4 placebo responders had a confirmed partial response at Cycle 16, Day 28, after 4 cycles of Koselugo treatment.[3]

‡Primary analysis. DCO August 5, 2024.[3]

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Embryo-Fetal Toxicity. Koselugo can cause fetal harm when administered during pregnancy. In animal studies, administration of selumetinib to mice during organogenesis caused reduced fetal weight, adverse structural defects, and effects on embryo-fetal survival at approximate exposures >5 times the human exposure at the clinical dose of 25 mg/m^2 twice daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Koselugo and for 1 week after the last dose.

Please see additional Important Safety Information throughout and the full Prescribing Information for Koselugo (selumetinib).

CI=confidence interval; DCO=data cutoff; ICR=independent central review; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas; REiNS=Response Evaluation in Neurofibromatosis and Schwannomatosis.

Koselugo® (selumetinib)
10 mg & 25 mg capsules
5 mg & 7.5 mg oral granules

Data on chronic PN-related pain

Limitations of analysis

The key secondary endpoint below did not reach statistical significance. Due to hierarchical testing, the endpoints lower in the hierarchy were also not significant. Therefore, these results are observational in nature and should be interpreted with caution.

LS mean change in PAINS-pNF score from baseline to Cycle 12 in patients who had a baseline PAINS-pNF pain intensity score ≥3[3]*

Koselugo twice daily

LS mean
−2.0
(95% CI: −2.6, −1.4)
(n=42)

Placebo twice daily

LS mean
−1.3
(95% CI: −1.8, −0.7)
(n=42)

- The difference did not reach statistical significance and results should be interpreted with caution

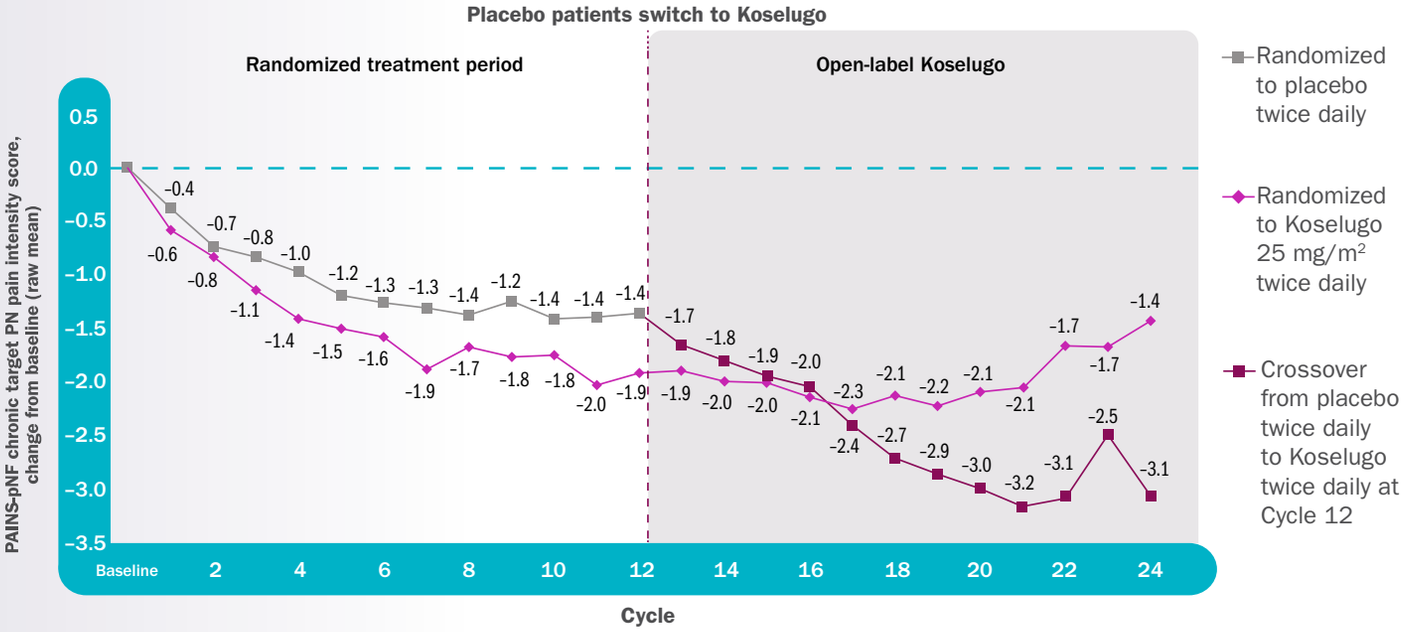
*At baseline, 70% (50/71) of patients in the Koselugo group and 72% (53/74) of patients in the placebo group had a PAINS-pNF chronic target PN score ≥3. In the randomized period, a clinically meaningful difference defined as a change of 2 points was estimated based on PAINS-pNF, which is an NF1-specific adaptation of the NRS-11 scale. During the study, participants completed a daily e-diary to rate their worst target PN pain intensity over approximately the past 24 h by selecting a number between 0 (no tumor pain) and 10 (worst tumor pain possible).[3]

Supplementary, descriptive analysis: change in pain intensity score over time[3]

Limitations of analysis

The graph below shows the raw mean change from baseline in PAINS-pNF chronic target PN pain intensity score over time for the pain full analysis set. The results are descriptive in nature and should therefore be interpreted with caution.

Change from baseline in PAINS-pNF chronic target PN pain intensity score over time, pain full analysis set[3]



Number of patients																								
Koselugo	50	49	48	48	48	48	47	45	45	45	45	41	44	44	40	40	39	33	28	23	20	15	13	11	7
Placebo	53	53	53	53	50	49	48	48	48	47	46	45	44	41	41	41	42	35	31	26	23	18	13	10	8

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

ADVERSE REACTIONS

Common adverse reactions ≥40% in pediatric patients include vomiting, diarrhea, increased CPK, dry skin, paronychia, nausea, dermatitis acneiform, and pyrexia.

Common adverse reactions ≥40% in adult patients include rash (all), dermatitis acneiform, and diarrhea.

Please see additional Important Safety Information throughout and the full Prescribing Information for Koselugo (selumetinib).

CI=confidence interval; LS=least squares; NF1=neurofibromatosis type 1; NRS-11=Numeric Rating Scale-11; PAINS-pNF=Pain Intensity Scale for Plexiform Neurofibromas; PN=plexiform neurofibromas.

Koselugo (selumetinib) has a well-characterized safety profile[3]

The safety profile of Koselugo evaluated over **~1.8 years in KOMET** was generally consistent with that observed in the SPRINT study in pediatric patients.[1,3,23†]

The most common adverse reactions (≥40%) in KOMET were rash (all), rash (acneiform), and diarrhea[1]

No new safety signals were observed in the adult population, and most AEs were mild or moderate (Grade 1 or 2).[3]

Serious adverse reactions occurred in 14% of patients who received Koselugo; only cellulitis occurred in more than 1 patient (2.8%).[1]

†This statement reflects exposure to Koselugo in 74 pediatric patients who received a dosage ranging from 20 mg/m^2 to 30 mg/m^2 orally twice daily in the SPRINT Phase 1 and Phase 2 Stratum 1 studies. At the DCO of February 2021, the median duration of exposure to Koselugo was 4.4 years (range: 28 days to 7.7 years).[24] In KOMET, 145 patients were randomized to receive Koselugo 25 mg/m^2 or placebo twice-daily for 12 cycles (28-day cycles), after which placebo patients crossed over to receive open-label Koselugo. At the DCO of August 2024, median total duration of exposure was 554 days (approximately 18.2 months) in patients randomized to Koselugo.[1,3]

KOMET study adverse reactions (≥20%) in patients who received Koselugo compared with placebo[1]

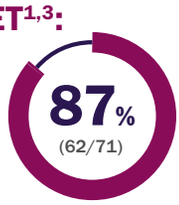
	Randomized to Koselugo† (n=71)		Randomized to placebo† (n=74)	
Adverse reactions	All Grades (%)	Grades ≥3 (%)	All Grades (%)	Grades ≥3 (%)
Skin and subcutaneous tissue				
Rash (all)§	85	4.2	23	0
Rash acneiform‖	66	2.8	11	0
Musculoskeletal and connective tissue				
Musculoskeletal pain¶	23	0	22	0
Gastrointestinal				
Diarrhea	42	0	12	0
Vomiting	25	0	8	0
Nausea	25	0	16	0
General				
Edema#	21	0	1.4	0
Fatigue**	24	0	14	0

†ADRs of patients during the 12-cycle (48 weeks) randomization period.
§Rash (all) included acne, dermatitis, dermatitis acneiform, erythema, exfoliative rash, rash, rash erythematous, rash follicular, rash maculopapular, rash pruritic, rash pustular, urticaria, rash macular, and rash papular.
‖Rash (acneiform) included acne and dermatitis acneiform.
¶Musculoskeletal pain included arthralgia, back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, and pain in extremity.
#Edema included localized edema, edema, edema peripheral, and peripheral swelling.
**Fatigue included asthenia and fatigue.

Adverse reactions can be manageable and may not require discontinuation[1]

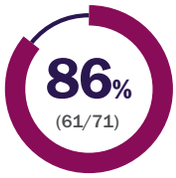
Patients (N=137) received Koselugo for a median duration of 11 months (range: 10 days to 31 months).[1]

In KOMET[1,3]:



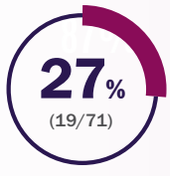
of patients did not permanently discontinue Koselugo due to AEs

Adverse reactions resulting in permanent discontinuation included dermatitis acneiform, cellulitis, nausea, wound, neurofibrosarcoma, neurofibrosarcoma recurrent, psychiatric decompensation, ulcerative keratitis, and nail disorder



of patients did not require dose reduction due to AEs

Adverse reactions requiring a dosage reduction in ≥2 patients were paronychia, increased CPK, increased ALT, increased AST, rash, and alopecia



of patients required dose interruption due to AEs but reinitiated therapy††

Adverse reactions requiring a dosage interruption in ≥2 patients were increased CPK, rash, headache, abdominal pain, nausea, and COVID-19

††These patients may have discontinued at a later date.

Please see additional Important Safety Information throughout and the full Prescribing Information for Koselugo (selumetinib).

AE=adverse event; ADR=adverse drug reaction; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; DCO=data cutoff.

Indication & Important Safety Information

INDICATION

KOSELUGO is indicated for the treatment of adult and pediatric patients 1 year of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Left Ventricular Dysfunction. Koselugo can cause cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥10% below baseline. In the pediatric safety pool, Grade 2 LVEF decrease occurred, as well as decreased LVEF of ≥20% resulting in dose interruption and dose reduction. The median time to first occurrence of LVEF decrease was approximately 12 months. In the adult population, Grade 2 LVEF decrease occurred, with decreased LVEF resulting in dose interruption. The median time to first occurrence of LVEF decrease was approximately 4 months. Assess ejection fraction by echocardiogram prior to initiating treatment, every 3 months during the first year of treatment, every 6 months thereafter, and as clinically indicated. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction. In patients who interrupt Koselugo for decreased LVEF, obtain an echocardiogram or a cardiac MRI every 3 to 6 weeks until resolution. Upon resolution of decreased LVEF, obtain an echocardiogram or a cardiac MRI every 2 to 3 months.

Ocular Toxicity. Koselugo can cause ocular toxicity, including retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED), and blurred vision. In the pediatric safety pool, blurred vision, photophobia, cataracts, ocular hypertension, and retinal tear occurred. Blurred vision resulted in dose interruption. RPED occurred in the pediatric population during treatment with Koselugo and resulted in permanent discontinuation. In the adult population, blurred vision and vitreous floaters occurred in patients receiving Koselugo. Conduct ophthalmic assessments prior to initiating Koselugo, at regular intervals during treatment, and for new or worsening visual changes. Permanently discontinue Koselugo in patients with RVO. Withhold Koselugo in patients with RPED, conduct ophthalmic assessments every 3 weeks until resolution, and resume Koselugo at a reduced dose.

Gastrointestinal Toxicity. Koselugo can cause gastrointestinal toxicities, including diarrhea and colitis. In the pediatric safety pool (N=134), diarrhea occurred in 59% of patients, in addition to diarrhea resulting in permanent discontinuation and dose interruption. In the adult population (N=71), diarrhea occurred in 42% of patients who received Koselugo, in addition to diarrhea resulting in dose interruption. The median time to first onset of diarrhea was approximately 2 months in the pediatric safety pool and 1 month in the adult population. Advise patients to start an anti-diarrheal agent (eg, loperamide) and to increase fluid intake immediately after the first episode of diarrhea. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Skin Toxicity. Koselugo can cause severe rashes, including dermatitis acneiform. In the pediatric safety pool (N=134), rash occurred in 68% of patients. The most frequent rashes included dermatitis acneiform (47%) and maculopapular rash (31%). Pruritus, alopecia, and eczema occurred. In the adult population (N=71), rash occurred in 85% of patients who received Koselugo. The most frequent rash included dermatitis acneiform (66%). Alopecia and pruritus occurred in patients who received Koselugo. Grade 3 rash and rash resulting in dose interruption and dose reduction occurred in both the pediatric safety pool and the adult population. Permanent discontinuation also occurred in the adult population. Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Increased Creatine Phosphokinase (CPK). Koselugo can cause increased CPK, myalgia, and rhabdomyolysis. In the pediatric safety pool (N=134), increased CPK, based on laboratory data, occurred in 73% of patients, including Grade 3 or 4. In the adult population (N=71), increased CPK, based on laboratory data, occurred in 70% of patients who received Koselugo, including Grade 3 or 4. Increased CPK resulted in dose interruption and dose reduction in both the pediatric safety pool and adult population. Increased CPK concurrent with myalgia occurred in both populations, including one patient who permanently discontinued Koselugo for myalgia in the pediatric safety pool. Obtain serum CPK prior to initiating Koselugo, periodically during treatment, and as clinically indicated. If increased CPK occurs, evaluate for rhabdomyolysis or other causes. Withhold, reduce dose, or permanently discontinue Koselugo based on severity of adverse reaction.

Increased Levels of Vitamin E and Risk of Bleeding (Koselugo Capsules). Koselugo capsules contain vitamin E, which can inhibit platelet aggregation and antagonize vitamin K-dependent clotting factors. Supplemental vitamin E is not recommended if daily vitamin E intake (including the amount of vitamin E in Koselugo and supplement) will exceed the recommended or safe limits due to increased risk of bleeding. An increased risk of bleeding may occur in patients who are co-administered vitamin-K antagonists or anti-platelet antagonists with Koselugo capsules. Monitor for bleeding in these patients and increase international normalized ratio (INR) monitoring in patients taking a vitamin-K antagonist. Perform anticoagulant assessments more frequently and adjust the dose of vitamin-K antagonists or anti-platelet agents as appropriate. Koselugo oral granules do not contain vitamin E.

Embryo-Fetal Toxicity. Koselugo can cause fetal harm when administered during pregnancy. In animal studies, administration of selumetinib to mice during organogenesis caused reduced fetal weight, adverse structural defects, and effects on embryo-fetal survival at approximate exposures >5 times the human exposure at the clinical dose of 25 mg/m^2 twice daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Koselugo and for 1 week after the last dose.

ADVERSE REACTIONS

Common adverse reactions ≥40% in pediatric patients include vomiting, diarrhea, increased CPK, dry skin, paronychia, nausea, dermatitis acneiform, and pyrexia.

Common adverse reactions ≥40% in adult patients include rash (all), dermatitis acneiform, and diarrhea.

DRUG INTERACTIONS

Effect of Other Drugs on Koselugo

Concomitant use of Koselugo with a strong or moderate CYP3A4 inhibitor or fluconazole increased selumetinib plasma concentrations, which may increase the risk of adverse reactions. Avoid coadministration with Koselugo. If coadministration cannot be avoided, reduce Koselugo dosage.

Concomitant use of Koselugo with a strong or moderate CYP3A4 inducer decreased selumetinib plasma concentrations, which may reduce Koselugo efficacy. Avoid concomitant use with Koselugo.

SPECIAL POPULATIONS

Pregnancy & Lactation. Verify the pregnancy status of patients of reproductive potential prior to initiating Koselugo. Due to the potential for adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with Koselugo and for 1 week after the last dose.

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or at https://us-aereporting.astrazeneca.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information for Koselugo (selumetinib) at https://alexion.com/Documents/koselugo_uspi.pdf.

Please see additional Important Safety Information throughout and the full Prescribing Information for Koselugo (selumetinib).

Koselugo®
(selumetinib)
10 mg & 25 mg capsules
5 mg & 7.5 mg oral granules

Koselugo (selumetinib) comes with a team

ONESOURCE®
Personalized Patient Support from Alexion

OneSource™ is a free, personalized support program offered by Alexion. Whether your patient is newly diagnosed or has had NF1 for some time, our specialists are available to provide support throughout their journey.

The OneSource team helps your patients start and stay on Koselugo

Support services include:

- Navigating health insurance coverage
- Ensuring continuous access to Koselugo
- Providing personalized disease and treatment education
- Hosting events to connect the NF1 PN community
- Providing educational resources

Your patients can pay as little as $0 for Koselugo if they have commercial insurance through the OneSource CoPay program.*

Patients and providers can contact OneSource via email: **OneSource@Alexion.com** or phone: **1-888-765-4747**, 8:30 AM–8:00 PM ET, Monday to Friday.

Enroll your patients in OneSource today! Download the enrollment form **here**.

Follow the steps in our How to Access Koselugo Guide to get your patients started on Koselugo. Download the Guide **here**.

*Please refer to the full CoPay Terms and Conditions at **www.AlexionOneSource.com/KosCopay**.

NF1=neurofibromatosis type 1; PN=plexiform neurofibromas.

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Koselugo is the only therapy proven to deliver significant PN volume reduction vs placebo in adults with NF1 PN[3]*

The FIRST

FDA-approved therapy for patients aged 1 year and older with symptomatic, inoperable NF1 PN[1,2]

of real-world experience

in pediatric patients[1,25†]

Well-characterized safety profile

evaluated for ~1.8 years in KOMET and 7.7 years in pediatric patients in SPRINT[1,3,24‡]

Continuous dosing

with no mandatory monthly dosing interruptions[§] and an option for patients who have difficulty swallowing whole capsules[1]

[§]Dose adjustments may be necessary based on individual safety and tolerability.[1]

*In the KOMET Phase 3 study, 20% (14/71; 95% CI: 11, 31) of patients receiving Koselugo and 5% (4/74; 95% CI: 2, 13) of patients receiving placebo saw a ≥20% decrease in the size of their PN volume from baseline by the end of Cycle 16, confirmed by 3D MRI scan (*P*=0.011).[1]

Discover how Koselugo may help your adult patients with symptomatic, inoperable NF1 PN at Koselugohcp.com.

[†]Since FDA approval: April 10, 2020.[1,25]

[‡]This statement reflects exposure to Koselugo in 74 pediatric patients who received a dosage ranging from 20 mg/m^2 to 30 mg/m^2 orally twice daily in the SPRINT Phase 1 and Phase 2 Stratum 1 studies. At the DCO of February 2021, the median duration of exposure to Koselugo was 4.4 years (range: 28 days to 7.7 years).[24] In KOMET, 145 patients were randomized to receive Koselugo 25 mg/m^2 or placebo twice-daily for 12 cycles (28-day cycles), after which placebo patients crossed over to receive open-label Koselugo. At the DCO of August 2024, median total duration of exposure was 554 days (range: 454 to 657 days) in patients randomized to Koselugo.[1,3]

INDICATION

KOSELUGO is indicated for the treatment of adult and pediatric patients 1 year of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS associated with Koselugo include Left Ventricular Dysfunction, Ocular Toxicity, Gastrointestinal Toxicity, Skin Toxicity, Increased Creatine Phosphokinase (CPK), Increased Levels of Vitamin E and Risk of Bleeding (Koselugo Capsules), and Embryo-Fetal Toxicity.

ADVERSE REACTIONS

Common adverse reactions ≥40% in pediatric patients include vomiting, diarrhea, increased CPK, dry skin, paronychia, nausea, dermatitis acneiform, and pyrexia.

Common adverse reactions ≥40% in adult patients include rash (all), dermatitis acneiform, and diarrhea.

DRUG INTERACTIONS include strong/moderate CYP3A4 inhibitors or fluconazole and strong/moderate CYP3A4 inducers.

Please see additional Important Safety Information throughout and the full Prescribing Information for Koselugo (selumetinib).

3D=three-dimensional; CI=confidence interval; DCO=data cutoff; FDA=Food and Drug Administration; MRI=magnetic resonance imaging; NF1=neurofibromatosis type 1; PN=plexiform neurofibromas.

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