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Updated efficacy and safety of vimseltinib in patients with tenosynovial giant cell tumor: 1-year follow-up from the MOTION phase 3 trial

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Declaration of interests

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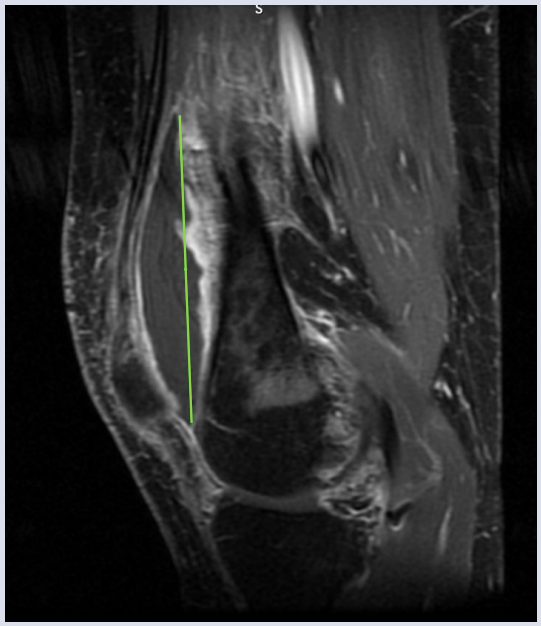
Tenosynovial giant cell tumor (TGCT): locally aggressive neoplasm driven by CSF1R and treated with vimseltinib

- TGCT is a locally aggressive neoplasm caused by dysregulation of the *CSF1* gene leading to overproduction of CSF1[1,2]
- Patients with TGCT experience pain, stiffness, and decreased physical function of affected joints; not all patients have disease that is amenable to surgery[1,3,4]
- Systemic treatment options are limited, and none are approved in Europe
- Patients require therapies with manageable toxicity due to the need for long-term treatment[1]
  - An unmet need remains for an effective CSF1R-targeted therapy with a favorable safety profile
- Vimseltinib is an investigational, oral, switch-control tyrosine kinase inhibitor specifically designed to selectively and potently inhibit CSF1R[5,6]



TGCT in the right knee

CSF1, colony-stimulating factor 1; CSF1R, CSF1 receptor; TGCT, tenosynovial giant cell tumor.

1) Stacchiotti S, et al. *Cancer Treat Rev*. 2023;112:102491. 2) West RB, et al. *Proc Natl Acad Sci USA*. 2006;103(3):690-5. 3) Mastboom MJ, et al. *Interact J Med Res*. 2018;7(1):e4. 4) Lin F, et al. *J Health Econ Outcomes Res*. 2022;9(1):68-74. 5) Smith BD, et al. *Mol Canc Ther*. 2021;20(11);2098-109. 6) Caldwell TM, et al. *Bioorg Med Chem Lett*. 2022;74:128928.

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MOTION trial design: an international, randomized, double-blind, placebo-controlled phase 3 study

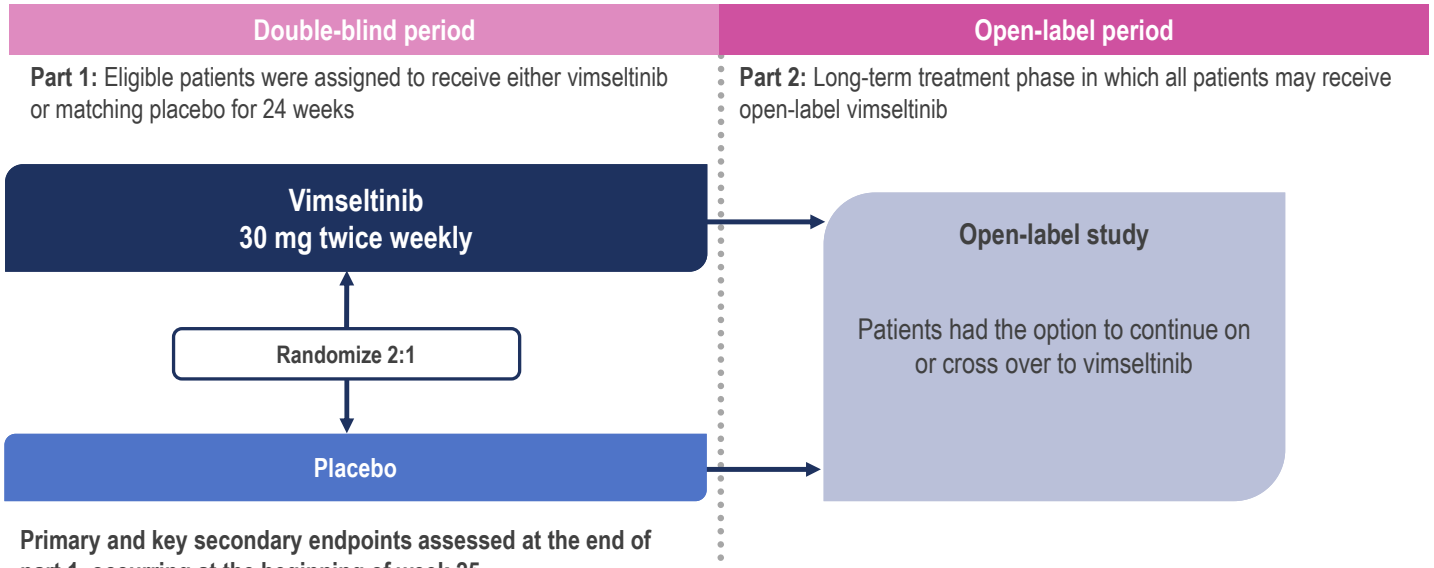
Key eligibility criteria

Patients ≥18 years old with a confirmed diagnosis of symptomatic TGCT for which surgical resection would potentially cause worsening of functional limitation or severe morbidity

Previous treatment with imatinib or nilotinib was allowed

Randomization was stratified by geographical region and tumor location

Clinicaltrials.gov identifier: NCT05059262



Primary endpoint: ORR by independent radiological review (IRR) using RECIST v1.1 at week 25
Powered to detect a 30% difference between treatment arms

Secondary endpoints: ORR by IRR using TVS at week 25; mean change from baseline at week 25 in active ROM, PROMIS-PF, worst stiffness NRS, and EQ-VAS; and BPI worst pain response at week 25.

Data cutoff: February 22, 2024.

BPI, Brief Pain Inventory; EQ-VAS, EuroQol Visual Analogue Scale; NRS, numeric rating scale; ORR, objective response rate; PROMIS-PF, Patient-Reported Outcomes Measurement Information System Physical Function; ROM, range of motion; TGCT, tenosynovial giant cell tumor; TVS, Tumor Volume Score.

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Patient demographics and baseline characteristics

	Vimseltinib n = 83	Placebo n = 40
Age, years, median (IQR)	45 (33–53)	43 (31–53)
Sex		
Female	46 (55)	27 (68)
Male	37 (45)	13 (33)
Race		
White	59 (71)	21 (53)
Asian	1 (1)	4 (10)
Black or African American	4 (5)	0
Other[a]	19 (23)	15 (38)
Affected joint		
Knee	56 (67)	27 (68)
Ankle	9 (11)	6 (15)
Hip	11 (13)	1 (3)
Other[b]	7 (8)	6 (15)
Prior TGCT surgery or procedure[c]	64 (77)	27 (68)
Prior TGCT systemic therapy	19 (23)	9 (23)[d]
Imatinib	16 (19)	7 (18)
Nilotinib	2 (2)	4 (10)
Other[e]	1 (1)	0

- In total, 118 patients received vimseltinib
  - In the vimseltinib arm, 73/83[f] patients continued to receive treatment in part 2
  - In the placebo arm, 35/40 patients crossed over to vimseltinib in part 2
- At the updated data cutoff (February 2024), 79 (67%) patients remain on treatment

Data obtained from Gelderblom H, et al. *The Lancet.* 2024;403(10445):2709-19. Data shown as n (%) unless otherwise noted.
[a]Includes not reported and unknown. [b]Includes foot, wrist, hand, shoulder, elbow, and temporomandibular joint. [c]All patients had histologically confirmed TGCT per diagnostic biopsy or existing pathology report; diagnostic biopsies were not recorded as a prior surgery or procedure. [d]Two patients in the placebo arm received both imatinib and nilotinib. [e]Includes an investigational agent (BP 27 672). [f]One patient randomized to vimseltinib continued to part 2 but did not receive treatment.
AE, adverse event; IQR, interquartile range; IRR, independent radiological review; PD, progressive disease; TGCT, tenosynovial giant cell tumor.

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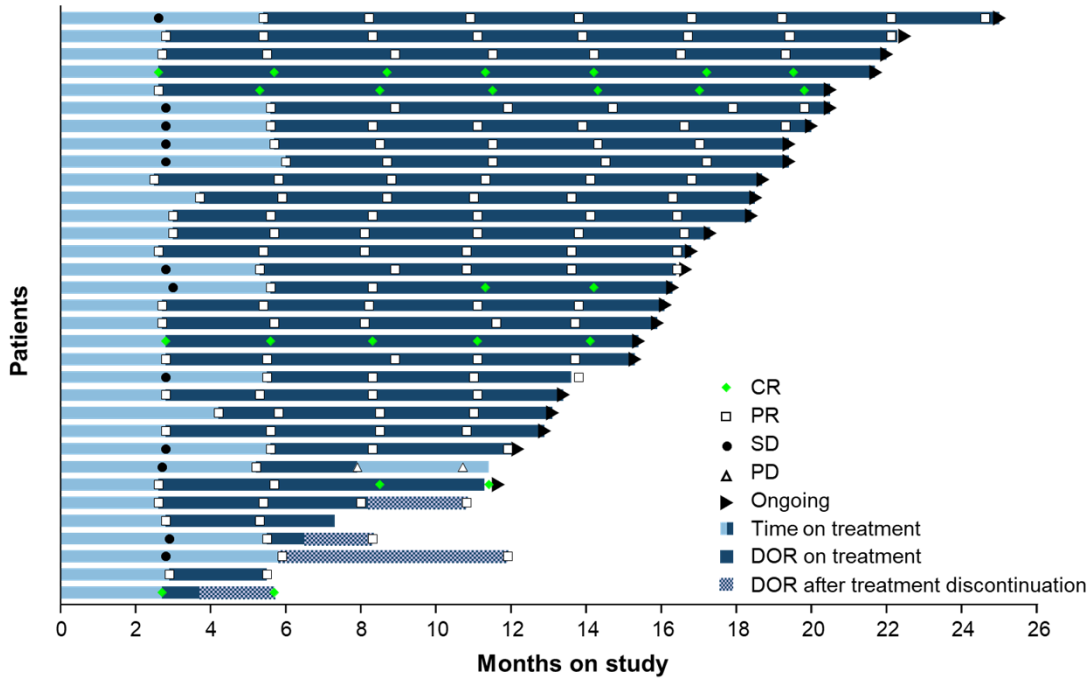
Vimseltinib demonstrated durable antitumor activity per RECIST v1.1 with ≥1 year of follow-up



At week 25	Vimseltinib n = 83	Placebo n = 40
Overall response using RECIST v1.1		
CR	4 (5)	0
PR	29 (35)	0
SD	42 (51)	33 (83)
NE	8 (10)	7 (18)
ORR using RECIST v1.1	33 (40)	0
Treatment difference, % (95% CI), *P*-value[a]	40 (29 to 51), ***P* <0.0001**	

At the time of data cutoff in part 2, the median DOR[b] for the 33 responders was still not reached (range, 2.5+ to 19.4+ months) and 12 of the responses lasted ≥12 months

Data cutoff in part 2: February 22, 2024. Data in the table were obtained from Gelderblom H, et al. *The Lancet*. 2024;403(10445):2709-19. Data cutoff in part 1: August 22, 2023.
Using RECIST v1.1 by IRR; includes all available follow-up visits for patients with objective responses. Patients who did not have an assessment at the end of part 1 for any reason or whose week 25 assessment after the first dose in the open-label period or outside of the visit window of ±14 days were assessed as NE and a nonresponder.
[a]An unstratified exact CI was utilized. [b]Based on Kaplan-Meier estimate. DOR is defined as the time from first imaging result showing response to disease progression or death by any cause.
CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

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Vimseltinib demonstrated durable antitumor activity per TVS with ≥1 year of follow-up

- The irregular growth and shape of TGCT can make measurement with linear methods, like RECIST, difficult[1]
- Tumor Volume Score (TVS) is a TGCT-specific semiquantitative MRI scoring system that estimates tumor volume[1]
- TVS response corresponds to ≥50% reduction in estimated tumor volume
- ORR by TVS at week 25 may predict long-term best overall response by RECIST

At week 25	Vimseltinib n = 83	Placebo n = 40
Overall response using TVS		
CR	4 (5)	0
PR	52 (63)	0
SD	19 (23)	34 (85)
PD	0	1 (3)
NE	8 (10)	5 (13)
ORR using TVS	56 (67)	0
Treatment difference, % (95% CI), *P*-value	67 (56 to 77), ***P* <0.0001**	

At the time of data cutoff in part 2, the median DOR[a] for the 56 responders was still not reached (range, 2.5+ to 19.4+ months) and 23 of the responses lasted ≥12 months

Data cutoff in part 2: February 22, 2024. Data in the table were obtained from Gelderblom H, et al. *The Lancet.* 2024;403(10445):2709-19. Data cutoff in part 1: August 22, 2023. Data shown as n (%) unless otherwise noted. Patients who did not have an assessment at the end of part 1 for any reason or whose week 25 assessment after the first dose in the open-label period or outside of the visit window of ±14 days were assessed as NE and a nonresponder.

[a]Based on Kaplan-Meier estimate. DOR is defined as time from first imaging result showing response to disease progression or death by any cause.

CI, confidence interval; CR, complete response; DOR, duration of response; MRI, magnetic resonance imaging; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TGCT, tenosynovial giant cell tumor; TVS, Tumor Volume Score.

1) Peterfy C, et al. *Future Oncol*. 2022;18(12):1449-59.

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Vimseltinib provided statistically significant and clinically meaningful improvements versus placebo in part 1

- Clinically meaningful improvements in secondary endpoints could translate to impactful differences in quality of life, such as being able to bathe independently, climb stairs without assistance, or perform tasks for employment[1]
- Symptomatic benefit was not limited to patients with objective RECIST responses; patients receiving vimseltinib who had stable disease also had meaningful improvements in active ROM and PRO measures

At week 25	Vimseltinib n = 83	Placebo n = 40	*P*-values
Active Range of Motion			
% Mean change from baseline (SE)	18.4 (6.5)	3.8 (7.2)	***P* = 0.0077**
PROMIS-Physical Function			
Mean change from baseline (SE)	4.6 (1.0)	1.3 (0.9)	***P* = 0.0007**
Worst stiffness Numeric Rating Scale			
Mean change from baseline (SE)	−2.1 (0.2)	−0.3 (0.3)	***P* <0.0001**
EQ-Visual Analogue Scale			
Mean change from baseline (SE)	13.5 (2.4)	6.1 (2.9)	***P* = 0.0155**
BPI worst pain			
n (% Response rate[a])	40 (48)	9 (23)	***P* = 0.0056**

Data obtained from Gelderblom H, et al. *The Lancet.* 2024;403(10445):2709-19. Data cutoff in part 1: August 22, 2023.
[a]Responder: Experienced at least a 30% decrease in mean BPI worst pain and did not experience a 30% or greater increase in narcotic analgesic use; Mean change from baseline and standard errors are estimated using a mixed model for repeated measures.
BPI, Brief Pain Inventory; EQ, EuroQol; PRO; patient-reported outcome; PROMIS, PRO Measurement Information System; RECIST, Response Evaluation Criteria in Solid Tumors; ROM, range of motion; SE, standard error.
1) Mastboom, MJ et a. *Interact J Med Res*. 2018;7:e4.

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Vimseltinib continued to be well tolerated with ≥1 year of follow-up with few discontinuations due to TEAEs

TEAEs in ≥15% of patients in either treatment arm	Vimseltinib → vimseltinib (combined parts 1 + 2) n = 83		Placebo → vimseltinib n = 35		Vimseltinib total (vimseltinib and crossover) N = 118	
Preferred term, n (%)	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Periorbital edema	39 (47)	3 (4)	17 (49)	1 (3)	56 (47)	4 (3)
Pruritis	29 (35)	3 (4)	10 (29)	2 (6)	39 (33)	5 (4)
Asthenia	27 (33)	1 (1)	8 (23)	1 (3)	35 (30)	2 (2)
Face edema	28 (34)	1 (1)	7 (20)	0	35 (30)	1 (1)
Blood CPK increased	26 (31)	10 (12)	8 (23)	4 (11)	34 (29)	14 (12)
Fatigue	30 (36)	1 (1)	4 (11)	0	34 (29)	1 (1)
AST increased	22 (27)	1 (1)	11 (31)	0	33 (28)	1 (1)
Arthralgia	23 (28)	0	9 (26)	0	32 (27)	0
Headache	24 (29)	1 (1)	8 (23)	1 (3)	32 (27)	2 (2)
Hypertension	18 (22)	6 (7)	10 (29)	4 (11)	28 (24)	10 (8)
Nausea	22 (27)	0	5 (14)	0	27 (23)	0
Rash	22 (27)	0	5 (14)	0	27 (23)	0
Rash maculopapular	20 (24)	2 (2)	6 (17)	0	26 (22)	2 (2)
Edema peripheral	17 (20)	0	7 (20)	0	24 (20)	0
Diarrhea	15 (18)	1 (1)	7 (20)	0	22 (19)	1 (1)
ALT increased	12 (14)	0	9 (26)	0	21 (18)	0
COVID-19	16 (19)	1 (1)	3 (9)	0	19 (16)	1 (1)
Generalized edema	14 (17)	1 (1)	4 (11)	0	18 (15)	1 (1)
Insomnia	6 (7)	1 (1)	6 (17)	0	12 (10)	1 (1)

Data cutoff: February 22, 2024. [a]Reflects treatment discontinuations at data cutoff; AEs are attributed to part 1 or part 2 based on AE start date.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease-2019; CSF1R, colony-stimulating factor 1 receptor; CPK, creatine phosphokinase; TEAE, treatment-emergent AE.

1) Pognan F, et al. *Curr Res Toxicol*. 2022;3:100091. 2) Radi ZA, et al. *Am J Pathol*. 2011;179(1):240-7.

- Most TEAEs were grade 1/2
- Serum enzyme elevations were consistent with the known mechanism of action of CSF1R inhibitors[1,2]
- TEAEs led to treatment discontinuation in 8% (9/118) of all patients receiving vimseltinib[a]
- There was no evidence of cholestatic hepatotoxicity, drug-induced liver injury, or hair/skin hypopigmentation
- Median (range) treatment duration was 14.4 (1.5–25.0) and 8.2 (0.8–18.3) months for the randomized vimseltinib and vimseltinib crossover groups, respectively

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MOTION 1-year follow-up continued to demonstrate clinically meaningful benefits of vimseltinib in patients with TGCT

- Vimseltinib provided statistically significant and clinically meaningful improvements vs placebo for the primary and all 6 key secondary endpoints, including ORR per TVS, active ROM, physical function, stiffness, health status, and worst pain in part 1
- Significantly more patients receiving vimseltinib experienced objective tumor response by IRR using RECIST v1.1 or TVS than those receiving placebo
- Updated results from part 2 demonstrated sustained tumor responses with vimseltinib and a safety profile consistent with the known safety profile of vimseltinib
- Vimseltinib was well tolerated with manageable adverse events and no evidence of cholestatic hepatotoxicity, drug-induced liver injury, or hair/skin hypopigmentation
- If approved, vimseltinib offers an effective systemic treatment for patients with TGCT and provides proven functional health and symptomatic benefits to a population living with substantial morbidity and limited treatment options

IRR, independent radiological review; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ROM, range of motion; TGCT, tenosynovial giant cell tumor; TVS, Tumor Volume Score.

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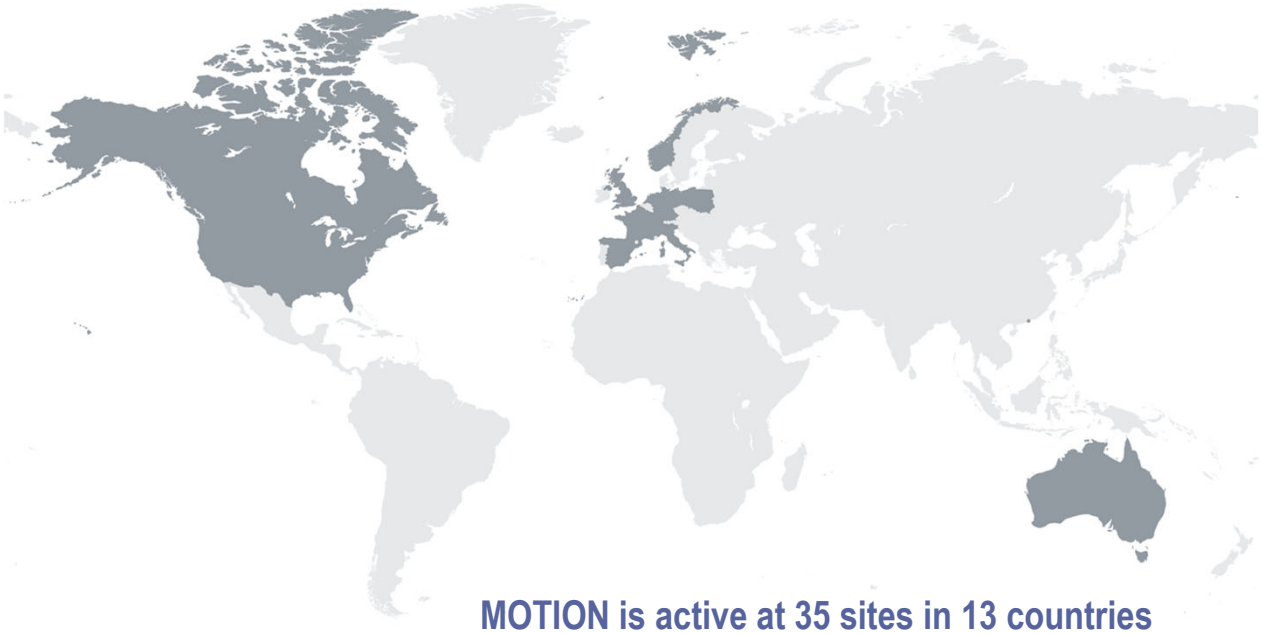

MOTION is active at 35 sites in 13 countries

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