A Mixed-Methods Analysis to Define Minimum Clinically Importance Differences (MCIDs) in Range of Motion, Physical Function, and Worst Stiffness in Patients with Tenosynovial Giant Cell Tumor (TGCT)

Heather Gelhorn[1], Katelyn N Cutts[1], Tsion Fikre[1], Yipin Han[1], Christopher Tait[2], Nicholas Zeringo[2], Amanda Saunders[2], Brooke Harrow[2]

[1]Patient-Centered Research, Evidera, Bethesda, MD, USA
[2]Deciphera Pharmaceuticals, LLC, Waltham, MA, USA

Disclosures

- HG, KNC, TF, and YH are employees of Evidera who were contracted by Deciphera to conduct the research study.
- CT, NZ, AS, and BH are employees of Deciphera.

Background and Study Objectives

Background

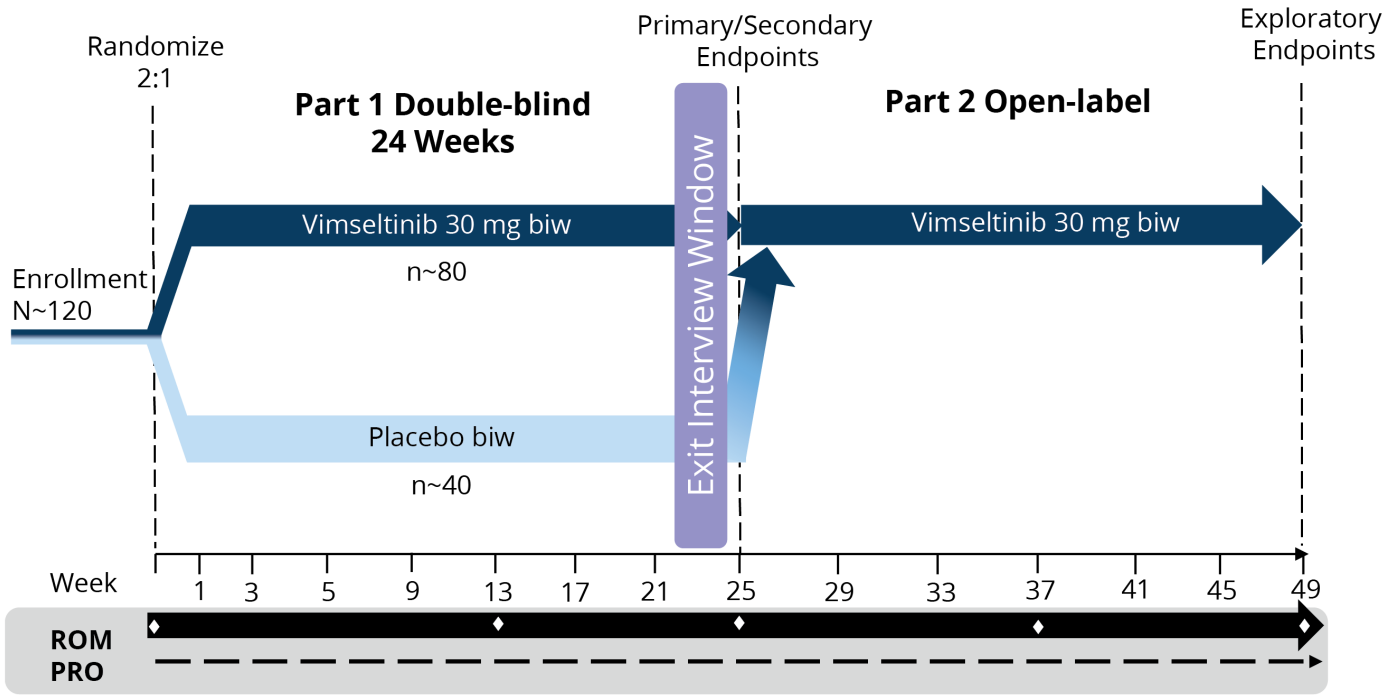
- Tenosynovial giant cell tumor (TGCT) is a locally aggressive neoplasm that involves the synovium, bursae, or tendon sheath. Tumor location varies and is often associated with joint destruction, pain, stiffness, and limited range of motion (ROM).
- Previous research in TGCT demonstrated content validity, psychometric properties and thresholds for meaningful change (PROMIS-PF and worst stiffness NRS).[1-4]

Objective

To define a meaningful change in clinical outcome assessments (COAs) measuring active range of motion, physical function and stiffness among patients with TGCT using a mixed-methods approach, gathering both quantitative and qualitative data (i.e., clinical trial exit interviews) on meaningful change directly from patients.

1. Gelhorn HL, et al. *Clin Ther*. 2016;38(4):778-793
2. Gelhorn HL, et al. *J Patient Rep Outcomes*. 2019;3(1):6.
3. Speck RM, et al. *J Patient Rep Outcomes*. 2020;4(1):61
4. Tap WD, et al. *Clin Cancer Res*. 2022;28(2):298-307

MOTION[1] is an international, randomized, double-blind, placebo-controlled phase 3 study of vimseltinib, an investigational CSF1R inhibitor in patients with TGCT



Patient population and eligibility criteria:

- Histologically confirmed, symptomatic tenosynovial giant cell tumor.
- Surgical resection will potentially cause worsening functional limitations or severe morbidity.
- No prior use of systemic therapy targeting CSF1 or CSF1R (except imatinib and nilotinib).

Primary Endpoint
ORR, including CR and PR per RECIST v1.1 at week 25 by IRR
Key Secondary Endpoints
ORR per TVS at week 25 by IRR
Change from baseline in active ROM of the affected joint, relative to a reference standard, at week 25
Change from baseline in the PROMIS-PF score at week 25
Change from baseline in the Worst Stiffness NRS score at week 25
Change from baseline in EQ-VAS at week 25
Response of at least a 30% improvement in the mean BPI Worst Pain NRS score without a 30% or greater increase in narcotic analgesic use at week 25

Abbreviations: BIW = twice weekly; BPI = Brief Pain Inventory; CR= complete response; CSF1/CSF1R = anti-colony-stimulating factor 1/colony-stimulating factor 1 receptor; IRR = independent radiological review; NRS = numeric rating scale; ORR = objective response rate; PR = partial response; PRO = patient-reported outcome; PROMIS-PF = Patient-reported Outcomes Measurement Information System Physical Function; RECIST = Response Evaluation Criteria in Solid Tumors ; ROM = range of motion; TGCT = tenosynovial giant cell tumor; TVS = tumor volume score; VAS = visual analog scale

1. Gelderblom H, et al. The Lancet. 2024;403(10445):2709-19

Outcome Measures and Anchors

- **Patient-Reported Outcomes Measurement Information System (PROMIS)-Physical Functioning (PF) form:** a 15-item questionnaire specific to patients with TGCT.
- **Active Range of Motion (ROM):** ROM for the affected joint was assessed using goniometry.
- **Worst Stiffness Numeric Rating Scale (NRS):** a single item evaluating worst stiffness in the past 24 hours on a scale from 0 (no stiffness) to 10 (worst imaginable).
- **Patient Global Impression of Severity (PGIS):** two single items evaluating the severity of tumor-related physical functioning and limited ROM at the site of the tumor on a 5-point scale ranging from “none” to “very severe.”
- **Patient Global Impression of Change (PGIC):** three single items evaluating change over time of tumor-related physical functioning, ROM, and overall at the site of the tumor on a 5-point scale ranging from “very much improved” to “very much worsened”.

Abbreviations: TGCT = tenosynovial giant cell tumor

Qualitative Exit Interviews

- Qualitative embedded exit interviews were conducted within 28 days prior to the end of Part 1 visit (week 25) and prior to unblinding during MOTION.
- Exit interview participants were cognitively debriefed on the COA measures of interest and asked about meaningful change.
  - Patients were randomized to one of three groups: PROMIS-PF, PGIS/PGIC- PF and ROM, and Worst Stiffness NRS.
  - Patients randomized to debrief on the PGIS/PGIC were asked about the minimal amount of change in the patient global impression of change anchors they would consider to be meaningful for the following items:

PGIC-Physical Function: "*How has your tumor-related physical functioning changed since the start of the trial? Please focus on your ability to do daily activities such as walking, climbing stairs, or carrying groceries.*" *Response options ranging from "very much improved " to "very much worse".*

PGIC-Range of Motion: *"Please focus on your range of motion – how far and how naturally you can bend, straighten, and pivot the joint at the site of your tumor (i.e., affected joint). Choose the response below that best describes the overall change in your range of motion since the start of the trial." Response options ranging from "very much improved " to "very much worse".*

Abbreviations: COA = clinical outcome assessment; NRS = numeric rating scale; PGIC = patient global impression of change; PGIS = patient global impression of severity; PROMIS-PF = Patient-reported Outcomes Measurement Information System Physical Function; ROM = range of motion

Quantitative Analysis

- Qualitative results from the exit interviews were used for defining the primary anchor categories for the quantitative analyses.
- Anchor- and distribution-based methods were used to estimate thresholds for meaningful change for PROMIS-PF, ROM, and Worst Stiffness.
  - Correlations were assessed to evaluate appropriateness of anchors.
  - The responder definition point estimates were derived from the minimal meaningful change group(s) for each anchor, as identified by the majority of patients in the exit interviews.
- Triangulation of these point estimates was then used to converge on a single point estimate for each responder definition.
- All analyses were conducted on blinded data prior to trial primary analysis.

Abbreviations: PROMIS-PF = Patient-reported Outcomes Measurement Information System Physical Function; ROM = range of motion

Sample Disposition

- A total of 123 patients were randomized in MOTION, with n=96[1] (78%) completing an exit interview.

Interview Sample	PROMIS-PF	PGIS and PGIC for PF and ROM	Worst Stiffness NRS
Interviews Completed	33*	33	26

Abbreviations: NRS = numeric rating scale; PGIC = patient global impression of change; PGIS = patient global impression of severity; PROMIS-PF = Patient-reported Outcomes Measurement Information System Physical Function; ROM = range of motion
*includes six patients with upper-extremity tumors and 27 patients with lower-extremity tumors per randomization stratification factors.
[1] N=4 participants were excluded from the final qualitative interview sample due to audio quality issues, and not experiencing stiffness (n=1).

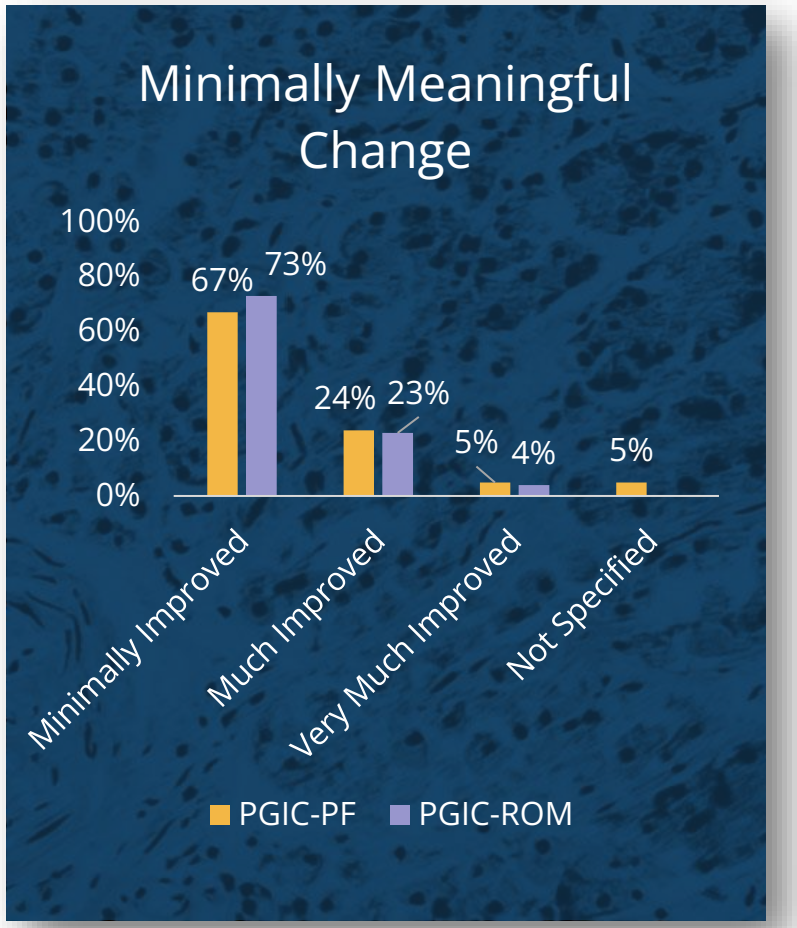
- All MCID analyses were conducted using an interim data cut comprising approximately 75% of the sample (n=93).

MCID Analysis Sample	PROMIS-PF	Active ROM	Worst Stiffness NRS
Baseline and Week 25	71	81	73

Abbreviations: MCID = minimum clinically important difference; NRS = numeric rating scale; PROMIS-PF = Patient-reported Outcomes Measurement Information System Physical Function; ROM = range of motion

Qualitative Input on Meaningful Change in PGIC-PF and PGIC–ROM

A majority of patients felt a minimal improvement was meaningful and would have an impact on their ability to perform daily activities



Subject 1, hip: *Even again,* ***minimally improved****, if . . . I could* ***exercise for a little bit longer or I could climb steps without using a rail****. Even if I could just have that more minimal improvement, that would've been enough to just feel satisfied with the treatment… just living with chronic pain 24/7, you just* ***look for the little moments where you have a bit of relief and a bit of a break****.*

Subject 2, foot: *Especially when you have kids, that* ***minimal change*** *may be* ***able to run with my kids, play with my kids****. . . . being able to spend time with your kids* ***is very meaningful to me****…Even though it's a minimal change . . . it means a lot to me because I can do a lot with that.* ***Even going to work right now is very easy*** *for me.*

Key portions of the quote are bolded for emphasis.

Abbreviations: PGIC-PF = patient global impression of change – physical functioning; PGIC-ROM = patient global impression of change – range of motion

MCID: Correlations between Anchors and PRO Change Scores

All patient reported anchors, had an appropriate association (r ≥ 0.30) with the measures

COA Anchor	Change in PROMIS-PF score from Baseline to Week 25			Change in ROM Assessment score from Baseline to Week 25			Change in Worst Stiffness NRS from Baseline to Week 25		
	n	r[a]	p-value	n	r[a]	p-value	n	r[a]	p-value
Change in PGIS-PF from baseline to week 25	71	-0.43	0.0002	–	–	–	-	-	-
PGIC-PF at week 25	71	-0.54	<0.0001	–	–	–	-	-	-
Change in PGIS-ROM from baseline to week 25	-	-	-	67	-0.34	0.0045	-	-	-
PGIC-ROM at week 25	–	–	–	68	-0.39	0.0010	-	-	-
PGIC-Overall condition at week 25	71	-0.46	<0.0001	68	-0.38	0.0012	67	0.41	0.0006

[a] Spearman's rank sum correlation

Abbreviations: COA = clinical outcome assessment; MCID = minimum clinically important difference; NRS = numeric rating scale; PF = physical functioning; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; ROM = range of motion.

Anchor-based Analyses: Active ROM

For the change in PGIS-ROM, the primary anchor, the mean change from baseline in active ROM assessment for patients with a **1-point improvement was 9.0** (SD=13.5). For PGIC-ROM at Week 25, the mean change from baseline in active ROM assessment among patients reporting "**minimally improved" was 6.0** (SD=22.0).

Score	Any Improvement	3-Point Improvement	2-Point Improvement	1-Point Improvement	No Change (0-Point Change)	1-Point Worsening	2-Point Worsening	3-Point Worsening
Change in PGIS-ROM From Baseline to Week 25								
n	30	1	8	21	31	5	1	0
Mean (SD)	15.3 (28.7)	23.7 (–)	30.9 (49.8)	**9.0 (13.5)**	6.8 (20.5)	7.7 (39.0)	-10.0 (–)	–
Score	**Any Improvement**	**Very Much Improved**	**Much Improved**	**Minimally Improved**	**No Change**	**Minimally Worse**	**Much Worse**	**Very Much Worse**
PGIC-ROM at Week 25								
n	46	8	23	15	15	5	2	0
Mean (SD)	14.5 (29.2)	34.7 (48.0)	13.0 (22.3)	**6.0 (22.0)**	4.2 (10.0)	4.3 (20.7)	-14.4 (15.1)	–
PGIC-Overall Condition at Week 25								
n	47	12	23	12	15	5	1	0
Mean (SD)	14.3 (29.0)	29.1 (39.3)	9.0 (23.7)	**9.4 (22.6)**	3.8 (14.0)	-0.1 (15.2)	-3.7 (–)	–

Abbreviations: PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; ROM = range of motion; SD = standard deviation

Based on the qualitative input from the exit interview study, 1-point improvement in PGIS and minimally improved on PGIC were used as the primary anchor category as noted in bold and yellow highlight.

Anchor-based Analyses: PROMIS-PF

For the change in PGIS-PF, the primary anchor, the mean change from baseline in PROMIS-PF score among patients with a **1-point improvement was 4.4** (SD=4.1). The mean change from baseline in PROMIS-PF score among patients reporting "**minimally improved" on the PGIC-PF was 2.6** (SD=4.1).

Score	Any Improvement	3-Point Improvement	2-Point Improvement	1-Point Improvement	No Change (0-Point Change)	1-Point Worsening	2-Point Worsening	3-Point Worsening
Change in PGIS-PF From Baseline to Week 25								
n	36	2	8	26	29	6	0	0
Mean (SD)	6.0 (5.8)	22.5 (9.2)	7.3 (2.5)	**4.4 (4.1)**	2.2 (4.9)	1.8 (5.3)	–	–
	Any Improvement	**Very Much Improved**	**Much Improved**	**Minimally Improved**	**No Change**	**Minimally Worse**	**Much Worse**	**Very Much Worse**
PGIC-PF at Week 25								
n	52	13	24	15	13	5	1	0
Mean (SD)	5.4 (5.8)	9.7 (7.2)	4.9 (4.7)	**2.6 (4.1)**	0.8 (3.5)	0.4 (4.2)	-1.0 (–)	–
PGIC-Overall Condition at Week 25								
n	51	14	25	12	14	5	1	0
Mean (SD)	5.4 (5.9)	8.7 (7.1)	4.8 (5.1)	**2.9 (4.3)**	0.5 (3.5)	2.2 (4.3)	-1.0 (–)	–

Abbreviations: PF = physical functioning; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = standard deviation

Based on the qualitative input from the exit interview study, 1-point improvement in PGIS and minimally improved on PGIC were used as the primary anchor category as noted in bold and yellow highlight.

Anchor-based Analyses: Worst Stiffness

- There was no PGIS or PGIC specific to stiffness included in the MOTION study.
- The mean change in Worst Stiffness NRS among patients reporting “minimally improved” on the PGIC-Overall Condition at Week 25 was -0.9 (SD=1.3) and -2.3 (SD=1.8) for patients reporting “much improved.”

Score	PGIC-Overall Condition at Week 25							
	Any Improvement	Very Much Improved	Much Improved	Minimally Improved	No Change	Minimally Worse	Much Worse	Very Much Worse
n	46	11	24	11	15	5	1	0
Mean (SD)	-2.2 (2.1)	-3.4 (2.8)	**-2.3 (1.8)**	**-0.9 (1.3)**	-0.6 (1.9)	-1.4 (1.5)	-0.2 (–)	–

Abbreviations: NRS = numeric rating scale; PGIC = Patient Global Impression of Change; SD = standard deviation

MCID: Triangulation

Measure	Type of Assessment	Criteria	Responder Definition Value	Selected MCID Definition
Active ROM	Anchor-based methods	Change in PGIS-ROM from baseline to week 25	9.0 to 30.9	**10%**
		PGIC-ROM at week 25	6.0 to 13.0	
		PGIC-overall condition at week 25	9.0 to 9.4	
	Distribution-based methods	$0.25*SD_{SC}$	7.38	
		$0.50*SD_{SC}$	14.75	
		SEM	9.33	
PROMIS-PF	Anchor-based methods	Change in PGIS-PF from baseline to week 25	4.4 to 7.3	**3-point**
		PGIC-PF at week 25	2.6 to 4.9	
		PGIC-overall condition at week 25	2.9 to 4.8	
	Distribution-based methods	$0.25*SD_{SC}$	1.45	
		$0.50*SD_{SC}$	2.89	
		SEM	2.00	
Worst Stiffness	Anchor-based methods	PGIC-overall condition at week 25	-0.9 to –2.3	**-2-point**
	Distribution-based methods	$0.25*SD_{SC}$	-0.50	
		$0.50*SD_{SC}$	-0.99	
		SEM	-0.58	

Abbreviations: MCID = minimum clinically important difference; NRS = numeric rating scale; PF = physical functioning; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; ROM = range of motion; SD_{SC} = standard deviation - screening; SEM = standard error of measurement

Note: A negative value indicates improving stiffness.

Conclusion

- Combined evidence from anchor and distribution-based methods supported by patient insights from qualitative interviews informed the final selection of MCIDs of:
  - +10% for active ROM
  - +3 points for PROMIS-PF
  - -2 points for Worst Stiffness NRS

- The MCID reflects the patient experience with treatment and demonstrates the importance of the treatment changes from the patient perspective, which is especially critical for TGCT.
- These thresholds were used in the analysis of COA data from the recently published Phase 3 trial of vimseltinib in TGCT to determine whether the magnitude of the changes were meaningful from the patient perspective. The results were clinically significant for all COA endpoints including ROM, PROMIS-PF and Worst Stiffness NRS.[1]

1. Gelderblom H, et al. The Lancet. 2024;403(10445):2709-19

Abbreviations: COA= clinical outcome assessment; MCID = miminum clinically important difference; NRS = numeric rating scale; PROMIS-PF = Patient-Reported Outcomes Measurement Information System Physical Function; ROM = range of motion; TGCT = Tenosynovial Giant Cell Tumor

Acknowledgments

We thank the patients and their families and caregivers, the investigators, and the investigational site staff for the MOTION phase 3 study.

The MOTION study is sponsored by Deciphera Pharmaceuticals, LLC.