Anchor-Based Method to Determine Minimal Clinically Important Improvement (MCII) For a Novel Autologous Therapy Used to Treat Osteoarthritis

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INTRODUCTION: Assessment of both pain and functional improvement, coupled with determining whether the improvement is clinically meaningful for the patient, are necessary to evaluate the clinical efficacy of treatments for osteoarthritis (OA). The minimal clinically important improvement (MCII) is the smallest change in measurement that signifies a meaningful improvement in a patient's condition. Instead of a general responder criterion defined by a fixed-point improvement in patient reported outcomes (PROs), Tubach et al. defined a method whereby the specific MCII for a particular therapy is determined by anchoring pain and functional outcome scores to patient global impressions by asking the patients directly how they rate their own improvement (1). Tubach's method suggests that the MCII for an oral NSAID may be different than the MCII for a specific intra-articular injection. Following the method outline by Tubach, a MCII was established for a novel intra-articular therapy (Autologous Protein Solution (APS) obtained by using the nSTRIDE® Kit, Zimmer Biomet) in a pilot study and then used in larger clinical studies to determine the percentage of responders.

METHODS: Three clinical studies were utilized to evaluate the effect of a single injection of APS in subjects with mild to moderate knee OA. All clinical studies were approved by ethics committees and subjects signed informed consents before enrollment. Studies were conducted in Europe (post-market) and US (IDE, BQ180271). In the pilot study (PROGRESS II: NCT02138890), subjects were asked at the 12-month follow-up visit to rate their improvement using a Patient Global Impression of Improvement scale (PGI-I) ("Very Much Improved", "Improved", "Minimally Improved", "No Change", "Minimally Worse", "Much Worse", and "Very Much Worse"). WOMAC (LK3.1) pain (0-20) and function (0-68) score changes from baseline to 12 months were then calculated for subjects scoring themselves as "minimally improved". The MCII was established from the 25th percentile distribution of WOMAC pain and function scores (improvement from baseline). The 25th percentile of the distribution of WOMAC pain scores (improvement from baseline) for these subjects corresponds to a score achieved by 75% of the patients reporting a "minimally improved" outcome (2). Applying this MCII prospectively, the number of responders were calculated in two independent clinical trials with similar study designs (PROGRESS IV: NCT02905240; IDE 17069/11 and PROGRESS V: NCT03182374). Data is presented as mean ± standard deviation.

RESULTS: The MCIIs were derived using the anchor-based method with the PGI-I and WOMAC pain and function outcomes. In PROGRESS II, the mean improvement in WOMAC pain and function scores increased with each increasing patient rating (Table 1). The MCII was established as a 2.0 point improvement in WOMAC pain and a 7.5 point improvement in WOMAC function (Table 2). For comparison, the MCII that would be established using the anchor question of "much improved" is also provided (Table 2). Applying these MCII thresholds to larger cohorts of subjects in similarly designed trials achieved context-specific responder rates (Table 3).

DISCUSSION: The pilot study data enabled the development of an MCII that is context-specific, as it has the similar patient population, time points, baseline characteristics, baseline symptom severity, and intervention as the larger, confirmatory studies. These factors are important to consider in establishing a MCII (2). Utilization of responder comparisons using anchor-based MCII is gaining traction over the traditional approach of determining statistical significance between treatment groups in interventional studies (3). This is because the margin of measured improvement between treatments may meet the threshold of statistical significance (typically $p < 0.05$) even when the improvement is below the threshold of clinical detection by the patients. Therefore, comparing the statistical significance of responder rates (e.g. percentage of patients meeting MCII criteria) between groups addresses this concern. One limitation of this work is that no comparative or control data is represented in this analysis. This evaluation was used to define an MCII for this particularly therapy, but without comparative data, is not useful in determining effectiveness.

CLINICAL RELEVANCE: Regulatory agencies and payers are now more interested in clinical importance improvement in PROs versus direct statistical comparisons. Results from this study can be utilized in randomized, blinded controlled studies to compare responder rates between treatment and control cohorts.

REFERENCES: 1.Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Annals of the Rheumatic Diseases. 2005;64(1):34-7. 2.Bannuru RR, Vaysbrot EE, McIntyre LF. Did the American Academy of Orthopaedic Surgeons osteoarthritis guidelines miss the mark? Arthroscopy. 2014;30(1):86-9.3.Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg. 2013;21(9):571-6.

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Table 1. WOMAC Pain and Function scores per category of the transition PGI-I question

Transition Question	N	WOMAC pain mean improvement from baseline to 12 months	WOMAC function mean improvement from baseline to 12 months
Very Much Worse	1	-1.0	-7.0
Much Worse	1	1.5	4.5
Minimally Worse	5	3.2	3.8
No Change	6	4.2	7.4
Minimally Improved	9	5.8	15.8
Much Improved	18	8.4	25.3
Very Much Improved	4	10.9	37.8

Table 2. MCII Improvement from baseline to 12 months

Transition question	MCII for WOMAC Pain improvement	MCII for WOMAC Function improvement
Based on 25th percentile of the PGI - "Minimally Improved" subjects	2.0	7.5
Based on 25th percentile of the PGI - "Much Improved" subjects	7.0	20

Table 3. Percent responders that meet the MCII at 12 months (Per protocol population).

Study	Category	WOMAC Pain Responders at 12 months (%(n))	Average WOMAC Pain point improvement of subjects at 12 months	WOMAC Function Responders at 12 months (%(n))	Average WOMAC Function point improvement at 12 months
PROGRESS IV	Meets MCII	82.5% (127/154)	7.3 ± 3.3	75.3% (116/154)	24.7 ± 11.3
	Below MCII	17.5% (27/154)	-0.89 ± 1.6	24.7% (38/154)	-1.1 ± 7.1
PROGRESS V	Meets MCII	74.8% (83/111)	6.3 ± 3.3	71.2% (79/111)	20.2 ± 10.8
	Below MCII	25.2% (28/111)	-0.39 ± 1.3	28.8% (32/111)	-0.30 ± 7.0