Osteoarthritis and Cartilage 33 (2025) 383–390

Osteoarthritis and Cartilage

Exploring a novel outcome measure of symptom progression in knee osteoarthritis utilizing a large randomized trial

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ARTICLE INFO

Article history:
Received 19 January 2024
Accepted 12 December 2024

Keywords:
Osteoarthritis
Knee
Sprifermin
Fibroblast growth factor 18
Treatment outcome

SUMMARY

Objectives: Explore a newly defined composite measure of symptom progression for knee osteoarthritis (KOA) in a large, randomized study of a potential disease-modifying osteoarthritis drug (DMOAD).
Design: Using longitudinal KOA studies, a potential composite endpoint of time to symptom progression was defined as the first occurrence of worsening of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain of ≥10 points with no improvement (≤9 point decrease) in WOMAC Function (0–100 scale). A post hoc analysis explored discrimination and association with structural outcomes in the sprifermin FORWARD trial through Years 3 and 5. All treatment arms of the intent-to-treat population were analyzed.
Results: Among the 549 FORWARD participants, 442 (80.5%) completed Year 3, and 378 (68.9%) completed Year 5. Sprifermin showed dose-dependent benefits in the time to symptom progression at Year 3 with hazard ratio (95% CI) for each sprifermin treatment arm vs placebo as follows: 100 μg every 6 months (Q6M), 0.51 (0.28, 0.93); 100 μg Q12M, 0.69 (0.40, 1.20); 30 μg Q6M, 0.89 (0.53, 1.50); and 30 μg Q12M, 0.80 (0.47, 1.35). Similar findings were seen through Year 5 and for a subgroup based on modern clinical trial inclusion criteria. There were increased numbers of knee replacements in symptom progressors (n=8, 5.6%) vs non-progressors (n=7, 1.7%).
Conclusions: The symptom progression endpoint discriminated between placebo and treatment responses in a post hoc analysis of a Phase 2 investigational DMOAD KOA trial. The endpoint requires validation and further exploration in DMOAD clinical trials.
Trial number: NCT01919164

Introduction

Osteoarthritis (OA) ranks among the most common causes of chronic pain and physical disability globally, with a high burden on healthcare systems and society due to reduced work productivity and early retirement.[1–4] Consistently, the therapeutic priority for individuals with knee OA (KOA) is to avoid disability and the need for knee replacement (KR).[5–8] Physicians, experts, and regulators agree

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https://doi.org/10.1016/j.joca.2024.12.003

with the need for new disease-modifying OA drugs (DMOADs) that might intervene in both the structural and symptomatic progression of OA, in line with patient expectations.[9–11] Treatment goals related to slowing OA structural progression are to significantly delay/prevent joint failure ('joint survival', eg, no KR) but also to reduce the deterioration of function and worsening of pain ('feel').[10] The challenge in developing a DMOAD that is primarily structurally modifying (ie, without direct analgesic properties) is how to best measure feeling (pain), function, and joint survival with our currently available tools in a clinical trial which is feasible (eg, number of participants, duration) to conduct. The initial focus for a potential DMOAD may need to be demonstration of a delay in symptom worsening rather than improvement, which is in line with both regulatory guidance and patient goals.[5–8,10,11]

Considerations when developing a novel endpoint addressing symptoms in KOA clinical trials would include understanding minimum clinically meaningful changes (improvement or worsening) in pain and function as well as their relationship to structural progression. Further, as the endpoint would need to address both pain and function which may have different trajectories in KOA, likely a composite measure would be required.

The objective of this study was to develop a potential composite measure of symptom progression for use in KOA trials of DMOADs and apply the proposed endpoint to one of the few studies where structural change was demonstrated, the sprifermin FORWARD study. This endpoint would represent a first step in determining novel endpoints for the evaluation of DMOAD effectiveness.

Methods

Endpoint derivation

To derive the endpoint, data from studies reporting minimum clinically meaningful changes (improvement or worsening) in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain and Physical Function subscale scores (WOMAC Pain, WOMAC Function) were compiled (Supplementary Table 1). In several analyses, clinically meaningful changes in WOMAC Pain and Function subscales were defined as approximately 10 points in multiple studies (0–100 scale, higher numbers worse).[12–17]

Next, natural history studies of KOA evaluating the use of a clinically important worsening (9–10 points, 0–100 scale) in WOMAC Pain or Function in association with clinical outcomes of symptom worsening, cartilage thickness worsening, or KR were then identified.[18–20] Wirth et al, using the Osteoarthritis Initiative (OAI) database, reported that symptomatic progression, defined as worsening of WOMAC Pain of ≥9 points, was associated with concurrent loss in cartilage thickness during the period from 2 to 4 years post-baseline.[20] As a corollary, Deveza et al showed in OAI that individuals with cartilage thickness loss over 2 years vs stable thickness were more likely to be symptomatic progressors (defined by WOMAC Pain increase of > 9 points over 2 years) and more likely to undergo KR in the next 4 years (5.6% vs 1.5%, respectively).[18] The association of episodes of deterioration of pain and/or function with KR was also seen in the Dutch Cohort Hip and Cohort Knee (CHECK) early OA cohort.[19] A first episode of deterioration, defined as a > 9-point increase in WOMAC Pain or WOMAC Function, when adjusted for duration of follow-up in those that received KR vs those that did not (median 4.5 vs 9 years follow-up, respectively), was associated with an increased likelihood of receiving KR (odds ratio [OR] 3.2 [95% confidence interval {CI} 1.4–7.2] for WOMAC Pain; OR 2.3 [95% CI 1.1–5.0] for WOMAC Function).

Taken together, a time-to-symptom progression endpoint was defined as the first occurrence of worsening of WOMAC Pain by ≥10 points with no improvement of WOMAC Function by > 9 points (0–100 scale, higher numbers indicating worse symptoms). The symptom progression endpoint includes both pain and function components because, although unlikely, worsening pain with improved function could occur. The primary driver of the composite endpoint was pain, since, generally, studies report worsening pain as a predictor of worsened function but not the converse.[21,22] Worsening pain has also been shown to be predictive of structural progression and/or KR, but worsening function has rarely been identified as a predictor of these outcomes.[18–20,23,24] With respect to worsening function, self-reported functional impairment may not worsen over time due to modifications of behavior in response to increased pain (response shift).[25] Further, the proportion of individuals who have worsened on function but not pain or vice versa has not been reported for the individual studies.

Pain was also the driver of the endpoint since pain and functional progression in KOA have been reported to have different trajectories. Based on various analyses of data from OAI and the Multicenter Osteoarthritis Study, whereas pain in KOA continues to worsen with time with acceleration in the 2 years prior to KR, function in KOA remains relatively stable until worsening in the 2 years before KR.[23,26–29]

Endpoint populations analyzed

FORWARD was a Phase 2, multicenter, randomized, double-blind, placebo (PBO)-controlled, parallel-group, dose-finding, five-year trial of the safety and efficacy of sprifermin (NCT01919164), the design and results of which are reported elsewhere.[30,31] Briefly, participants aged 40–85 years with symptomatic radiographic KOA (Kellgren-Lawrence [KL] grade 2 or 3, medial minimum joint space width [mJSW] ≥2.5 mm, and WOMAC Pain question 1 (WOMAC A1) score of 4 to 9 [0–10 scale, higher scores indicating worse pain]) in the target knee were randomized (1:1:1:1:1) to receive three once-weekly intra-articular injections (1 cycle) of sprifermin 30 μg Q6M (x4 cycles total [x4]) or Q12M (x2 cycles total [x2]); sprifermin 100 μg Q6M (x4) or Q12M (x2); or PBO (saline) for 18 months.[30] The primary endpoint was change in total femorotibial joint cartilage thickness from baseline to 2 years as measured by quantitative magnetic resonance imaging (qMRI). WOMAC Total and Pain were secondary endpoints. The WOMAC was collected every 3 months (Q3M) and MRI Q6M through Year 2 and then at least Q12M through Year 5, respectively. The intent-to-treat population (ITT; all randomized participants) was used for WOMAC analyses; the modified ITT (mITT; all ITT participants with one baseline and at least one post-treatment qMRI assessment) was used for qMRI efficacy analyses. All participants gave written informed consent. In FORWARD, sprifermin demonstrated its ability to dose-dependently increase cartilage thickness in participants with KOA but did not prospectively show a difference from PBO in the magnitude of pain reduction or functional improvement at the 2-year primary endpoint.[30]

When applying the novel defined endpoint, in addition to utilizing the full ITT, we evaluated a population reflective of the enriched KOA populations of more recent clinical trials, termed the 'subgroup-at-risk' (SAR), published elsewhere.[32] Briefly, several publications were identified to explore an enrichment strategy, ie, selection of populations identified as having a risk for structural and symptomatic KOA progression, to utilize in future trials to potentially increase the probability of demonstrating both structural and symptomatic benefits over PBO.[20,24,33–35] Based on the studies identified, the enriched population required the presence of more advanced structural and symptomatic disease: having more pronounced but not complete cartilage loss with a resultant increased likelihood of experiencing a decrease in cartilage thickness over time without intervention, as well as a sufficient degree of pain that permitted the detection of a clinically meaningful change in pain scores from baseline.[18,24,32–34,36–41] The SAR was then identified

through post hoc analysis of the FORWARD study and had the following characteristics at baseline: 1) mJSW between 1.5 to 3.5 mm, inclusive (mJSW defined as the minimum of the lateral or medial JSW); and 2) moderate-to-severe knee pain, defined as WOMAC Pain of 40 to 90 points in the target knee.[32] The SAR (all randomized subgroup participants) was used for WOMAC analyses; the modified SAR (mSAR; all SAR participants with one baseline and at least one post-treatment qMRI assessment) was used for qMRI efficacy analyses.

Endpoint application

To test the potential utility of the novel symptom progression endpoint (first occurrence of worsening of WOMAC Pain by ≥10 points with no improvement of WOMAC Function by > 9 points), it was then applied to the FORWARD study population to assess its discrimination with respect to symptomatic outcomes but also its association with structural outcomes. Time to symptom progression was evaluated over 3 and 5 years using a survival analysis. The 3-year time frame was chosen for the primary analysis of time-to-symptom progression as it was the period in which symptom improvement was detected in the SAR in a previously published analysis; it was also used for the association of symptom progression with cartilage thickness outcomes as FORWARD participants, since no longer treated between Year 2 and Year 3, began to lose accrued cartilage.[31,32] The data were also analyzed to evaluate the association of symptom progression with KR outcomes, which had a low incidence in FORWARD over the 5-year trial period, likely due to the trial eligibility criteria.

Additional analyses included least squares mean change from baseline in WOMAC Pain and in WOMAC Function using analysis of variance at each time point; the percentage of participants who improved ≥10 points on WOMAC Pain and on WOMAC Function was also analyzed using a Chi-square test at each time point.

The populations analyzed for time-to-symptom progression were the ITT and the SAR; the SAR was included to evaluate if an enrichment strategy for KOA progressors would allow the proposed endpoint to detect more pronounced differences between the sprifermin treatment arms and PBO. Analyses evaluating mean change from baseline and ≥10-point improvements in WOMAC Pain and WOMAC Function focused on the individual sprifermin 100 μg arms only compared to PBO since these were the treatment arms shown to have the most cartilage growth in FORWARD and the most improvement in WOMAC Pain or WOMAC Function in the previous SAR analysis.[32] The populations analyzed for time-to-symptom progression at Year 3 by change in cartilage thickness (decrease or no change/increase from the original study baseline at Year 2) were the mITT and mSAR. The entire ITT and entire SAR (all treatment arms combined) were analyzed for the association of symptom progression with KR incidence.

Missing data were not imputed for any analysis. All p-values and hazard ratios (HRs) reported were nominal; there was no adjustment for multiplicity.

Results

The ITT (N=549) and the SAR (N=161) baseline characteristics are provided for reference in Table I.[30–32] In the ITT, 441 participants were randomized to sprifermin treatment and 108 to PBO. Three-hundred eighty-seven (87.8%) participants in the sprifermin groups and 87 (80.6%) in the PBO group completed the Year 2 visit; 360 (81.6%) and 82 (75.9%) completed the Year 3 visit, and 313 (71.0%) and 65 (60.2%) completed the Year 5 visit, respectively. Of the 161 individuals comprising the SAR, 127 were randomized to sprifermin treatment and 34 to PBO. One-hundred twenty (94.4%) participants in the sprifermin groups and 28 (82.4%) in the PBO group completed the Year 2 visit; 114 (89.8%) and 26 (76.5%) completed the Year 3 visit, and 101 (79.6%) and 19 (55.9%) completed the Year 5 visit, respectively.

Overall, ITT participants' mean age was 64.1 years; 69.0% were female, and 80.0% were White individuals. Baseline mean body mass index (BMI) was 29.3 kg/m^2 with 39.7% of participants being obese (BMI ≥30 kg/m^2). Most participants had KL grade 2 (69.0%). Mean medial mJSW was 4.21 mm, and the mean WOMAC A1 score was 5.6 (0–10 scale, higher scores worse). The SAR baseline characteristics were similar to those of the ITT with the exception that the SAR had more females (78.9%), a higher mean BMI (35.8 kg/m^2), and, as expected, more severe KOA by KL grade (53% KL grade 3), medial mJSW (3.46 mm), and pain than the ITT (mean WOMAC A1 score 6.2).

Compared to PBO, sprifermin treatment as a whole showed numerical dose-dependent benefits in the time-to-symptom progression in the ITT (Fig. 1A; p=0.21) by Year 3. The HR (95% CI) values for time to symptom progression at Year 3 for each sprifermin treatment arm vs PBO in the ITT were as follows: 100 μg Q6M, 0.51 (0.28, 0.93); 100 μg Q12M, 0.69 (0.40, 1.20); 30 μg Q6M, 0.89 (0.53, 1.50); and 30 μg Q12M, 0.80 (0.47, 1.35). The time to symptom progression results for sprifermin 100 μg Q6M were nominally significantly different vs PBO, but there were no significant differences in the risk of symptom progression from baseline in the novel composite endpoint for the other sprifermin treatment arms. The number of individuals experiencing symptom progression through Year 3 is presented in Supplementary Table 2.

Likewise, clinically meaningful changes in the slowing of symptom progression were seen for the SAR in the sprifermin arms compared to PBO, but earlier and with more pronounced differences (Fig. 1B) compared to the ITT (Fig. 1A), with the 100 μg Q6M arm results being nominally significant and showing the most separation in both the ITT and SAR.[12–17] The HR (95% CI) values for time to symptom progression at Year 3 for each sprifermin treatment arm vs PBO in the SAR were as follows: 100 μg Q6M, 0.28 (0.09, 0.86); 100 μg Q12M, 0.44 (0.0.17, 1.16); 30 μg Q6M, 0.33 (0.11, 1.00); and 30 μg Q12M, 0.51 (0.21, 1.24). Additionally, similar results were noted through Year 5 in the ITT and the SAR (Supplementary Figure 1 and Supplementary Figure 2).

In contrast, for both the sprifermin 100 μg arms, improvements of ≥10 points in WOMAC Pain or WOMAC Function were not present for the ITT at all time points, but in the SAR, these results were nominally significant starting at Year 1 through Year 3 for WOMAC Pain and at Year 3 for WOMAC Function (Supplementary Table 3). Mean changes in WOMAC Pain and WOMAC Function were not significant for the ITT, but in the SAR, both sprifermin 100 μg arms for WOMAC Pain and the 100 μg Q12M arm for WOMAC Function were associated with nominally significant improvements by Year 3 (Supplementary Table 4).

Sensitivity analyses were performed using a 20-point worsening in WOMAC Pain with no improvement by > 9 points in WOMAC Function at Year 3. While numerically, there continued to be trends for a dose-dependent benefit with sprifermin treatment compared with PBO, the number of individuals with this degree of worsening on WOMAC Pain were too few to be able to detect a statistically significant benefit for sprifermin in either the ITT or SAR. An analysis by sex was also performed. Although males in both the ITT and SAR PBO groups (n=168 and n=34, respectively) had more progression utilizing the composite endpoint than females (n=379 and n=127, respectively), the same degree of dose-dependent treatment responses were seen for both sexes (data not shown).

When evaluating the association of changes in cartilage thickness from baseline at Year 2 (Supplementary Figures 3–6) with symptom progression at Year 3, symptom progression for individuals on PBO was similar regardless of a decrease or no change/increase in cartilage thickness in both the mITT and mSAR. When evaluating the association of decreased cartilage thickness from baseline with

Characteristic	ITT (N=549)					SAR (N=161)				
	Placebo	Sprifermin (n=441)				Placebo	Sprifermin (n=127)			
	(n=108)	30 μg×2 (n=110)	30 μg×4 (n=111)	100 μg×2 (n=110)	100 μg×4 (n=110)	(n=34)	30 μg×2 (n=36)	30 μg×4 (n=27)	100 μg×2 (n=31)	100 μg×4 (n=33)
Mean age, years (SD)	63.5 (8.5)	65.2 (8.4)	63.2 (8.4)	63.4 (9.1)	65.2 (8.0)	62.2 (7.7)	65.3 (8.1)	65.9 (6.1)	66.0 (7.9)	66.8 (7.0)
Female, n (%)	76 (70.4)	73 (66.4)	80 (72.1)	77 (70.0)	73 (66.4)	24 (70.6)	27 (75.0)	22 (81.5)	26 (83.9)	28 (84.8)
Asian race, n (%)	21 (19.4)	22 (20.0)	23 (20.7)	23 (20.9)	21 (19.1)	7 (20.6)	6 (16.7)	6 (22.2)	10 (32.3)	5 (15.2)
White race, n (%)	87 (80.6)	88 (80.0)	88 (79.3)	87 (79.1)	89 (80.9)	27 (79.4)	30 (83.3)	21 (77.8)	21 (67.7)	28 (84.8)
Hispanic/Latino, n (%)	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean BMI (kg/m^2) (SD)	30.1 (6.1)	29.5 (5.3)	28.9 (5.5)	28.5 (5.2)	29.6 (5.1)	31.1 (6.8)	30.9 (6.5)	30.1 (6.3)	29.3 (5.4)	31.3 (5.0)
BMI ≥ 30, n (%)	48 (45.7)	46 (43.0)	41 (38.0)	38 (35.8)	45 (42.1)	15 (44.1)	19 (54.3)	10 (37.0)	12 (38.7)	19 (57.6)
KL Grade 2, n (%)	74 (68.5)	73 (66.4)	77 (69.4)	77 (70.0)	78 (70.9)	14 (41.2)	17 (47.2)	12 (44.4)	14 (45.2)	19 (57.6)
Mean medial mJSW, mm (SD)	4.20 (1.30)	4.11 (1.14)	4.23 (1.28)	4.33 (1.23)	4.23 (1.07)	3.57 (1.35)	3.32 (0.86)	3.49 (0.82)	3.40 (0.77)	3.51 (0.74)
Mean WOMAC A1 score, 0–10 (SD)	5.6 (1.4)	5.6 (1.4)	5.6 (1.4)	5.5 (1.2)	5.8 (1.4)	6.2 (1.4)	6.0 (1.4)	6.1 (1.3)	6.2 (1.2)	6.4 (1.0)
Mean WOMAC Pain score, 0–100 (SD)	46.5 (14.4)	46.8 (15.4)	45.9 (15.7)	45.2 (15.5)	48.2 (16.5)	54.8 (11.5)	55.3 (10.3)	52.1 (10.9)	58.3 (11.4)	57.9 (10.6)
Mean WOMAC Function score, 0–100 (SD)	46.1 (17.5)	45.0 (18.8)	45.3 (16.0)	41.5 (17.7)	46.7 (19.9)	55.7 (14.4)	52.4 (17.4)	50.3 (16.2)	53.8 (12.8)	59.7 (10.8)

×2, every 12 months for 2 cycles; ×4, every 6 months for 4 cycles; BMI, body mass index; ITT, intent-to-treat population; KL, Kellgren-Lawrence; mJSW, minimum joint space width; N, number in entire analysis set; n, number in sample; SAR, subgroup at risk population; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table I Osteoarthritis and Cartilage

Baseline Characteristics by Treatment Arm – FORWARD Study - ITT and SAR.

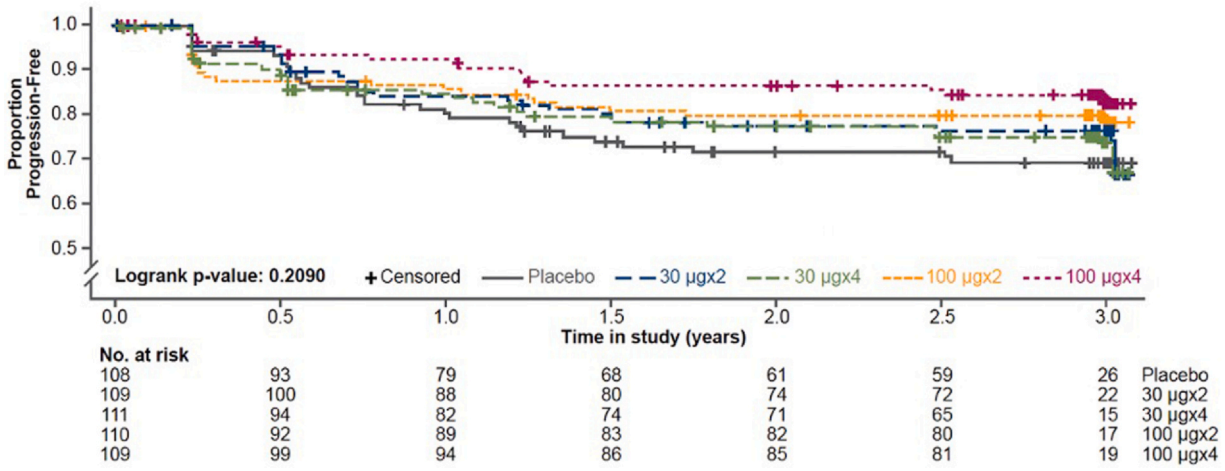

Fig. 1 Osteoarthritis and Cartilage

A. Time to Symptom Progression up to Year 3 – FORWARD Study (ITT). B. Time to Symptom Progression up to Year 3 – FORWARD Study (SAR). ×2, every 12 months for 2 cycles; ×4, every 6 months for 4 cycles; ITT, intent to treat population; No., number; SAR, subgroup at risk population.

symptom progression in both the mITT and mSAR, sprifermin treatment resulted in less symptom progression than treatment with PBO (logrank p-value < 0.05 for mITT and mSAR); the HR (95% CI) values at Year 3 for each sprifermin treatment arm vs PBO in the mITT were as follows: 100 μg Q6M, 0.43 (0.14, 1.29); 100 μg Q12M, 0.25 (0.06, 1.07); 30 μg Q6M, 0.67 (0.30, 1.52); and 30 μg Q12M, 0.1.38 (0.69, 2.76) (Supplementary Figure 3 and Supplementary Figure 4). These changes were more pronounced in the mSAR, with HR (95% CI) values < 0.001 (< 0.001, NA) for each of the sprifermin 100 μg arms vs PBO. With no change/increase in cartilage thickness, each of the sprifermin 100 μg arms showed no significant difference versus PBO in the mITT and the mSAR (Supplementary Figure 5 and Supplementary Figure 6).

The symptom progression endpoint was also associated with increased numbers of KR in symptom progressors (n=8, 5.6%) vs non-progressors (n=7, 1.7%) at Year 5 with similar trends apparent at Year 3 (n=5, 4.1% vs n=2, 0.5%). These associations were more pronounced in the SAR (Year 5: n=5, 11.9% vs n=0, 0%; Year 3: n=2. 5.7% vs n=0, 0%).

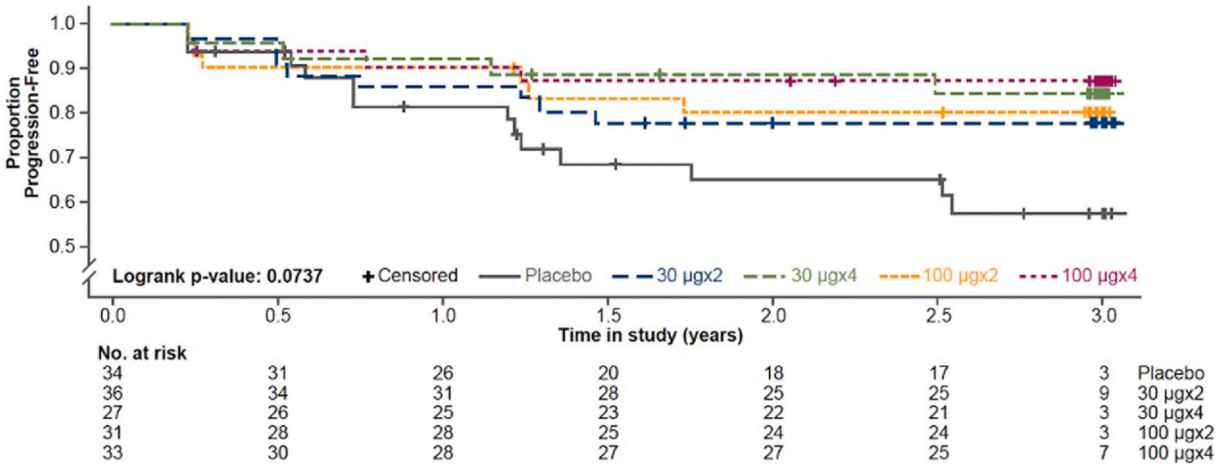

Fig. 1 Osteoarthritis and Cartilage

(*continued*)

Discussion

Using data from several natural history studies, we derived a novel composite measure to define symptom progression in KOA. In this post hoc analysis, this endpoint was able to discriminate between active and PBO arms of a potential DMOAD in a randomized clinical trial and was also associated with subsequent KR.

The use of a composite outcome measure evaluating pain and function in a clinical trial of KOA may serve to minimize multiplicity issues in analyses. Time to symptom progression was chosen rather than a straight proportional analysis because the outcome of interest is not only whether symptom progression occurred but also when that progression occurred. As individuals with OA wish to delay disease progression, a straight proportional analysis at a single time point would not clearly capture the aspect of time in the delay of OA progression, making the proposed endpoint a more patient-centric outcome measure.[5,42] Further, the use of this composite endpoint as defined with a time-to-event analysis is in accordance with the United States Food and Drug Administration (FDA) Guidance "*Multiple endpoints in clinical trials*".[43] A composite measure was also of interest since co-primary endpoints to evaluate changes in WOMAC Pain and WOMAC Function separately could result in improvements for either being met by different study participants. Thereby, results would not accurately reflect the overall response to the drug. Although unlikely, a participant could improve on pain and worsen on function or vice versa, thereby potentially having individuals with a perceived net benefit on therapy captured in a co-primary endpoint analysis.

With respect to the investigational DMOAD, sprifermin, the delay in symptom progression (worsening in pain without improvement in function) was apparent with the highest dose sprifermin treatment arm compared to PBO in the ITT and also in the SAR. Further, in evaluating the DMOAD properties of sprifermin, ie, the association of symptom progression with structural progression, separation between the sprifermin arms and PBO was seen for cartilage thickness outcomes in both populations. There was also a numerical increase in the incidence of KR in those with symptom progression compared to those without.

When evaluating symptom improvement (instead of symptom progression), differentiation of sprifermin from PBO was detected, but only in the SAR, with a lag in functional as compared to pain improvement. This lag is not surprising, as it would be expected that pain would need to improve first to allow for function to improve, and functional limitations that were a consequence of the disease process, eg, loss of muscle strength and stamina, would need time to recover after disease progression has subsided on therapy.[7] This lag may impact a trial's ability to ascertain functional improvements in KOA of a potential DMOAD within a trial period.

The ability to detect differences in symptom progression in both the enriched and the entire FORWARD populations suggests that symptom progression as defined by our endpoint may be a more sensitive measure than improvement to evaluate the effect of a DMOAD. One caveat is that because the SAR had higher WOMAC Pain scores at baseline, it raises the possibility that any improvement detected might reflect regression to the mean. However, evaluating symptom progression with a time-to-event analysis should minimize the impact of regression to the mean on the results.

With respect to the relationship of the endpoint to structural outcomes, this generally may be difficult to discern due to the small degree of cartilage thickness change associated with sprifermin treatment. In the current study, individuals with a decrease in cartilage thickness on sprifermin compared to PBO had a reduction in symptom progression, possibly due to the potential for improved biomechanical properties of cartilage occurring with sprifermin treatment that would not be captured by qMRI.[44] Though the highest dose sprifermin-treated arms consistently demonstrated less symptom progression than the PBO-treated group, the treatment effect of sprifermin over PBO was more pronounced in the subset of participants with a concurrent decrease in cartilage thickness than those with no change/increase in cartilage thickness. As the number of participants in the PBO subset with no change/increase in cartilage thickness was small, and because having no change/increase in cartilage thickness in the PBO group was unexpected, no firm conclusions can be drawn with respect to symptom progression in those with no change/increase in cartilage thickness.

When evaluating the relationship of the endpoint to KR incidence, even if the basis for receipt of KR is multifactorial, the numerical increase in KR incidence in those with symptom progression compared to those without is informative. In this study, it showed the potential association of symptom progression with the occurrence of end-stage OA, as randomization should have ensured all factors affecting the outcome of KR receipt would be similarly distributed among the treated groups.

There are limitations in the current study. First, a systematic literature review or a consensus approach was not used to derive the endpoint, and few therapeutic DMOAD trials exist that are large enough with data available in which to apply the endpoint. Further, there were a small number of participants in the SAR overall (with only 34 in the PBO arm) and a small number of individuals who received KR in the study (n=15 at Year 5). The use of post hoc analysis of observed data without imputation for missing data or correction for multiplicity testing also may have overestimated results. Also, while the FORWARD study enrolled a broad OA population, the SAR also had some baseline imbalances with outliers that may have affected the reported outcomes. Regardless, the SAR results appeared to be consistent with those of the ITT.

The novel symptom progression endpoint of KOA employed in this study discriminated between active treatment and PBO, especially in a population subset more typical of modern DMOAD trials. This symptom progression endpoint, not yet validated, bears further exploration prospectively in DMOAD clinical studies as a composite measure of joint pain and function. We hope this study will encourage further research into novel patient-relevant endpoints for DMOAD studies.

Role of the funding source

The FORWARD Trial was funded by EMD Serono. Post hoc analysis and medical writing support were funded by Formation Bio Inc.

Author contributions

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Responsibility for the integrity of the work as a whole: PGC, NG; Conception and design: NG, KS. Analysis and interpretation of the data: All authors. Drafting of the article: NG. Critical revision of the article for important intellectual content: All authors.

Conflict of interest

PGC: Speakers bureau: AbbVie, Novartis, Consultant of: AbbVie, AstraZeneca, Biosplice, BMS, Eli Lilly, Galapagos, Genascence, GSK, Grunenthal, Levicept, Merck, Novartis, Pfizer, Regeneron, Stryker, and UCB; NK: Consultant of: Formation Bio; D.H. Consultant of: Lilly, Novartis, Pfizer, TissueGene, TLCBio; AG: Consultant of: AstraZeneca, Grunenthal, Levicept, Novartis, Organogenesis, Pfizer, Regeneron, TissueGene, Formation Bio, Employee of: Owner, Boston Imaging Core Lab (BICL); MH: Consultant for: Formation Bio; KS: Shareholder of: Formation Bio, Consultant of: Formation Bio, Employee of: Former employee of Formation Bio; JC: Consultant of: Former consultant of Formation Bio; CK: Employee of: Formation Bio, MJ: Consultant of: Former consultant of Formation Bio; LZ; Employee of: Formation Bio; NG: Shareholder of: UCB, Consultant of: Centrexion, Formation Bio, Former consultant of: Ampio. Employee of: Former employee of Formation Bio.

Acknowledgments

The authors would like to acknowledge the contributions of the FORWARD participants and clinic staff. Medical writing assistance was provided by Judy Wiles, Trish Rawn, and Selma Tse of Facet Communications Inc. Statistical assistance was provided by Christine Pan and Peter Song of CPAN, Inc. Final formatting support was provided by Alexandra Dulle and Mary Heckler of Formation Bio. PGC is supported in part by the National Institute for Health and Care Research (NIHR) Leeds Biomedical Research Centre (NIHR203331). The views expressed are those of the authors and not necessarily those of the National Health Service (NHS), the NIHR or the Department of Health.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2024.12.003.

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