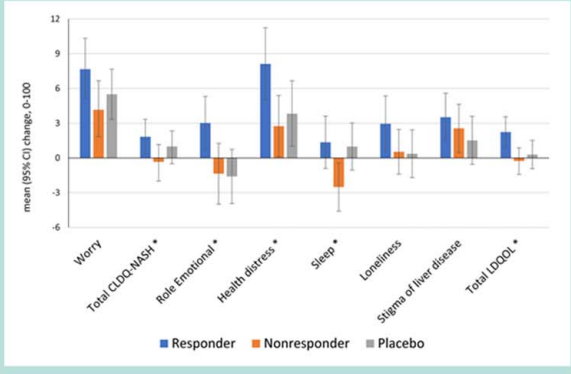
Health-related quality of life (HRQL) assessments in a 52-week, double-blind, randomized, placebo-controlled phase III study of resmetirom (MGL-3196) in patients with metabolic dysfunction–associated steatohepatitis (MASH) and fibrosis

VISUAL ABSTRACT

Health-related quality of life (HRQL) assessments in a 52-week, double-blind, randomized, placebo-controlled phase III study of resmetirom (MGL-3196) in patients with metabolic dysfunction–associated steatohepatitis (MASH) and fibrosis



*Changes in select HRQL scores in subjects with (Responder) vs. without (Nonresponder) fibrosis improvement or NASH resolution response to treatment with resmetirom (*p<0.05) vs. placebo.*

- Of the 966 subjects (ITT cohort in MAESTRO-NASH), n=323 received resmetirom 100 mg, n=322 resmetirom 80 mg, and n=321 placebo.
- After 52 weeks of treatment with resmetirom (100 mg or 80 mg), subjects who met the primary histologic endpoints (improvement of fibrosis or resolution of NASH) experienced improvement in several HRQL domains (Figure).
- Similar improvements in HRQL were observed in histologic responders from 100 mg and 80 mg resmetirom groups separately, contrasted by no improvements in placebo and in nonresponders.
- Histologic responders with baseline F3 had similar or more pronounced improvements of HRQL in comparison to responders with baseline F1B/F2 stage.
- In conclusion, MASH/NASH patients who achieved improvement of fibrosis or resolution of MASH with resmetirom experienced clinically meaningful and statistically significant improvements in multiple domains of HRQL.

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ORIGINAL ARTICLE

Health-related quality of life (HRQL) assessments in a 52-week, double-blind, randomized, placebo-controlled phase III study of resmetirom (MGL-3196) in patients with metabolic dysfunction–associated steatohepatitis (MASH) and fibrosis

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Abstract

Background and Aims: Resmetirom, liver-directed thyroid-hormone receptor-β agonist, received approval for metabolic dysfunction–associated steatohepatitis (MASH) treatment. We assessed health-related quality of life (HRQL) in patients with MASH treated with resmetirom.

Approach and results: Patients with MASH/NASH without cirrhosis and with confirmed/suspected fibrosis were enrolled in a 54-month double-blind randomized placebo-controlled phase III clinical trial with serial biopsy assessments at baseline and week 52 (MAESTRO-NASH, NCT03900429). HRQL was assessed using Chronic Liver Disease Questionnaire-NASH (CLDQ-NAFLD) and Liver Disease Quality of Life (LDQOL). Baseline HRQL score changes by treatment group (resmetirom 80 mg, resmetirom 100 mg, or placebo) and histological response (improvement of fibrosis without worsening of NAS or resolution of MASH/NASH without worsening of fibrosis) were compared after 52 weeks. Included were 966 intention-to-treat patients: 323 received resmetirom 100 mg, 322 resmetirom 80 mg, and 321 placebo. By weeks 24 and 52, patients receiving 80 or 100 mg resmetirom experienced HRQL improvement in CLDQ-NAFLD Worry domain (mean +0.21 to +0.24, $p < 0.05$). At week 52, subjects who met histologic endpoints after treatment with resmetirom (100 mg and 80 mg pooled) experienced HRQL improvement in CLDQ-NAFLD Worry +0.46 (41% met minimal clinically important difference [MCID]), LDQOL domains: Role Emotional +3.0 (28% met MCID), Health Distress +8.1 (38% MCID), Stigma +3.5 (39% MCID), and total LDQOL +2.2

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; FI, fibrosis improvement; HRQL, health-related quality of life; ITT, intention-to-treat; LDQOL, Liver Disease Quality of Life; MASH, metabolic dysfunction–associated steatohepatitis; MCID, minimal clinically important difference; NAS, NAFLD activity score; NR, NASH resolution; PDFF, proton density fat fraction; PRO, patient-reported outcome; WPAI, Work Productivity and Activity Impairment.

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(35% MCID) (all $p < 0.05$). Similar improvements were noted in histologic responders from 100 mg or 80 mg resmetirom groups when separated—no improvements in placebo or nonresponders. Baseline F3 histologic responders had similar/more pronounced HRQL improvements.

Conclusions: Patients with MASH/NASH with fibrosis improvement or the resolution of MASH with resmetirom experienced clinically meaningful and statistically significant HRQL improvements.

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease, formerly known as NAFLD, is the most common cause of chronic liver disease and a leading cause of HCC and indication for liver transplantation.[1–3] From the spectrum of metabolic dysfunction–associated steatotic liver disease/NAFLD, those who show steatohepatitis (metabolic dysfunction–associated steatohepatitis [MASH] or NASH) can have a more progressive liver disease. As of the early 2020s, the global prevalence of NAFLD/metabolic dysfunction–associated steatotic liver disease was estimated at 38%, including 5%–6% of MASH/NASH.[1] Patients with MASH/NASH and significant fibrosis (stages 2 or 3, F2-F3) are at an increased risk for adverse clinical outcomes.[4,5] In addition to adverse clinical outcomes, these patients report impairment of health-related quality of life (HRQL) and are responsible for significant economic burden.[6,7]

Impairment of HRQL in MASH/NASH has been demonstrated in comparison to both the general population and to patients with simple steatosis but was the most pronounced in patients with advanced fibrosis and cirrhosis.[8–11] In turn, some studies have shown that improvement of fibrosis and/or fibrosis noninvasive test scores can be associated with some improvement of select generic and disease-specific HRQL scores in MASH/NASH.[12–15]

Resmetirom is an oral, liver-directed thyroid hormone receptor-β selective agonist that is now approved for the treatment of adult patients with MASH/NASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3).[16,17] Data from the phase II clinical trial of patients with NASH supported not only the potential efficacy and safety of resmetirom in adults with NASH but also the improvement of some aspects of HRQL.[16] Data from the phase III clinical trial of resmetirom in adults with biopsy-confirmed NASH (MAESTRO-NASH) showed that 80 and 100 mg resmetirom led to NASH resolution with no worsening of fibrosis in 25.9% and 29.9% as compared to 9.7% of those in the placebo group ($p < 0.001$).[17] Furthermore, fibrosis improvement by at least 1 stage with no worsening of the NAFLD activity score was achieved in 24.2% and 25.9% receiving resmetirom as compared with 14.2% of the placebo group ($p < 0.001$).[17] In the phase III trial in patients with NASH without cirrhosis, resmetirom had a good safety profile.[17] The aim of this study is to assess the impact of resmetirom on HRQL from the data collected as a part of the MAESTRO-NASH clinical trial.

METHODS

The study presents a prespecified analysis of HRQL data collected in phase III, randomized, double-blind, placebo-controlled study of resmetirom with serial biopsy assessments in subjects with noncirrhotic NASH and confirmed or suspected fibrosis (MAESTRO-NASH, NCT03900429).[17] To be included in this clinical trial, subjects were required to have $\geq$3/5 metabolic risk factors by International Diabetes Federation, controlled attenuation parameter $\geq$280 dB/m, liver stiffness by vibration controlled transient elastography $\geq$8.5 kPa, or a historic liver biopsy within 6 months of randomization with histologic evidence of NASH (NAFLD Activity Score $\geq$4 with a score of $\geq$1 for steatosis, hepatocyte ballooning, and lobular inflammation). Full eligibility criteria have been published elsewhere.[17]

Per the clinical trial's protocol,[17] subjects were randomized 1:1:1, stratified by type 2 diabetes status (presence/absence) and fibrosis stage (F1/F2/F3), to receive resmetirom 80 mg, resmetirom 100 mg, or placebo administered orally once daily. In this study, the F1 population was considered exploratory, while the F2/F3 population, including F1B, was the primary intention-to-treat (ITT) population specified for all analyses; for this purpose, F1B patients were considered equivalent to the F2 patients. Two central pathologists assessed baseline and week 52 biopsies for histologic scores on NASH and fibrosis; magnetic resonance imaging (MRI)-proton density fat fraction (PDFF) assessments were also performed at baseline and week 52. The dual primary histologic endpoints at week 52 were NASH resolution (achievement of a hepatocyte ballooning score of 0, lobular inflammation score of 0 or 1, and a $\geq$2-point NAS reduction) with no worsening of fibrosis (NASH

Resolution [NR] response) OR fibrosis improvement by ≥1 stage with no worsening of NAS (Fibrosis Improvement [FI] response).[17] An additional response endpoint (MRI-PDFF response) was defined as a ≥30% reduction in MRI-PDFF percent from baseline to week 52.

Patient-reported outcomes

The HRQL was assessed using the Chronic Liver Disease Questionnaire (CLDQ-NAFLD), Liver Disease Quality of Life (LDQOL) instruments, and Work Productivity and Activity Impairment (WPAI) instrument.[18–20] The instruments were completed on the first day of treatment before the initiation of any treatment-related activities and then at weeks 24 and 52.

The CLDQ-NAFLD/NASH is a validated NAFLD/NASH-specific instrument that includes 36 items and 6 domains (Abdominal symptoms, Activity, Emotional health, Fatigue, Systemic symptoms, and Worry).[18] All items and domain scores range from 1 to 7, and higher scores indicate better quality of life. In this manuscript, where specified, the CLDQ-NAFLD scores were renormalized to 0–100 for illustrative purposes.

The LDQOL is a 2-part HRQL instrument that includes 72 items and 17 domains: the first 36 items and 8 domains are generic (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health), and the remaining 36 items and 9 domains are liver disease–specific (Symptoms of liver disease, Effects of liver disease, Concentration/memory, Health distress, Sexual Function, Sleep, Loneliness, Hopelessness, and Stigma of liver disease).[19] All domain scores range from 0 to 100, and higher scores indicate better quality of life.

The WPAI is used to assess impairment in work productivity due to both absenteeism (missed hours of work due to a health problem) and presenteeism (self-reported impaired productivity while working) in employed subjects, activities other than work in all subjects.[20] Higher WPAI scores, ranging from 0 to 100, correspond to greater impairments in work productivity or activity.

For all HRQL instruments, the minimal clinically important difference (MCID) in a score was defined as 5% of the score range size, that is, 0.3 for the domains of CLDQ-NAFLD, 5.0 for the domains LDQOL, and 5.0 for the domains of WPAI.[18–21] Using those, meeting MCID was defined as an increase of ≥MCID from baseline for the CLDQ-NAFLD and LDQOL domain scores or a decrease by ≥MCID for the WPAI scores.

Statistical analysis

The sample size for the MAESTRO-NASH study was chosen to yield a power of >90% for the primary histologic endpoints.[17] Clinical and demographic parameters, as well as all HRQL scores, were summarized as N (%) or mean ± SD for the subjects included in the modified ITT population of MAESTRO-NASH.[17] Only observed HRQL data at each study time point were used.

The mixed-effects models for repeated measures that included both weeks 24 and 52 HRQL measurements were used to estimate the effect of treatment on changes in HRQL scores from subjects' own baseline levels for each HRQL domain separately. The mixed-effects models for repeated measures included adjustment for the baseline HRQL value and stratification factors (the presence of diabetes and baseline fibrosis stage), treatment regimen as a fixed effect (reference regimen: placebo), and subject as a random effect, and yielded least-square mean estimates for the HRQL score changes at weeks 24 and 52 with 97.5% CIs. Assessments of changes in HRQL scores in other predefined clinical groups (by the presence of histologic or MRI-PDFF response) were performed by means of arithmetic means, which were compared between the subgroups using the Mann-Whitney test, and to zero (which would indicate no significant change from baseline) using Wilcoxon signed-rank test for matched pairs. In addition, the proportions of subjects meeting MCID were calculated.

All analyses were conducted in SAS 9.4 (SAS Institute). All participants provided written informed consent before enrollment. This study was done in accordance with the ethical principles of the Declaration of Helsinki and was consistent with the International Conference on Harmonisation Good Clinical Practice and applicable regulatory requirements. The institutional review boards or independent ethics committees of each study center approved the study and all amendments.

RESULTS

There were 966 subjects included in the ITT population MAESTRO-NASH[17] that included the primary analysis population based on the central pathologists reassessed baseline fibrosis stage of F1B (moderate fibrosis), F2 or F3 at the time of the primary baseline, and week 52 biopsy read. Eighty-four patients were rescored by 2 central pathologists as baseline F1 (including F1A, F1C, or a combination of F1A/C plus F1B) and were considered exploratory. The mean (±SD) age was 57±11 years; 44% were male, and 67% had type 2 diabetes. In addition, 62% had fibrosis stage F3 at baseline while 33% had F2 and 5% had F1B; also, 84% had baseline NAS score ≥5.[17] Of the included ITT subjects, 323 received resmetirom 100 mg, 322 resmetirom 80 mg, and 321 received placebo. The HRQL scores of subjects who have both baseline and postbaseline measurements (n = 776

with CLDQ-NAFLD, n = 796 with LDQOL, and n = 310 with WPAI) are shown in Supplemental Table S1, http://links.lww.com/HEP/I659.

Histologic response and HRQL

There were 125 (50%) subjects in the resmetirom 100 mg group, 109 (42%) in the 80 mg group, and 53 (19%) in the placebo group who met the primary histologic endpoint of improvement of histologic fibrosis OR resolution of NASH as measured through baseline/week 52 paired biopsies (available for n = 782; of those, n = 696 had CLDQ-NAFLD and n = 714 had LDQOL).[17] Subjects who met FI and/or NR (100 mg and 80 mg pooled) experienced significant improvement in several HRQL scores: mean change from baseline to week 52 (95% CI) in Worry of CLDQ-NAFLD was +0.46 (0.31–0.62) (40% met MCID), Role Emotional of LDQOL +3.0 (0.7–5.3) (29% met MCID), Health Distress of LDQOL +8.1 (5.0–11.2) (38% met MCID), Stigma of LDQOL +3.5 (1.5–5.6) (38% met MCID), and total LDQOL +2.2 (0.9–3.6) (36% met MCID) (all $p < 0.05$) (Table 1, Supplemental Tables S2, S5, and S6, http://links.lww.com/HEP/I659, Figure 1, and Supplemental Figure S1, http://links.lww.com/HEP/I660). Similar improvements in these HRQL scores were observed in treatment responders from the 100 mg and 80 mg resmetirom groups studied separately, contrasted by no improvements or smaller improvements in both the placebo group and resmetirom nonresponders (Table 2 and Figure 1). In other domains of CLDQ-NAFLD and LDQOL, the MCID was met by 28%–42% of resmetirom responders (Supplemental Tables S7 and S8, http://links.lww.com/HEP/I659). The changes in HRQL scores of treatment responders were similar for all definitions of histologic treatment response (FI, NR, and FI and/or NR) (Table 1,

TABLE 1 Changes in HRQL scores in resmetirom-treated subjects with primary histologic response (FI only, NR only, and NR and/or FI) versus placebo

HRQL score	FI with 100 mg	FI with 80 mg	Placebo
N with CLDQ-NAFLD	66	65	229
Worry	0.42 (0.16–0.69)[a]	0.50 (0.24–0.75)[a]	0.33 (0.20–0.46)[a]
N with LDQOL	71	67	235
General Health (GH)	3.04 (−0.02 to 6.10)[a]	0.13 (−3.28 to 3.55)	1.16 (−0.61 to 2.92)
Role Emotional (RE)	1.76 (−1.81 to 5.33)	3.23 (−0.10 to 6.56)[a,b]	−1.60 (−3.93 to 0.74)
Health distress	6.69 (1.09–12.29)[a]	9.14 (3.69–14.60)[a]	3.83 (1.00–6.66)[a]
Stigma of liver disease	2.82 (−0.79 to 6.43)	4.66 (1.09–8.24)[a]	1.52 (−0.55 to 3.60)
Total LDQOL	0.83 (−1.40 to 3.06)	3.03 (0.67–5.39)[a,b]	0.30 (−0.92 to 1.52)
HRQL score	NR with 100 mg	NR with 80 mg	Placebo
N with CLDQ-NAFLD	72	60	229
Worry	0.38 (0.12–0.65)[a]	0.39 (0.15–0.63)[a]	0.33 (0.20–0.46)[a]
N with LDQOL	77	63	235
Role Emotional (RE)	3.35 (−0.69 to 7.40)[b]	0.33 (−3.29 to 3.95)	−1.60 (−3.93 to 0.74)
Health distress	6.66 (1.70–11.61)[a]	7.34 (2.21–12.47)[a]	3.83 (1.00–6.66)[a]
Total LDQOL	0.88 (−1.43 to 3.19)	2.50 (0.33–4.66)[a]	0.30 (−0.92 to 1.52)
HRQL score	NR and/or FI with 100 mg	NR and/or FI with 80 mg	Placebo
N with CLDQ-NAFLD	100	89	229
Worry	0.51 (0.28–0.75)[a]	0.40 (0.21–0.60)[a]	0.33 (0.20–0.46)[a]
N with LDQOL	108	92	235
General Health (GH)	2.88 (0.14–5.61)[a]	0.28 (−2.50 to 3.06)	1.16 (−0.61 to 2.92)
Role Emotional (RE)	3.32 (−0.06 to 6.69)[a,b]	2.67 (−0.40 to 5.74)[b]	−1.60 (−3.93 to 0.74)
Health distress	8.33 (3.93–12.74)[a]	7.88 (3.50–12.26)[a]	3.83 (1.00–6.66)[a]
Loneliness	2.92 (−0.29 to 6.13)[a]	2.99 (−0.68 to 6.66)	0.37 (−1.68 to 2.42)
Stigma of liver disease	2.60 (−0.30 to 5.51)	4.62 (1.72–7.52)[a]	1.52 (−0.55 to 3.60)
Total LDQOL	1.84 (−0.06 to 3.75)	2.71 (0.91–4.51)[a,b]	0.30 (−0.92 to 1.52)

Note: Each cell shows the mean change from baseline to week 52 with 95% CI.

[a]$p < 0.05$ versus zero change (within-treatment comparison indicates significant change from baseline).

[b]$p < 0.05$ versus placebo. Only statistically significant changes ($p < 0.05$ in comparison to zero or placebo) are included; all HRQL domains are shown in Supplemental Tables S5 and S6, http://links.lww.com/HEP/I659.

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; FI, fibrosis improvement; HRQL, health-related quality of life; LDQOL, Liver Disease Quality of Life; NR, NASH resolution.

Supplemental Tables S2, S5, and S6, http://links.lww.com/HEP/I659). Similar trends were observed when responders to resmetirom were compared to placebo responders only (Supplemental Table S9, http://links.lww.com/HEP/I659).

Of the ITT cohort, 62% had F3 at baseline, and the remaining subjects had F2 or F1B (Supplemental Table S2, http://links.lww.com/HEP/I659). At baseline, subjects with F3 had lower HRQL scores in multiple HRQL domains in comparison to F1B/F2 ($p < 0.05$ for Physical Functioning, Role Physical, General Health, Social Functioning, and Effects of liver disease) (Supplemental Table S2, http://links.lww.com/HEP/I659). The F3 group also had a significantly lower employment rate (51% vs. 65%, $p = 0.019$), but there was no difference in work productivity among patients with NASH with F3 who were employed ($p > 0.05$) (Supplemental Table S2, http://links.lww.com/HEP/I659).

Treatment responders (NR and/or FI) 100 mg and 80 mg pooled populations with baseline F3, compared with baseline F1B/F2, had similar or more pronounced improvements in some HRQL domains including Worry, CLDQ-NAFLD +0.54 (0.33–0.75) in F3 versus +0.32 (0.10–0.54) in F1B/F2; Role Emotional, LDQOL +3.8 (0.9–6.7) in F3 versus +1.7 (−2.1 to 5.5) in F1B/F2; Health Distress, LDQOL +8.4 (4.3–12.6) versus +7.6 (2.9–12.3) in F1B/F2 (Figure 2, Supplemental Figure S2, http://links.lww.com/HEP/I660).

MRI-PDFF response and HRQL

There were 160 (72.1%) subjects in the resmetirom 100 mg group, 146 (62.7%) in the 80 mg group, and 58 (25.1%) in the placebo group who met the MRI-PDFF response endpoint (total observed n = 686). Treatment nonresponders experienced worsening of Role Physical and Bodily Pain, LDQOL, −4.8 (−8.3 to −1.3) and −3.8 (−7.5 to −0.1), respectively, as compared with MRI-PDFF responders who showed improvement or no change, −0.3 (−2.7 to 2.1), +2.2 (−0.3 to 4.7), respectively (both $p < 0.05$) (Figure 3).

Resmetirom treatment effect on HRQL

By treatment week 24, subjects receiving either dose of resmetirom experienced generally similar changes in HRQL scores from baseline levels when compared to placebo: all but one $p > 0.05$ (Supplemental Table S3, http://links.lww.com/HEP/I659). The highest rate of meeting MCID was observed for the Worry scores (38% in 100 mg, 46% in 80 mg, and 39% in placebo). By treatment week 52, changes in HRQL scores remained similar across the 3 treatment arms ($p > 0.05$ when compared to placebo) (Supplemental Table S4, http://links.lww.com/HEP/I659). The proportions of subjects meeting the MCID ranged from 23% (Social

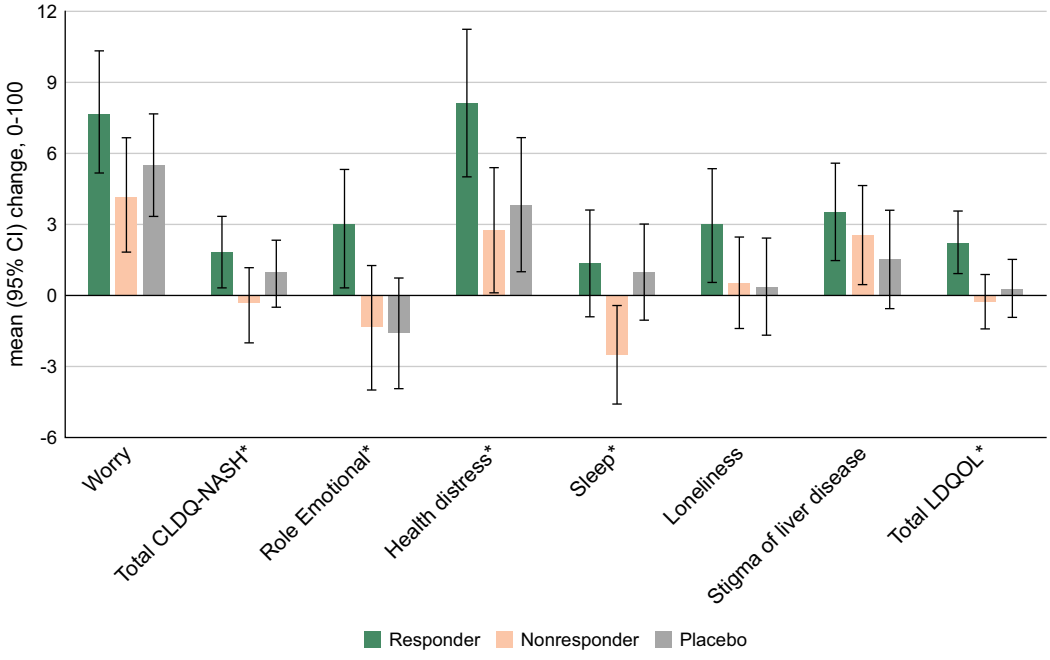

FIGURE 1 Changes in HRQL scores in subjects with (responder) versus without a response (nonresponder) on either primary histologic endpoint (NR or FI) to treatment with resmetirom (*$p < 0.05$) versus placebo; mean HRQL score change (renormalized from the original scale to 0–100 where applicable) from baseline to week 52 with 95% CI. Only statistically significant changes from baseline to week 52 ($p < 0.05$ in comparison to zero or to nonresponders or placebo) are shown; changes in all HRQL domains in their original scales are shown in Supplemental Figure S1, http://links.lww.com/HEP/I660. Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; FI, fibrosis improvement; HRQL, health-related quality of life; LDQOL, Liver Disease Quality of Life; NR, NASH resolution.

TABLE 2 Changes in HRQL scores in resmetirom-treated subjects (100 mg and 80 mg pooled) with the primary histologic response (FI only, NR only, and FI and/or NR) versus placebo

HRQL score	FI (100 mg and 80 mg pooled)	Placebo
N with CLDQ-NAFLD	131	229
Worry	0.46 (0.28–0.64)[a]	0.33 (0.20–0.46)[a]
N with LDQOL	138	235
Role Emotional (RE)	2.48 (0.03–4.92)[a,b]	−1.60 (−3.93 to 0.74)
Health distress	7.88 (3.98–11.78)[a]	3.83 (1.00–6.66)[a]
Stigma of liver disease	3.71 (1.18–6.25)[a]	1.52 (−0.55 to 3.60)
HRQL score	NR (100 mg and 80 mg pooled)	Placebo
N with CLDQ-NAFLD	132	229
Worry	0.39 (0.21–0.57)[a]	0.33 (0.20–0.46)[a]
N with LDQOL	140	235
Health distress	6.96 (3.41–10.52)[a]	3.83 (1.00–6.66)[a]
HRQL score	NR and/or FI (100 mg and 80 mg pooled)	Placebo
N with CLDQ-NAFLD	189	229
Worry	0.46 (0.31–0.62)[a]	0.33 (0.20–0.46)[a]
Total CLDQ-NAFLD score	0.11 (0.02–0.20)[a]	0.06 (−0.03 to 0.14)
N with LDQOL	200	235
Role Emotional (RE)	3.02 (0.72–5.32)[a,b]	−1.60 (−3.93 to 0.74)
Health distress	8.13 (5.01–11.24)[a,b]	3.83 (1.00–6.66)[a]
Loneliness	2.95 (0.54–5.36)[a]	0.37 (−1.68 to 2.42)
Stigma of liver disease	3.53 (1.47–5.59)[a]	1.52 (−0.55 to 3.60)
Total LDQOL	2.24 (0.92–3.56)[a,b]	0.30 (−0.92 to 1.52)
N with WPAI	59	67
Activity impairment	−3.73 (−7.40 to −0.06)[a]	−3.43 (−8.48 to 1.61)

Note: Each cell shows the mean change from baseline to week 52 with 95% CI.
[a]$p < 0.05$ versus zero change (within-treatment comparison indicates significant change from baseline).
[b]$p < 0.05$ versus placebo. Only statistically significant changes ($p < 0.05$ in comparison to zero or placebo) are included; all HRQL domains are shown in Supplemental Tables S5 and S6, http://links.lww.com/HEP/I659.
Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; FI, fibrosis improvement; HRQL, health-related quality of life; LDQOL, Liver Disease Quality of Life; NR, NASH resolution; WPAI, Work Productivity and Activity Impairment.

Functioning in the placebo arm) to 46% (Abdominal symptoms in the 80 mg arm).

DISCUSSION

This is an in-depth analysis of HRQL in patients with histologic MASH/NASH who were treated with resmetirom. Our data show that, in comparison to patients receiving a placebo, those who achieved primary histologic response with resmetirom experienced significant improvements in several aspects of their HRQL when the histologic response was defined as resolution of MASH/NASH or improvement of fibrosis or meeting any of the 2; in fact, the latter was associated with more pronounced HRQL improvement in comparison to either of the individual histologic endpoints. Furthermore, among resmetirom-treated groups, there was no dose dependency, so changes in HRQL scores were similar between 100 and 80 mg doses.

Among those who achieved primary histologic response with either dose or resmetirom, the improvements in HRQL were observed in the areas of worry, role emotion, health distress, and stigma as measured by the respective domains of the validated HRQL questionnaires. Some of these improvements were also associated with higher proportions of patients meeting MCID among treatment responders: in comparison to placebo, histologic response was associated with a higher proportion of patients meeting the MCID threshold for the total LDQOL score (34.8% among those with fibrosis response, 35.5% with a primary histologic response of FI and/or NR, vs. 25.1% in placebo, both $p < 0.05$). In addition, in comparison to nonresponders, those with primary histologic response had a higher chance of meeting MCID for the domains of Health Distress (38.0% vs. 28.4%) and Loneliness (41.5% vs. 31.0%) as well as the total LDQOL score (35.5% vs. 21.6%) (all $p < 0.05$). Altogether, these data suggest that achieving histologic improvement, especially

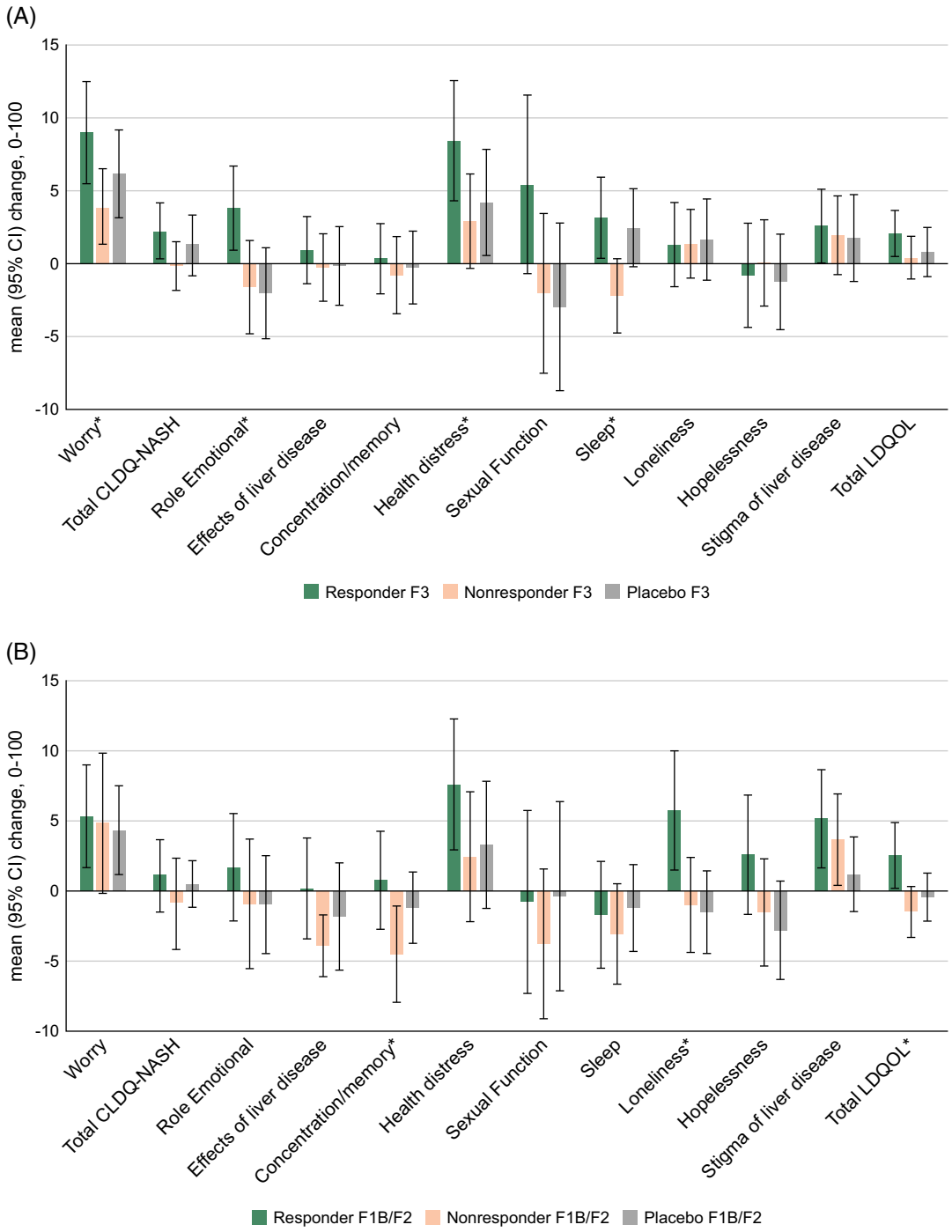

FIGURE 2 Changes in HRQL scores in (A) F3 and (B) F1B/F2 subjects with (responder) versus without a response (nonresponder) on either primary histologic endpoint (NR or FI) to treatment with resmetirom (*$p < 0.05$) versus placebo; mean HRQL score change (renormalized from the original scale to 0–100 where applicable) from baseline to week 52 with 95% CI. Only HRQL scores with statistically significant changes from baseline to week 52 ($p < 0.05$ in comparison to zero or to nonresponders or placebo) in either F3 or F1B/F2 group are shown; changes in all HRQL domains in their original scales are shown in Supplemental Figure S2, http://links.lww.com/HEP/I660. Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; FI, fibrosis improvement; HRQL, health-related quality of life; LDQOL, Liver Disease Quality of Life; NR, NASH resolution.

improvement of fibrosis, in the presence of a favorable safety profile for the drug could lead to a better quality of life.

In this study, we found that subjects with baseline F3 had lower HRQL scores in some domains than those with baseline F1B/F2. This finding is interesting on its own since it is sometimes suggested that, after accounting for associated comorbidities such as obesity and diabetes, noncirrhotic MASH/NASH is asymptomatic and, therefore, not linked to HRQL impairment

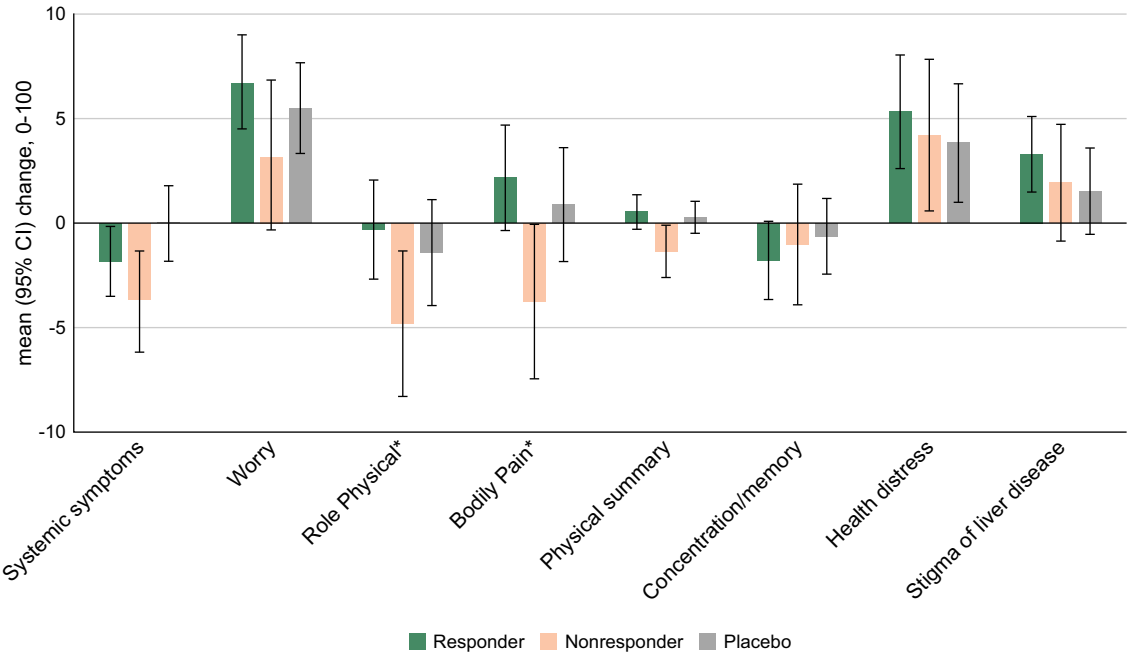

FIGURE 3 Changes in HRQL scores in subjects with versus without MRI-PDFF response to resmetirom (*$p < 0.05$); mean HRQL score change (renormalized from the original scale to 0–100 where applicable) from baseline to week 52 with 95% CI. Only statistically significant changes from baseline to week 52 ($p < 0.05$ in comparison to zero or to nonresponders or placebo) are shown; changes in all HRQL domains in their original scales are shown in Supplemental Figure S3, http://links.lww.com/HEP/I660. Abbreviations: HRQL, health-related quality of life; PDFF, proton density fat fraction.

until the patient progresses to cirrhosis. However, in this study, which used a very well-characterized population, we observed impairment in HRQL scores in subjects with F3, which was consistent across multiple physical health-related domains. Given that, we also analyzed the data separately by the baseline fibrosis stage. In this context, we found that improvements in HRQL scores in treatment responders with baseline F3 were similar or more pronounced in some domains when compared to HRQL changes in patients with F1B/F2. Since the study did not enroll subjects with cirrhosis or more advanced liver disease, further studies are needed to assess HRQL trends in patients with cirrhosis due to MASH/NASH.

When the overall treatment effect of resmetirom was evaluated in comparison to the placebo, we found that HRQL score changes by weeks 24 and 52 were largely similar in resmetirom and placebo patients. In fact, the most prominent improvements were observed in the Worry domain, similar in magnitude in all treatment groups, contrasted by similar worsening in Social Functioning; the latter could be explained by the COVID-19 pandemic, which started soon after the study was initiated. It is important to note that changes in HRQL scores could be a reflection of safety and efficacy. The fact that resmetirom-treated groups had similar scores to the placebo group suggests that resmetirom side effect profile is favorable and similar to the placebo. In terms of efficacy, our data demonstrate that histologic responders had clinically relevant improvements in scores (MCID) and improvements in a number of HRQL scores. In fact, this response was seen across histologic disease severity as determined by stages of fibrosis. Finally, it is also important to note that there were no differences between weeks 24 and 52 patient-reported outcome (PRO) responses, suggesting that the impact of resmetirom on PROs can be seen as early as week 24.

Although our analysis primarily focused on histologic response, we assessed the association of the response by MRI-PDFF with HRQL scores. In this context, patients with MRI-PDFF response maintained better scores in Bodily Pain and Role Physical than the subjects who did not achieve an MRI-PDFF response. Since the stage of fibrosis is more consistently predictive of the long-term outcomes, the association of PRO improvement with fibrosis improvement may have important clinical implications.[22] On the other hand, this finding does not mean that changes in noninvasive tests such as MRI-PDFF would not capture some other aspects of HRQL and patients' well-being in long-term follow-up. More data are needed to show the clinical relevance of MRI-PDFF or other noninvasive tests in predicting patients' experience with the disease and its treatment.

The mechanisms by which resmetirom could improve HRQL in patients with MASH are not known. Although these mechanisms cannot be elucidated in this study, it is plausible that this may be a manifestation of

resmetirom-associated reduction in the hepatic and/or systemic inflammation or an improvement in the metabolic milieu. In fact, improvement of inflammatory cytokine profile has been associated with improvement of fatigue and other aspects of HRQL.[23] Further studies are needed to prospectively collect PROs along with metabolic and inflammatory biomarkers in resmetirom-treated patients to test this hypothesis.

It is important to note that the inclusion of PROs in clinical trials of MASH brings patients' experience with the treatment regimen. In this context, several previous studies have shown that improvement of fibrosis and/or its surrogates can lead to improvement of PROs in patients with MASH/NASH.[12–15] While pharmacological options for patients with MASH remain limited, other interventions that have resulted in the improvement of metabolic comorbidities (eg, weight loss) can also bring about better HRQL.[24,25] In the context of those prior findings, the data from our study reinforce the fact that drugs such as resmetirom, with confirmed efficacy and a good safety profile, should lead to the improvement of HRQL scores. Ultimately, the inclusion of the PRO endpoints collected through validated instruments as a part of all clinical trials of new drugs for MASH remains an important part of full assessments of efficacy and safety.

The limitations of our study include the use of data collected from enrollees of a clinical trial with strict inclusion/exclusion criteria and close monitoring of subjects throughout the study duration, a homogenous study population that lacked important subpopulations, including subjects with major comorbidities and those without access to a clinical trial site, a limited selection of clinical outcomes to correlate with HRQL scores, and a relatively short follow-up duration.

In summary, our analysis of HRQL data collected in a phase III study of resmetirom for patients with non-cirrhotic MASH/NASH suggests improvements in some aspects of HRQL that meet both nominal statistical significance and clinical relevance (MCID) with the absence of substantial negative HRQL effects related to drug side effects. The HRQL response was especially prominent in those who achieved a histologic response, regardless of the specific definition of response and resmetirom dose. The HRQL domains with the most pronounced improvement were reflective of patients' overall well-being in the context of their disease (eg, health distress and role emotional). These HRQL data support the potential for resmetirom to provide comprehensive benefits to patients with MASH/NASH with liver fibrosis.

AUTHOR CONTRIBUTIONS

Zobair M. Younossi: conceptualization; funding acquisition; methodology; supervision; and writing—original draft. Maria Stepanova: data curation; formal analysis; writing—original draft. Andrei Racila: data curation; software; resources; validation; writing—review and editing. Linda Henry: resources and writing—review and editing. Dominic Labriola: methodology; supervision; writing—review and editing; and validation. Rebecca Taub: conceptualization; funding acquisition; supervision; writing—review & editing; and validation. Fatema Nader: project administration; resources; writing—review and editing. All authors made substantial contributions to the conception and design, acquisition of data, analysis and interpretation of data, and drafting of the article or revising it critically for important intellectual content. All authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST

Zobair M. Younossi consults and received grants from Abbott, Boehringer Ingelheim, Bristol Myers Squibb, CymaBay, GENFIT, Gilead, GlaxoSmithKline, Intercept, Ipsen, Madrigal, Merck, Novo Nordisk, Siemens, Terns, and Viking. Dominic Labriola is employed by and owns stock in Madrigal. She owns stock in Bristol Myers Squibb. Rebecca Taub is employed by and owns stock in Madrigal. The remaining authors have no conflicts to report.

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