Effectiveness of a digital health application for multiple sclerosis (*levidex*): randomized controlled trial (LAMONT)

Clinical investigation report following ISO 14155:2020

Investigational device

levidex

Study design

- pragmatic
- randomized (simple randomization)
- controlled (two arms)
- online

Study population

470 patients with multiple sclerosis (MS), aged 18 and above, who reported impaired MS-specific health-related quality of life (total score of the Hamburg Quality of Life Questionnaire for Multiple Sclerosis [HALEMS] ≥ 2).

Statement

This clinical investigation was performed in accordance with ISO 14155:2020 and the ethical principles in the Declaration of Helsinki.

Sponsor

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Study registration number

ClinicalTrials.gov ID: NCT06090305

Date

22.04.2025

Version

3.0

Summary of the revision history

Version	Date	Changes
2	18.12.2024	● In version 2, results from the analysis of the full data set are presented, leading to changes in chapters 1, 2, 4, 5 and 6. ● An appendix was created. ● All changes are highlighted in yellow.
3	22.04.2025	● Details on the randomization procedure were added, leading to revisions in chapter 4. ● Details on the implementation of the jump-to-reference imputation were added, leading to revisions in chapter 4. ● Minor transcription errors in chapter 5 were corrected without impact on results. ● Comparisons of baseline characteristics of dropouts and completers by study group were added, resulting in changes in chapter 5. ● Odds Ratios were added as effect size estimates in the analyses of DMD use, leading to changes in chapter 5. ● The methodology for comparing days on sick leave, sick pay, and inpatient treatment was clarified, leading to revisions in chapter 5. ● Subgroup analyses based on DMD use were added for all confirmatory endpoints, including corresponding forest plots, leading to revisions in chapter 5 and the appendix. ● All changes were highlighted in orange.

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1. Summary

1.1. Title of the clinical investigation

Effectiveness of a digital health application for multiple sclerosis (*levidex*): randomized controlled trial (LAMONT)

1.2. Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system. According to current estimates, more than 700,000 people are affected in Europe. Worldwide, more than 2.5 million people suffer from MS [1], which causes significant socioeconomic costs depending on the severity of the disease [2]. Symptomatology is varied and dominated by sensory and motor impairments of the upper and lower extremities, fatigue, visual and cognitive disturbances, and emotional impairment [3]. Currently available drug therapies for MS ("disease-modifying drugs", DMDs) are mainly aimed at reducing the relapse rate and slowing the progression of neurological impairment, while also presenting notable challenges due to their side effects [4]. According to the current European guideline on pharmacological MS treatment, specific drugs are recommended for the different forms of MS [5]. In addition to or independent of drug therapy, non-pharmacological treatment methods can alleviate certain MS symptoms such as fatigue and depressive symptoms. In addition to cognitive behavioral therapy (CBT) approaches, specific psychological techniques such as acceptance-and-commitment therapy, interpersonal therapy, or motivational interviewing have been studied. Systematic reviews and meta-analyses show treatment success on different symptom complexes in MS, such as fatigue [6], [7], depression [7], [8], subjectively perceived cognitive deficits [9], and an increase in quality of life [7], [10]. A meta-analysis on psychosocial interventions showed positive immunomodulatory effects of CBT, in particular, on the immune system in a number of indications including MS [11]. A promising approach of psychological interventions is the special case of digital health apps (DiGA). Among others, the use of DiGA *deprexis*, which is based on CBT, led to a reduction in comorbid depressive symptomatology in patients with MS [12]. There is also evidence of the effectiveness of the DiGA *elevida* developed by the applicant for patients with MS and fatigue [13]. Finally, a randomized controlled trial (RCT) with 421 patients with MS or Clinically Isolated Syndrome (CIS) showed significant and clinically relevant effects of the DiGA *levidex* [14], [15] on MS-specific health-related quality of life [16]. The observed effect sizes must be interpreted within the context of MS as a complex and severe condition. Notably, the effects of *levidex* on MS-specific quality of life align with the effects of DMDs on this outcome, even those classified as most effective [17], [18], [19]. This indicates that, given the nature of the condition, comparably smaller intervention effects are to be anticipated, while still being meaningful to patients.

In conclusion, nonpharmacological interventions whose benefits have been demonstrated in clinical trials may be a useful adjunct to usual care (for example, with DMDs) because of their positive risk-benefit profile. Psychological treatment approaches, especially CBT, show positive effects. These have been demonstrated primarily for depressive symptoms, fatigue, and disease-related quality of life. Specifically, the digital intervention *levidex* showed

promising effects on MS-specific health-related quality of life, days on sick leave and instrumental activities of daily living in the study submitted for provisional listing in the DiGA registry [16].

The present RCT was conducted to support the permanent listing in the DiGA registry and aimed to further assess the effectiveness of the fully automated, internet-based intervention program *levidex* when used in conjunction with treatment-as-usual (TAU) compared to TAU alone.

1.3. Purpose of the clinical investigation

The purpose of this clinical investigation was to assess the effectiveness of the fully automated digital health application *levidex* in adult patients with MS in terms of improving health-related quality of life.

1.4. Description of the clinical investigation population

The study population consisted of adult patients with MS who reported impaired health-related quality of life.

1.5. Clinical investigation method

Recruitment of patients was achieved through an online campaign, newsletters and physicians. Interested participants were directed to a study website providing information about the trial and details about participation. First Patient First Visit was 2023-11-09. Last Patient Last Visit was on 2024-12-06.

1.6. Results of the clinical investigation

1.6.1. Primary endpoint

The intention-to-treat (ITT) analysis showed that after 6 months of using *levidex*, patients in the TAU + *levidex* intervention group had better MS-specific health-related quality of life than patients in the TAU-only control group: the estimated baseline-adjusted difference between the groups after 6 months was -0.10 points on the Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HALEMS) total score (95 % CI = [-0.18, -0.03], p = .008; d = 0.26).

The improvement in MS-specific health-related quality of life was confirmed in a conservative 'jump-to-reference' (J2R) sensitivity analysis, where missing values were imputed assuming that, following drop-out, participants in the intervention group behave like those in the control group: here, the estimated baseline-adjusted group difference in MS-specific health-related quality of life was -0.09 points on the HALEMS total score (95% CI = [-0.16, -0.03]; p = .003; d = 0.24).

Results of the responder analysis based on a minimal clinically important difference (MCID) of 0.22 points reduction on the HALEMS [20] showed that more patients in the intervention

group (39.5%) than in the control group (27.8%) achieved clinically relevant improvements in MS-specific health-related quality of life after 6 months (χ^2 = 7.19, *p* = .007, Odds Ratio (OR) = 1.69; 95% CI = [1.15; 2.50]). Thus, clinically relevant improvements in quality of life were 69% more likely in the intervention than in the control group. The pattern of results corresponds to a Number Needed to Treat (NNT) of 9.

1.6.2. Secondary Endpoints

After 6 months, the ITT analysis showed significant reductions in the intervention group compared to the control group for the secondary endpoint depressive symptoms (estimated baseline-adjusted difference on the PHQ-9 total score = -0.8 points; 95% CI = [-1.4, -0.1], *p* = .025; *d* = 0.21). There were also significant improvements in social and work-related functioning (estimated baseline-adjusted group difference on the WSAS total score = -1.8; 95% CI = [-2.9; -0.6], *p* = .003; *d* = 0.30), and significant improvements in MS-specific health-related quality of life assessed with the MusiQoL (estimated baseline-adjusted group difference on the MusiQoL global index score = 2.1; 95% CI = [0.3; 3.9], *p* = .020; *d* = 0.23). There were no significant reductions in anxiety symptoms (estimated baseline-adjusted group difference on the GAD-7 total score = -0.5; 95% CI = [-1.2; 0.2], *p* = .205; *d* = 0.13). Due to the planned gatekeeping strategy, all following planned secondary endpoints will therefore be considered exploratory. No significant improvement in instrumental activities of daily living (estimated baseline-adjusted group difference on the FAI total score = 0.8; 95% CI = [-0.1; 1.8], *p* = .097; *d* = 0.17) were observed.

For the time point after 3 months assessing intermediate effects, significant improvements in the primary endpoint MS-specific health-related quality of life were observed in the ITT analysis: the estimated baseline-adjusted difference between the groups after 3 months was -0.11 points on the HALEMS total score (95 % CI = [-0.18, -0.05], *p* < .001; *d* = 0.32). This was confirmed in a conservative J2R analysis: here, the estimated baseline-adjusted group difference in MS-specific health-related quality of life was -0.10 points on the HALEMS total score (95% CI = [-0.16; -0.04]; *p* < .001; *d* = 0.29).

1.7. Conclusion

Results of this clinical investigation show that the use of *levidex* in addition to TAU leads to significant and clinically relevant improvements in MS-specific health-related quality of life compared to TAU alone after 6 months in patients with MS. Regarding the primary endpoint, i.e., MS-specific health-related quality of life, *levidex* has an NNT of 9. This is comparable to studies investigating the effect of commonly prescribed DMDs on health-related quality of life, which report NNT values ranging from 7 to 145, with most falling between 7 and 19 [17], [18], [19]. Given that MS is a severe chronic disease significantly affecting quality of life, and considering that all participants in the current trial were at least moderately impaired in their health-related quality of life (with an inclusion cut-off of 2 ≥ on the HALEMS total score, approximating an Expanded Disability Status Scale [EDDS] score of ≥ 3), effects of this magnitude are to be expected. This is corroborated by the observation that even DMDs in the highest efficacy category (Category 3) do not demonstrate greater effectiveness than *levidex* in enhancing health-related quality of life.

levidex also showed significant intervention effects on a broad spectrum of patient-relevant outcomes, i.e., depression, social and work-related functioning and quality of life as measured by the MusiQoL. The results' robustness was confirmed by J2R sensitivity analyses.

All patients in the intervention group registered to use *levidex*. User satisfaction was very high at both time points, with Net Promoter Scores (NPS) ranging from 31.5 to 35.6. No adverse events or device deficiencies were observed and patient satisfaction with *levidex* was high. The risk-benefit ratio therefore appears to be positive.

1.8. Date of the clinical investigation

First Patient First Visit: 2023-11-09

1.9. Completion date of the clinical investigation

Last Patient Last Visit: 2024-12-06

2. Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system. According to current estimates, more than 700,000 people are affected in Europe. Worldwide, more than 2.5 million people suffer from MS [1], which causes significant socioeconomic costs depending on the severity of the disease [2]. Symptomatology is varied and dominated by sensory and motor impairments of the upper and lower extremities, fatigue, visual and cognitive disturbances, and emotional impairment [3]. Currently available drug therapies for MS ("disease-modifying drugs", DMDs) are mainly aimed at reducing the relapse rate and slowing the progression of neurological impairment, while also presenting notable challenges due to their side effects [4]. According to the current European guideline on pharmacological MS treatment, specific drugs are recommended for the different forms of MS [5]. In addition to or independent of drug therapy, non-pharmacological treatment methods can alleviate certain MS symptoms such as fatigue and depressive symptoms. In addition to cognitive behavioral therapy (CBT) approaches, specific psychological techniques such as acceptance-and-commitment therapy, interpersonal therapy, or motivational interviewing have been studied. Systematic reviews and meta-analyses show treatment success on different symptom complexes in MS, such as fatigue [6], [7], depression [7], [8], subjectively perceived cognitive deficits [9], and an increase in quality of life [7], [10]. A meta-analysis on psychosocial interventions showed positive immunomodulatory effects of CBT, in particular, on the immune system in a number of indications including MS [11]. A promising approach of psychological interventions is the special case of digital health apps (DiGA). Among others, the use of DiGA *deprexis*, which is based on CBT, led to a reduction in comorbid depressive symptomatology in patients with MS [12]. There is also evidence of the effectiveness of the DiGA *elevida* developed by the applicant for patients with MS and fatigue [13]. Finally, a randomized controlled trial (RCT) with 421 patients with MS or Clinically Isolated Syndrome (CIS) showed significant and clinically relevant effects of the DiGA *levidex* [14], [15] on MS-specific health-related quality of life [16]. The observed effect sizes must be

interpreted within the context of MS as a complex and severe condition. Notably, the effects of *levidex* on MS-specific quality of life align with the effects of DMDs on this outcome, even those classified as most effective [17], [18], [19]. This indicates that, given the nature of the condition, comparably smaller intervention effects are to be anticipated, while still being meaningful to patients.

In conclusion, nonpharmacological interventions whose benefits have been demonstrated in clinical trials may be a useful adjunct to usual care (for example, with DMDs) because of their positive risk-benefit profile. Psychological treatment approaches, especially CBT, show positive effects. These have been demonstrated primarily for depressive symptoms, fatigue, and disease-related quality of life. Specifically, the digital intervention *levidex* showed promising effects on MS-specific health-related quality of life, days on sick leave and instrumental activities of daily living in the study submitted for provisional listing in the DiGA registry [16].

The present RCT was conducted to support the permanent listing in the DiGA registry and aimed to further assess the effectiveness of the fully automated, internet-based intervention program *levidex* when used in conjunction with treatment-as-usual (TAU) compared to TAU alone.

3. Investigational device and methods

3.1. Investigational device description

levidex is an interactive online program for independent use by users with MS or CIS. It focuses on recognized treatment elements of CBT.

levidex is based on proprietary software of the developing company (broca®), with access via password-protected and https-encrypted websites. The program can be used on conventional web-browsers on desktop PCs, tablets and smartphones. Users receive access to the program by 12-digit personal codes (vouchers), provided by the developer. Data protection and data security are ensured by compliance with legal regulation, such as GDPR in Europe. After initial registration and consent of general terms and conditions users can log into the program using their email address and personal password at any time. The program is set up as an adaptive- and responsive-web-design pulling a layout template for a specific device, adapting to dimension and resolution of the display used. This results in high flexibility of usage regardless of the available hardware.

levidex consists of 16 modules, most of which contain treatment methods from CBT and health behavior change, and can be completed in about 30-60 minutes each.

The program is dialog-based. This means that *levidex* offers the user brief therapeutically helpful information, and the user then selects the one that most interests them and/or best suits the individual situation from a fixed number of predetermined response options. *levidex* then empathically responds to this response option and subsequently conveys the next piece of information, to which the user can in turn respond, and so on.

To improve physical health, the program contains content units (e.g., psychoeducation, cognitive restructuring, behavioral activation exercises) with information and suggestions for

dealing with MS/CIS, stress management, sleep, nutrition, and sports/exercise. Content is delivered in individual modules. Program texts are accompanied by illustrations, photos and audio recordings as well as various worksheets and summaries (PDF documents). Underlying evidence is provided in the form of edited short summaries appropriate for the target audience. Moreover, optional daily short text messages (SMS) are sent as reminders and to motivate and support users in their daily lives. The program also offers a symptom tracking function; that is, users are invited to complete embedded questionnaires at regular intervals in order to self-monitor changes over time.

In detail, the following contents are conveyed:

Psychological well-being

Emotions are addressed as a central component of psychological well-being. Various behavioral therapy techniques and exercises are used to improve mental and physical well-being and have a positive impact on the immune system. There is a special focus on managing stress, which is addressed with problem-solving techniques, mindfulness-based methods, and other behavioral therapy strategies.

Nutrition coach

The influence of nutritional habits on inflammatory processes in the body is taught in a scientifically sound manner. An inventory of the current diet is the basis for possible behavioral changes in the future in order to nutritionally counteract increased inflammatory processes. Self-reflection and mental contrasting are important components of the therapeutic process.

Exercise and physical activity

A current physical activity profile and potential physical limitations are collected. The influence of physical activity on the body and the immune system is clearly discussed. Together, realistic goals are set and pursued in the long term; motivational hurdles are addressed and worked on therapeutically.

Optimize sleep quality

Sleep quality is a decisive factor for an immune system in balance. Chronotype-appropriate measures are designed to improve sleep quality. Among other things, an analysis of sources of disturbance as well as an individual sleep plan should promote an improvement of sleep in everyday life.

Long-term support

The deepening of individual topics over a longer period of time is intended to bring about a sustainable change in behavior. Typical obstacles to implementation are repeatedly addressed and worked on therapeutically in order to be overcome in the long term.

3.2. Intended purpose

levidex is intended to provide therapeutic methods and exercises based on evidence-based psychological and psychotherapeutic therapies for patients with MS or CIS to help them managing their MS or CIS.

levidex is intended as a self-application supplemental to care-as-usual for patients 18 years of age or older.

levidex is neither intended to replace treatment provided by a health care provider nor to provide information which is used to make decisions with diagnosis or therapeutic purposes.

4. Clinical investigation plan

4.1. Clinical investigation objectives

The primary objective of this study was to evaluate the effectiveness of the fully automated digital health application *levidex* in improving MS-specific health-related quality of life in patients with MS in addition to usual care (primary endpoint). Moreover, the effects of *levidex* were examined in terms of improvements in depressive symptoms, social and work-related functioning, anxiety, instrumental activities of daily living (secondary endpoints) as well as DMD intake, sick leave/sick pay and inpatient treatment (exploratory endpoints). The primary time point for the evaluation of the effectiveness of *levidex* was after 6 months (T2). An additional time point was assessed after 3 months (T1) to assess early effects. The control group received access to *levidex* after T2.

Hypotheses are:

PH_0: The use of *levidex* in addition to TAU does not lead to differences in MS-specific health-related quality of life after six months, measured by the HALEMS, compared to TAU only.
PH_A: The use of *levidex* in addition to TAU leads to differences in MS-specific health-related quality of life after six months, measured by the HALEMS, compared to TAU only.

$SH1_0$: The use of *levidex* in addition to TAU does not lead to differences in depressive symptoms after six months, measured by the PHQ-9, compared to TAU only.
$SH1_A$: The use of *levidex* in addition to TAU leads to differences in depressive symptoms after six months, measured by the PHQ-9, compared to TAU only.

$SH2_0$: The use of *levidex* in addition to TAU does not lead to differences in social and work-related functioning after six months, measured by the WSAS, compared to TAU only.
$SH2_A$: The use of *levidex* in addition to TAU leads to differences in social and work-related functioning after six months, measured by the WSAS, compared to TAU only.

$SH3_0$: The use of *levidex* in addition to TAU does not lead to differences in MS-specific health-related quality of life after six months, measured by the MusiQoL, compared to TAU only.
$SH3_A$: The use of *levidex* in addition to TAU leads to differences in MS-specific health-related quality of life after six months, measured by the MusiQoL, compared to TAU only.

$SH4_0$: The use of *levidex* in addition to TAU does not lead to differences in anxiety symptoms after six months, measured by the GAD-7, compared to TAU only.
$SH4_A$: The use of *levidex* in addition to TAU leads to differences in anxiety symptoms after six months, measured by the GAD-7, compared to TAU only.

$SH5_0$: The use of *levidex* in addition to TAU does not lead to differences in instrumental activities of daily living after six months, measured by the FAI, compared to TAU only.
$SH5_A$: The use of *levidex* in addition to TAU leads to differences in instrumental activities of daily living after six months, measured by the FAI, compared to TAU only.

$EH1_0$: The use of *levidex* in addition to TAU does not lead to differences in MS-specific health-related quality of life domains after six months, measured by the HALEMS subscales, compared to TAU only.
$EH1_A$: The use of *levidex* in addition to TAU leads to differences in MS-specific health-related quality of life domains after six months, measured by the HALEMS subscales, compared to TAU only.

$EH2_0$: The use of *levidex* in addition to TAU does not lead to differences in DMD usage after six months, measured by the overall DMD intake as well as DMD intake classified according to efficacy in the past three months, compared to TAU only.
$EH2_A$: The use of *levidex* in addition to TAU leads to differences in DMD usage after six months, measured by the overall DMD intake as well as DMD intake classified according to efficacy in the past three months, compared to TAU only.

$EH3_0$: The use of *levidex* in addition to TAU does not lead to differences in sick days after six months, measured by the number of sick days in the past three months, compared to TAU only.
$EH3_A$: The use of *levidex* in addition to TAU leads to differences in sick days after six months, measured by the number of sick days in the past three months, compared to TAU only.

$EH4_0$: The use of *levidex* in addition to TAU does not lead to differences in days on sick pay after six months, measured by the number of days on sick pay in the past three months, compared to TAU only.
$EH4_A$: The use of *levidex* in addition to TAU leads to differences in days on sick pay after six months, measured by the number of days on sick pay in the past three months, compared to TAU only.

$EH5_0$: The use of *levidex* in addition to TAU does not lead to differences in days in inpatient treatment after six months, measured by the number of days in inpatient treatment in the past three months, compared to TAU only.
$EH5_A$: The use of *levidex* in addition to TAU leads to differences in days in inpatient treatment after six months, measured by the number of days in inpatient treatment in the past three months, compared to TAU only.

4.2. Clinical investigation design

- Pragmatic
- Randomized (simple randomization performed automatically via an external computerized tool using computer-generated random numbers)
- Controlled (two arms)
- Online (no traditional physical investigation site)

4.3. Clinical investigation endpoints

4.3.1. Primary endpoint

- MS-specific health-related quality of life (assessed with the total score of the Hamburg Quality of Life Questionnaire for Multiple Sclerosis [HALEMS], German version [20], [21])

4.3.2. Secondary endpoints

- Depressive symptoms (assessed with the total score of the Patient Health Questionnaire [PHQ-9], German version [22])
- Social and work-related functioning (assessed with the total score of the Work and Social Adjustment Scale [WSAS], German version [23])
- MS-specific health-related quality of life (assessed with the global index score of the Multiple Sclerosis International Quality of Life [MusiQoL], German version [24], [25])
- Anxiety symptoms (assessed with the total score of the Generalized Anxiety Disorder Scale [GAD-7], German Version [26])
- Instrumental activities of daily living (assessed with the total score of the Frenchay Activities Index [FAI], German version [27])

4.3.3. Exploratory endpoints

- HALEMS subscales (cognition; fatigue; lower limb mobility; upper limb mobility; communication; mood)
- Intake of DMDs overall in the last 3 months
- Intake of DMDs classified according to efficacy (efficacy category 1-3 according to current German clinical guideline [28]) in the last 3 months
- Number of days on sick leave/sick pay in the last 3 months
- Number of days in inpatient treatment in the last 3 months

4.4. Control group

Participants in the control group received usual medical care in consultation with their respective treating team. Following the pragmatic study design, usual medical care was supposed to reflect the reality of care and may therefore have comprised all forms of outpatient care, including treatment by a primary care physician or specialist, intake of DMDs and other medication, psychotherapy (such as CBT), as well as no treatment at all [29], [30].

4.5. Ethical considerations

This study was reviewed and approved by the ethics committee of the Hamburg chamber of physicians (Ärztekammer Hamburg; reference number 2023-101078-BO-ff). The clinical investigation was conducted in accordance with the ethical principles in the Declaration of Helsinki. Prior to participation, detailed patient information was provided and informed consent was obtained.

An ethics amendment specifying the interim analysis presented in version 1 of this report was approved by the ethics committee on 2024-09-06.

4.6. Data quality assurance

Data were collected online using secure, internationally recognized survey software (LimeSurvey). The survey software was programmed such that valid possible responses and response ranges were predefined for every question. Quality of the data and procedures

were checked every week (e.g., participants were contacted in time to complete the questionnaires). In addition, a daily backup of the data was performed. These will be stored in anonymized, read-only form after the study is completed. The data will be retained for 10 years.

4.7. Subject population for the clinical investigation

Inclusion criteria:

- Age ≥ 18
- Impaired health-related quality of life (total score of the Hamburg Quality of Life Questionnaire for Multiple Sclerosis [HALEMS] ≥ 2)*
- Specialist treatment in the last three months before study inclusion
- Diagnosis of MS (relevant ICD-10-GM diagnoses G35.x), confirmed by a medical document or equivalent certificate
- Sufficient cognitive and motor skills to use an online program
- Consent to participate
- Sufficient knowledge of the German language
- Access to the Internet

* to include patients in the study whose quality of life is impaired, we set a cut-off value of HALEMS total score ≥ 2 as an inclusion criterion. This cut-off approximates an Expanded Disability Status Scale (EDSS) score of ≥ 3, reflecting at least moderate disability in MS [21], [31].

Exclusion criteria:

- Presence of severe impairment of independence or abilities (degree of care [“Pflegegrad”, § 15 SGB XI] ≥ 3)

4.8. Treatment allocation schedule

Simple randomization (no blocked randomization, no stratification) was performed automatically using computer-generated random numbers and concealed from study staff.

4.9. Concomitant medications/treatment

All participants received usual medical care in consultation with their respective treating team. Following the pragmatic study design, usual medical care was supposed to reflect the reality of care and may therefore have comprised all forms of outpatient care, including treatment by a primary care physician or specialist, intake of DMDs and other medication, psychotherapy (such as CBT), as well as no treatment at all [29], [30].

4.10. Duration of follow-up

The total duration of follow-up was 6 months.

4.11. Statistical design

Analysis of intervention effects at T2 was performed by calculating an ANCOVA: the respective outcome at 6 months served as the dependent variable, the treatment condition (intervention vs. control group) as the independent variable, and the baseline values of the respective outcome as the covariate. Treatment effects (independent variable: treatment condition), i.e., baseline-adjusted mean group differences between the intervention and control group in the respective outcome variable at T2, are reported on the original scale, along with the corresponding 95% CI. The corresponding *p*-value of the treatment effect from the ANCOVA was used to determine statistical significance of the results. Between-group effects (Cohen's *d* [32], [33]) were determined based on the difference in baseline-adjusted mean values between the intervention group and the control group at T2, respectively.

Tests of intermediate treatment effects at T1 were performed analogously with baseline as covariate. Stability of effects was tested using paired *t*-tests for each group.

The primary analysis was performed as an intention-to-treat (ITT) analysis with multiple imputation under 'missing at random' (MAR) assumption [34], [35]. The ITT analysis provides an estimation of the treatment effect for all subjects randomized [34]. Missing data points at T1/T2 were imputed using the respective variable values at baseline as well as group membership and other sociodemographic and clinical variables (age, sex, MS type, concomitant psychotherapy at baseline, antidepressant use at baseline). The ITT analysis was implemented following a computationally efficient implementation for bootstrapped maximum likelihood multiple imputation using the *R* packages *bootImpute* [36] and *mice* [37]. In detail, 1,000 bootstrap samples of the incomplete dataset (with the variables mentioned above) were generated for each outcome variable and then the relevant outcome variable was imputed twice with the *mice* package with default settings (i.e., using predictive mean matching with a pool of 5 candidate values) as recommended.

In addition, a conservative sensitivity analysis based on reference-based multiple imputation (J2R imputation) was calculated. Under reference-based imputation, patients who drop out of the intervention group are assumed to no longer participate in the intervention and their outcomes from that point on are assumed to be the same as those of the control group [38], [39]. J2R sensitivity analysis was implemented with a computationally efficient implementation for bootstrapped maximum likelihood multiple imputation using the *bootImpute* and *mlmi* packages in *R* [36]. Specifically, the function *refBasedCts* (*mlmi* package) was used with the argument 'type = "J2R"' to perform the reference-based imputation [40].

Moreover, an exploratory per-protocol (PP) analysis was planned [35], [41]. For PP analyses, the dataset was filtered based on the variable 'voucher activated'. Individuals in the intervention group who did not activate the voucher to activate *levidex* were planned to be excluded from the PP dataset. Because all participants in the intervention group activated their voucher, this would have resulted in the same analysis as the primary ITT analysis and was therefore not conducted.

Analysis of exploratory outcomes (medication; number of days in sick leave/pay; number of days in inpatient treatment) were conducted based on complete data in the form of χ^2-tests to examine between group effects at T1 and T2.

Operationally, all results were considered statistically significant at the two-sided 5% level. This is equivalent to using a one-sided *p*-value (nominal $\alpha = 0.025$) and a one-sided 2.5% overall significance level [42]. All analyses were performed with *R*, version 4.4.1 [43]. No correction for multiple testing was applied.

4.12. Amendments to the CIP

The CIP was amended on 2024-08-23, to include the interim analysis presented in version 1 of this report. The amendment was approved by the ethics committee on 2024-09-06.

5. Results

5.1. Clinical investigation initiation date

First Patient First Visit: 2023-11-09

5.2. Clinical investigation completion/suspension date

Last Patient Last Visit: 2024-12-06

5.3. Disposition of subjects

Study participants were recruited through an online campaign, newsletters, flyers, and through physicians from November 2023 through June 2024. A total of 3355 people were interested in participation and were screened for eligibility. Of these, 470 met inclusion criteria and were randomized to the intervention (n = 215) and control group (n = 255). The investigational device *levidex* was provided free of charge by its developer and manufacturer, GAIA. The intervention group received access immediately after randomization, while the control group was offered access to *levidex* after 6 months. *levidex* is an internet-based application that does not require any installation. However, internet access and an up-to-date internet browser are required to use *levidex*.

5.4. Accountability of subjects

In total, 470 participants were included in the study.

Figure 1 summarizes the flow of participants through the study. As described in section 4.11, missing data were imputed for ITT and J2R analyses.

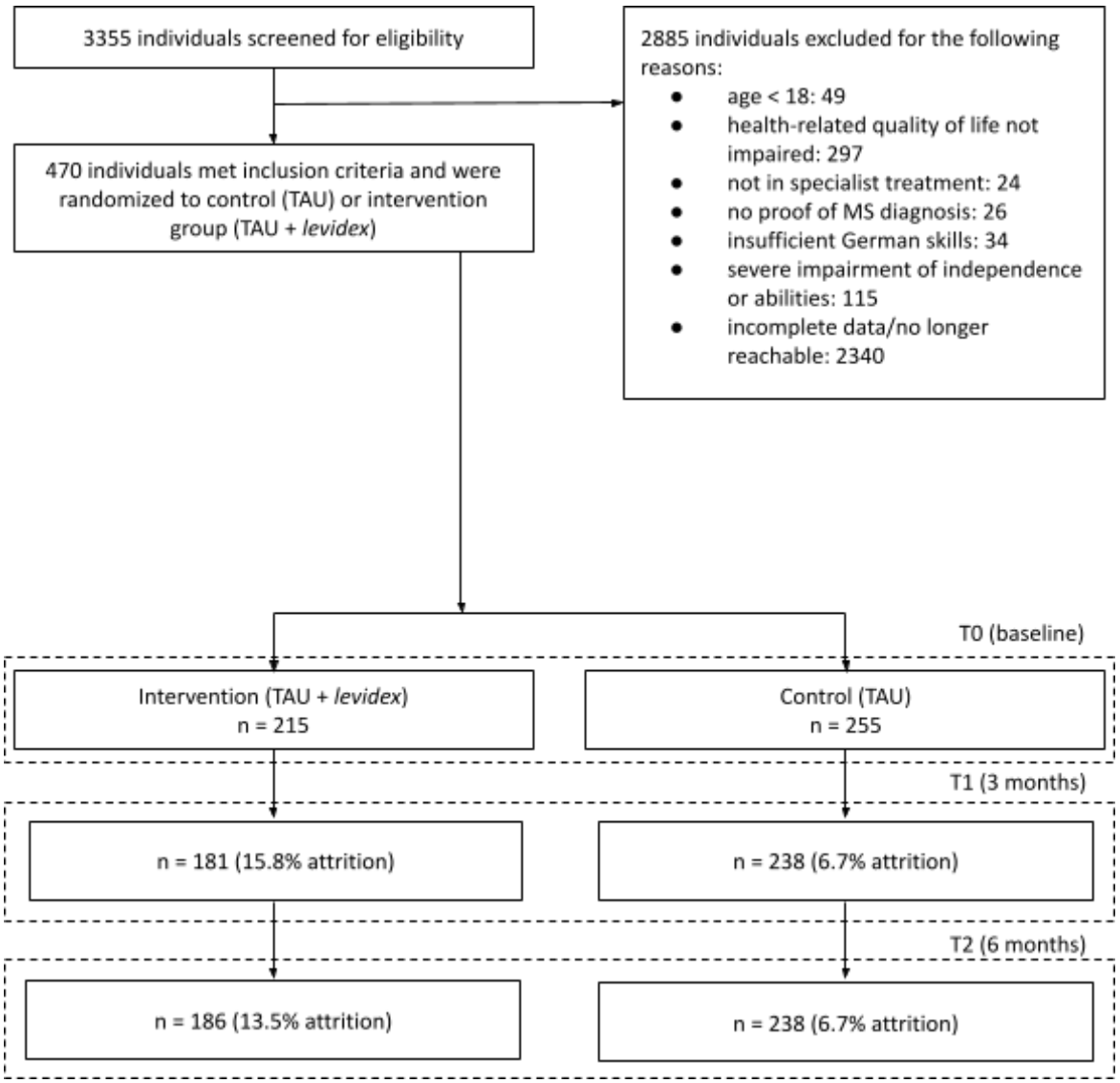

Figure 1 | Flow of participants through the study.

5.4.1. Subjects who did not pass the screening test

A total of 3355 people were initially screened for eligibility. Of these, 2885 had to be excluded for the following reasons after the online questionnaire:

- age < 18: 49
- health-related quality of life not impaired: 297
- not in specialist treatment: 24
- no proof of MS diagnosis: 26
- insufficient German skills: 34
- severe impairment of independence or abilities: 115
- incomplete data/no longer reachable: 2340

5.4.2. Subjects lost to follow-up

Table 1 | Number of patients lost to follow-up by time point and study group.

Time point	Control	*levidex*
up to T1	16 (6.3%)	28 (13.0%)
up to T2	14 (5.5%)	21 (9.8%)

5.4.3. Subjects withdrawn or discontinued from the clinical investigation

Table 2 | Number of patients withdrawn from the clinical investigation by time point and study group.

Time point	Control	*levidex*
up to T1	1 (0.4%)	6 (2.8%)
up to T2	3 (1.2%)	8 (3.7%)

5.4.4. Comparison of dropouts and completers

Table 3 | Comparison of baseline characteristics of dropouts and completers for the total sample and separately for the intervention and control group. Values represent mean (SD) unless stated otherwise.

	Total			**Control**			***levidex***		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
	n = 46	n = 424		n = 17	n = 238		n = 29	n = 186	
Age	44.83 (10.32)	46.82 (10.64)	t = -1.24, p = .220	46.66 (9.80)	47.57 (10.80)	t = -0.37, p = 0717	43.75 (10.64)	45.86 (10.38)	t = -1.00, p = 0.325
Age category (n [%])			χ^2 = 4.10, p = .535			χ^2 = 1.83, p = 0.873			χ^2 = 5.60, p = 0.348
18-15	0 (0.0)	6 (1.4)		0 (0.0)	5 (2.1)		0 (0.0)	1 (0.5)	
26-35	9 (19.6)	55 (13.0)		1 (5.9)	27 (11.3)		8 (27.6)	28 (15.1)	
36-45	12 (26.1)	130 (30.7)		6 (35.3)	65 (27.3)		6 (20.7)	65 (34.9)	
46-55	16 (34.8)	127 (30.0)		6 (35.3)	79 (33.2)		10 (34.5)	48 (25.8)	
56-65	9 (19.6)	93 (21.9		4 (23.5)	53 (22.3)		5 (17.2)	40 (21.5)	
> 65	0 (0.0)	13 (3.1)		0 (0.0)	9 (3.8)		0 (0.0)	4 (2.2)	

	Total			Control			*levidex*		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
Sex (n [%])			χ^2 = 0.46, *p* = .498			χ^2 = 0.05, *p* = .826			χ^2 = 4.09, *p* = .043
male	10 (21.7)	75 (17.7)		3 (17.6)	55 (23.1)		7 (24.1)	20 (10.8)	
female	36 (78.3)	349 (82.3)		14 (82.4)	183 (76.9)		22 (75.9)	166 (89.2)	
intersexual	0 (0)	0 (0)		0 (0)	0 (0)				
Family situation (n [%])			χ^2 = 6.11, *p* = .106			χ^2 = 7.62, *p* = .054			χ^2 = 3.07, *p* = .380
never married	16 (34.8)	125 (29.5)		4 (23.5)	68 (28.6)		12 (41.4)	57 (30.6)	
married / registered civil partnership	20 (43.5)	251 (59.2)		7 (41.2)	138 (58.0)		13 (44.8)	113 (60.8)	
divorced / registered partnership annulled	9 (19.6)	45 (10.6)		5 (29.4)	30 (12.6)		4 (13.8)	15 (8.1)	
widowed / registered partner deceased	1 (2.2)	3 (0.7)		1 (5.9)	2 (0.8)		0 (0.0)	1 (0.5)	
Education (n [%])			χ^2 = 0.81, *p* = .976			χ^2 = 1.68, *p* = .892			χ^2 = 1.72, *p* = .886
Hauptschulabschluss	1 (2.2)	9 (2.1)		1 (5.9)	7 (2.9)		0 (0.0)	2 (1.1)	
Realschulabschluss	5 (10.9)	49 (11.6)		1 (5.9)	30 (12.6)		4 (13.8)	19 (10.2)	
Fachhochschulreife	4 (8.7)	29 (6.8)		2 (11.8)	18 (7.6)		2 (6.9)	11 (5.9)	
Abitur (A-levels)	6 (13.0)	42 (9.9)		2 (11.8)	26 (10.9)		4 (13.8)	16 (8.6)	
completed vocational training	11 (23.9)	116 (27.4)		4 (23.5)	70 (29.4)		7 (24.1)	46 (24.7)	
completed university studies	19 (41.3)	179 (42.2)		7 (41.2)	87 (36.6)		12 (41.4)	92 (49.5)	

	Total			Control			*levidex*		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
Employment (n [%])			X^2 = 8.78, p = .458			X^2 = 13.99, p = .123			X^2 = 3.17, p = .869
not employed	16 (34.8)	121 (28.5)		6 (35.3)	75 (31.5)		10 (34.5)	46 (24.7)	
employed irregularly	1 (2.2)	6 (1.4)		1 (5.9)	2 (0.8)		0 (0.0)	4 (2.2)	
marginal employment	0 (0.0)	19 (4.5)		0 (0.0)	15 (6.3)		0 (0.0)	4 (2.2)	
employed part-time	17 (37.0)	136 (32.1)		7 (41.2)	66 (27.7)		10 (34.5)	70 (37.6)	
employed full-time	11 (23.9)	127 (30.0)		2 (11.8)	71 (29.8)		9 (31.0)	56 (30.1)	
in vocational training	0 (0.0)	4 (0.9)		0 (0.0)	3 (1.3)		0 (0.0)	1 (0.5)	
in retraining	0 (0.0)	2 (0.5)		0 (0.0)	1 (0.4)		0 (0.0)	1 (0.5)	
on parental leave	0 (0.0)	7 (1.7)		0 (0.0)	3 (1.3)		0 (0.0)	4 (2.2)	
partial retirement	1 (2.2)	1 (0.2)		1 (5.9)	1 (0.4)		0 (0.0)	0 (0.0)	
voluntary military service	0 (0.0)	1 (0.2)		0 (0.0)	1 (0.4)		0 (0.0)	0 (0.0)	
Ethnicity (multiple answers possible; n [%])									
white	44 (95.7)	416 (98.1)	X^2 = 0.31, p = .575	17 (100.0)	234 (98.3)	X^2 = 0.0, p = 1	27 (93.1)	182 (97.8)	X^2 = 0.70, p = .402
black	0 (0.0)	1 (0.2)	X^2 = 0.0, p = 1	0 (0.0)	0 (0.0)	*n/a*	0 (0.0)	1 (0.5)	X^2 = 0.0, p = 1
middle eastern	3 (6.5)	8 (1.9)	X^2 = 2.14, p = .144	1 (5.9)	6 (2.5)	X^2 = 0.00, p = .959	2 (6.9)	2 (1.1)	X^2 = 2.01, p = .156
south asian	0 (0.0)	2 (0.5)	X^2 = 0.0, p = 1	0 (0.0)	1 (0.4)	X^2 = 0.0, p = 1	0 (0.0)	1 (0.5)	X^2 = 0.0, p = 1
latin american	0 (0.0)	1 (0.2)	X^2 = 0.0, p = 1	0 (0.0)	0 (0.0)	*n/a*	0 (0.0)	1 (0.5)	X^2 = 0.0, p = 1
unknown	0 (0.0)	1 (0.2)	X^2 = 0.0, p = 1	0 (0.0)	1 (0.4)	X^2 = 0.0, p = 1	0 (0.0)	0 (0.0)	*n/a*

	Total			Control			*levidex*		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
prefer not to answer	0 (0.0)	1 (0.2)	X^2 = 0.0, p = 1	0 (0.0)	0 (0.0)	*n/a*	0 (0.0)	1 (0.5)	X^2 = 0.0, p = 1
MS type (n [%])			X^2 = 1.98, p = .576			X^2 = 1.90, p = .594			X^2 = 1.59, p = .662
RRMS	28 (60.9)	264 (62.3)		9 (52.9)	145 (60.9)		19 (65.5)	119 (64.0)	
PPMS	10 (21.7)	63 (14.9)		5 (29.4)	43 (18.1)		5 (17.2)	20 (10.8)	
SPMS	7 (15.2)	79 (18.6)		3 (17.6)	41 (17.2)		4 (13.8)	38 (20.4)	
unspecified	1 (2.2)	18 (4.2)		0 (0.0)	9 (3.8)		1 (3.4)	9 (4.8)	
MS duration (in years)	12.41 (9.17)	11.72 (9.86)	t = 0.48, p = .633	14.60 (10.39)	11.49 (10.01)	t = 1.20, p = .247	11.13 (8.30)	12.03 (9.68)	t = -0.53, p = 0.600
Stage of disability (PDDS)			X^2 = 4.09, p = .769			X^2 = 5.68, p = .578			X^2 = 2.19, p = .949
normal	2 (4.3)	22 (5.2)		0 (0.0)	12 (5.0)		2 (6.9)	10 (5.4)	
mild disability	4 (8.7)	68 (16.0)		0 (0.0)	36 (15.1)		4 (13.8)	32 (17.2)	
moderate disability	14 (30.4)	111 (26.2)		6 (35.3)	61 (25.6)		8 (27.6)	50 (26.9)	
gait disability	13 (28.3)	88 (20.8)		5 (29.4)	50 (21.0)		8 (27.6)	38 (20.4)	
early cane	7 (15.2)	67 (15.8)		3 (17.6)	36 (15.1)		4 (13.8)	31 (16.7)	
late cane	2 (4.3)	38 (9.0)		1 (5.9)	23 (9.7)		1 (3.4)	15 (8.1)	
bilateral support	3 (6.5)	23 (5.4)		2 (11.8)	16 (6.7)		1 (3.4)	7 (3.8)	
wheelchair/scooter	1 (2.2)	7 (1.7)		0 (0.0)	4 (1.7)		1 (3.4)	3 (1.6)	
bedridden	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Currently in psychotherapy (n [%])	13 (28.3)	97 (22.9)	X^2 = 0.67, p = .413	5 (29.4)	50 (21.0)	X^2 = 0.26, p = .611	8 (27.6)	47 (25.3)	X^2 = 0.07, p = .790
Number of sessions in last 3 months	2.85 (6.81)	1.27 (2.91)	t = 1.56, p = .126	1.59 (3.00)	1.32 (3.13)	t = 0.36, p = .726	3.59 (8.24)	1.20 (2.60)	t = 1.54, p = 0.133
Currently in physiotherapy (n [%])	23 (50.0)	218 (51.4)	X^2 = 0.03, p = .855	11 (64.7)	129 (54.2)	X^2 = 0.71, p = .400	12 (41.4)	89 (47.8)	X^2 = 0.42, p = .516
Number of	7.00 (9.71)	7.75	t = -0.49, p	7.82	8.13 (10.86)	t = -0.12,	6.52	7.26 (9.45)	t = -0.39,

	Total			Control			*levidex*		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
sessions in last 3 months		(10.26)	= .624	(10.16)		p = .907	(9.58)		p = 0.698
Number of massages in last 3 months	1.85 (3.40)	1.80 (4.76)	t = 0.09, p = .931	2.00 (3.41)	1.88 (4.86)	t = 0.13, p = .896	1.76 (3.45)	1.69 (4.64)	t = 0.09, p = .929
Currently in rehabilitation (n [%])	6 (13.0)	32 (7.5)	χ^2 = 1.69, p = .194	3 (17.6)	15 (6.3)	χ^2 = 1.62, p = .203	3 (10.3)	17 (9.1)	χ^2 = 0.0, p = 1
Currently taking DMDs (multiple answers possible; n [%])									
any DMD	22 (47.8)	239 (56.4)	χ^2 = 1.23, p = .268	8 (47.1)	136 (57.1)	χ^2 = 0.66, p = .418	14 (48.3)	103 (55.4)	χ^2 = 0.51, p = .475
DMD of efficacy category 1[a]	8 (17.4)	92 (21.7)	χ^2 = 0.46, p = .498	3 (17.6)	45 (18.9)	χ^2 = 0.0, p = 1	5 (17.2)	47 (25.3)	χ^2 = 0.50, p = .480
DMD of efficacy category 2[b]	8 (17.4)	41 (9.7)	χ^2 = 2.65, p = .104	2 (11.8)	22 (9.2)	χ^2 = 0.0, p = 1	6 (20.7)	19 (10.2)	χ^2 = 2.68, p = .102
DMD of efficacy category 3[c]	6 (13.0)	106 (25.0)	χ^2 = 3.27, p = .071	3 (17.6)	69 (29.0)	χ^2 = 0.53, p = .468	3 (10.3)	37 (19.9)	χ^2 = 0.95, p = .331
Currently taking antidepressants (n [%])	8 (17.4)	71 (16.7)	χ^2 = 0.01, p = .911	4 (23.5)	40 (16.8)	χ^2 = 0.14, p = .707	4 (13.8)	31 (16.7)	χ^2 = 0.01, p = .905
Days on sick leave (last 3 months; n [%])			χ^2 = 2.69, p = .442			χ^2 = 4.48, p = .214			χ^2 = 0.71, p = .871
0 days	18 (39.1)	166 (39.2)		6 (35.3)	90 (37.8)		12 (41.4)	76 (40.9)	
1-5 days	6 (13.0)	76 (17.9)		3 (17.6)	46 (19.3)		3 (10.3)	30 (16.1)	
6-10 days	4 (8.7)	58 (13.7)		0 (0.0)	35 (14.7)		4 (13.8)	23 (12.4)	
> 10 days	18 (39.1)	124 (29.2)		8 (47.1)	67 (28.2)		10 (34.5)	57 (30.6)	

	Total			Control			*levidex*		
	Dropouts	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**	**Dropouts**	**Completers**	**Statistical comparison**
Days on sick pay (last 3 months; n [%])			X^2 = 3.07, *p* = .381			X^2 = 1.40, *p* = .706			X^2 = 8.83, *p* = .032
0 days	41 (89.1)	367 (86.6)		14 (82.4)	207 (87.0)		27 (93.1)	160 (86.0)	
1-5 days	0 (0.0)	9 (2.1)		0 (0.0)	5 (2.1)		0 (0.0)	4 (2.2)	
6-10 days	1 (2.2)	2 (0.5)		0 (0.0)	2 (0.8)		1 (3.4)	0 (0.0)	
> 10 days	4 (8.7)	46 (10.8)		3 (17.6)	24 (10.1)		1 (3.4)	22 (11.8)	
Days in inpatient treatment (last 3 months; n [%])			X^2 = 1.16, *p* = .763			X^2 = 1.65, *p* = .648			X^2 = 2.51, *p* = .473
0 days	38 (82.6)	352 (83.0)		12 (70.6)	195 (81.9)		26 (89.7)	157 (84.4)	
1-5 days	2 (4.3)	32 (7.5)		2 (11.8)	19 (8.0)		0 (0.0)	13 (7.0)	
6-10 days	3 (6.5)	19 (4.5)		1 (5.9)	11 (4.6)		2 (6.9)	8 (4.3)	
> 10 days	3 (6.5)	21 (5.0)		2 (11.8)	13 (5.5)		1 (3.4)	8 (4.3)	
HALEMS total score	2.82 (0.58)	2.68 (0.48)	*t* = 1.58, *p* = .121	2.89 (0.68)	2.66 (0.45)	*t* = 1.35, *p* = .193	2.79 (0.53)	2.71 (0.52)	*t* = 0.72, *p* = .475
PHQ-9 total score	11.54 (4.09)	11.15 (4.44)	*t* = 0.62, *p* = .540	11.59 (4.82)	11.02 (4.36)	*t* = 0.47, *p* = .641	11.52 (3.69)	11.32 (4.55)	*t* = 0.26, *p* = .794
WSAS total score	19.98 (8.92)	18.57 (8.16)	*t* = 1.03, *p* = .310	22.12 (8.32)	18.25 (8.30)	*t* = 1.85, *p* = .080	18.72 (9.15)	18.98 (7.97)	*t* = -0.14, *p* = .888
MusiQoL global index score	51.07 (14.85)	55.78 (13.02)	*t* = -2.07, *p* = .044	49.55 (16.77)	56.00 (12.41)	*t* = -1.55, *p* = .138	51.96 (13.84)	55.50 (13.80)	*t* = -1.28, *p* = .208
GAD-7 total score	8.89 (5.49)	8.24 (4.48)	*t* = 0.78, *p* = .440	7.76 (5.39)	7.70 (4.08)	*t* = 0.05, *p* = .963	9.55 (5.54)	8.92 (4.87)	*t* = 0.58, *p* = .568
FAI total score	27.28 (8.27)	28.87 (7.52)	*t* = -1.25, *p* = .217	25.35 (7.42)	28.69 (7.73)	*t* = -1.79, *p* = .090	28.41 (8.65)	29.10 (7.25)	*t* = -0.41, *p* = .687

[a] efficacy category 1 according to the current German clinical guideline [28]: dimethyl fumarate / diroximel fumarate, glatirameroids, interferon-beta, teriflunomide; [b] efficacy category 2 according to the current German clinical guideline [28]: cladribine, fingolimod, ozanimod, ponesimod, siponimod; [c] efficacy category 3 according to the current German

clinical guideline [28]: alemtuzumab, natalizumab, ocrelizumab, ofatumumab, rituximab, ublituximab.

5.5. Subject demographics and clinical characteristics

Table 4 below presents an overview of the participants' characteristics at T0.

Table 4 | Subject demographics and clinical characteristics at baseline. Values represent mean (SD) unless stated otherwise.

	Total	**Control**	***levidex***
	n = 470	n = 255	n = 215
Age	46.63 (10.62)	47.51 (10.72)	45.58 (10.41)
Age category (n [%])			
18-25	6 (1.3)	5 (2.0)	1 (0.5)
26-35	64 (13.6)	28 (11.0)	36 (16.7)
36-45	142 (30.2)	71 (27.8)	71 (33.0)
46-55	143 (30.4)	85 (33.3)	58 (27.0)
56-65	102 (21.7)	57 (22.4)	45 (20.9)
> 65	13 (2.8)	9 (3.5)	4 (1.9)
Sex (n [%])			
male	85 (18.1)	58 (22.7)	27 (12.6)
female	385 (81.9)	197 (77.3)	188 (87.4)
intersexual	0 (0)	0 (0)	0 (0)
Family situation (n [%])			
never married	141 (30.0)	72 (28.2)	69 (32.1)
married / registered civil partnership	71 (57.7)	145 (56.9)	126 (58.6)
divorced / registered partnership annulled	54 (11.5)	35 (13.7)	19 (8.8)
widowed / registered partner deceased	4 (0.9)	3 (1.2)	1 (0.5)
Education (n [%])			
Hauptschulabschluss	10 (2.1)	8 (3.1)	2 (0.9)
Realschulabschluss	54 (11.5)	31 (12.2)	23 (10.7)
Fachhochschulreife	33 (7.0)	20 (7.8)	13 (6

	Total	Control	*levidex*
Abitur (A-levels)	48 (10.2)	28 (11.0)	20 (9.3)
completed vocational training	127 (27.0)	74 (29.0)	53 (24.7)
completed university studies	198 (42.1)	94 (36.9)	104 (48.4)
Employment (n [%])			
not employed	137 (29.1)	81 (31.8)	56 (26.0)
employed irregularly	7 (1.5)	3 (1.2)	4 (1.9)
marginal employment	19 (4.0)	15 (5.9)	4 (1.9)
employed part-time	153 (32.6)	73 (28.6)	80 (37.2)
employed full-time	138 (29.4)	73 (28.6)	65 (30.2)
in vocational training	4 (0.9)	3 (1.2)	1 (0.5)
in retraining	2 (0.4)	1 (0.4)	1 (0.5)
on parental leave	7 (1.5)	3 (1.2)	4 (1.9)
partial retirement	2 (0.4)	2 (0.8)	0 (0.0)
in voluntary military service	1 (0.2)	1 (0.4)	0 (0.0)
Ethnicity (multiple answers possible; n [%])			
white	460 (97.9)	251 (98.4)	209 (97.2)
black	1 (0.2)	0 (0.0)	1 (0.5)
middle eastern	11 (2.3)	7 (2.7)	4 (1.9)
south asian	2 (0.4)	1 (0.4)	1 (0.5)
latin american	1 (0.2)	0 (0.0)	1 (0.5)
unknown	1 (0.2)	1 (0.4)	0 (0.0)
prefer not to answer	1 (0.2)	0 (0.0)	1 (0.5)
MS type (n [%])			
RRMS	292 (62.1)	154 (60.4)	138 (64.2)
PPMS	73 (15.5)	48 (18.8)	25 (11.6)
SPMS	86 (18.3)	44 (17.3)	42 (19.5)
unspecified	19 (4.0)	9 (3.5)	10 (4.7)
MS duration (in years)	11.79 (9.79)	11.69 (10.05)	11.91 (9.49)
Stage of disability (PDDS)			

	Total	Control	*levidex*
normal	24 (5.1)	12 (4.7)	12 (5.6)
mild disability	72 (15.3)	36 (14.1)	36 (16.7)
moderate disability	125 (26.6)	67 (26.3)	58 (27.0)
gait disability	101 (21.5)	55 (21.6)	46 (21.4)
early cane	74 (15.7)	39 (15.3)	35 (16.3)
late cane	40 (8.5)	24 (9.4)	16 (7.4)
bilateral support	26 (5.5)	18 (7.1)	8 (3.7)
wheelchair/scooter	8 (1.7)	4 (1.6)	4 (1.9)
bedridden	0 (0.0)	0 (0.0)	0 (0.0)
Currently in psychotherapy (n [%])	110 (23.4)	55 (21.6)	55 (25.6)
Number of sessions in last 3 months	1.42 (3.51)	1.34 (3.12)	1.53 (3.92)
Currently in physiotherapy (n [%])	241 (51.3)	140 (54.9)	101 (47.0)
Number of sessions in last 3 months	7.67 (10.20)	8.11 (10.79)	7.16 (9.45)
Number of massages in last 3 months	1.80 (4.64)	1.89 (4.78)	1.70 (4.49)
Currently in rehabilitation (n [%])	38 (8.1)	18 (7.1)	20 (9.3)
Currently taking DMDs (multiple answers possible; n [%])			
any DMD	261 (55.5)	144 (56.5)	117 (54.4)
DMD of efficacy category 1[a]	100 (21.3)	48 (18.8)	52 (24.2)
DMD of efficacy category 2[b]	49 (10.4)	24 (9.4)	25 (11.6)
DMD of efficacy category 3[c]	112 (23.8)	72 (28.2)	40 (18.6)
Currently taking antidepressants (n [%])	79 (16.8)	44 (17.3)	35 (16.3)
Days on sick leave (last 3 months; n [%])			
0	184 (39.1)	96 (37.6)	88 (40.9)
1-5	82 (17.4)	49 (19.2)	33 (15.3)

	Total	Control	*levidex*
6-10	62 (13.2)	35 (13.7)	27 (12.6)
> 10	142 (30.2)	75 (29.4)	67 (31.2)
Days on sick pay (last 3 months; n [%])			
0	408 (86.8)	221 (86.7)	187 (87.0)
1-5	9 (1.9)	5 (2.0)	4 (1.9)
6-10	3 (0.6)	2 (0.8)	1 (0.5)
> 10	50 (10.6)	27 (10.6)	23 (10.7)
Days in inpatient treatment (last 3 months; n [%])			
0	390 (83.0)	207 (81.2)	183 (85.1)
1-5	34 (7.2)	21 (8.2)	13 (6.0)
6-10	22 (4.7)	12 (4.7)	10 (4.7)
> 10	24 (5.1)	15 (5.9)	9 (4.2)
HALEMS total score	2.70 (0.49)	2.68 (0.47)	2.72 (0.52)
PHQ-9 total score	11.19 (4.41)	11.05 (4.38)	11.34 (4.44)
WSAS total score	18.71 (8.23)	18.51 (8.34)	18.94 (8.12)
MusiQoL global index score	55.32 (13.27)	55.57 (12.81)	55.02 (13.83)
GAD-7 total score	8.30 (4.59)	7.71 (4.17)	9.01 (4.96)
FAI total score	28.72 (7.60)	28.47 (7.74)	29.01 (7.44)

[a] efficacy category 1 according to the current German clinical guideline [28]: dimethyl fumarate / diroximel fumarate, glatirameroids, interferon-beta, teriflunomide; [b] efficacy category 2 according to the current German clinical guideline [28]: cladribine, fingolimod, ozanimod, ponesimod, siponimod; [c] efficacy category 3 according to the current German clinical guideline [28]: alemtuzumab, natalizumab, ocrelizumab, ofatumumab, rituximab, ublituximab.

5.6. CIP compliance

The CIP was complied with throughout the duration of the clinical investigation. An amendment specifying the interim analysis presented in version 1 of this report was submitted to the ethics committee and approved prior to conducting the analyses. The interim analysis was performed due to a regulatory deadline for submitting data on the effectiveness of *levidex* by 2024-10-06.

5.7. Analysis

The means at follow-ups (T1 and T2) presented in the tables below are unadjusted for baseline. Please note that because all participants in the intervention group registered for *levidex*, which was defined as the relevant criterion for PP analyses, no additional PP analyses were conducted.

5.7.1. Primary endpoint

- MS-specific health-related quality of life (assessed with the HALEMS total score)

Table 5 | Results of the primary endpoint MS-specific quality of life (HALEMS)

Time		**Control**			***levidex***			**ANCOVA**			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	255	2.68	0.47	215	2.72	0.51	-	-	-	-
	T1	255	2.65	0.56	215	2.57	0.55	-0.11 (-0.18, -0.05)	< .001	0.03	0.32 (0.13, 0.52)
	T2	255	2.66	0.58	215	2.60	0.57	-0.10 (-0.18, -0.03)	.008	0.02	0.26 (0.07, 0.45)
J2R	T0	255	2.68	0.47	215	2.72	0.51	-	-	-	-
	T1	255	2.66	0.57	215	2.60	0.56	-0.10 (-0.16, -0.04)	< .001	0.02	0.29 (0.13, 0.44)
	T2	255	2.67	0.58	215	2.62	0.58	-0.09 (-0.16, -0.03)	.003	0.02	0.24 (0.08, 0.4)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

To evaluate the clinical significance of the findings, we performed an analysis of responders at T2 using an MCID of 0.22 points on the HALEMS total score [20]. A significantly higher proportion of participants in the intervention group reached this criterion than in the control group (85/215 [39.5%] vs. 71/255 [27.8%]; χ^2 = 7.19, *p* = .007, OR = 1.69, 95% CI = [1.15; 2.50]).

Table 6 | Responder rate of MS-specific health-related quality of life at T2 by study group

	Control (n = 255)	***levidex* (n = 215)**	Statistical comparison	Odds Ratio (95% CI)[a]
responder (n [%])	71 (27.8%)	85 (39.5%)	χ^2 = 7.19, *p* = .007	1.69 (1.15, 2.50)

[a] calculated using unconditional maximum likelihood estimation (Wald). An Odds Ratio (OR) > 1 signifies a higher likelihood of the event occurring in the intervention group.

5.7.2. Secondary endpoints

- Depressive symptoms (assessed with the PHQ-9 total score)

Table 7 | Results of the secondary endpoint depressive symptoms (PHQ-9)

Time	**Control**			***levidex***			**ANCOVA**			
	n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]

ITT	T0	255	11.0	4.4	215	11.3	4.4	-	-	-	-
	T1	255	9.8	4.4	215	9.9	4.5	-0.2 (-0.9, 0.5)	.630	0	0.05 (-0.15, 0.24)
	T2	255	10.1	4.5	215	9.5	4.6	-0.8 (-1.4, -0.1)	.025	0.01	0.21 (0.03, 0.4)
J2R	T0	255	10.9	4.3	215	11.2	4.6	-	-	-	-
	T1	255	9.9	4.4	215	9.9	4.5	-0.1 (-0.7, 0.4)	.627	0	0.04 (-0.12, 0.20)
	T2	255	10.1	4.4	215	9.7	4.6	-0.6 (-1.2, -0.1)	.027	0.01	0.18 (0.02, 0.33)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

A standardized mean difference (SMD) between groups at T2 of at least *d* = 0.24 was considered as the criterion to evaluate clinical relevance of the findings [44]. Given that the between-group SMD was *d* = 0.21, results show that the additional use of *levidex* did not result in clinically significant reductions in depressive symptoms compared to TAU alone. In accordance, a responder analysis based on an MCID of 5 points [45] shows that a comparable proportion of participants in the intervention group and control group reached this criterion (48/215 [22.3%] vs. 52/255 [20.4%]; $\chi^2 = 0.26$, $p = .610$, OR = 1.12, 95% CI = [0.72, 1.75]).

Table 8 | Responder rate of depressive symptoms at T2 by study group

	Control (n = 255)	***levidex* (n = 215)**	Statistical comparison	Odds Ratio (95% CI)[a]
responder (n [%])	52 (20.4%)	48 (22.3%)	$\chi^2 = 0.26$, $p = .610$	1.12 (0.72, 1.75)

[a] calculated using unconditional maximum likelihood estimation (Wald). An Odds Ratio (OR) > 1 signifies a higher likelihood of the event occurring in the intervention group.

- Social and work-related functioning (assessed with the WSAS total score)

Table 9 | Results of the secondary endpoint social and work-related functioning (WSAS)

Time		**Control**			***levidex***			**ANCOVA**			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	255	18.5	8.3	215	19.0	8.1	-	-	-	-
	T1	255	18.2	9.2	215	17.0	8.5	-1.7 (-2.7, -0.6)	.002	0.04	0.30 (0.11, 0.49)
	T2	255	18.7	9.2	215	17.3	8.8	-1.8 (-2.9, -0.6)	.003	0.04	0.30 (0.10, 0.50)
J2R	T0	255	18.5	8.3	215	19.0	8.1	-	-	-	-
	T1	255	18.3	9.3	215	17.3	8.7	-1.4 (-2.3, -0.5)	.002	0.02	0.25 (0.09, 0.42)
	T2	255	18.6	9.2	215	17.6	8.9	-1.4 (-2.3, -0.5)	.002	0.02	0.25 (0.09, 0.4)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

A between-group difference of at least 3 points at T2 was defined as the criterion to evaluate clinical relevance of the findings in the CIP [46], [47]. Given that the between-group difference was 1.8 points, this criterion suggests that the additional use of *levidex* does not result in a clinically significant improvement of social and work-related functioning. By contrast, a responder analysis based on a MCID of 8 points [48] shows that a significantly higher proportion of participants in the intervention group reached this criterion than in the control group (34/215 [15.8%] vs. 16/255 [6.3%]; χ^2 = 11.2, p < .001, OR = 2.80, 95% CI = [1.50, 5.24]), suggesting clinically relevant effects of *levidex* on social and work-related functioning.

Table 10 | Responder rate of social and work-related functioning at T2 by study group

	Control (n = 255)	***levidex* (n = 215)**	Statistical comparison	Odds Ratio (95% CI)[a]
responder (n [%])	16 (6.3%)	34 (15.8%)	χ^2 = 11.2, p < .001	2.80 (1.50, 5.24)

[a] calculated using unconditional maximum likelihood estimation (Wald). An Odds Ratio (OR) > 1 signifies a higher likelihood of the event occurring in the intervention group.

- MS-specific health-related quality of life (assessed with the MusiQoL global index score)

Table 11 | Results of the secondary endpoint MS-related quality of life (MusiQoL)

Time		**Control**			***levidex***			**ANCOVA**			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	p-value	Partial η^2	Cohen's d (95% CI)[b]
ITT	T0	255	55.6	12.8	215	55.0	13.8	-	-	-	-
	T1	255	56.8	13.3	215	57.9	14.2	1.5 (-0.1, 3.1)	.071	0.01	0.18 (-0.02, 0.38)
	T2	255	56.0	13.6	215	57.7	14.5	2.1 (0.3, 3.9)	0.02	0.02	0.23 (0.04, 0.43)
J2R	T0	255	55.5	12.8	215	55.0	13.8	-	-	-	-
	T1	255	56.8	13.4	215	57.6	14.3	1.2 (-0.1, 2.5)	.067	0.01	0.15 (-0.01, 0.31)
	T2	255	56.0	13.3	215	57.4	14.4	1.9 (0.5, 3.3)	.008	0.01	0.21 (0.06, 0.36)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

A responder analysis was conducted as specified in the CIP based on the criterion of improvement of at least half a standard deviation from T0 to T2 (0.5 x 14.75 = 7.375, see [25]) showed a significantly higher responder rate in the intervention than in the control group (68/215 [31.6%] vs. 56/255 [22.0%]; χ^2 = 5.61, p = .018, OR = 1.64, 95% CI = [1.09, 2.48]).

Table 12 | Responder rate of MS-specific health-related quality of life at T2 by study group

	Control (n = 255)	***levidex* (n = 215)**	Statistical comparison	Odds Ratio (95% CI)[a]

responder (n [%])	56 (22.0%)	68 (31.6%)	$X^2 = 5.61$, $p = .018$	1.64 (1.09, 2.48)

[a] calculated using unconditional maximum likelihood estimation (Wald). An Odds Ratio (OR) > 1 signifies a higher likelihood of the event occurring in the intervention group.

- Anxiety symptoms (assessed with the GAD-7 total score)

Table 13 | Results of the secondary endpoint anxiety symptoms (GAD-7)

Time		**Control**			***levidex***			**ANCOVA**			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	255	7.7	4.2	215	9.0	4.9	-	-	-	-
	T1	255	7.0	4.1	215	8.1	4.8	0.2 (-0.5, 0.9)	.537	0	-0.06 (-0.26, 0.13)
	T2	255	7.4	4.5	215	7.8	4.9	-0.5 (-1.2, 0.2)	.205	0.01	0.13 (-0.07, 0.33)
J2R	T0	255	7.7	4.1	215	9.0	4.9	-	-	-	-
	T1	255	7.0	4.1	215	8.1	4.7	0.2 (-0.4, 0.7)	.511	0	-0.06 (-0.22, 0.11)
	T2	255	7.4	4.4	215	7.8	4.7	-0.5 (-1, 0.1)	.088	0.01	0.14 (-0.02, 0.29)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

Since a gatekeeping testing strategy was planned as a multiplicity control [49], all following secondary endpoints were considered exploratory given that no significant effects were observed for anxiety symptoms measured with the GAD-7.

5.7.3. Exploratory endpoints

- Instrumental activities of daily living (assessed with the FAI total score)

Table 14 | Results of the secondary endpoint instrumental activities of daily living (FAI)

Time		**Control**			***levidex***			**ANCOVA**			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	255	28.5	7.7	215	29.0	7.4	-	-	-	-
	T1	255	28.6	7.7	215	29.4	8.0	0.4 (-0.5, 1.3)	.418	0	0.08 (-0.11, 0.28)
	T2	255	28.4	7.9	215	29.6	8.1	0.8 (-0.1, 1.8)	.097	0.01	0.17 (-0.03, 0.36)
J2R	T0	255	28.4	7.7	215	29.0	7.4	-	-	-	-
	T1	255	28.6	7.6	215	29.4	8.0	0.3 (-0.4, 1.1)	.395	0	0.07 (-0.24, 0.09)
	T2	255	28.3	7.9	215	29.3	8.2	0.6 (-0.2, 1.3)	.163	0.01	-0.12 (-0.28, 0.05)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- HALEMS subscale ‘cognition’

Table 15 | Results of the exploratory endpoint HALEMS subscale ‘cognition’

Time		Control			*levidex*			ANCOVA			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	255	2.82	0.89	215	2.96	0.96	-	-	-	-
	T1	255	2.80	0.93	215	2.82	1.03	-0.09 (-0.22, 0.03)	.151	0.01	0.14 (-0.05, 0.34)
	T2	255	2.81	0.93	215	2.81	0.97	-0.1 (-0.23, 0.03)	.121	0.01	0.14 (-0.04, 0.33)
J2R	T0	255	2.82	0.89	215	2.96	0.96	-	-	-	-
	T1	255	2.81	0.93	215	2.84	1.03	-0.08 (-0.19, 0.02)	.131	0.01	0.13 (-0.04, 0.29)
	T2	255	2.82	0.93	215	2.85	0.97	-0.07 (-0.18, 0.03)	.182	0	0.11 (-0.05, 0.26)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- HALEMS subscale ‘fatigue’

Table 16 | Results of the exploratory endpoint HALEMS subscale ‘fatigue’

Time		Control			*levidex*			ANCOVA			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	255	3.21	0.84	215	3.26	0.95	-	-	-	-
	T1	255	3.23	0.95	215	3.06	0.94	-0.2 (-0.34, -0.06)	.004	0.02	0.29 (0.09, 0.48)
	T2	255	3.18	0.93	215	3.09	0.96	-0.12 (-0.26, 0.02)	.098	0.01	0.17 (-0.03, 0.37)
J2R	T0	255	3.21	0.84	215	3.26	0.95	-	-	-	-
	T1	255	3.24	0.96	215	3.10	0.95	-0.18 (-0.29, -0.06)	.004	0.02	0.24 (0.08, 0.41)
	T2	255	3.19	0.93	215	3.11	0.97	-0.12 (-0.23, 0)	.046	0.01	0.16 (0, 0.32)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- HALEMS subscale ‘mobility lower limb’

Table 17 | Results of the exploratory endpoint HALEMS subscale ‘mobility lower limb’

Time		Control			*levidex*			ANCOVA			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	255	2.74	1.08	215	2.69	1.04	-	-	-	-
	T1	255	2.71	1.10	215	2.51	1.02	-0.16 (-0.26, -0.05)	.004	0.02	0.28 (0.1, 0.47)
	T2	255	2.73	1.13	215	2.56	1.08	-0.14 (-0.26, -0.01)	.028	0.01	0.22 (0.03, 0.42)
J2R	T0	255	2.72	1.09	215	2.70	1.04	-	-	-	-

	T1	255	2.70	1.10	215	2.55	1.04	-0.13 (-0.22, -0.04)	.005	0.02	0.24 (0.08, 0.4)
	T2	255	2.72	1.13	215	2.60	1.09	-0.11 (-0.21, -0.01)	.035	0.01	0.18 (0.02, 0.34)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- HALEMS subscale ‘mobility upper limb’

Table 18 | Results of the exploratory endpoint HALEMS subscale ‘mobility upper limb’

Time		**Control**			***levidex***			**ANCOVA**			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	255	1.84	0.73	215	1.89	0.81	-	-	-	-
	T1	255	1.88	0.83	215	1.75	0.75	-0.11 (-0.2, -0.02)	.012	0.02	0.24 (0.06, 0.42)
	T2	255	1.87	0.79	215	1.88	0.84	-0.03 (-0.12, 0.05)	.46	0	0.07 (-0.11, 0.25)
J2R	T0	255	1.84	0.73	215	1.89	0.81	-	-	-	-
	T1	255	1.89	0.83	215	1.82	0.76	-0.1 (-0.18, -0.03)	.005	0.01	0.22 (0.07, 0.37)
	T2	255	1.88	0.80	215	1.87	0.82	-0.05 (-0.12, 0.03)	.207	0	0.1 (-0.05, 0.25)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- HALEMS subscale ‘communication’

Table 19 | Results of the exploratory endpoint HALEMS subscale 'communication’

Time		**Control**			***levidex***			**ANCOVA**			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	255	2.58	0.82	215	2.63	0.89	-	-	-	-
	T1	255	2.54	0.85	215	2.55	0.87	-0.02 (-0.13, 0.08)	.649	0	0.04 (-0.15, 0.23)
	T2	255	2.67	0.85	215	2.60	0.92	-0.11 (-0.22, 0)	.052	0.01	0.19 (0, 0.38)
J2R	T0	255	2.58	0.82	215	2.64	0.89	-	-	-	-
	T1	255	2.54	0.86	215	2.55	0.87	-0.03 (-0.12, 0.06)	.543	0	0.05 (-0.11, 0.2)
	T2	255	2.68	0.86	215	2.61	0.94	-0.11 (-0.2, -0.02)	.021	0.01	0.19 (0.03, 0.35)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- HALEMS subscale ‘mood’

Table 20 | Results of the exploratory endpoint HALEMS subscale ‘mood’

Time		**Control**			***levidex***			**ANCOVA**			
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Partial η^2	Cohen's *d* (95% CI)[b]
ITT	T0	255	2.89	0.76	215	2.89	0.82	-	-	-	-

	T1	255	2.73	0.82	215	2.67	0.79	-0.06 (-0.18, 0.05)	.277	0.01	0.1 (-0.08, 0.29)
	T2	255	2.71	0.80	215	2.63	0.82	-0.08 (-0.2, 0.03)	.166	0.01	0.14 (-0.06, 0.33)
J2R	T0	255	2.89	0.76	215	2.89	0.82	-	-	-	-
	T1	255	2.73	0.82	215	2.68	0.80	-0.05 (-0.15, 0.04)	.258	0	0.09 (-0.07, 0.25)
	T2	255	2.71	0.79	215	2.64	0.82	-0.07 (-0.17, 0.03)	.162	0.01	0.12 (-0.05, 0.28)

[a] Group difference on original scale 3/6 months after baseline, adjusted for baseline scores.
[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- Intake of DMDs

Table 21 | Results of the exploratory endpoints intake of DMDs overall and intake of DMDs classified according to efficacy at T1 and T2

		Control		***levidex***			**X^2-Test**	
	Time	n	yes (n, %)	n	yes (n, %)	Odds Ratio[d] (95% CI)	**X^2**	***p*-value**
intake of DMDs overall	T1	238	124 (52.1)	181	106 (58.6)	1.30 (0.88, 1.92)	1.73	0.188
	T2	238	123 (51.7)	186	105 (56.5)	1.21 (0.82, 1.78)	0.96	0.328
intake of DMDs category 1[a]	T1	238	42 (17.6)	181	45 (24.9)	1.54 (0.96, 2.48)	3.25	0.071
	T2	238	37 (15.5)	186	43 (23.1)	1.63 (1.00, 2.66)	3.91	0.048
intake of DMDs category 2[b]	T1	238	17 (7.1)	181	21 (11.6)	1.71 (0.87, 3.34)	2.48	0.115
	T2	238	20 (8.4)	186	18 (9.7)	1.17 (0.60, 2.28)	0.21	0.649
intake of DMDs category 3[c]	T1	238	65 (27.3)	181	41 (22.7)	0.78 (0.50, 1.22)	1.18	0.278
	T2	238	66 (27.7)	186	44 (23.7)	0.81 (0.52, 1.26)	0.90	0.342

[a] efficacy category 1 according to the current German clinical guideline [28]: dimethyl fumarate / diroximel fumarate, glatirameroids, interferon-beta, teriflunomide; [b] efficacy category 2 according to the current German clinical guideline [28]: cladribine, fingolimod, ozanimod, ponesimod, siponimod; [c] efficacy category 3 according to the current German clinical guideline [28]: alemtuzumab, natalizumab, ocrelizumab, ofatumumab, rituximab, ublituximab; [d] calculated using unconditional maximum likelihood estimation (Wald). An Odds Ratio (OR) > 1 signifies a higher likelihood of the event occurring in the intervention group.

- Days on sick leave, on sick pay, in inpatient treatment

Table 22 | Results of the exploratory endpoints days on sick leave, on sick pay, and in inpatient treatment at T1 and T2

		Control		**levidex**		**Wilcoxon-Rank Sum Test with continuity correction**	
	Time	n	mean (SD)	n	mean (SD)	*W*	*p*-value
Days on sick leave (mean, SD)	T1	238	15.4 (28.7)	181	18.8 (31.4)	19500	.078
	T2	237	13.3 (26.8)	186	15.8 (28.9)	21080	.411
Days on sick pay (mean, SD)	T1	238	7.2 (22.9)	181	10.8 (27.4)	19722	.019
	T2	238	5.2 (19.3)	186	7.2 (23.3)	22216	.904
Days in inpatient treatment (mean, SD)	T1	238	1.5 (5.8)	181	1.4 (5.4)	21356	.797
	T2	237	1.6 (6.8)	186	1.8 (9.9)	21837	.775

5.7.4. Use of *levidex*

All participants in the intervention group (215/215; 100%) registered to use *levidex*. Over the study period, participants completed an average of 10 modules (SD = 5) out of 16 possible modules. While all modules were available to all users, they had the option to skip modules if they did not apply to them. Patients demonstrated an average of 25.1 days (SD = 23.7) with active use in the program over the study period.

5.7.5. User satisfaction

User satisfaction was assessed with the NPS. Participants in the intervention group were asked how likely they were to recommend *levidex* to a friend or colleague with MS [50]. Responses were scored on an 11-point Numerical Rating Scale ranging from 0 = 'I would definitely not recommend the program' to 10 = 'I would definitely recommend the program'. Following the traditional approach to calculating the NPS yielded a score of 35.6 at T1 and a score of 31.5 at T2, indicating very high user satisfaction at both time points.

The ZUF-8 [51] was evaluated as an alternative measure of user satisfaction in the intervention group. At T1, the mean total score on this measure was 25.5 (SD = 4.1), which translates to a mean item score of 3.2. At T2, the mean total score on this measure was 25.3 (SD = 5.0), which translates to a mean item score of 3.2. These results therefore reflect high user satisfaction as well (item scores range from 1 to 4 and are oriented from negative to positive).

5.7.6. Adverse events and adverse device effects

No adverse events or adverse device effects were observed.

A safety analysis based on complete observations investigated the proportion of patients whose quality of life had deteriorated to a clinically significant extent (defined by an MCID of 0.22 [20]) compared to baseline after 6 months. In the intervention group, 40/186 [21.5%] showed a deterioration in MS-specific health-related quality of life, compared to 57/238 [23.9%] in the control group (χ^2 = 0.35, p = .552). Thus, there was no statistically significant difference in the proportion of deterioration between the two study groups.

5.8. Device deficiencies and serious adverse events

Device deficiencies or serious adverse events were not observed.

5.9. Subgroup analyses for special populations

Subgroup analyses were conducted following the ITT principle for the primary endpoint HALEMS total score at T2 (6 months, primary time point for the analysis of effectiveness). An overview of the results of the subgroup analyses presented in tables 23-28 and in the form of a forest plot in figure 2 (Cohen's *d*) and in figure 3 (adjusted mean difference) in the appendix. The means at T2 presented in tables 23-28 are unadjusted for baseline.

- Sex

Table 23 | Subgroup analysis based on sex for the primary endpoint MS-specific health-related quality of life at T2

Time	**Control**			***levidex***			**ANCOVA**		
	n	mean	SD	n	mean	SD	Treatment effect	*p*-value	Cohen's *d* (95% CI)[b]

								(95% CI)[a]		
women (n = 385)	T0	197	2.67	0.46	188	2.73	0.52	-	-	-
	T2	197	2.65	0.55	188	2.59	0.58	-0.11 (-0.19, -0.03)	.007	0.28 (0.08, 0.49)
men (n = 85)	T0	58	2.70	0.50	27	2.69	0.47	-	-	-
	T2	58	2.70	0.64	27	2.67	0.51	-0.02 (-0.17, 0.13)	.830	0.04 (-0.36, 0.44)

[a] Group difference on original scale at T2, adjusted for baseline scores.

[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

Further data on the effectiveness of *levidex* in men is presented in the appendix.

- Age

Table 24 summarizes the effects of subgroup analyses based on age for the primary endpoint MS-specific health-related quality of life at T2. Of note, in the analysis only a total of 13 individuals (9 in the control group and 4 in the intervention group) were above 65 years old. Due to this small sample size, the computations and results from the ANCOVA were unstable. Therefore, we opted to provide descriptive statistics only for this particular subgroup.

Table 24 | Subgroup analysis based on age for the primary endpoint MS-specific health-related quality of life at T2

Time		**Control**			***levidex***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
18-65 years (n = 457)	T0	246	2.67	0.47	211	2.73	0.52	-	-	-
	T2	246	2.65	0.58	211	2.60	0.58	-0.10 (-0.17, -0.02)	.012	0.25 (0.06, 0.45)
> 65 years (n = 13)	T0	9	3.00	0.35	4	2.49	0.20	-	-	-
	T2	9	3.09	0.35	4	2.49	0.36	-	-	-

[a] Group difference on original scale at T2, adjusted for baseline scores.

[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- MS subtype

Table 25 summarizes the effects of subgroup analyses based on MS subtype for the primary endpoint MS-specific health-related quality of life at T2. Of note, in the analysis only a total of 19 individuals (9 in the control group and 10 in the intervention group) had the diagnosis G35.9 'Multiple sclerosis, unspecified'. Due to this small sample size, the computations and results from the ANCOVA were unstable. Therefore, we opted to provide descriptive statistics only for this particular subgroup.

Table 25 | Subgroup analysis based on MS subtype for the primary endpoint MS-specific health-related quality of life at T2

	Time	**Control**			***levidex***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
RRMS (n = 292)	T0	154	2.63	0.46	138	2.70	0.52	-	-	-
	T2	154	2.58	0.55	138	2.55	0.59	-0.09 (-0.19, 0)	.057	0.24 (-0.01, 0.49)
PPMS (n = 73)	T0	48	2.69	0.40	25	2.76	0.56	-	-	-
	T2	48	2.74	0.51	25	2.69	0.55	-0.11 (-0.28, 0.05)	.168	0.34 (-0.15, 0.83)
SPMS (n = 86)	T0	44	2.82	0.51	42	2.79	0.48	-	-	-
	T2	44	2.88	0.63	42	2.76	0.45	-0.09 (-0.24, 0.06)	.219	0.26 (-0.16, 0.68)
unspecified (n = 19)	T0	9	2.84	0.55	10	2.63	0.45	-	-	-
	T2	9	2.67	0.69	10	2.53	0.54	-	-	-

[a] Group difference on original scale at T2, adjusted for baseline scores.

[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- Psychotherapy status

Table 26 | Subgroup analysis based on psychotherapy status at baseline for the primary endpoint MS-specific health-related quality of life at T2

	Time	**Control**			***levidex***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
not in psycho-therapy (n = 360)	T0	200	2.69	0.48	160	2.69	0.51	-	-	-
	T2	200	2.68	0.58	160	2.58	0.57	-0.10 (-0.18, -0.02)	.016	0.26 (0.05, 0.47)
in psycho-therapy (n = 110)	T0	55	2.63	0.40	55	2.81	0.52	-	-	-
	T2	55	2.60	0.57	55	2.65	0.59	-0.10 (-0.27, 0.07)	.238	0.25 (-0.16, 0.66)

[a] Group difference on original scale at T2, adjusted for baseline scores.

[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- Antidepressant use

Table 27 | Subgroup analysis based on antidepressant use at baseline for the primary endpoint MS-specific health-related quality of life at T2

	Time	Control			*levidex*			ANCOVA		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
on anti-depressants (n = 79)	T0	44	2.91	0.45	35	2.77	0.49	-	-	-
	T2	44	2.95	0.52	35	2.58	0.61	-0.25 (-0.41, -0.08)	.004	0.66 (0.21, 1.1)
not on anti-depressants (n = 391)	T0	211	2.63	0.46	180	2.71	0.52	-	-	-
	T2	211	2.61	0.57	180	2.60	0.57	-0.07 (-0.15, 0.01)	.093	0.18 (-0.03, 0.4)

[a] Group difference on original scale at T2, adjusted for baseline scores.

[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

- DMD use

Table 28 | Subgroup analysis based on DMD use at baseline for the primary endpoint MS-specific health-related quality of life at T2

	Time	Control			*levidex*			ANCOVA		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
on any DMD (n = 261)	T0	144	2.67	0.46	117	2.70	0.52	-	-	-
	T2	144	2.64	0.57	117	2.62	0.57	-0.06 (-0.15, 0.04)	0.233	0.15 (-0.10, 0.40)
not on DMD (n = 209)	T0	111	2.70	0.47	98	2.75	0.51	-	-	-
	T2	111	2.69	0.58	98	2.57	0.58	-0.16 (-0.27, -0.05)	0.006	0.39 (0.12, 0.66)

[a] Group difference on original scale at T2, adjusted for baseline scores.

[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

Subgroup analyses based on DMD use for the other confirmatory endpoints and corresponding forest plots based on adjusted mean differences are provided in the appendix.

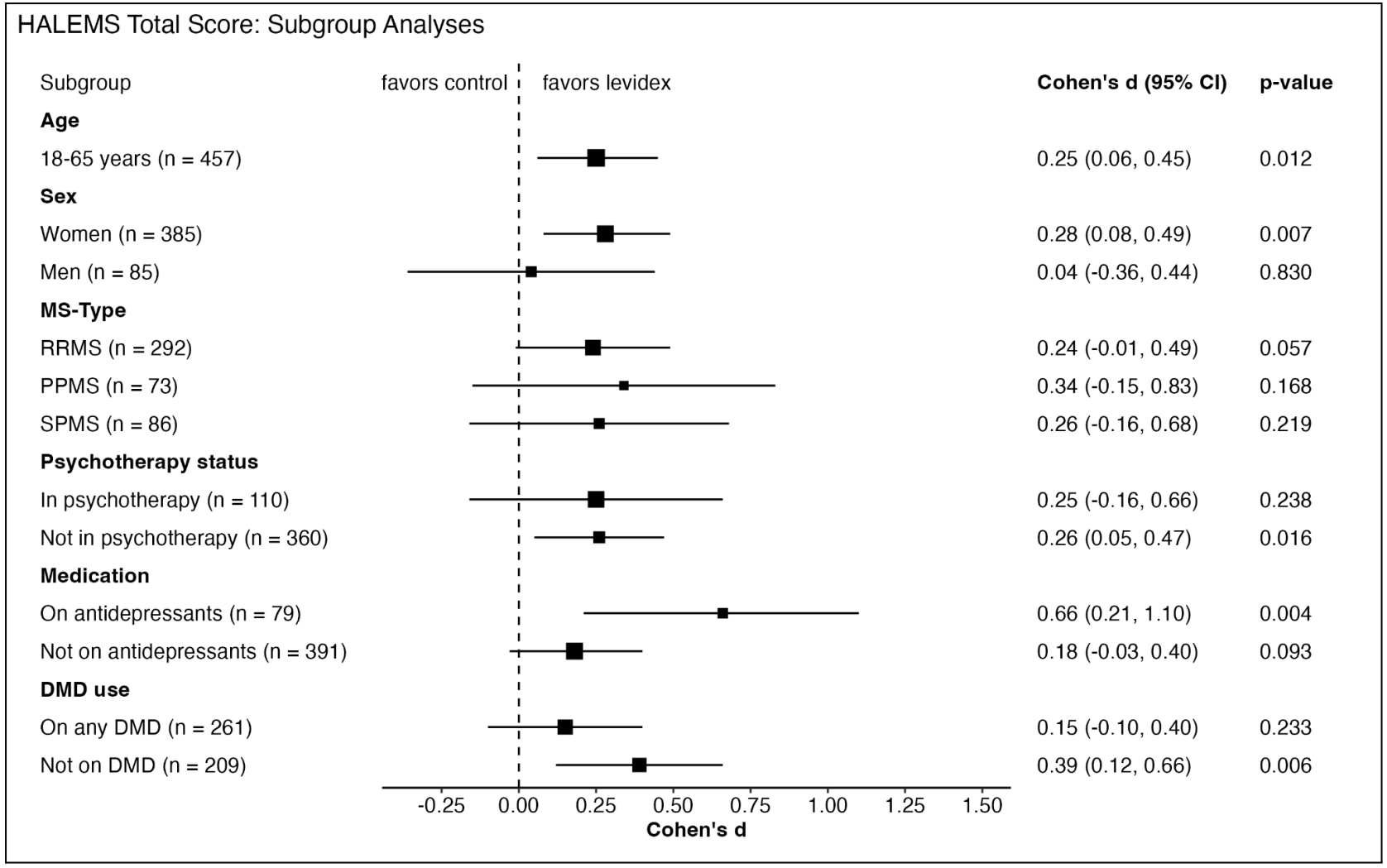

Figure 2 | Forest plot of effect sizes (Cohen's *d*) for the primary endpoint health-related quality of life, assessed with the HALEMS total score. *p*-values are derived from the ANCOVA.

5.10. Listings of deaths and reasons for deaths

Deaths and reasons thereof were not recorded during this clinical investigation.

6. Discussion and overall conclusions

6.1. Clinical performance, effectiveness and safety results

After 6 months, the *levidex* intervention group displayed significant improvements in MS-specific health-related quality of life, depressive symptoms, and social and work-related functioning compared to the control group. These effects were mostly already present after 3 months, suggesting continued effectiveness of *levidex*. The robustness of the results was confirmed by conservative J2R sensitivity analyses. Regarding the primary endpoint, i.e., MS-specific health-related quality of life after 6 months, *levidex* has an NNT of 9, which is comparable to the effects of DMDs on MS-specific health-related quality of life. No adverse events or device effects were observed. Patients rated their satisfaction with the program as very high.

6.2. Assessment of benefits and risks

In this clinical investigation report, use of *levidex* in addition to TAU was shown to be significantly more effective in improving MS-specific health-related quality of life, depressive symptoms, and social and work-related functioning in patients with MS than TAU alone. In contrast, *levidex* had no effects on anxiety symptoms and instrumental activities of daily living. No adverse events or device effects were observed. Therefore, the benefit-risk ratio is positive.

6.3. Discussion of the clinical relevance of the results

MS patients often do not receive the psychosocial support they need [52]. Inadequate treatment may be due to disease-related barriers such as transportation difficulties, physical immobility, fatigue and MS exacerbations that make personalized treatment difficult [52], [53]. DiGAs such as *levidex* represent a promising opportunity to provide access to effective, evidence-based interventions for MS patients: Among others, the use of the DiGA *deprexis*, which is based on CBT, led to a reduction in comorbid depressive symptomatology in patients with MS [12]. There is also evidence of the effectiveness of *elevida*, a DiGA developed by the applicant for patients with MS and fatigue [13]. Finally, a previously conducted RCT on the effectiveness of *levidex* showed that it has significant and clinically relevant effects on MS-specific health-related quality of life and participation in instrumental activities of daily living [16]. The results of the present RCT are in line with these previous studies on the use of DiGAs in patients with MS: As in the first RCT investigating the effectiveness of *levidex* [16], the present study showed that *levidex* has significant positive effects on MS-specific health-related quality of life after 3 months and 6 months. Clinically relevant improvements in quality of life after 6 months were 69% more likely in the intervention than in the control group, corroborating *levidex'* positive impact further. Taken together with positive signals that already emerged during the development and feasibility phases [14], [15], both RCTs provide compelling evidence for *levidex*' effectiveness on MS-specific health-related quality of life.

These effects on MS-specific health-related quality of life are comparable to the effects of classic psychological interventions, which show meta-analytic effects of - depending on the study - *d* = 0.24 [54] or ranging from Hedge's *g* = 0.23 to *g* = 0.82 [55] for self-management interventions and of *d* = 0.39 [56] for mindfulness interventions. Importantly, due to the high scalability of fully automated digital interventions such as *levidex*, even slightly smaller effects are able to have a large public health effect by reaching a considerably larger group of patients. The effects observed for *levidex* in the present trial are comparable to other studies on digital interventions in MS, where the use of *deprexis*, which is primarily aimed at reducing depressive symptoms, led to effects of *d* = 0.33 on HALEMS fatigue and thinking and of *d* = 0.27 on HALEMS subscale mobility lower limbs after 9 weeks (comparable to *d* = 0.29 for fatigue and thinking and *d* = 0.28 for mobility lower limbs after 12 weeks in the present trial) [12]. Another digital intervention for depression in MS yielded effects of *d* = 0.29 on health-related quality of life [57]. The use of *elevida*, which is primarily aimed at reducing fatigue in MS, also showed significant effects on these subscales, although no effect sizes are reported [13]. Finally, the previous trial on the effectiveness of *levidex* showed effects of *d* = 0.23 on MS-specific health-related quality of life [16], which is comparable to the results obtained in the present study.

It is also necessary to set the results in relation with effects achieved by DMD treatments, which usually are accompanied with a higher risk for adverse effects compared to behavioral interventions. There is meta-analytic evidence for medication to have effects of around *d* = 0.34 on health-related quality of life in MS [54]. In the group of different DMDs, these effects range from small within-group effects of *d* = 0.16 on the MusiQoL for IFNbeta [58] to Odds ratios for clinically relevant response of OR = 1.93 for dimethyl fumarate [59] and OR = 2.26 for fingolimod [17]. Importantly, in the latter study, HALEMS change score was -0.02 for 1.25mg fingolimod and -0.01 for 5mg fingolimod [17], which is ten times smaller than the change of -0.10 on the HALEMS total score after 6 months that we observed in the current trial. Natalizumab and alemtuzumab showed responder Odds ratios in the range of OR = 1.39 to OR = 1.69 [18], [19], and are thus comparable with the effect of *levidex* (OR = 1.69). The NNT of 9 for *levidex* is comparable to studies investigating the effect of commonly prescribed DMDs on health-related quality of life, which report NNT values ranging from 7 to 145, with most falling between 7 and 19 [17], [18], [19]. Given that MS is a severe chronic disease with a significant impact on quality of life, effects of this magnitude are to be expected, even for DMDs categorized within the highest efficacy group (Category 3).

Regarding depressive symptoms, classic psychotherapy for depression in patients with MS has meta-analytic effects ranging from *d* = 0.45 - 0.61 [8], [60]. Digital interventions aiming at reducing depression in patients with MS, such as *amiria*, had effects ranging from *d* = 0.53 to *d* = 0.97 [12], [61], [62], which are higher than the effects observed in the present RCT. However, it has to be noted that in contrast to those interventions, *levidex* is not specifically aimed at reducing depressive symptoms; therefore, the observed significant effect of *d* = 0.21 is within the range of expected results.

Moreover, *levidex* had significant effects on social and work-related functioning. These findings complement the improvements in MS-specific health-related quality of life by highlighting enhancements in specific aspects of daily functioning, which are highly relevant

outcomes for patients. This underscores the broad positive impact of *levidex* on overall well-being for individuals with MS.

Subgroup analyses revealed that whereas women using *levidex* show statistically significant and small improvements in MS-specific health-related quality of life, this is not the case for men. Given that the existing literature does not indicate less effectiveness of psychological interventions for patients with MS in males compared to females [63], [64], [65], we decided to inspect potential sex differences in a subsample of the first RCT on *levidex* [16] that complies to similar inclusion criteria as the ones of the present RCT (i.e., cut-off of ≥ 2 on the HALEMS total score). Results of these subgroup analyses and pooled meta-analytic effects are reported in the appendix. Not enough participants over 65 years of age participated in the present study to draw robust conclusions regarding the effectiveness of *levidex* in that population, but descriptively, the effect appears to be smaller than in participants aged 18-65. Given that life expectancy is reduced in patients with MS [66] and that due to the progressive nature of the disease, older participants were more likely to meet exclusion criteria such as a degree of care ("Pflegegrad") ≥ 3, the pool of potentially eligible participants older than 65 was reduced. The use of *levidex* was descriptively somewhat more effective in participants taking antidepressants at baseline, compared with those not on antidepressants. More subgroup analyses revealed that *levidex* has comparable effectiveness irrespective of MS subtype and concomitant psychotherapy.

The exploratory analyses investigating the differential intake of DMDs at T1 and T2 showed that significantly more participants of the intervention group took DMDs of category 1 (lowest efficacy category) at T2, compared to the control group. This finding, however, mirrors the pattern observed at baseline, where descriptively, more patients randomized to the intervention group took DMDs of the efficacy category 1, whereas more patients randomized to the control group took DMDs of the highest efficacy category 3. Therefore, the use of *levidex* presumably did not influence DMD intake, but baseline group differences were sustained later on in the study. Importantly, since the higher use of category 1 DMDs in the intervention group is balanced by higher use of category 3 DMDs in the control group, as evidenced by the lack of differences between in the groups in DMD intake overall across all time points, it is highly unlikely that differential DMD use affected other endpoints. DMDs of category 3 are, by definition, the most effective medications; thus, if anything, the pattern of medication intake indicates that the intervention group was treated less intensively across all time points.

Of note, user satisfaction with *levidex* was very high, with an NPS up to 35.6. This result compares very favorably to previously published NPS ratings for digital health interventions for chronic conditions, which averaged at 9.5 [67] and 20 [68], respectively.

In summary, *levidex* stands out favorably when compared to existing treatment options for various outcomes in MS. Specifically for the primary endpoint of MS-specific health-related quality of life, *levidex* achieved a significant and clinically relevant effect which is comparable to that of DMDs or other digital interventions. Significant effects of *levidex* were also demonstrated on depressive symptoms, as well as social and work-related functioning, outcomes with high relevance to patients. Accordingly, patient satisfaction with the program

was very high. While resource-intensive face-to-face psychotherapy for patients with MS is potentially slightly more effective, due to a shortage in therapy places waiting lists for such face-to-face psychotherapy exceed several months [69]. Digital interventions such as *levidex* can offer low-threshold help for patients.

Taken together with previous findings, the present clinical investigation provides compelling evidence that *levidex* significantly improves MS-specific health-related quality of life, depressive symptoms, as well as social and work-related functioning in adult patients with MS.

6.4. Specific benefits or special precautions required for individual subjects or groups considered to be at risk

Using *levidex* in addition to TAU was found to be more effective in improving MS-specific health-related quality of life compared to TAU alone. *levidex* should only be used as an adjunct to usual care, not as a substitute for it.

6.5. Implications for the conduct of future clinical investigations

This clinical investigation affirms the feasibility of online studies assessing the efficacy of fully automated interventions for MS. The very positive user feedback highlights a willingness in the target population to embrace fully automated digital solutions. Future studies might explore whether certain patient profiles or patients in specific care settings yield greater benefits from *levidex*.

6.6. Limitations of the clinical investigation

A potential limitation of the current RCT involves the differing attrition rates between the intervention and control groups. Despite being relatively low, especially compared to the expected dropout rate of 25%, the distinct attrition rates pose a challenge in interpreting our results. It is plausible that participants in the intervention group used the provided intervention until they felt they had gained sufficient benefits. As a result, some of them may have chosen not to continue investing their time in the study, given their perception that the intervention was no longer necessary. This aligns with the well-documented “good enough effect” documented extensively in classic psychotherapy research [70], [71], and more recently, also for digital interventions [72]. Additional limitations include the study’s reliance on self-report measures, which can be considered a methodological disadvantage due to the inherent subjectivity and potential for recall biases. However, this inherently subjective nature of the quality of life construct also serves as an advantage, allowing for a more personalized understanding of the patient experience and emphasizing the importance of individual perspectives in assessing well-being. Additionally, patient-reported outcomes are relevant and feasible, capturing aspects of quality of life that might be overlooked by objective measures.

Notwithstanding these potential limitations, our study establishes that *levidex* significantly improves MS-specific health-related quality of life, depressive symptoms, and social and work-related outcomes.

7. Abbreviated terms and definitions

ANCOVA	Analysis of covariance
CBT	Cognitive behavioral therapy
CI	Confidence interval
CIS	Clinically isolated syndrome
DiGA	Digital health application
DMD	Disease-modifying drug
ITT	Intention-to-treat
J2R	Jump-to-reference
MAR	Missing at random
MCID	Minimal clinically relevant difference
MS	Multiple sclerosis
NNT	Number needed to treat
NPS	Net promoter score
OR	Odds ratio
PP	Per protocol
RCT	Randomized controlled trial
SMD	Standardized mean difference
T1	3 months after randomization
T2	6 months after randomization
TAU	Treatment-as-usual

8. Ethics

This study and its amendment was reviewed and approved by the ethics committee of the Hamburg chamber of physicians (Ärztekammer Hamburg; reference number 2023-101078-BO-ff). The clinical investigation was conducted in accordance with the ethical principles in the Declaration of Helsinki. Prior to participation, detailed patient information was provided and informed consent was obtained.

9. Investigators and administrative structure of clinical investigation

This clinical investigation was primarily conducted as an online trial without a traditional physical investigation site. Study management including patient recruitment and data acquisition was conducted by the sponsor. No funding was provided by the sponsor.

Principal investigator:

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- role: scientific lead and coordinator of the trial

Sponsor:

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Sponsor's representative: PD Dr. Gitta Jacob, gitta.jacob@gaia-group.com

- role: trial management, online data acquisition and analyses

External organizations:

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- role: Co-PI, consulting cooperation partner, trial design and analyses

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11. Appendix

- Effectiveness of *levidex* in men using data from the first *levidex* RCT

To further investigate the effects of *levidex* in men, we analyzed data from male participants in the first levidex RCT [16]. To maximize comparability between populations, we applied a HALEMS total cutoff score of ≥ 2 to the data, yielding a total of 71 eligible participants. As shown in table 27 below, this analysis revealed significant effects for men with impaired health-related quality of life in the first levidex RCT. To synthesize the findings, we pooled the effect size estimates from the first and current levidex RCTs using a random-effects meta-analytic model implemented with the *R* package *metafor* [16], applying default settings. The resulting overall meta-analytic effect size was $d = 0.37$ (95% CI = [-0.29, 1.03], $p = .269$), suggesting a similar effect size as in women (see figure 2).

Table 29 | Effectiveness of *levidex* in men for the primary endpoint MS-specific health-related quality of life (HALEMS total score) at T2 (6 months follow-up) in the first *levidex* RCT [16].

	Time	**Control**			***levidex***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
men (n = 71)	T0	36	2.92	0.59	35	2.84	0.61	-	-	-
	T2	36	3.00	0.64	35	2.62	0.69	-0.31 (-0.51, -0.11)	.002	0.71 (0.27, 1.15)

[a] Group difference on original scale at T2, adjusted for baseline scores.

[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

Table 30 | Subgroup analysis based on DMD use at baseline for the secondary endpoint depressive symptoms at T2

	Time	**Control**			***levidex***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
on any DMD (n = 261)	T0	144	11.2	4.3	117	11.6	4.4	-	-	-
	T2	144	10.2	4.4	117	10.0	4.5	-0.4 (-1.2, 0.4)	0.358	0.11 (-0.13, 0.36)
not on DMD (n = 209)	T0	111	10.9	4.4	98	11.1	4.4	-	-	-
	T2	111	10.1	4.6	98	9.0	4.7	-1.2 (-2.2, -0.2)	0.018	0.33 (0.06, 0.59)

[a] Group difference on original scale at T2, adjusted for baseline scores.

[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

Table 31 | Subgroup analysis based on DMD use at baseline for the secondary endpoint social and work-related functioning at T2

	Time	**Control**			***levidex***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
on any DMD (n = 261)	T0	144	17.5	8.1	117	18.1	7.8	-	-	-
	T2	144	17.5	8.9	117	16.7	8.1	-1.3 (-2.7, 0.1)	0.078	0.23 (-0.02, 0.48)
not on DMD (n = 209)	T0	111	19.8	8.4	98	19.9	8.3	-	-	-
	T2	111	20.2	9.5	98	18.0	9.4	-2.3 (-4.0, -0.7)	0.005	0.39 (0.11, 0.67)

[a] Group difference on original scale at T2, adjusted for baseline scores.

[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

Table 32 | Subgroup analysis based on DMD use at baseline for the secondary endpoint MS-specific health-related quality of life at T2

	Time	**Control**			***levidex***			**ANCOVA**		
		n	mean	SD	n	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
on any DMD (n = 261)	T0	144	56.4	12.9	117	55.7	14.8	-	-	-
	T2	144	56.3	14.1	117	57.5	15.0	1.8 (-0.4, 4.0)	0.110	0.21 (-0.05, 0.46)
not on DMD (n = 209)	T0	111	54.5	12.5	98	54.2	12.3	-	-	-
	T2	111	55.6	12.9	98	57.9	14.0	2.5 (-0.2, 5.1)	0.067	0.26 (-0.02, 0.53)

[a] Group difference on original scale at T2, adjusted for baseline scores.

[b] based on baseline-adjusted values; positive values show effects in favor of the intervention group.

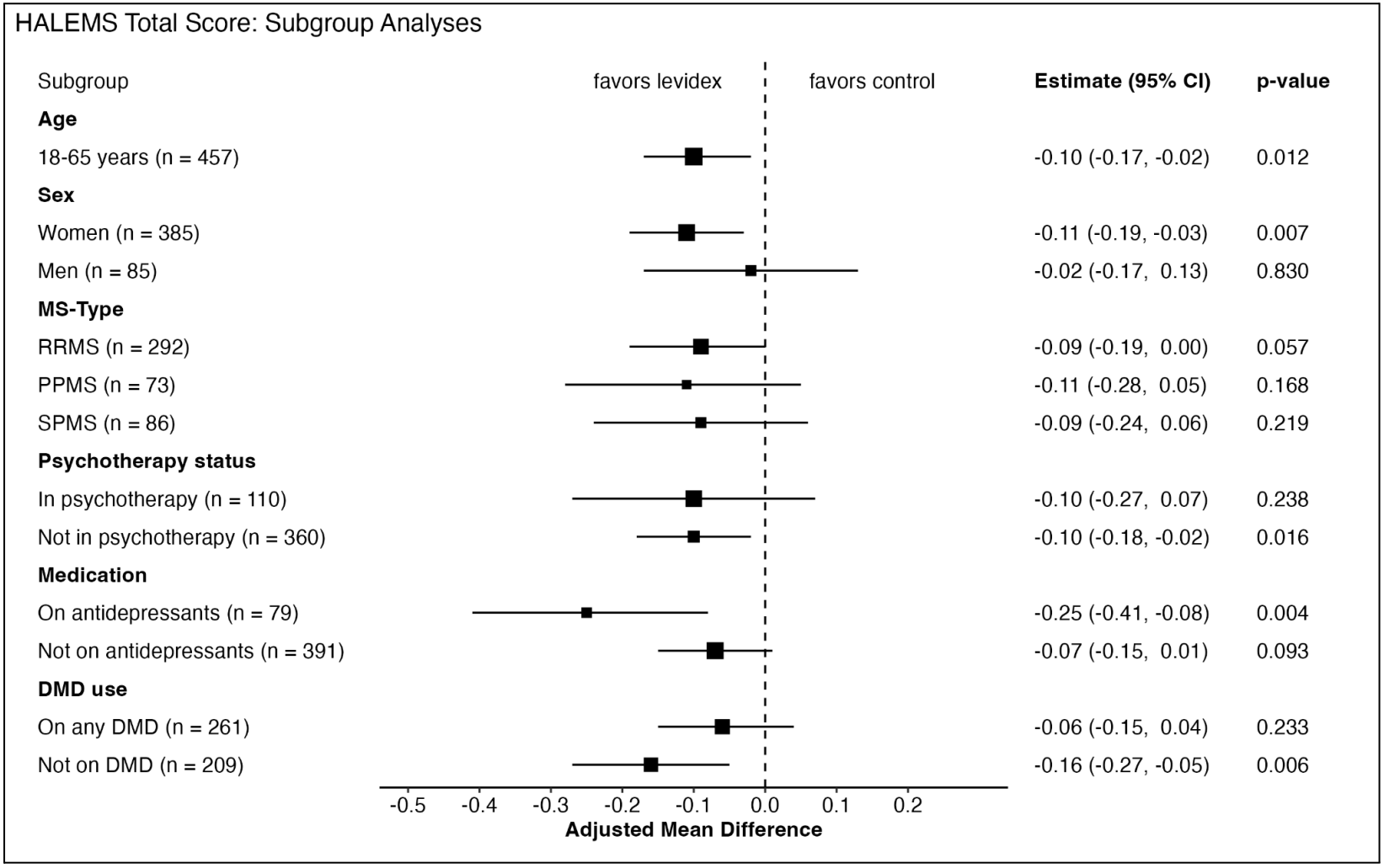

Figure 3 | Forest plot of adjusted mean differences for the primary endpoint MS-specific health-related quality of life, assessed with the HALEMS total score. *p*-values are derived from the ANCOVA.

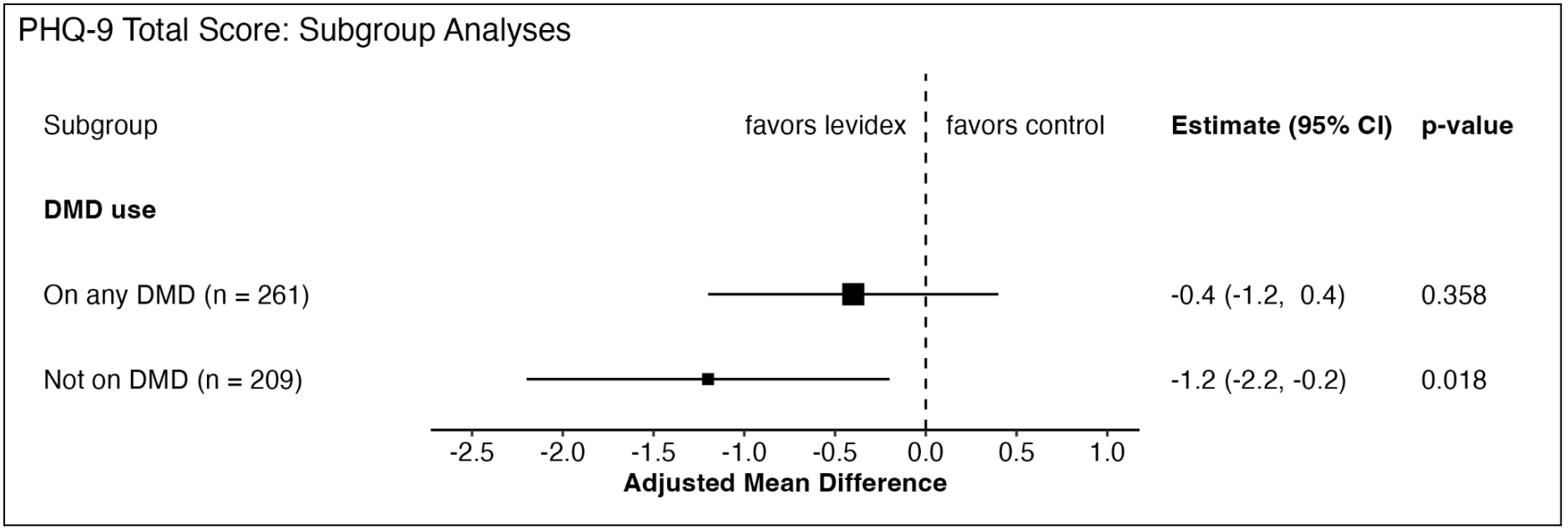

Figure 4 | Forest plot of adjusted mean differences for the secondary endpoint depressive symptoms, assessed with the PHQ-9 total score. *p*-values are derived from the ANCOVA.

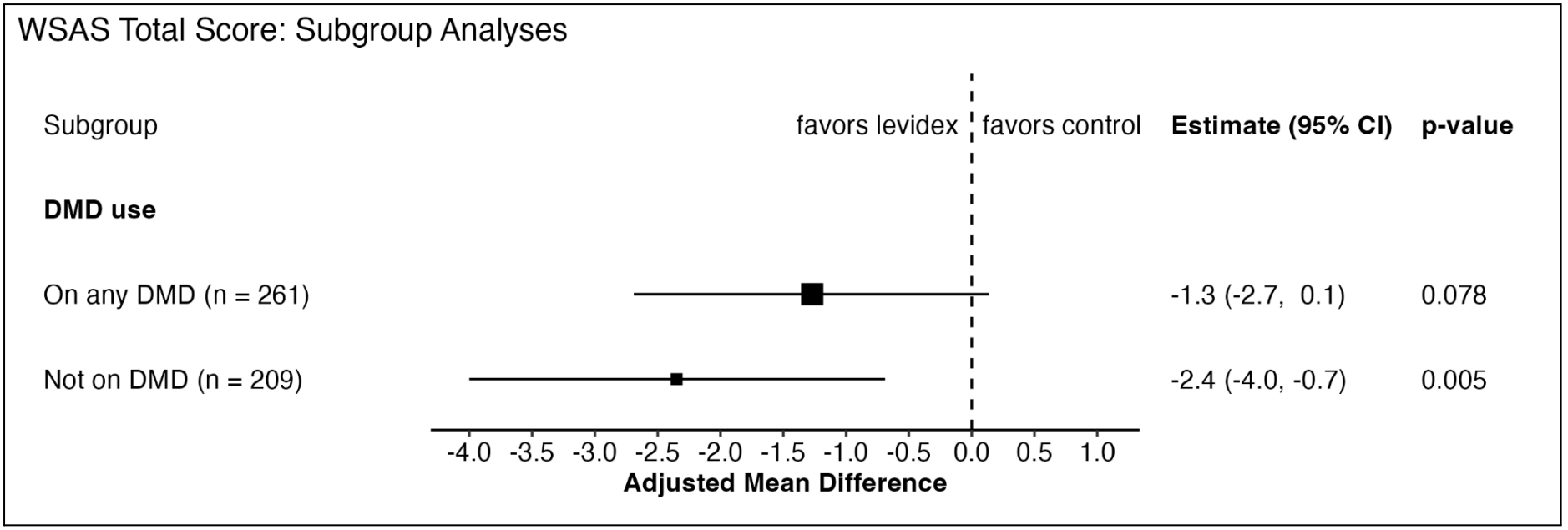

Figure 5 | Forest plot of adjusted mean differences for the secondary endpoint social and work-related functioning, assessed with the WSAS total score. *p*-values are derived from the ANCOVA.

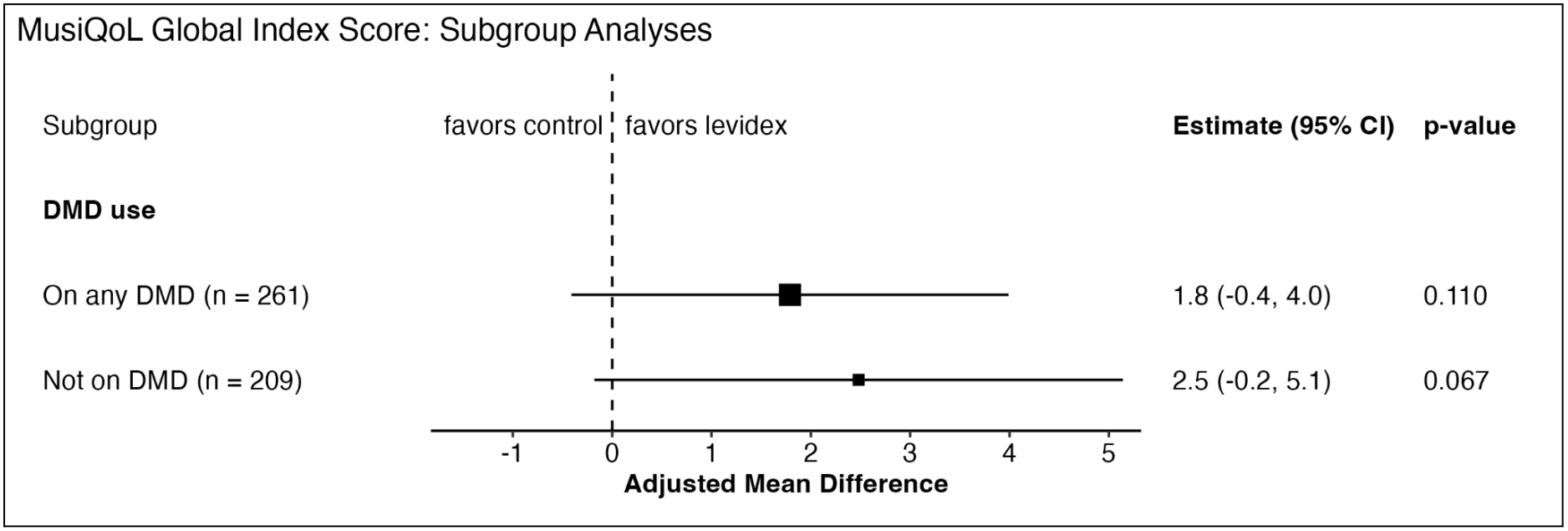

Figure 6 | Forest plot of adjusted mean differences for the secondary endpoint MS-specific health-related quality of life, assessed with the MusiQoL global index score. *p*-values are derived from the ANCOVA.