Effectiveness of **P**riovi, **A** **D**igital Self-help Tool, **I**n **P**atients with **B**orderline **P**ersonality **D**isorder – a single-blinded Randomized Controlled Trial (EPADIP-BPD)

Clinical investigation report following ISO 14155:2020

Investigational device

priovi

Study design

randomized
controlled
single-blind
Online

Study population

580 patients of all sexes, aged 18 and above, with a diagnosis of borderline personality disorder (BPD) and at least moderate BPD symptom severity (Borderline Symptom List-23 (BSL-23) ≥ 1.07)

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

German Clinical Trials Register ID: DRKS00028888

Date

24.01.2024

Version

5.0

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1. Summary

1.1 Title of the clinical investigation

Effectiveness of **P**riovi, **A** **D**igital Self-help Tool, **I**n **P**atients with **B**orderline **P**ersonality **D**isorder – a single-blinded Randomized Controlled Trial (EPADIP-BPD)

1.2 Introduction

Borderline personality disorder (BPD) is a mental disorder characterized by pervasive instability in interpersonal relationships, self-image, emotion regulation, and impulse control [1], [2]. With an administrative 1-year prevalence of 0.34% in Germany, it is the most common personality disorder in clinical settings [2], [3]. BPD is associated with marked impairments in psychosocial and occupational functioning, increased risk for both psychiatric and somatic comorbidities, and a high mortality rate due to suicide and poor physical health [2], [4]–[6]. As a result, in Germany, life expectancy of patients with BPD is reduced by up to 9 years [2]. BPD not only poses an immense burden on those affected, but is also costly to society: In Germany, the treatment costs for BPD amount to an average of 31,000€ per patient and year [7] and exceed the costs of many other mental disorders, such as major depressive disorder, by far [8]. Inpatient treatment accounts for a large portion of these costs [7], but can be significantly reduced through effective psychotherapeutic treatment [9], [10], i. e., disorder-specific approaches such as schema therapy [11], [12].

However, even in well-developed Western European health-care systems, less than 25% of patients with BPD have access to such psychotherapy [13], [14], despite it being recommended as the first-line treatment for BPD in the relevant clinical guidelines [15], [16] and representing patients' preferred treatment option in psychiatric settings [17]. Reasons for this treatment gap include high costs of treatment and unavailability of trained psychotherapists. In one study involving more than 150 psychotherapists in Munich, Germany, for example, over 20% refused "on principle" to treat patients with BPD [18]. This underscores the need to find ways to provide evidence-based, disorder-specific psychotherapeutic interventions to more BPD patients [19], [20].

One innovative, promising means of addressing the existing treatment gap in BPD is through digital health apps (DiGAs) [21], [22]. DiGAs offer flexible, cost-efficient access to mental health care, and can foster a sense of empowerment in patients [20], [23]. However, there have been concerns about the safety of DiGAs in patients with BPD given the prevalence of self-harming behavior (e. g., suicidality, severe self-injury) in this population. Hence, a previous randomized controlled trial (RCT) by Klein et al. (2021) investigated the safety and effectiveness of a preliminary version of the self-guided, Internet-based intervention program *priovi* (which is based on schema therapy) in a group of patients with BPD who received either psychotherapy or psychiatric care [24]. Patients were included only after their psychiatrist or psychotherapist certified their eligibility for the study. The study demonstrated that *priovi* was safe to use in patients with BPD, as no adverse effects were reported. Moreover, positive effects were found in favor of the intervention group that had access to *priovi*, but these effects narrowly missed achieving statistical significance (p = 0.08). A possible explanation could be that *priovi* did not reach its full potential because the

participants included in the study by Klein et al. [24] received unusually high-quality routine treatment. It could also be that the trial was underpowered. Alternatively, the lack of significant empirical effectiveness could reflect shortcomings in the program. Thus, following the results of Klein et al. [24], *priovi* underwent revisions to improve the program further.

As a first step, a preliminary single-arm study was conducted using the revised version of *priovi*, involving 153 patients. The primary endpoint was the BSL-23, a measure of BPD symptoms. Over the three-month follow-up period, significant reductions in BPD symptoms were observed in the primary ITT analysis using the BSL-23 [d = 0.92, 95% confidence interval (CI): 0.74 - 1.11; $p < 0.001$]. Additionally, as secondary endpoints, changes in quality of life were assessed using the Mental and Physical Health sum score of the SF-12, both of which also exhibited significant effects.

Building upon the single-arm study, the current RCT aimed to investigate the effectiveness of the revised *priovi* when compared to usual medical care in an RCT setting.

1.3 Purpose of the clinical investigation

The purpose of this clinical investigation was to assess the effectiveness and safety of the DiGA *priovi* in adult patients with BPD.

1.4 Description of the clinical investigation population

The study population consisted of 580 adult patients of all sexes with a diagnosis of BPD and at least moderate BPD symptom severity (Borderline Symptoms List-23 (BSL-23) mean score ≥ 1.07). Subjects were excluded given a diagnosis of substance use disorder or psychotic disorder (with the exception of non-transitory paranoid ideas related to the BPD).

1.5 Clinical investigation method

Participants were motivated to participate in a pragmatic, parallel RCT via an online campaign. Recruitment started in May 2022 and ended in October 2022. Participants who met the inclusion criteria were randomized to the intervention or control group. The intervention group received access immediately after randomization, while the control group was provided with information regarding freely available self-help online material and was offered access to *priovi* after 6 months. All participants received usual medical care (TAU) in consultation with their respective treatment team during the study period. Following the pragmatic study design, usual medical care should reflect the reality of care, and may therefore include all forms of outpatient care, including treatment by a primary care physician or specialist, psychotherapy (such as CBT, schema therapy, etc.), as well as no treatment at all.

1.6 Results of the clinical investigation

1.6.1 Primary endpoint

The ITT analysis showed that after 3 months, patients in the TAU + *priovi* intervention group reported significantly lower BPD symptom severity, as assessed with the BSL-23 mean score, than patients in the TAU-only control group (group × time interaction effect from the Linear Mixed Model = -0.19, 95% CI = [-0.30, -0.09], $p < 0.001$; $d = 0.24$). This significant effect was maintained through to the 6 months-follow-up (group × time interaction effect = -0.09, 95% CI = [-0.15, -0.02], $p = 0.011$; $d = 0.15$). The overall pattern of results was confirmed in a conservative 'jump-to-reference' (J2R) sensitivity analysis where imputation of missing values was performed under the assumption that participants in the intervention group, post drop out, exhibit behavior akin to those in the control group (3 months: group × time interaction effect = -0.17, 95% CI = [-0.27, -0.07], $p < 0.001$; $d = 0.21$; 6 months: group × time interaction effect = -0.08, 95% CI = [-0.13, -0.02], $p = 0.007$; $d = 0.12$). Uncontrolled data from the 12-month follow-up demonstrated a continual decrease in BPD severity in the intervention group.

Analysis of treatment responders indicated that reliable improvements in BPD severity were significantly more frequent in the *priovi* intervention group than in the control group after 3 months (24.0% vs. 15.6%; Odds Ratio (OR) = 1.71, 95% CI = [1.10, 2.64]; $\chi^2 = 5.86$, $p = 0.016$), suggesting that the effects of *priovi* on BPD severity can be considered clinically relevant.
There was no significant difference in the proportion of patients experiencing deterioration of BPD symptoms between the intervention group (1.9%) and the control group (1.1%; OR = 1.65, 95% CI = [0.39, 6.99]; $\chi^2 = 0.11$, $p = 0.738$).

There was no significant difference in the proportion of patients achieving remission at 3 months between the *priovi* intervention group (0.007%) and the control group (0.004%; OR = 1.98, 95% CI = [0.18, 21.94]; $\chi^2 < 0.001$, $p = 1$). However, as we have already detailed in our previous communication, assessing remission after just 3 months of treatment may not provide meaningful insights in the context of BPD, as research consensus consistently suggests that substantial periods, typically several years, are typically required to achieve complete remission.

1.6.2 Secondary endpoints

The ITT analysis revealed significantly reduced levels of depressive symptoms, as assessed by the PHQ-9 total score, within the *priovi* intervention group when compared to the control group after 3 months (group × time interaction effect = -1.0, 95% CI = [-1.8, -0.3], $p = 0.009$; $d = 0.21$) and 6 months (group × time interaction effect = -0.5, 95% CI = [-0.9, -0.1], $p = 0.025$; $d = 0.16$). These results were confirmed by the more conservative J2R sensitivity analysis (3 months: group × time interaction effect = -0.9, 95% CI = [-1.6, -0.2], $p = 0.007$; $d = 0.19$; 6 months: group × time interaction effect = -0.5, 95% CI = [-0.8, -0.1], $p = 0.012$; $d = 0.15$).

Analysis of treatment responders based on a minimally clinically important difference (MCID) of 5 points indicated that reliable improvements in depressive symptoms were significantly more frequent in the *priovi* intervention group than in the control group after 3 months (38.3% vs. 24.8%; $\chi^2 = 11.18$, $p < 0.001$), suggesting that the effects of *priovi* on depressive symptoms can be considered clinically relevant.

The ITT-analysis also indicated that the *priovi* intervention group exhibited notably reduced levels of anxiety, as measured by the GAD-7 total score, in comparison to the control group after 3 months (group × time interaction effect = -0.7, 95% CI = [-1.4, -0.1], $p = 0.030$; $d = 0.23$) and 6 months (group × time interaction effect = -0.5, 95% CI = [-0.9, -0.1], $p = 0.025$; $d = 0.24$). These findings were supported by the more conservative J2R sensitivity analysis (3 months: group × time interaction effect = -0.6, 95% CI = [-1.2, -0.01], $p = 0.035$; $d = 0.21$; 6 months: group × time interaction effect = -0.4, 95% CI = [-0.7, -0.1], $p = 0.019$; $d = 0.22$).

The ITT-analysis showed no significant difference between the groups in psychological quality of life, as assessed with the SF-12 Mental sum score, at 3 months (group × time interaction effect = 0.4, 95% CI = [0, 0.9], $p = 0.065$; $d = 0.18$) and 6 months (group × time interaction effect = 0.2, 95% CI = [-0.1, 0.4], $p = 0.276$; $d = 0.10$). Comparable patterns of results emerged in the J2R analysis (3 months: group × time interaction effect = 0.4, 95% CI = [0, 0.8], $p = 0.056$; $d = 0.16$; 6 months: group × time interaction effect = 0.2, 95% CI = [-0.1, 0.4], $p = 0.160$; $d = 0.11$).

Likewise, the ITT analysis demonstrated no significant differences between the groups in terms of social and work-related functioning, measured by the WSAS, throughout the follow-up period (3 months: group × time interaction effect = -0.9, 95% CI = [-2.0, 0.2], $p = 0.109$; $d = 0.12$; 6 months group × time interaction effect = -0.4, 95% CI = [-1.1, 0.2], $p = 0.220$; $d = 0.08$).

Assessment of the clinical course of the study groups with a Poisson mixed model analysis showed a significant decrease in suicide attempts in the *priovi* group compared to the control group after 3 months (group × time interaction effect = -0.86, 95% CI = [-1.55, -0.18], $p = 0.014$) and 6 months (group × time interaction effect = -0.82, 95% CI = [-1.26, -0.38], $p < 0.001$). Regarding hospitalizations, there were no significant differences in frequency between the *priovi* group and the control group at 3 months (group × time interaction effect = 0.03, 95% CI = [-0.32, 0.38], $p = 0.864$) or 6 months (group × time interaction effect = 0.18, 95% CI = [-0.09, 0.44], $p = 0.190$). Similarly, there was no significant difference in the frequency of other life-threatening events (3 months: group × time interaction effect = -0.02, 95% CI = [-0.18, 0.14], $p = 0.791$; 6 months: group × time interaction effect = -0.04, 95% CI = [-0.16, 0.08], $p = 0.539$).

Users reported very high satisfaction with *priovi* throughout the follow-up period.

1.7 Conclusion

In conclusion, following 3 months of access to *priovi*, the intervention group demonstrated significantly reduced BPD severity in comparison to the control group, substantiated by

clinical significance in the responder analysis. *priovi* also yielded significant effects on depression and anxiety. Intervention effects were sustained at the 6-month follow-up. The results' robustness was confirmed by the J2R sensitivity analysis. Uncontrolled data from the 12-month follow-up showed a continual reduction in BPD severity in the intervention group.

Notably, the *priovi* group reported significantly fewer suicide attempts throughout the follow-up, indicating a more positive clinical trajectory. No significant differences between the intervention and control group were observed regarding hospitalizations or life-threatening events.

Patient satisfaction with *priovi* was very high.

1.8 Date of the clinical investigation initiation

- May 2022 (start of data collection)

1.9 Completion date of the clinical investigation

- November 2023 (completion of data collection for 12-month follow-up)

2. Introduction

BPD is a mental disorder characterized by pervasive instability in interpersonal relationships, self-image, emotion regulation, and impulse control [1], [2]. With an administrative 1-year prevalence of 0.34% in Germany, it is the most common personality disorder in clinical settings [2], [3]. BPD is associated with marked impairments in psychosocial and occupational functioning, increased risk for both psychiatric and somatic comorbidities, and a high mortality rate due to suicide and poor physical health [2], [4]–[6]. As a result, in Germany, life expectancy of patients with BPD is reduced by up to 9 years [2]. BPD not only poses an immense burden on those affected, but is also costly to society: In Germany, the treatment costs for BPD amount to an average of 31,000€ per patient and year [7] and exceed the costs of many other mental disorders, such as major depressive disorder, by far [8]. Inpatient treatment accounts for a large portion of these costs [7], but can be significantly reduced through effective psychotherapeutic treatment [9], [10], i. e., disorder-specific approaches such as schema therapy [11], [12].

However, even in well-developed Western European health-care systems, less than 25% of patients with BPD have access to such psychotherapy [13], [14], despite it being recommended as the first-line treatment for BPD in the relevant clinical guidelines [15], [16] and representing patients' preferred treatment option in psychiatric settings [17]. Reasons for this treatment gap include high costs of treatment and unavailability of trained psychotherapists. In one study involving more than 150 psychotherapists in Munich, Germany, for example, over 20% refused "on principle" to treat patients with BPD [18]. This underscores the need to find ways to provide evidence-based, disorder-specific psychotherapeutic interventions to more BPD patients [19], [20].

One innovative, promising means of addressing the existing treatment gap in BPD is through DiGAs [21], [22]. DiGAs offer flexible, cost-efficient access to mental health care, and can foster a sense of empowerment in patients [20], [23]. However, there have been concerns about the safety of DiGAs in patients with BPD given the prevalence of self-harming behavior (e. g., suicidality, severe self-injury) in this population. Hence, a previous randomized RCT by Klein et al. (2021) investigated the safety and effectiveness of a preliminary version of the self-guided, Internet-based intervention program *priovi* (which is based on schema therapy) in a group of patients with BPD who received either psychotherapy or psychiatric care [24]. Patients were included only after their psychiatrist or psychotherapist certified their eligibility for the study. The study demonstrated that priovi was safe to use in patients with BPD, as no adverse effects were reported. Moreover, positive effects were found in favor of the intervention group that had access to *priovi*, but these effects narrowly missed achieving statistical significance ($p = 0.08$). A possible explanation could be that *priovi* did not reach its full potential because the participants included in the study by Klein et al. [24] received unusually high-quality routine treatment. It could also be that the trial was underpowered. Alternatively, the lack of significant empirical effectiveness could reflect shortcomings in the program. Thus, following the results of Klein et al. [24], *priovi* underwent revisions to improve the program further.

As a first step, a preliminary single-arm study was conducted using the revised version of *priovi*, involving 153 patients. The primary endpoint was the BSL-23, a measure of BPD symptoms. Over the three-month follow-up period, significant reductions in BPD symptoms

were observed in the primary ITT analysis using the BSL-23 [d = 0.92, 95% confidence interval (CI): 0.74 - 1.11; $p < 0.001$]. Additionally, as secondary endpoints, changes in quality of life were assessed using the Mental and Physical Health sum score of the SF-12, both of which also exhibited significant effects.

Building upon the single-arm study, the current RCT aimed to investigate the effectiveness of the revised *priovi* when compared to usual medical care in an RCT setting.

3. Investigational device and methods

3.1 Investigational device description

priovi is a self-guided, Internet-based intervention program based on schema therapy for patients with BPD [11], [12], [25]. *priovi* consists of 10 modules that provide psychoeducation about BPD and introduce psychotherapeutic exercises, methods and techniques. Content is presented playfully and tailored to the user's reported needs and interests.

priovi has one main function and several supporting secondary functions. The main function consists of a "simulated dialogue". This means that *priovi* presents the user brief text passages, and users then select a response option that interests them most or best suits their individual situation. *priovi* then responds emphatically to this response and conveys the next piece of information, to which the user can then respond in turn, and so on. In this way, a communication dynamic evolves. Patients are also motivated to complete simple homework tasks. Users can pause *priovi* at any time and continue from the point where they left off. Users are reminded regularly to take breaks.

In addition to the dialogues, which are at the core of the program, *priovi* offers a range of features including media such as audio recordings to guide therapeutic exercises or explain specific content in more detail and PDF-materials (worksheets and summary sheets), tailored motivational short text messages delivered as SMS (optional) or via email, as well as self-monitoring questionnaires to track target behaviors.

The content of the treatment modules is presented in table 1.

Table 1 | Structure and content of *priovi*.

Module	Description
1	**Onboarding I** The user is introduced to the program and receives important information on the user instructions, functions of *priovi*, symptoms of BPD and potential reasons for developing BPD, e.g., physical or sexual abuse. This is supported by two audios in case the user is emotionally upset, anxious or sad. In between, the participant can decide whether to take breaks. At the end of the module, the user is prompted to reward themselves for completing the module.
2	**Onboarding II** This module expands knowledge of BPD and therapeutic options. Theories and findings on disorder-specific needs are presented (e.g., safety, healthy human attachments). The user is introduced to schema therapy, an integrative form of psychotherapy that incorporates concepts and approaches from Cognitive Behavior Therapy (CBT). There are different schema modes that describe different emotional stages of the patient. The

most important are child modes (vulnerable & angry child), harmful parent modes (punitive & demanding), coping modes (distant protector), healthy modes (happy child & healthy adult). Cognitive, emotional and behavioral methods can be used to apply schema therapy. In between, the user can decide to take breaks.

3 Child modes

This module provides detailed information about the so-called child modes. The user is informed about how to identify child modes. They are introduced to “Lea”, a fictional person with BPD, to improve comprehension of module content during the program. An audio gives examples of “child mode situations” of Lea. In between, the user can decide whether to take breaks.

4 Parent modes/Adult modes

This module provides detailed information about the so-called dysfunctional parent modes and the healthy adult mode. The user is informed about how parent modes develop and how to recognize parent modes. An audio gives examples of “parent mode situations” of Lea. Quiz questions support practice in identifying parent modes. In between, the user can decide to take breaks.

5 Coping modes

This module provides detailed information about the so-called coping modes. The user is informed about how and which coping modes result from parent/child modes. Forms of coping modes are avoidance (distant protector mode), overcompensation, submission/sacrifice. The user can choose to look at specific modes more in detail. Information is provided on the distant protector mode, i.e., reasons for its development and consequences. Again, a comic strip and case histories (in the form of 3 audios) contribute to better comprehension. In between, the participant can decide whether to take breaks.

6 Onboarding Phase II

The user is introduced to the second phase of priovi, where adaptive coping methods tailored to different schema modes are practiced. They can choose the schema mode most important for themselves and which exercises to complete. The exercises have different levels of difficulty. The aim of the exercises is to develop a “mode-toolbox” out of which every user can choose a method the next time they need to deal with any schema mode. All of the following modules start with a small exercise to help recall information about the different modes.

7 Coping modes exercises

The first training module is about coping modes. Tailored cognitive/cognitive-behavioral trainings are provided for the modes of

		avoidance (distant protector mode), overcompensation, submission/sacrifice based on the choice of the participant, e.g., an audio about personal experiences with the distant protector mode and writing a pro/contra list about (dis-)advantages of it. They can decide to take a break before the next dialogue.
8	**Child modes exercises**	The second training module is about child modes. Tailored cognitive/cognitive-behavioral trainings are provided for the “vulnerable” and “angry” child mode using the example of Lea and different audios, e.g., an audio in which the participant can practice saying good things about him/herself or using the “healthy adult” coping method to improve how he/she deals with criticism. They can decide to take a break before the next unit.
9	**Parent modes exercises**	The third training module is about child modes. Tailored cognitive/cognitive-behavioral trainings are provided for the “punitive” and “demanding” parent mode using the example of Lea again and, for example, an audio that helps practice the "healthy adult" coping method to improve mastery of tasks without being mentally overwhelmed. At the end of the module, the user is prompted to take a break and reward themselves for finishing the exercises.
10	**Finish**	The last module intends to motivate the user (e.g., using an audio) to continue practicing the different coping methods in situations where he/she experiences a specific schema mode again in the future. Further use of the program is explained.

3.2 Intended purpose

priovi is intended to provide therapeutic methods and exercises based on evidence-based psychological and psychotherapeutic therapies for patients with borderline personality disorder, to help them managing their borderline personality disorder.

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

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

4. Clinical investigation plan

4.1 Clinical investigation objectives

The primary objective of this trial was to evaluate the effectiveness of the self-guided, Internet-based intervention *priovi* in lowering BPD symptoms in adult patients with BPD when used in addition to TAU. Moreover, the effects of *priovi* were examined in terms of improvements in psychological quality of life, depression, anxiety, social and work-related functioning, as well as with regard to the clinical course (number of suicide attempts, number of hospitalization, number of life-threatening events). The primary time point for the evaluation of the effectiveness of *priovi* was after 3 months (T1). Additional follow-ups were conducted after 6 (T2) and 12 months (T3) to assess the stability of effects. The control group received access to *priovi* after T2.

4.2 Clinical investigation design

- Randomized (simple randomization performed automatically via an external computerized tool)
- Controlled (two arms)
- Single-blind (referring to the study investigators, not the study participants)
- Online (no traditional physical investigation site)

4.3 Clinical investigation endpoints

4.3.1 Primary endpoint

- Severity of BPD symptoms (assessed with the BSL-23 mean score [26]) at T1

4.3.2 Secondary endpoints

- Responder rate of BPD symptoms

  Given the lack of a published MCID for the primary endpoint, the BSL-23 mean score, responder were defined by a change of borderline symptom severity on the BSL-23 total score following both conditions: (i) reaching the psychometric criterion of a reliable change index (RCI; relevant *z*-score = 1.96 for a 95% CI) [27] and (ii) a change of BSL-23-total score towards a less severe grade from T0 to T1 [28]. Deteriorators were defined accordingly by both, (i) reaching RCI and (ii) a change of BSL-23-total score towards a more severe grade from T0 to T1. Non-responders were defined as no change of the BPD severity grade, even if the RCI was reached.
- Remission rate of BPD symptoms

  Remission of borderline symptoms was defined as reaching a BSL-23 mean score of < 0.28 (corresponding to “none or low” BPD severity following the classification proposed in [28]) at T1. Patients with BSL-23 mean scores ≥ 0.28 at T1 were defined as not in remission. As already mentioned above, remission of BPD after 3 months of treatment would be completely unexpected.

- Psychological quality of life (assessed with the SF-12 mental sum score [29])
- Depression (assessed with the PHQ-9 sum score [30]–[32])
- Anxiety (assessed with the GAD-7 sum score [33], [34])
- Social and work-related functioning (assessed with the WSAS sum score [35])
- Clinical Course (number of suicide attempts in the past 3 months, number of hospitalizations in the past 3 months, number of life-threatening events in the past 3 months)

4.4 Control group

Participants in the control group received information regarding freely available self-help online material in addition to usual medical care (TAU) in consultation with their respective treatment team. Following the pragmatic study design, usual medical care should reflect the reality of care, and may therefore include all forms of outpatient care, including treatment by a primary care physician or specialist, psychotherapy (such as CBT, schema therapy, etc.), as well as no treatment at all. After 6 months (T2), the control group received access to *priovi*.

4.5 Ethical considerations

This study was approved by the ethics committee of the Medical Faculty of the University Lübeck (reference number 22-012). The study was pre-registered in the German Clinical Trials Register (DRKS) on April 27, 2022, with the registration number DRKS00028888.

4.6 Data quality assurance

Data were collected online using a secure, internationally recognized survey software (www.easyfeedback.de). 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 two weeks (e. g., participants were contacted in time to complete the questionnaires). Regular record-checking took place using a codebook with appropriate metadata. In addition, a daily backup of the data was performed. These were stored in anonymized, read-only form after the study was completed. The data will be retained for 10 years.

4.7 Subject population for the clinical investigation

Inclusion criteria:

- Age ≥ 18 years
- Diagnosis of BPD (ICD-10-GM-code: F60.31; assessed by a structured clinical interview [SCID-5-PD] conducted by telephone)
- At least moderate severity of BPD symptoms (BSL-23 mean score ≥ 1.07 [26], [28])
- Consent to participation

Exclusion criteria:

- Diagnosis of a substance use disorder
- Diagnosis of a psychotic disorder (with the exception of non-transitory paranoid ideas related to the BPD where the ability to test reality is mostly preserved)

4.8 Treatment allocation schedule

Simple randomization (no blocked randomization, no stratification) was performed automatically via an external computerized tool and concealed from study staff.

4.9 Concomitant medications/treatment

All participants received usual medical care (TAU) in consultation with their respective treatment team. Following the pragmatic study design, usual medical care should reflect the reality of care, and may therefore include all forms of outpatient care, including treatment by a primary care physician or specialist, psychotherapy (such as CBT, schema therapy, etc.), as well as no treatment at all.

4.10 Duration of follow-up

The duration of follow-up for the data reported on in this clinical investigation was 12 months.

4.11 Statistical design

All statistical analyses were performed with *R*, version 4.3.0 [36].

The primary outcome was analyzed using a linear mixed model analysis, with assessment time points modeled as ln(t+1), where t represented time from randomization in months. The model included a random intercept for each participant to account for interindividual differences, and the following fixed effects: time and intervention group as main effects, as well as group × time interaction for testing the slope difference between groups. The primary hypothesis was tested using T0 as pre-intervention and T1 as post-intervention time points. The covariance structure was chosen based on Akaike's Information Criterion (AIC) from a fixed set of candidate structures. The primary study hypothesis was tested on the group × time interaction. These analyses were repeated for secondary outcomes.

The main analysis was conducted as an ITT analysis following the principle 'analyze as randomized' [37], [38]. Missing values for continuous outcomes were substituted using multiple imputations. The imputation method was based on Fully Conditional Specification, where each incomplete variable was imputed by a separate model [39]. To ensure congeniality between the imputation and the analysis model, the group variable was included in the imputation model [40]. Other predictor variables for the imputation model included age, marital status, education, employment status, and psychotherapy at baseline. An additional reference-based sensitivity analysis (i.e., imputing data with the J2R method [41], [42]) was conducted following procedures for ITT-analysis.

Count data (such as the count of suicide attempts, hospitalizations, and life-threatening events) were subjected to the appropriate analysis method using a Poisson mixed model. This model incorporated a random intercept term for each participant, enabling the consideration of interindividual variations. The model included the following fixed effects: time and group as primary factors, and an interaction term between time and group. The hypothesis was tested on the group × time interaction.

All results were considered statistically significant at the two-sided 5% level.

4.12 Amendments to the CIP

The CIP was amended on March 3, 2023, to include the following additional specifications in the statistical analyses, as requested by the BfArM during the discussion on the provisional admission of *priovi* to the DiGA-registry:

- Details regarding the timing of data collection for secondary endpoints were added (Sections 1.4 and 6.1.c).
- A criterion for remission was added (Sections 1.4, 6.1.c, and 6.1.d).
- The classification of severity grades for borderline personality disorder was updated (Section 6.1.d).
- Subgroup analyses were included (Section 7.1).

5. Results

5.1 Accountability of subjects

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.

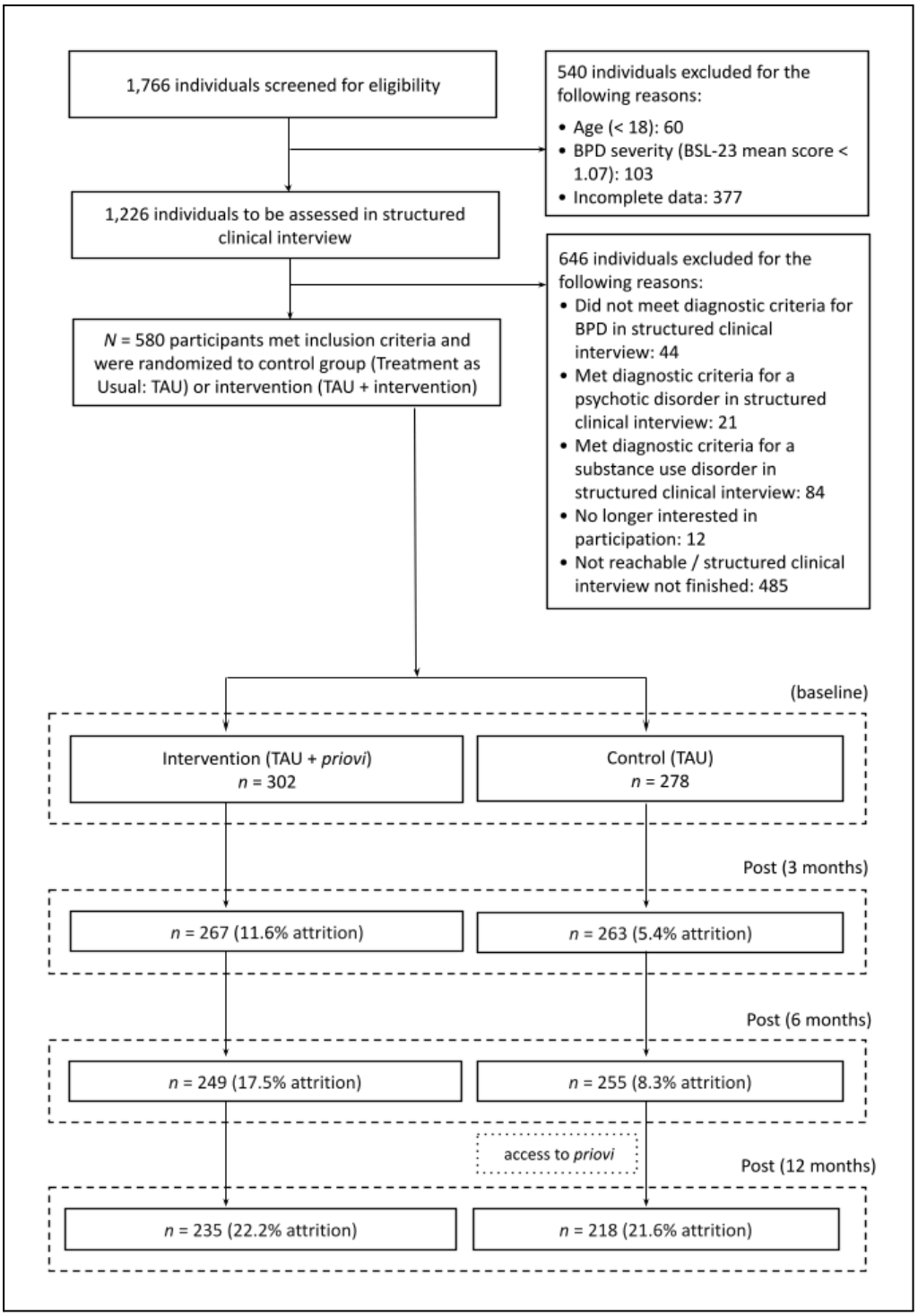

Figure 1 | Flow of participants through the study.

5.1.1 Subjects who did not pass the screening test

A total of 1,766 people were initially screened for eligibility. Of these, 540 had to be excluded in the online questionnaire for the following reasons:

- Age (< 18): 60
- BPD severity (BSL-23 mean score < 1.07): 103
- Incomplete data: 377

Thus, 1,226 people were to be assessed for eligibility in a structured clinical interview (SCID-5-PD) conducted via telephone. Of these, 646 were excluded for the following reasons:

- Did not meet diagnostic criteria for BPD in structured clinical interview: 44
- Met diagnostic criteria for psychotic disorder in structured clinical interview: 21
- Met diagnostic criteria for substance use disorder in structured clinical interview: 84
- No longer interested in participation: 12
- Not reachable / structured clinical interview not finished: 485

5.1.2 Subjects lost to follow-up

- up to T1: 45
- up to T2: 68
- up to T3: 115

5.1.3 Subjects withdrawn or discontinued from the clinical investigation

- up to T1: 5
- up to T2: 8
- up to T3: 12

As shown in table 13 below, participants who dropped out of the study up to T1 for any reason were significantly more likely to be men and participants with more severe BPD symptoms at baseline.

Table 2 | Comparison of baseline characteristics of subjects who dropped out of the study up to T1 for any reason and those who did not.

	Dropout (n = 50)	**Non-Dropout (n = 530)**	**Statistical comparison**
Age	29.3 (10.0)	31.5 (9.0)	$t = 1.49$, $p = 0.141$
Sex (male; n, %)	9 (18.0)	41 (7.7)	$X^2 = 6.11$, $p = 0.013$
BSL-23 mean score	2.51 (0.56)	2.31 (0.65)	$t = -2.30$, $p = 0.025$
Ever had psychotherapy (n, %)	46 (92.0)	506 (95.5)	$X^2 = 1.37$, $p = 0.242$

	Dropout (n = 50)	Non-Dropout (n = 530)	Statistical comparison
Currently in psychotherapy (n, %)	24 (48.0)	239 (45.1)	$X^2 = 0.15$, $p = 0.702$
Currently taking any psycholeptic / psychoanaleptic medication* (n, %)	20 (40.0)	277 (52.3)	$X^2 = 2.75$, $p = 0.097$

* ATC classification codes N05 / N06

5.2 Clinical investigation initiation date

- May 2022 (start of data collection)

5.3 Clinical investigation completion/suspension date

- November 2023 (completion of data collection for 12-month follow-up)

5.4 Disposition of subjects

Study participants were recruited through an online campaign from May through October 2022. A total of 1,766 people were interested in participation, provided informed consent and were screened for participation. A structured clinical interview was to be conducted with 1,226 of them to determine further specific diagnostic inclusion criteria. Of these, 580 met inclusion criteria and were randomized to the intervention (n = 302) and control group (n = 278). The investigational device *priovi* 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 *priovi* after 6 months. *priovi* 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 *priovi*.

5.5 Subject demographics and clinical characteristics

Table 3 | Subject demographics and clinical characteristics. Values represent mean (standard deviation [SD]) unless stated otherwise.

	priovi **(n = 302)**	**control (n = 278)**	**Whole Sample (N = 580)**
Age	31.10 (9.22)	31.55 (9.06)	31.32 (9.14)
Sex (male; n, %)	29 (9.6)	21 (7.6)	50 (8.6)
Gender (n, %)			

	priovi (n = 302)	control (n = 278)	Whole Sample (N = 580)
female	268 (88.7)	252 (90.6)	520 (89.7)
male	26 (8.6)	21 (7.6)	47 (8.1)
diverse	8 (2.6)	5 (1.8)	13 (2.2)
Family situation (n, %)			
divorced / registered partnership annulled	21 (7.0)	11 (4.0)	32 (5.5)
living in partnership, longer than 2 years	66 (21.9)	72 (25.9)	138 (23.8)
living in partnership, shorter than 2 years	68 (22.5)	64 (23.0)	132 (22.8)
married / registered civil partnership	42 (13.9)	42 (15.1)	84 (14.5)
single	105 (34.8)	87 (31.3)	192 (33.1)
widowed / registered partner deceased	0 (0)	2 (0.7)	2 (0.3)
Education (n, %)			
no school-leaving qualification	3 (1.0)	5 (1.8)	8 (1.4)
Hauptschulabschluss	21 (7.0)	12 (4.3)	33 (5.7)
Realschulabschluss	57 (18.9)	41 (14.7)	98 (16.9)
Fachhochschulreife	25 (8.3)	20 (7.2)	45 (7.8)
Abitur (A-levels)	43 (14.2)	45 (16.2)	88 (15.2)
completed vocational training	63 (20.9)	78 (28.3)	141 (24.3)
completed university studies	74 (24.5)	73 (26.3)	147 (25.3)
other education	16 (5.3)	4 (1.4)	20 (3.4)

	priovi (n = 302)	control (n = 278)	Whole Sample (N = 580)
Employment (n, %)			
not employed	100 (33.1)	85 (30.6)	185 (31.9)
marginal employment (mini job)	14 (4.6)	15 (5.4)	29 (5.0)
employed part-time	55 (18.2)	53 (19.1)	108 (18.6)
employed full-time	87 (28.8)	89 (32.3)	176 (30.3)
other form of employment	46 (15.2)	36 (12.9)	82 (14.1)
Ever had psychotherapy (n, %)	285 (94.4)	267 (96.0)	552 (95.2)
Currently in psychotherapy (n, %)	138 (45.7)	125 (45.0)	263 (45.3)
Currently taking any psycholeptic / psychoanaleptic medication* (n, %)	157 (52.0)	140 (50.4)	297 (51.2)
Regular medication (multiple answers possible; n, %)			
Antidepressants	131 (43.4)	128 (46.0)	259 (44.7)
Antipsychotics	36 (11.9)	41 (14.7)	77 (13.3)
Sedatives	16 (5.3)	6 (2.2)	22 (3.8)
Psychostimulants	9 (3.0)	11 (4.0)	20 (3.4)
Antiepileptics	10 (3.3)	4 (1.4)	14 (2.4)
Anxiolytics	6 (2.0)	6 (2.2)	12 (2.1)
Medication as needed (multiple answers possible; n, %)			
Antipsychotics	15 (5.0)	22 (7.9)	37 (6.4)
Sedatives	20 (6.6)	13 (4.7)	33 (5.7)
Anxiolytics	17 (5.6)	10 (3.6)	27 (4.7)

	priovi (n = 302)	control (n = 278)	Whole Sample (N = 580)
Antidepressants	5 (1.7)	7 (2.5)	12 (2.1)

* Anatomical Therapeutic Chemical (ATC) classification codes N05 / N06

Table 4 | Relevant treatment characteristics over the course of the clinical investigation.

	priovi	control	Statistical comparison
T1	n = 267	n = 263	
Currently in psychotherapy (n, %)	142 (53.2)	147 (55.9)	$\chi^2 = 0.39$, $p = 0.531$
Currently taking any psycholeptic / psychoanaleptic medication* (n, %)	147 (55.1)	147 (55.9)	$\chi^2 = 0.04$, $p = 0.846$
Regular medication (multiple answers possible; n, %)			
Antidepressants	119 (44.6)	125 (47.5)	$\chi^2 = 0.47$, $p = 0.494$
Antipsychotics	38 (14.2)	41 (15.6)	$\chi^2 = 0.19$, $p = 0.661$
Sedatives	17 (6.4)	8 (3.0)	$\chi^2 = 3.26$, $p = 0.071$
Psychostimulants	7 (2.6)	10 (3.8)	$\chi^2 = 0.59$, $p = 0.441$
Antiepileptics	9 (3.4)	5 (1.9)	$\chi^2 = 1.11$, $p = 0.291$
Anxiolytics	7 (2.6)	4 (1.5)	$\chi^2 = 0.79$, $p = 0.374$
Medication as needed (multiple answers possible; n, %)			
Antipsychotics	9 (3.4)	13 (4.9)	$\chi^2 = 0.82$, $p = 0.364$
Sedatives	13 (4.9)	14 (5.3)	$\chi^2 = 0.06$, $p = 0.812$
Anxiolytics	7 (2.6)	9 (3.4)	$\chi^2 = 0.29$, $p = 0.590$
Antidepressants	3 (1.1)	7 (2.7)	$\chi^2 = 1.69$, $p = 0.193$
	priovi	control	Statistical comparison
T2	n = 249	n = 255	

	priovi	control	Statistical comparison
Currently in psychotherapy (n, %)	151 (60.6)	142 (55.7)	$\chi^2 = 1.27$, $p = 0.259$
Currently taking any psycholeptic / psychoanaleptic medication* (n, %)	136 (54.6)	135 (52.9)	$\chi^2 = 0.14$, $p = 0.706$
Regular medication (multiple answers possible, % yes)			
Antidepressants	112 (45.0)	116 (45.5)	$\chi^2 = 0.01$, $p = 0.908$
Antipsychotics	32 (12.9)	34 (13.3)	$\chi^2 = 0.03$, $p = 0.873$
Sedatives	14 (5.6)	7 (2.7)	$\chi^2 = 2.61$, $p = 0.106$
Psychostimulants	8 (3.2)	15 (5.9)	$\chi^2 = 2.06$, $p = 0.151$
Antiepileptics	8 (3.2)	8 (3.1)	$\chi^2 < 0.01$, $p = 0.961$
Anxiolytics	6 (2.4)	2 (0.8)	$\chi^2 = 2.13$, $p = 0.144$
Medication as needed (multiple answers possible; n, %)			
Antipsychotics	7 (2.8)	11 (4.3)	$\chi^2 = 0.83$, $p = 0.363$
Sedatives	17 (6.8)	13 (5.1)	$\chi^2 = 0.67$, $p = 0.412$
Anxiolytics	8 (3.2)	5 (2.0)	$\chi^2 = 0.79$, $p = 0.375$
Antidepressants	6 (2.4)	4 (1.6)	$\chi^2 = 0.46$, $p = 0.498$

* ATC classification codes N05 / N06

5.6 CIP compliance

The CIP was complied with throughout the duration of the clinical investigation.

5.7 Analysis

5.7.1 Primary endpoint

- Severity of BPD symptoms (assessed with the BSL-23 mean score [26])

Table 5 | Results of the primary endpoint severity of BPD symptoms (BSL-23 mean score)

Time	control		*priovi*		Linear Mixed Model		
	mean	SD	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]

ITT	T0	2.32	0.64	2.34	0.64	-	-	-
	T1	1.94	0.78	1.74	0.83	-0.19 (-0.3, -0.09)	<. 001	0.24 (0.07, 0.42)
	T2	1.77	0.86	1.64	0.84	-0.09 (-0.15, -0.02)	0.011	0.15 (-0.03, 0.32)
J2R	T0	2.32	0.64	2.34	0.64	-	-	-
	T1	1.93	0.78	1.76	0.83	-0.17 (-0.27, -0.07)	<. 001	0.21 (0.05, 0.36)
	T2	1.76	0.85	1.66	0.85	-0.08 (-0.13, -0.02)	0.007	0.12 (-0.03, 0.27)

[a]group × time interaction effect on original scale 3 (T1)/6 (T2) months after baseline.
[b] based on observed values; positive values show effects in favor of the intervention group.

5.7.2 Secondary endpoints

- Responder rate at T1

Significantly more participants in the *priovi*-group were classified as responders (24.0%) after 3 months based on the definition described in section 4.3.2 than in the control group (15.6%; OR = 1.71, 95% CI = [1.10, 2.64]; $\chi^2 = 5.86$, $p = 0.016$).
There was no significant difference in the rate of patients experiencing deterioration of BPD symptoms as defined in section 4.3.2 between the *priovi*-group (1.9%) and the control group (1.1%; OR = 1.65, 95% CI = [0.39, 6.99]; $\chi^2 = 0.11$, $p = 0.738$). For details, see table 6.

- Remission rate at T1

As anticipated, hardly any patient showed BSL values indicating remission of BPD after 3 months. Accordingly, there was no significant difference between the *priovi* intervention group (0.007%) and the control group (0.004%; OR = 1.98, 95% CI = [0.18, 21.94]; $\chi^2 < 0.001$, $p = 1$; see also table 6).

- Responder rate at T2

More participants in the *priovi*-group were classified as responders (30.1%) after 6 months than in the control group (22.7%; OR = 1.46, 95% CI = [0.98, 2.18]), but the difference did not reach statistical significance ($\chi^2 = 3.53$, $p = 0.060$).
There was no significant difference in the rate of patients experiencing deterioration of BPD symptoms between the *priovi*-group (1.6%) and the control group (0.4%; OR = 4.15, 95% CI = [0.46, 37.4]; $\chi^2 = 0.86$, $p = 0.355$). For details, see table 6.

- Remission rate at T2

As after 3 months, hardly any patient showed BSL values indicating remission of BPD after 6 months. Accordingly, there was no significant difference in the remission rate between the

priovi intervention group (2.4%) and the control group (2.7%; OR = 0.87, 95% CI = [0.29, 2.64]; $\chi^2 < 0.001$, $p = 1$; see also table 6).

Table 6 | Results of responder and remission analyses of the primary endpoint at T1 and T2

T1	**control (n = 263)**	***priovi* (n = 267)**	Odds Ratio (95% CI)[a]
responder analysis			
responder (n, %)	41 (15.6)	64 (24.0)	1.71 (1.10, 2.64)
deterioratior (n, %)	3 (1.1)	5 (1.9)	1.65 (0.39, 6.99)
non-responder (n, %)	219 (83.3)	198 (74.2)	0.58 (0.38, 0.88)
remission analysis			
remission (n, %)	1 (0.004)	2 (0.007)	1.98 (0.18, 21.94)
T2	**control (n = 255)**	***priovi* (n = 249)**	Odds Ratio (95% CI)[a]
responder analysis			
responder (n, %)	58 (22.7)	75 (30.1)	1.46 (0.98, 2.18)
deterioratior (n, %)	1 (0.4)	4 (1.6)	4.15 (0.46, 37.4)
non-responder (n, %)	196 (76.9)	170 (68.3)	0.65 (0.44, 0.96)
remission analysis			
remission (n, %)	7 (2.7)	6 (2.4)	0.87 (0.29, 2.64)

[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, while an OR < 1 signifies a lower likelihood in the intervention group.

- Psychological quality of life (assessed with the SF-12 mental sum score [29])

Table 7 | Results of the secondary endpoint psychological quality of life (SF-12 mental sum score)

	Time	**control**		***priovi***		**Linear Mixed Model**		
		mean	SD	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
ITT	T0	11.9	2.5	12.0	2.7	-	-	-
	T1	13.0	3.4	13.6	3.4	0.4 (0, 0.9)	0.065	0.18 (0.01, 0.34)
	T2	13.5	3.6	13.8	3.6	0.2 (-0.1, 0.4)	0.276	0.10 (-0.07, 0.27)

J2R	T0	11.9	2.5	12.0	2.7	-	-	-
	T1	13.0	3.4	13.5	3.5	0.4 (0, 0.8)	0.056	0.16 (0.01, 0.31)
	T2	13.4	3.6	13.8	3.6	0.2 (-0.1, 0.4)	0.16	0.11 (-0.03, 0.24)

[a]group × time interaction effect on original scale 3 (T1)/6 (T2) months after baseline.
[b] based on observed values; positive values show effects in favor of the intervention group.

- Depression (assessed with the PHQ-9 sum score [30]–[32])

Table 8 | Results of the secondary endpoint depression (PHQ-9 sum score)

	Time	**control**		***priovi***		**Linear Mixed Model**		
		mean	SD	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
ITT	T0	17.4	4.6	17.3	4.7	-	-	-
	T1	15.5	5.4	14.4	5.5	-1.0 (-1.8, -0.3)	0.009	0.21 (0.04, 0.38)
	T2	14.6	5.5	13.7	5.5	-0.5 (-0.9, -0.1)	0.025	0.16 (-0.01, 0.33)
J2R	T0	17.3	4.6	17.3	4.7	-	-	-
	T1	15.5	5.4	14.5	5.5	-0.9 (-1.6, -0.2)	0.007	0.19 (0.03, 0.35)
	T2	14.7	5.5	13.8	5.5	-0.5 (-0.8, -0.1)	0.012	0.15 (0, 0.30)

[a] group × time interaction effect on original scale 3 (T1)/6 (T2) months after baseline.
[b] based on observed values; positive values show effects in favor of the intervention group.

- Anxiety (assessed with the GAD-7 sum score [33], [34])

Table 9 | Results of the secondary endpoint anxiety (GAD-7 sum score)

	Time	**control**		***priovi***		**Linear Mixed Model**		
		mean	SD	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
ITT	T0	15.0	3.8	14.7	3.7	-	-	-
	T1	13.2	4.7	12.1	4.6	-0.7 (-1.4, -0.1)	0.030	0.23 (0.06, 0.41)
	T2	12.8	4.8	11.7	4.8	-0.5 (-0.9, -0.1)	0.025	0.24 (0.06, 0.42)
J2R	T0	15.0	3.8	14.7	3.7	-	-	-
	T1	13.2	4.7	12.2	4.6	-0.6 (-1.2, -0.01)	0.035	0.21 (0.05, 0.36)
	T2	12.8	4.8	11.8	4.8	-0.4 (-0.7, -0.1)	0.019	0.22 (0.07, 0.36)

[a]group × time interaction effect on original scale 3 (T1)/6 (T2) months after baseline.
[b] based on observed values; positive values show effects in favor of the intervention group.

- Social and work-related functioning (assessed with the WSAS sum score [35])

Table 10 | Results of the secondary endpoint social and work-related functioning (WSAS sum score)

	Time	control		*priovi*		Linear Mixed Model		
		mean	SD	mean	SD	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
ITT	T0	23.5	7.7	23.4	8.0	-	-	-
	T1	21.8	8.9	20.7	9.2	-0.9 (-2, 0.2)	0.109	0.12 (-0.05, 0.30)
	T2	21.1	9.4	20.3	9.5	-0.4 (-1.1, 0.2)	0.220	0.08 (-0.09, 0.25)
J2R	T0	23.5	7.7	23.4	8.0	-	-	-
	T1	21.8	9.0	20.8	9.2	-0.8 (-1.8, 0.2)	0.125	0.11 (-0.05, 0.27)
	T2	21.2	9.3	20.3	9.5	-0.4 (-1.0, 0.1)	0.125	0.09 (-0.06, 0.24)

[a]group × time interaction effect on original scale 3 (T1)/6 (T2) months after baseline.
[b] based on observed values; positive values show effects in favor of the intervention group.

- Clinical Course

Table 11 | Number of reported suicide attempts, hospitalizations and life-threatening events

	Time	control		*priovi*		Poisson Mixed Model	
		N	events (events per 100 persons)	N	events (events per 100 persons)	Treatment effect (95% CI)[a]	*p*-value
suicide attempts	T0	278	23 (8.3)	302	38 (12.6)	-	-
	T1	262	21 (8.0)	264	9 (3.4)	-0.86 (-1.55, -0.18)	0.014
	T2	254	29 (11.4)	249	11 (4.4)	-0.82 (-1.26, -0.38)	<. 001
hospitali-zations	T0	278	60 (21.6)	302	82 (27.2)	-	-
	T1	262	54 (20.6)	264	74 (28.0)	0.03 (-0.32, 0.38)	0.864
	T2	254	26 (10.0)	249	47 (18.9)	0.18 (-0.09, 0.44)	0.190
life-threa tening events	T0	278	425 (153)	302	378 (125)	-	-
	T1	262	310 (118)	264	260 (98.5)	-0.02 (-0.18, 0.14)	0.791

	T2	254	135 (53.1)	249	113 (45.4)	-0.04 (-0.16, 0.08)	0.539

[a]group × time interaction effect 3 (T1)/6 (T2) months after baseline.

- Number of suicide attempts

  The analysis utilizing the Poisson mixed model revealed a significant decrease in the number of suicide attempts over time within the *priovi* group compared to the control group, both up to T1 (group × time interaction effect = -0.86, 95% CI = [-1.55, -0.18], p = 0.014) and through T2 (group × time interaction effect = -0.82, 95% CI = [-1.26, -0.38], p < .001). Descriptively, we observed 57.5% fewer suicide attempts in the *priovi* group as compared to the control group after 3 months, and 61.3% fewer suicide attempts after 6 months.

- Number of hospitalizations

  The Poisson mixed model indicated that the number of hospitalizations did not differ between the *priovi* group and the control group, neither up to T1 group × time interaction effect = 0.03, 95% CI = [-0.32, 0.38], p = 0.864) nor through T2 (group × time interaction effect = 0.18, 95% CI = [-0.09, 0.44], p = 0.190).

- Number of life-threatening events

  The Poisson mixed model indicated that the number of life-threatening events did not differ between the *priovi* group and the control group, neither up to T1 (group × time interaction effect = -0.02, 95% CI [-0.18, 0.14], p = 0.791) nor through T2 (group × time interaction effect = -0.04, 95% CI [-0.16, 0.08], p = 0.539).

- Long-term follow-up of BPD symptoms at T3

Table 12 | Longitudinal development of BPD symptoms in the *priovi* group.

	Time	mean	SD	mean difference to T0 (95% CI)	*p*-value	Cohen's *d* (95% CI)[a]
ITT	T0	2.34	0.64	-	-	-
	T1	1.74	0.83	-0.60 (-0.69, -0.51)	< .001	0.82 (0.68, 0.96)
	T2	1.64	0.84	-0.70 (-0.80, -0.60)	< .001	0.90 (0.74, 1.05)
	T3	1.58	0.89	-0.76 (-0.86, -0.65)	< .001	0.89 (0.73, 1.04)

[a] pre-post effect size relative to T0; positive values indicate a reduction of symptoms.

Table 13 | BPD symptoms in the control group after receiving access to *priovi* following T2.

	Time	mean	SD	mean difference to T2 (95% CI)	*p*-value	Cohen's *d* (95% CI)[a]
ITT	T2	1.77	0.86	-	-	-
	T3	1.55	0.85	-0.21 (-0.30, -0.12)	< .001	0.30 (0.16, 0.43)

[a] pre-post effect size relative to T2; positive values indicate a reduction of symptoms.

- User Satisfaction

User satisfaction with *priovi* was assessed using the Net Promoter Score (NPS [43]). Participants in the intervention group were asked how likely they were to recommend *priovi* to a friend or colleague. Responses were recorded on an 11-point numeric 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 25.0 at T1, which reflects very high user satisfaction with *priovi*. At T2, the NPS was even slightly higher at 31.0, underscoring participants' consistent and sustained satisfaction with *priovi*.

5.7.4 Adverse events and adverse device effects

No adverse events or adverse device effects were observed.

5.8 Device deficiencies and serious adverse events

Device deficiencies were not observed. Regarding serious adverse events, there was a statistically significant decrease in the number of suicide attempts in the intervention group compared to the control group. No significant differences were observed with respect to hospitalizations or life-threatening events.

5.9 Subgroup analyses for special populations

Subgroup analyses were conducted following the ITT principle for the primary endpoints at T1 (3 months, primary time point for the analysis of effectiveness). An overview of the results of the subgroup analyses in the form of a forest plot is given in figure 2.

- Baseline BPD severity

We examined subgroups based on the baseline severity of BPD symptoms, following the classification proposed in [28] for the BSL-23. The results are presented in table 14 below. Descriptively, treatment effects tended to increase with BPD severity, but the difference did not reach statistical significance ($p = 0.933$).

Of note, only a total of 19 individuals (6 in the control group and 13 in the intervention group) fell into the highest severity category ('extremely high' BPD severity [28]). Due to this small sample size, the computations and results from the linear mixed model were unstable. Therefore, we opted to provide descriptive statistics only for this particular subgroup:

	Time	**Control**		***priovi***	
		mean	SD	mean	SD
ITT	T0	3.51	0.05	3.69	0.18
	T1	2.91	0.74	2.97	0.85

Table 14 | Subgroup analysis based on baseline BPD severity (following the classification proposed in [28]) for the primary endpoint BPD severity (BSL-23 mean score) at T1.

ITT								
moderate n = 165			**high** n = 233			**very high** n = 163		
Linear Mixed Model			**Linear Mixed Model**			**Linear Mixed Model**		
Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
-0.17 (-0.35, 0.0)	0.053	0.20 (-0.13, 0.52)	-0.20 (-0.35, -0.05)	0.011	0.31 (0.04, 0.57)	-0.25 (-0.45, -0.05)	0.016	0.36 (0.05, 0.67)

[a]group × time interaction effect on original scale 3 months after baseline.
[b] based on observed values; positive values show effects in favor of the intervention group.

- Age

There was only one person aged 65 years and older in the sample at baseline; therefore, dedicated subgroup analyses based on age as specified in the CIP (18-65 years vs. > 65 years) were not possible. Exclusion of this individual yielded almost identical results to the main analysis on the primary endpoint, the BSL-23 mean score (estimated group difference = -0.19, 95% CI = [-0.30, -0.19], $p < .001$; $d = 0.24$).

- Sex

Subgroup analyses based on sex are reported in table 15 below. Regarding the primary endpoint of BPD severity at T1, the treatment effect was descriptively larger in men than in women, but the difference did not reach statistical significance ($p = 0.440$).

Table 15 | Subgroup analysis based on sex for the primary endpoint BPD severity (BSL-23 mean score) at T1.

ITT	
women	**men**

n = 530			n = 50		
Linear Mixed Model			**Linear Mixed Model**		
Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
-0.18 (-0.29, -0.07)	0.001	0.20 (0.02, 0.38)	-0.31 (-0.63, 0.01)	0.054	0.80 (0.22, 1.37)

[a]group × time interaction effect on original scale 3 months after baseline.
[b] based on observed values; positive values show effects in favor of the intervention group.

- Psychotherapy status

Table 16 below displays subgroup analyses based on psychotherapy status. For the primary endpoint of BPD severity at T1, participants in psychotherapy at baseline exhibited a larger treatment effect in comparison to those not in psychotherapy. However, this difference did not achieve statistical significance ($p = 0.685$).

Table 16 | Subgroup analysis based on psychotherapy status for the primary endpoint BPD severity (BSL-23 mean score) at T1.

ITT					
In psychotherapy n = 263			**Not in psychotherapy** n = 317		
Linear Mixed Model			**Linear Mixed Model**		
Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
-0.22 (-0.37, -0.07)	0.005	0.30 (0.06, 0.55)	-0.17 (-0.32, -0.03)	0.018	0.20 (-0.03, 0.43)

[a]group × time interaction effecton original scale 3 months after baseline.
[b] based on observed values; positive values show effects in favor of the intervention group.

- Medication

As displayed in table 17 below, for the primary endpoint of BPD severity at T1, the treatment effect on the original scale was descriptively smaller in those taking any substance from ATC classes N05 (psycholeptics) or N06 (psychoanaleptics) at baseline compared to those who did not, but the difference did not reach statistical significance ($p = 0.644$).

Table 17 | Subgroup analysis based on medication status for the primary endpoint BPD severity (BSL-23 mean score) at T1.

ITT	
On medication n = 297	**Not on medication** n = 283

Linear Mixed Model			Linear Mixed Model		
Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]	Treatment effect (95% CI)[a]	*p*-value	Cohen's *d* (95% CI)[b]
-0.17 (-0.32, -0.03)	0.021	0.25 (0.02, 0.48)	-0.22 (-0.37, -0.07)	0.004	0.25 (0.01, 0.50)

[a]group × time interaction effect on original scale 3 months after baseline.

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

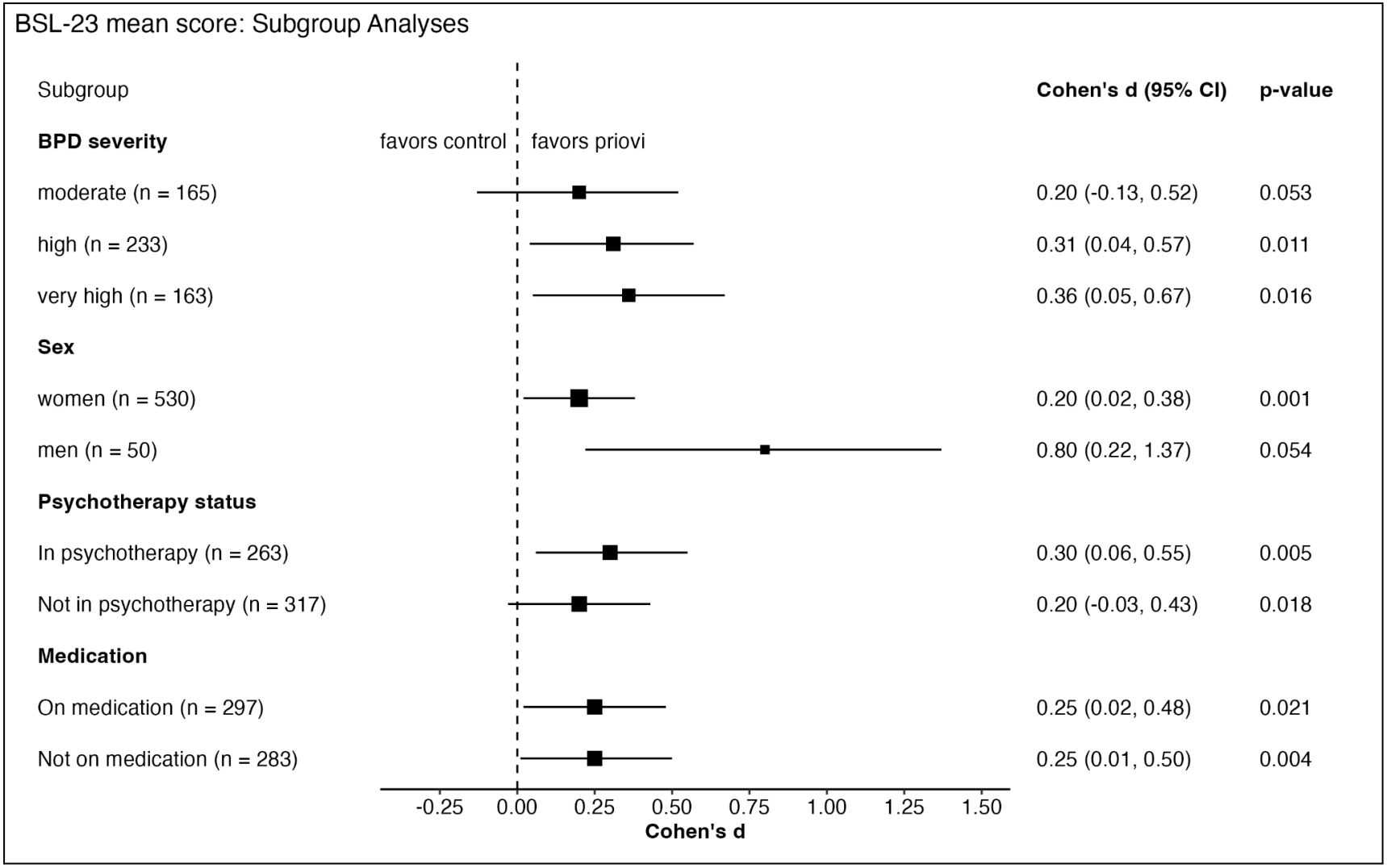

Figure 2 | Forest plot of effect sizes (Cohen's *d*) for the primary endpoint, the BSL-23 mean score. *p*-values are derived from the Linear Mixed Model.

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 3 months, the intervention group displayed significantly lower BPD severity levels than the control group. Responder analysis verified the clinical significance of these reductions. In addition, there were significant effects of *priovi* on depression and anxiety. Intervention effects remained evident at the 6-month follow-up. The robustness of the results was confirmed by the conservative J2R sensitivity analysis. Uncontrolled data from the 12-month follow-up demonstrated an ongoing decrease in BPD severity levels in the *priovi* group.

Additionally, the *priovi* group displayed a more positive clinical trajectory, reporting significantly fewer suicide attempts than the control group throughout the follow-up. No significant differences were observed regarding the number of hospitalizations and other life threatening-events.

Patient satisfaction with *priovi* was remarkably high after both 3 and 6 months.

6.2 Assessment of benefits and risks

This clinical investigation shows that the use of *priovi* in addition to TAU is effective and safe in reducing BPD severity as well as depression and anxiety for up to 6 months. Therefore, the benefit-risk ratio can be rated as positive.

6.3 Discussion of the clinical relevance of the results

The majority of patients with BPD, about 75%, do not have access to appropriate psychotherapeutic treatment in Western European health care systems [13], [19], even though the relevant clinical guidelines recommend psychotherapy as the first-line treatment for BPD [15], [16]. Flexible and convenient to use, DiGAs represent valuable tools in closing this treatment gap and thus have potential to reduce the vast individual and socioeconomic burden associated with BPD [7], [9], [22], [23]. Specifically, a previous RCT showed positive effects of a preliminary version of *priovi* in patients with BPD who received either psychotherapy or psychiatric care [24].

The results of the present RCT complement and extend these findings: Following a 3-month utilization of *priovi*, the intervention group exhibited significantly reduced BPD severity levels in comparison to the control group. Responder analysis verified the clinical significance of these reductions. Moreover, significant effects of *priovi* on depression and anxiety were observed. In addition, the number of suicide attempts were reduced by 57.5% in the *priovi* group as compared to the control group by 3 months. Intervention effects were maintained at the 6-month follow-up. Uncontrolled data from the 12-month follow-up showed continued effectiveness of *priovi*.

These findings, although highly promising, should be considered within the broader context of available treatment options, specifically face-to-face psychotherapy and off-label use of pharmacotherapy. We will discuss them separately for each confirmatory outcome.

In the realm of BPD-specific psychotherapy, meta-analytic evidence suggests that the most frequently studied approach, DBT, yields improvements of *d* = 0.36–0.60 in reducing BPD symptoms when compared to TAU [44]–[46]. DBT, much like other BPD-specific psychotherapeutic approaches, typically requires a significant allocation of resources, involving an average of approximately 40 to 100 face-to-face sessions administered by a highly trained professional over a span of 1 to 3 years [47]. In contrast, for more generic, non-BPD-specific psychotherapies like CBT, which are more common, the average effect size in reducing BPD symptoms compared to TAU is smaller (*d* = 0.24 [46], [48]). The literature on pharmacotherapy presents a mixed picture. The existing evidence is of very low certainty and does not indicate significant benefits in reducing BPD symptoms, and in some cases, potential adverse effects have been observed. For instance, medications such as olanzapine have been associated with increased incidents of self-injurious behavior and weight gain [49], [50].
Given the absence of evidence supporting the effectiveness of pharmacotherapy in treating BPD and the challenges in accessing psychotherapy, the results of our trial mark a notable development in BPD research: The observed effect size for *priovi* (*d* = 0.24) in reducing BPD severity is clinically relevant and comparable to the effects typically observed in non-BPD-specific psychotherapy. Of practical significance for strained healthcare systems is that these positive outcomes were achieved through a fully automated intervention, without drawing from already scarce psychotherapeutic resources, thus providing fast and safe access to an additional treatment element. Moreover, these findings gain further context as positive effects were also noted when *priovi* was used in conjunction with ongoing psychotherapy. Thus, the trial results affirm that *priovi* offers a safe and accessible adjunct to BPD treatment, providing valuable benefits to a patient population in significant need.

In addition to the positive results observed in reducing BPD severity, the use of *priovi* resulted in significant reductions in suicide attempts. This confirms that the beneficial effects on suicidal outcomes associated with face-to-face psychotherapy [44], [46], [48], [49] can translate to a fully automated, digital delivery format. In contrast, similar to BPD symptoms, the available evidence concerning the impact of pharmacotherapy on suicide-related outcomes is very uncertain, showing little to no discernible effects [49], [50]. Collectively, these findings underscore the role of *priovi* as a much-needed, low-threshold addition to the treatment spectrum for BPD.

In the context of treating depressive symptoms in individuals with BPD, the existing meta-analytic evidence from BPD-specific psychotherapy, more specifically DBT, indicates that the observed effects in comparison to TAU do not achieve statistical significance [44], [51]. Similarly, for non-BPD-specific psychotherapy (CBT), the meta-analytic evidence suggests no significant effect on depressive symptoms in BPD [44]. Evidence on treating depression in BPD with pharmacotherapy is inconclusive and of low certainty [49], [50]. Thus, the effect of *d* = 0.21 observed for *priovi* in improving depressive symptoms in

individuals with BPD appears to be a very favorable result within the context of the available evidence for the other treatment options.

Only a limited number of studies incorporate anxious symptoms as an outcome measure in BPD treatment research. Therefore, one meta-analysis resorted to examining a broader outcome category (general psychopathology, anxiety, and depression). This analysis suggested that psychotherapy, encompassing both BPD-specific and non-BPD-specific approaches, exhibits an effect size of $d = 0.32$ when compared to control conditions, with the majority involving TAU [48]. Available studies on pharmacotherapy suggest limited effectiveness in alleviating anxiety in BPD [49], [52]. Therefore, considering the available evidence, the effect size of $d = 0.23$ observed for *priovi* in reducing anxious symptoms among individuals with BPD can be considered a favorable result.

When considering quality of life outcomes, the data in the literature is quite limited [16]. In one meta-analysis, psychotherapy (mostly resource-intensive, BPD-specific approaches) demonstrated an average effect size of $d = 0.32$ in enhancing generic measures of quality of life compared to diverse control conditions [53]. Concerning medication, one RCT found that lamotrigine did not significantly impact the health-related quality of life in individuals with BPD [54]. Adding to the overall mixed picture, we found a small and statistically not significant effect of *priovi* on quality of life. A possible explanation for this pattern of results is that improvements in quality of life may follow improvements in symptoms and therefore take longer to become evident, aligning with the classic phase-model of psychotherapy outcomes [55].

The same applies to the outcome of psychosocial functioning. There is a general paucity of studies addressing functioning as an outcome within BPD treatment; specifically, we found no prior RCT investigating outcomes directly comparable to our endpoint of social and work-related functioning. BPD-specific psychotherapy, specifically DBT, when compared to TAU, shows a meta-analytic effect size of $d = 0.36$ for psychosocial functioning [44]. Conversely, in the case of non-BPD-specific psychotherapy (CBT) versus TAU, the reported effect size on psychosocial functioning, derived from a single study, is 0 [44], [51]. Similarly, pharmacotherapy has little to no effect on psychosocial functioning in BPD [49]. Again, our result adds to the overall mixed picture, as we found a small and statistically not significant effect of *priovi* on work and social functioning. Similar to quality of life outcomes, effects on social and work-related functioning may take longer to become evident [55].

In summary, *priovi* stands out favorably when compared to existing treatment options for various outcomes in BPD. Specifically, for the primary endpoint of BPD severity, *priovi* achieved a significant and clinically relevant effect. Additionally, significant reductions in suicide attempts and clinically relevant improvements in depression and anxiety were observed. Resource-intensive BPD-specific face-to-face psychotherapy, while potentially slightly more effective for some of the considered outcomes, is virtually inaccessible in the reality of care [13], [19]. Off-label pharmacotherapy comes with no conclusive benefits on core BPD symptoms, depression, anxiety, quality of life as well as social and work-related functioning. Thus, the highly prevalent use of pharmacotherapy in the treatment of patients with BPD [56] is not supported by the available evidence.

Taken together with previous findings, the present clinical investigation provides compelling evidence that *priovi* reduces BPD severity as well as depression and anxiety in adult patients with BPD significantly and to a clinically relevant extent.

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

Using *priovi* as in addition to TAU was found to be effective in reducing BPD severity, depression and anxiety as well as the frequency of suicide attempts in adult patients with BPD, compared to using TAU only. *priovi* 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

The current clinical investigation demonstrates the feasibility and safety of conducting online studies with patients diagnosed with BPD. The high satisfaction among participants with *priovi* underscores a general inclination within the target population to adopt digital solutions, highlighting promising avenues for digitizing other evidence-based treatments for BPD. Further studies could also investigate whether specific patients or patients in specific care settings benefit more from *priovi*.

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 for a severe and chronic disorder like BPD, 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” documented extensively in classic psychotherapy research [57], [58], and more recently, also for digital interventions [59].

Another conceivable limitation is the predominance of female participants in the patient sample. This skew might be due to an overall higher prevalence of diagnosed BPD in women than in men [60], as well as sex differences in help-seeking behaviors among patients with BPD [61]. From this perspective, the observed proportion of women in the sample (91.4%) aligns closely with the sex distribution in clinical settings: Data from the European Drug Safety Project (*Arzneimittelsicherheit in der Psychiatrie*), which regularly surveys psychiatric hospitals in Germany, Switzerland, and Austria, reported that 87.2% of all BPD patients in the monitored clinics were women [56]. Similarly, studies investigating the effectiveness of psychotherapeutic interventions in BPD often feature exclusively female or predominantly female participant samples [45], [51] (e.g., the mean proportion of women is 92.3% in the meta-analysis described in [45]). Taken together, these data suggest that the overrepresentation of female participants in our study mirrors real-world clinical patterns

and other research findings. Despite the relatively low percentage of male participants, our large sample size enabled us to recruit a total of 50 men, allowing us to draw meaningful conclusions about *priovi*'s effectiveness for men as well: The subgroup analysis highlighted an interesting trend where *priovi* displays - at least descriptively - greater effectiveness in men than in women. This could be due to the fact that men with BPD are often even more under-served in the health-care system than women with BPD [60]. As a result, digital solutions like *priovi* might hold particular appeal for them.

7. Abbreviated terms and definitions

ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BPD	borderline personality disorder
BSL-23	Borderline Symptom List - 23
CBT	Cognitive Behavioral Therapy
CI	confidence interval
DRKS	German Clinical Trials Register
DiGA	digital health application (“Digitale Gesundheitsanwedung”)
GAD-7	Gesundheitsbogen für Patienten - 7 Items
ITT	intent to treat
J2R	jump-to-reference
MCID	minimal clinically important difference
NPS	Net Promoter Score
OR	Odds Ratio
PDF	Portable Document Format
PHQ-9	Gesundheitsbogen für Patienten - 9 Items
RCI	Reliable Change Index
RCT	randomized controlled trial
SCID-5-PD	Structured clinical interview for DSM-5 - personality disorders
SD	standard deviation
SF-12	Short Form (12) Gesundheitsfragebogen
SMS	Short Message Service
TAU	treatment-as-usual
WSAS	Work and Social Adjustment Scale

8. Ethics

This study was approved by the ethics committee of the Medical Faculty of the University Lübeck (reference number 22-012).

9. Investigators and administrative structure of clinical investigation

This clinical investigation was conducted as an online trial without a traditional physical investigation site.

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- role: patient recruitment, trial management, online-data acquisition, telephone interviews, provision of the software, examination and evaluation of reports with regard to adverse effects

10. References

[1] K. Lieb, M. C. Zanarini, C. Schmahl, M. M. Linehan, and M. Bohus, “Borderline personality disorder,” *The Lancet*, vol. 364, no. 9432, pp. 453–461, 2004, doi: 10.1016/S0140-6736(04)16770-6.

[2] F. Jacobi, R. Grafiadeli, H. Volkmann, and I. Schneider, “Krankheitslast der Borderline-Persönlichkeitsstörung: Krankheitskosten, somatische Komorbidität und Mortalität,” *Nervenarzt*, vol. 92, no. 7, pp. 660–669, 2021, doi: 10.1007/s00115-021-01139-4.

[3] M. ten Have *et al.*, “Prevalence rates of borderline personality disorder symptoms: a study based on the Netherlands Mental Health Survey and Incidence Study-2,” *BMC Psychiatry*, vol. 16, no. 1, p. 249, Dec. 2016, doi: 10.1186/s12888-016-0939-x.

[4] B. F. Grant *et al.*, “Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions,” *J. Clin. Psychiatry*, vol. 69, no. 4, p. 533, 2008.

[5] T. T. Juurlink, F. Lamers, H. J. F. van Marle, J. R. Anema, and A. T. F. Beekman, “The role of borderline personality disorder symptoms on absenteeism & work performance in the Netherlands Study of Depression and Anxiety (NESDA),” *BMC Psychiatry*, vol. 20, no. 1, p. 414, 2020, doi: 10.1186/s12888-020-02815-6.

[6] A. E. Tate *et al.*, “Borderline personality disorder: associations with psychiatric disorders, somatic illnesses, trauma, and adverse behaviors,” *Mol. Psychiatry*, vol. 27, no. 5, pp. 2514–2521, 2022.

[7] T. Wagner *et al.*, “The societal cost of treatment-seeking patients with borderline personality disorder in Germany,” *Eur. Arch. Psychiatry Clin. Neurosci.*, vol. 272, no. 4, pp. 741–752, 2022, doi: 10.1007/s00406-021-01332-1.

[8] C. Krauth, J. T. Stahmeyer, J. J. Petersen, A. Freytag, F. M. Gerlach, and J. Gensichen, “Resource utilisation and costs of depressive patients in Germany: results from the primary care monitoring for depressive patients trial,” *Depress. Res. Treat.*, vol. 2014, 2014.

[9] T. Wagner *et al.*, “Societal cost-of-illness in patients with borderline personality disorder one year before, during and after dialectical behavior therapy in routine outpatient care,” *Behav. Res. Ther.*, vol. 61, pp. 12–22, 2014, doi: 10.1016/j.brat.2014.07.004.

[10] D. Meuldijk, A. McCarthy, M. E. Bourke, and B. F. S. Grenyer, “The value of psychological treatment for borderline personality disorder: Systematic review and cost offset analysis of economic evaluations,” *PloS One*, vol. 12, no. 3, p. e0171592, 2017, doi: 10.1371/journal.pone.0171592.

[11] J. E. Young, J. S. Klosko, and M. E. Weishaar, *Schema therapy: A practitioner’s guide*. New York: Guilford Press, 2003.

[12] G. A. Jacob and A. Arntz, *Schematherapie in der Praxis. 2. Auflage.* Weinheim: Beltz, 2015.

[13] M. L. Hermens, P. T. van Splunteren, A. van den Bosch, and R. Verheul, “Barriers to implementing the clinical guideline on borderline personality disorder in the Netherlands,” *Psychiatr. Serv.*, vol. 62, no. 11, pp. 1381–1383, 2011.

[14] E. A. Iliakis, A. K. I. Sonley, G. S. Ilagan, and L. W. Choi-Kain, “Treatment of borderline personality disorder: is supply adequate to meet public health needs?,” *Psychiatr. Serv.*, vol. 70, no. 9, pp. 772–781, 2019, doi: 10.1176/appi.ps.201900073.

[15] S. Simonsen *et al.*, “European guidelines for personality disorders: past, present and future,” *Borderline Personal. Disord. Emot. Dysregulation*, vol. 6, no. 1, p. 9, 2019, doi: 10.1186/s40479-019-0106-3.

[16] DGPPN e.V., “S3-Leitlinie Borderline-Persönlichkeitsstörung.” Nov. 14, 2022. [Online]. Available: https://register.awmf.org/assets/guidelines/038-015l_S3_Borderline-Persoenlichkeitsst%C3%B6rungen_2022-11.pdf

[17] R. K. McHugh, S. W. Whitton, A. D. Peckham, J. A. Welge, and M. W. Otto, “Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review,”

J. Clin. Psychiatry, vol. 74, no. 6, pp. 595–602, 2013, doi: 10.4088/JCP.12r07757.
[18] A. Jobst, S. Hörz, A. Birkhofer, P. Martius, and M. Rentrop, “Einstellung von Psychotherapeuten gegenüber der Behandlung von Patienten mit Borderline Persönlichkeitsstörung,” *Psychother. Psychosom. Med. Psychol.*, vol. 60, no. 3–4, pp. 126–131, 2010, doi: 10.1055/s-0029-1220764.
[19] P. Tusiani-Eng and F. Yeomans, “Borderline personality disorder: barriers to borderline personality disorder treatment and opportunities for advocacy,” *Psychiatr. Clin.*, vol. 41, no. 4, pp. 695–709, 2018, doi: 10.1016/j.psc.2018.07.006.
[20] K. M. Carroll and B. J. Rounsaville, “Computer-assisted Therapy in Psychiatry: Be Brave—It’s a New World,” *Curr. Psychiatry Rep.*, vol. 12, no. 5, pp. 426–432, 2010, doi: 10.1007/s11920-010-0146-2.
[21] E. Faßbinder, A. Hauer, A. Schaich, U. Schweiger, G. A. Jacob, and A. Arntz, “Integration of e-health tools into face-to-face psychotherapy for borderline personality disorder: a chance to close the gap between demand and supply?,” *J. Clin. Psychol.*, vol. 71, no. 8, pp. 764–777, 2015, doi: 10.1002/jclp.22204.
[22] S. L. Rizvi, C. D. Hughes, and M. C. Thomas, “The DBT Coach mobile application as an adjunct to treatment for suicidal and self-injuring individuals with borderline personality disorder: A preliminary evaluation and challenges to client utilization.,” *Psychol. Serv.*, vol. 13, no. 4, pp. 380–388, 2016, doi: 10.1037/ser0000100.
[23] M. Ballerstein and G. A. Jacob, “Einsatz und Wirksamkeit von Digitalen Gesundheitsanwendungen in der Patientenversorgung,” *PSYCH Up2date*, vol. 16, no. 04, pp. 278–283, 2022, doi: 10.1055/a-1684-6199.
[24] J. Klein *et al.*, “Effectiveness and safety of the adjunctive use of an internet-based self-management intervention for borderline personality disorder in addition to care as usual: results from a randomised controlled trial,” *BMJ Open*, vol. 11, p. e047771, Sep. 2021, doi: 10.1136/bmjopen-2020-047771.
[25] G. A. Jacob *et al.*, “A schema therapy–based ehealth program for patients with borderline personality disorder (priovi): naturalistic single-arm observational study,” *JMIR Ment. Health*, vol. 5, no. 4, p. e10983, 2018, doi: 10.2196/10983.
[26] M. Bohus *et al.*, “The short version of the Borderline Symptom List (BSL-23): development and initial data on psychometric properties,” *Psychopathology*, vol. 42, no. 1, pp. 32–39, 2009, doi: 10.1159/000173701.
[27] N. S. Jacobson and P. Truax, “Clinical significance: a statistical approach to defining meaningful change in psychotherapy research,” *J. Consult. Clin. Psychol.*, vol. 59, no. 1, pp. 12–19, 1991, doi: 10.1037//0022-006x.59.1.12.
[28] N. Kleindienst, M. Jungkunz, and M. Bohus, “A proposed severity classification of borderline symptoms using the borderline symptom list (BSL-23),” *Borderline Personal. Disord. Emot. Dysregulation*, vol. 7, p. 11, 2020, doi: 10.1186/s40479-020-00126-6.
[29] P. Hagell, A. Westergren, and K. Årestedt, “Beware of the origin of numbers: Standard scoring of the SF-12 and SF-36 summary measures distorts measurement and score interpretations,” *Res. Nurs. Health*, vol. 40, no. 4, pp. 378–386, 2017, doi: 10.1002/nur.21806.
[30] B. Löwe, J. Unützer, C. M. Callahan, A. J. Perkins, and K. Kroenke, “Monitoring depression treatment outcomes with the Patient Health Questionnaire-9,” *Med. Care*, vol. 42, no. 12, pp. 1194–1201, 2004, doi: 10.1097/00005650-200412000-00006.
[31] B. Löwe, K. Kroenke, W. Herzog, and K. Gräfe, “Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9),” *J. Affect. Disord.*, vol. 81, no. 1, pp. 61–66, 2004, doi: 10.1016/S0165-0327(03)00198-8.
[32] A. Martin, W. Rief, A. Klaiberg, and E. Braehler, “Validity of the Brief Patient Health Questionnaire Mood Scale (PHQ-9) in the general population,” *Gen. Hosp. Psychiatry*, vol. 28, no. 1, pp. 71–77, 2006, doi: 10.1016/j.genhosppsych.2005.07.003.
[33] B. Löwe *et al.*, “Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population,” *Med. Care*, vol. 46, no. 3, pp. 266–274, 2008, doi:

10.1097/MLR.0b013e318160d093.
[34] S. Kertz, J. Bigda-Peyton, and T. Bjorgvinsson, “Validity of the Generalized Anxiety Disorder-7 Scale in an acute psychiatric sample,” *Clin. Psychol. Psychother.*, vol. 20, no. 5, pp. 456–464, 2013, doi: 10.1002/cpp.1802.
[35] A. Heissel, J. Bollmann, M. Kangas, K. Abdulla, M. Rapp, and A. Sanchez, “Validation of the German version of the work and social adjustment scale in a sample of depressed patients,” *BMC Health Serv. Res.*, vol. 21, no. 1, p. 593, 2021, doi: 10.1186/s12913-021-06622-x.
[36] R Core Team, “R: A language and environment for statistical computing.” Vienna, Austria, 2022. [Online]. Available: https://cran.r-project.org/
[37] K. F. Schulz, D. G. Altman, D. Moher, and CONSORT Group, “CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials,” *BMJ*, vol. 340, p. c332, Mar. 2010, doi: 10.1136/bmj.c332.
[38] G. Eysenbach and CONSORT-EHEALTH Group, “CONSORT-EHEALTH: improving and standardizing evaluation reports of Web-based and mobile health interventions,” *J. Med. Internet Res.*, vol. 13, no. 4, p. e126, 2011, doi: 10.2196/jmir.1923.
[39] S. van Buuren and K. Groothuis-Oudshoorn, “mice: Multivariate Imputation by Chained Equations in R,” *J. Stat. Softw.*, vol. 045, no. i03, 2011, doi: 10.18637/jss.v045.i03.
[40] P. Hayati Rezvan, K. J. Lee, and J. A. Simpson, “The rise of multiple imputation: a review of the reporting and implementation of the method in medical research,” *BMC Med. Res. Methodol.*, vol. 15, no. 1, p. 30, Apr. 2015, doi: 10.1186/s12874-015-0022-1.
[41] J. R. Carpenter, J. H. Roger, and M. G. Kenward, “Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation,” *J. Biopharm. Stat.*, vol. 23, no. 6, pp. 1352–1371, 2013, doi: 10.1080/10543406.2013.834911.
[42] S. Cro, T. P. Morris, M. G. Kenward, and J. R. Carpenter, “Reference-based sensitivity analysis via multiple imputation for longitudinal trials with protocol deviation,” *Stata J.*, vol. 16, no. 2, pp. 443–463, 2016, doi: 10.1177/1536867X16016002.
[43] T. Keiningham, L. Aksoy, B. Cooil, T. Andreassen, and L. Williams, “A holistic examination of Net Promoter,” *J. Database Mark. Cust. Strategy Manag.*, vol. 15, pp. 79–90, 2008, doi: 10.1057/dbm.2008.4.
[44] O. J. Storebø *et al.*, “Psychological therapies for people with borderline personality disorder,” *Cochrane Database Syst. Rev.*, no. 5, 2020.
[45] M. Oud, A. Arntz, M. L. Hermens, R. Verhoef, and T. Kendall, “Specialized psychotherapies for adults with borderline personality disorder: A systematic review and meta-analysis,” *Aust. N. Z. J. Psychiatry*, vol. 52, no. 10, pp. 949–961, Oct. 2018, doi: 10.1177/0004867418791257.
[46] K. Setkowski *et al.*, “Which psychotherapy is most effective and acceptable in the treatment of adults with a (sub)clinical borderline personality disorder? A systematic review and network meta-analysis,” *Psychol. Med.*, vol. 53, no. 8, pp. 3261–3280, Jun. 2023, doi: 10.1017/S0033291723000685.
[47] C. Stiglmayr and H. Gunia, *Dialektisch-Behaviorale Therapie (DBT) zur Behandlung der Borderline-Persönlichkeitsstörung: Ein Manual für die ambulante Therapie*. Hogrefe Verlag, 2016.
[48] I. A. Cristea, C. Gentili, C. D. Cotet, D. Palomba, C. Barbui, and P. Cuijpers, “Efficacy of Psychotherapies for Borderline Personality Disorder: A Systematic Review and Meta-analysis,” *JAMA Psychiatry*, vol. 74, no. 4, pp. 319–328, Apr. 2017, doi: 10.1001/jamapsychiatry.2016.4287.
[49] J. M. Stoffers-Winterling *et al.*, “Pharmacological interventions for people with borderline personality disorder,” *Cochrane Database Syst. Rev.*, Feb. 2018, doi: 10.1002/14651858.CD012956.
[50] G. Gartlehner *et al.*, “Pharmacological treatments for borderline personality disorder: a systematic review and meta-analysis,” *CNS Drugs*, vol. 35, no. 10, pp. 1053–1067, 2021, doi:

10.1007/s40263-021-00855-4.
[51] J. M. Stoffers-Winterling *et al.*, “Psychotherapies for borderline personality disorder: a focused systematic review and meta-analysis,” *Br. J. Psychiatry*, pp. 1–15, 2022.
[52] J. Stoffers, B. A. Völlm, G. Rücker, A. Timmer, N. Huband, and K. Lieb, “Pharmacological interventions for borderline personality disorder,” *Cochrane Database Syst. Rev.*, no. 6, 2010, doi: 10.1002/14651858.CD005653.pub2.
[53] F. Chakhssi, J. M. Zoet, J. M. Oostendorp, M. L. Noordzij, and M. Sommers-Spijkerman, “Effect of psychotherapy for borderline personality disorder on quality of life: a systematic review and meta-analysis,” *J. Personal. Disord.*, vol. 35, no. 2, pp. 255–269, Apr. 2021, doi: 10.1521/pedi_2019_33_439.
[54] M. J. Crawford *et al.*, “The Clinical Effectiveness and Cost-Effectiveness of Lamotrigine in Borderline Personality Disorder: A Randomized Placebo-Controlled Trial,” *Am. J. Psychiatry*, vol. 175, no. 8, pp. 756–764, Aug. 2018, doi: 10.1176/appi.ajp.2018.17091006.
[55] K. I. Howard, R. J. Lueger, M. S. Maling, and Z. Martinovich, “A phase model of psychotherapy outcome: Causal mediation of change,” *J. Consult. Clin. Psychol.*, vol. 61, no. 4, pp. 678–685, 1993, doi: 10.1037/0022-006X.61.4.678.
[56] R. Bridler *et al.*, “Psychopharmacological treatment of 2195 in-patients with borderline personality disorder: A comparison with other psychiatric disorders,” *Eur. Neuropsychopharmacol.*, vol. 25, no. 6, pp. 763–772, Jun. 2015, doi: 10.1016/j.euroneuro.2015.03.017.
[57] M. Barkham *et al.*, “Dose-effect relations and responsive regulation of treatment duration: the good enough level,” *J. Consult. Clin. Psychol.*, vol. 74, no. 1, pp. 160–167, Feb. 2006, doi: 10.1037/0022-006X.74.1.160.
[58] J. J. Owen, J. Adelson, S. Budge, S. M. Kopta, and R. J. Reese, “Good-enough level and dose-effect models: Variation among outcomes and therapists,” *Psychother. Res. J. Soc. Psychother. Res.*, vol. 26, no. 1, pp. 22–30, 2016, doi: 10.1080/10503307.2014.966346.
[59] K. Lawler, C. Earley, L. Timulak, A. Enrique, and D. Richards, “Dropout From an Internet-Delivered Cognitive Behavioral Therapy Intervention for Adults With Depression and Anxiety: Qualitative Study,” *JMIR Form. Res.*, vol. 5, no. 11, p. e26221, Nov. 2021, doi: 10.2196/26221.
[60] P. Dehlbom *et al.*, “Gender differences in the treatment of patients with borderline personality disorder,” *Personal. Disord. Theory Res. Treat.*, vol. 13, no. 3, pp. 277–287, 2022, doi: 10.1037/per0000507.
[61] A. E. Skodol and D. S. Bender, “Why are women diagnosed borderline more than men?,” *Psychiatr. Q.*, vol. 74, pp. 349–360, 2003.