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ORIGINAL RESEARCH ARTICLE

Effectiveness and Tolerability of Vortioxetine Oral Drops Versus Oral Tablets in Major Depressive Disorder: An Analysis of a Real-World Cohort Study in Switzerland

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Abstract

Background The efficacy and tolerability of vortioxetine tablets for depression is established, but prospective data for the oral drop formulation were unavailable. This analysis compared the effectiveness, tolerability and dosing patterns of vortioxetine tablet and drop formulations for the treatment of major depressive episodes in Swiss real-world practice.

Methods A *post hoc* analysis of a prospective, non-interventional study in adults experiencing a major depressive episode (MDE) was conducted. Depression symptoms, functioning, dosing patterns and tolerability were assessed using unanchored Montgomery–Åsberg Depression Rating Scale items, the Clinical Global Impression-Severity (CGI-S) scale, a four-point functioning scale, and incidence of adverse drug reactions (ADRs). Statistical tests included two-sample *t*-tests, Fisher's exact test, Chi-square test and general linear modelling.

Results Of 225 patients, 60 (26.7%) initiated drops. Drops were more often prescribed for first MDE than tablets (65.0% [$n=39$] versus 46.1% [$n=76$]; $p=0.012$) and shorter MDE duration at baseline (2.9 versus 4.8 months; $p=0.02$). Mean CGI-S baseline scores were similar (drops: 5.0; tablets: 4.8). Both formulations improved depressive symptoms and functioning similarly. Drops were used in lower initial doses (4.2 mg/day) versus tablets (7.7 mg/day) ($p<0.001$) but in higher doses (> 10 mg/day) earlier during treatment (35% versus 13%, day 15). 'No or little effect' was significantly less frequent with drops (5.0%; $n=3$) versus tablets (23.6%; $n=39$) ($p<0.001$). ADR-related discontinuations were comparable (drops: 3.3%; tablets: 4.2%).

Conclusions This real-world analysis suggests that vortioxetine drops provide comparable control of depressive symptoms to tablets. The greater capacity for dose individualisation may be beneficial to patients.

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1 Introduction

Globally, major depressive disorder (MDD) is a significant contributor to the burden of disease, and depressive disorders affect approximately 280 million people according to 2019 estimates [1]. In addition to depressive symptoms, MDD is associated with cognitive impairment and impairment of everyday functioning, which may reduce workplace productivity, social functioning and overall quality of life [2–4]. Treatment with antidepressants is typically focussed on relieving mood symptoms, though the restoration of everyday functioning and the improvement of quality of life are also important considerations for the management of MDD [5, 6].

While tablets are the most common formulation of antidepressants, many patients with MDD report difficulty

Key Points

The severity of depressive symptoms decreased to a similar extent over approximately 8 weeks in patients who initiated vortioxetine tablets or oral drops, for the treatment of a major depressive episode in routine Swiss clinical practice.

Patients who initiated treatment with oral drops tended to increase the dose of vortioxetine earlier in the course of treatment. For these patients, significantly less drug ineffectiveness was reported.

Both formulations of vortioxetine were well tolerated by most patients, but greater control of dosing and titration with the drop formulation could be particularly beneficial for patients who are more susceptible to adverse events or reluctant to use antidepressant medication. Flexible, individualised dosing may contribute to perceived effectiveness of the medication. Furthermore, greater control of dosing by using an oral drop formulation has the potential to alleviate patient anxiety towards treatment.

swallowing pills, which can impact treatment adherence and effectiveness [7]. Lower acceptance and adherence to treatment can reduce effectiveness and lead to an increase of depression severity [7, 8]. Consequently, the availability of antidepressant formulations other than tablets may be of value to patients with depression [7].

Vortioxetine is an antidepressant with multimodal activity in the central nervous system [9–11], which is approved for the treatment of major depressive episodes in adults [11, 12]. The tablet formulation of vortioxetine is produced in four strengths: 5, 10, 15 and 20 mg [12]. The oral drop formulation of vortioxetine is also authorised in multiple countries, including those in the European Economic Area and Switzerland [12–14]. Each drop of oral solution contains 1 mg of vortioxetine [12, 14]. The bioequivalence of the tablet and drop formulations of vortioxetine has been demonstrated in healthy volunteers [13], and the multimodal activity of vortioxetine may expand its clinical profile in a dose-dependent manner [15], highlighting the potential utility of multiple formulations being available for vortioxetine. In addition, vortioxetine may be beneficial to patients with depression and comorbidities such as dementia [16], Alzheimer's disease [17], cardiovascular disease or diabetes [18], Parkinson's disease [19, 20] and some patients with bipolar depression [21]. Co-administration of vortioxetine with other drugs has been shown to be well tolerated, with few requirements for dose adjustment based on pharmacokinetic profiles [22], and the risk of withdrawal symptoms following discontinuation is low irrespective of dose [23, 24].

The efficacy, safety and tolerability of vortioxetine tablets for the treatment of MDD have been demonstrated in numerous short-term placebo- and active-controlled clinical trials [25–33], and in long-term open-label extension studies [24, 34]. Vortioxetine has also been associated with improvements in cognition and overall functioning [12, 35–38]. In addition to findings from controlled clinical trials, the effectiveness and tolerability of vortioxetine tablets in routine clinical practice have been established in various countries, with improvements observed in depressive symptoms, overall functioning, cognitive performance and health-related quality of life [39–41]. However, whilst the tablet formulation of vortioxetine is widely documented in literature, clinical data for the oral drop formulation for the treatment of MDD have been limited. To date, a small retrospective study conducted at a single centre in Italy has shown potential benefits of the drop formulation in patients with depression [42], but prospective data are needed.

A prospective, non-interventional cohort study was conducted to evaluate the effectiveness and tolerability of vortioxetine for the treatment of MDD in real-world practice in Switzerland. The full results of this study will be published elsewhere. The *post hoc* analysis presented here is the first prospective study to provide clinical data for the oral drop formulation of vortioxetine in patients with depression. This analysis aimed to compare the effectiveness and tolerability, dosing patterns and the characteristics of patients who initiated oral tablet versus oral drop formulation of vortioxetine for the treatment of major depressive episodes in Swiss clinical practice.

2 Methods

2.1 Study Design and Patient Population

This is a *post hoc* analysis of a prospective, non-interventional, uncontrolled, multicentre, real-world cohort study that evaluated the effectiveness and tolerability of vortioxetine (Brintellix®; manufactured by H. Lundbeck A/S) for the treatment of major depressive episodes in Swiss clinical practice.

Adult outpatients who were currently experiencing a major depressive episode and who were already scheduled to initiate treatment with vortioxetine (oral tablets or drops) were identified by their psychiatrist for inclusion in the study. Four study visits were scheduled during an observation period lasting approximately 8 weeks for each patient beginning from the initiation of vortioxetine: Visit 1 (baseline and treatment initiation), Visit

2 (approximately 2–3 weeks/15–22 days post baseline), Visit 3 (approximately 4–6 weeks/29–43 days post baseline) and Visit 4 (8 weeks/57 days post baseline) according to usual clinical practice. At each visit, patients were reviewed by their clinician who recorded assessment data on case report forms and adverse drug reaction (ADR) report forms.

Eligible patients were recruited for, and participated in, the study between 16 September 2019 and 30 September 2021. Adults aged ≥ 18 years who were receiving treatment as an outpatient in accordance with the summary of product characteristics (SmPC) for vortioxetine and were, currently, experiencing a major depressive episode were eligible for inclusion. Moreover, the decision to initiate treatment with vortioxetine (tablets or drops) must have been made at the discretion of the treating clinician, independent of inclusion in the study. Patients who were already receiving treatment with vortioxetine for the current depressive episode, had any contraindication to treatment with vortioxetine according to the SmPC, were a study staff member, or related to, or dependent on, the study staff, had previously been included in the study or were, currently, participating in an interventional study, were excluded.

On 2 April 2017, the Ethics Committee of the Canton of Zurich confirmed that the protocol for the real-world cohort study did not require specific ethics approval owing to its purely observational nature. As treating physicians had decided on treatment independently of the study and prior to inclusion, the study was not considered to fall under the definition of research in humans according to Swiss regulations. With the exception that this study was not registered (owing to its purely observational nature), this study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All patients provided written informed consent prior to participation in the study.

2.2 Endpoints

Demographic and clinical characteristics were recorded at baseline (Visit 1). Effectiveness endpoints included the sum of the unanchored Montgomery–Åsberg Depression Rating Scale (MADRS) item scores at baseline and at each study visit and the change in the sum of the unanchored MADRS items from baseline to each study visit. The MADRS is a clinician-rated scale used to determine the severity of ten depressive symptoms [43]. To reflect clinical practice in Switzerland, MADRS items were unanchored for this observation. This meant that items were scored on a simplified 7-point scale according to the severity of each symptom (0, none; 1, almost none; 2, mild; 3, moderate; 4, marked; 5, intense; 6, extreme) and did not use the anchors specified in the original MADRS. Mild depression was defined as a sum of the unanchored MADRS item scores of < 20, moderate as ≥ 20–29, and severe as ≥ 30; the maximum possible score was 60. The change in individual MADRS item scores from baseline to Visit 4 (approximately 8 weeks), and the MADRS response rate (proportion of patients with a ≥ 50% reduction in the sum of the unanchored MADRS items) and remission rate (proportion of patients with a sum of the unanchored MADRS items ≤ 10) at Visit 4 (approximately 8 weeks) were also assessed. The severity of depressive symptoms was also assessed at each visit using the Clinical Global Impression–Severity (CGI-S) scale.

Impairment of everyday functioning due to depression was assessed by clinicians at each visit across six domains: cognition, professional activities, family life, social and leisure activities, physical well-being and quality of life. The level of impairment was rated on a 4-point scale (none, mild, moderate, or severe). Clinician- and patient-rated assessment of efficacy at the end of observation was also assessed and was reported on a 4-point scale (very good, good, moderate or sufficient and inadequate or insufficient).

Dosing pattern analyses included the mean dose of vortioxetine received at treatment initiation and the mean prescribed dose of vortioxetine on each day of treatment, from baseline to Visit 4 (approximately 8 weeks). The proportions of patients receiving vortioxetine within specific dose ranges (≤ 5; > 5– ≤ 10; > 10– ≤ 15; > 15 mg/day) at each week, from baseline to Visit 4 were also reported.

The tolerability of vortioxetine was assessed by the incidence of ADRs, defined as adverse events for which a causal connection with the study drug cannot be ruled out, and defined special notifiable cases and reported via ADR report forms. The special notifiable cases to be reported were as follows: no or little effect; use in an unapproved indication (off-label use); overdose, misuse or abuse; drug interactions; use in paediatric patients; use during pregnancy or breastfeeding; incorrect use; occupational or accidental exposure; withdrawal symptoms; transmission of infectious diseases; unexpected positive effect; and transfer of the medicinal product via semen. Tolerability was also assessed by clinicians and patients at the end of observation using a 4-point scale (very good, good, moderate or sufficient and inadequate or insufficient).

2.3 Statistical Analysis

Baseline demographics and clinical characteristics, effectiveness outcomes, dosing patterns and tolerability outcomes were reported using descriptive statistics: mean (standard deviation [SD]) for continuous variables and numbers and percentages for categorical and binary variables.

All endpoints were compared between the group of patients who initiated vortioxetine oral tablets and the group who initiated oral drops. Results are presented according to the vortioxetine formulation (tablets or drops) reported at initiation of treatment regardless of possible subsequent formulation changes during the observation period, which were not known. Comparisons of baseline demographic and clinical characteristics were conducted using two-sample *t*-tests, chi-square tests or Fisher's exact tests. Changes from baseline to Visit 4 in the sum of the unanchored MADRS items, in the individual unanchored MADRS items, and in the severity of impairment of everyday functioning were compared between the tablet and drop groups using a general linear model with formulation (tablets or drops) and baseline value as variables. MADRS response and remission rates, and the incidence of ADRs/special notifiable cases were compared between the tablet and drop groups using a Fisher's exact test. A two-sample *t*-test was used to compare mean doses at treatment initiation between the tablet and drop groups and the sum of the unanchored MADRS items at each visit.

A p-value of < 0.05 was considered statistically significant. Missing data were handled using a mixed model for repeated measures for changes from baseline to Visit 4 in the sum of the unanchored MADRS items, individual MADRS items and impairment of functioning. For MADRS response and remission rates, missing data were imputed using last observation carried forward (LOCF), and an observed case method was used for the sum of the unanchored MADRS items at each visit. Data processing and statistical analysis were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 Results

3.1 Patients

A total of 226 patients initiated treatment with vortioxetine across 40 centres in Switzerland and were enrolled in the cohort study. Of the 225 patients for whom the formulation of vortioxetine was known, 165 (73.3%) initiated treatment with oral tablets and 60 (26.7%) initiated treatment with oral drops. Overall, 149 (90.3%) patients who initiated tablets and 53 (88.3%) patients who initiated drops completed approximately 8 weeks of treatment with vortioxetine. The mean (SD) duration of the observation period was 10.1 (5.5) weeks, with a median of 9 weeks.

Among patients who initiated tablets, reasons for not completing the observation period comprised ADRs ($n = 7$), non-adherence ($n = 5$), inadequate efficacy ($n = 2$) and hospitalisation, new workplace, patient decision and other/not specified (all $n = 1$). For the patients who initiated drops, reasons for not completing the observation period comprised patient decision ($n = 3$); ADRs, and therapy objectives achieved (both $n = 2$); and inadequate efficacy, and non-adherence (both $n = 1$). Treatment with vortioxetine was continued beyond the observation period of approximately 8 weeks for 141 (85.5%) patients who initiated tablets and for 53 (88.3%) patients who initiated drops. Baseline demographics and clinical characteristics for the study population are summarised in Table 1.

At baseline, patients who initiated drops had generally experienced depressive episodes with a shorter mean duration than patients who initiated tablets ($p = 0.016$) (Table 1). Moreover, a significantly higher proportion of patients who initiated drops (65.0%; $n = 39$) were experiencing their first major depressive episode than patients who initiated tablets (46.1%; $n = 76$) ($p = 0.012$). A numerically, but not statistically significantly, higher proportion of patients who initiated drops were considered to have severe depression according to clinical judgement (41.7%; $n = 25$) than patients who initiated tablets (26.7%; $n = 44$) (Table 1). At baseline, the mean sum of the unanchored MADRS items was comparable between patients who initiated drops (34.8 points) and for patients who initiated tablets (34.0 points) and was indicative of severe depression (≥ 30 points; Table 1). This was corroborated by mean CGI-S scores of 5.0 and 4.8 for oral drops and tablets, respectively, indicating marked illness (Table 1) [44].

3.2 Effectiveness

The severity of depression, as indicated by the mean sum of the unanchored MADRS items, decreased during the observation period in patients who initiated tablets and in patients who initiated drops (Fig. 1). The mean (SD) decreases in the sum of the unanchored MADRS items from baseline to Visit 4 did not differ significantly between the two formulations: 21.9 (10.0) with tablets and 22.7 (7.9) with drops. The mean scores for each of the ten individual unanchored MADRS items decreased from baseline to Visit 4 to a similar extent with the drop and tablet formulations (Table S1).

At Visit 4, the response rate was numerically, but not statistically significantly, higher in patients who initiated drops (80.0%; $n = 48$) than in those who initiated tablets (69.3%; $n = 113$) (Fig. 2). Remission rates at Visit 4 were similar in patients who initiated tablets (44.2%; $n = 72$) and in those who initiated drops (38.3%; $n = 23$) (Fig. 2).

With the tablet and drop formulations, the severity of impairment of everyday functioning decreased from baseline to Visit 4 across all six domains: impairment was most commonly rated as severe or moderate at baseline, and mild or none at Visit 4 (Fig. 3). At Visit 4, no patient who initiated the drop formulation had severe impairment in any of the six domains of functioning. No significant differences in severity of impairment were observed between the formulations.

Table 1 Baseline demographics and clinical characteristics by formulation initiated

	Vortioxetine formulation at treatment initiation		*p*-value
	Oral tablets ($n=165$)	Oral drops ($n=60$)	
Demographics			
Mean (SD) age at treatment initiation, years	43.4 (13.6)	43.0 (13.4)	0.848[a]
Female, *n* (%)	94 (57.0)	31 (51.7)	0.479[b]
Clinical characteristics			
Previous depressive episodes			
At least one previous depressive episode, *n* (%)	89 (53.9)	21 (35.0)	0.012[b]
Mean (SD) number of previous depressive episodes	3.4 (4.3) [$n=87$]	3.5 (3.4) [$n=20$]	0.960[a]
Mean (SD) age at first depressive episode, years	29.4 (12.2) [$n=88$]	23.6 (12.6) [$n=20$]	0.057[a]
Current depressive episode			
Mean (SD) duration of current depressive episode, weeks	21.1 (33.3) [$n=164$]	12.7 (17.8)	0.016[a]
Mean (SD) sum of the unanchored MADRS items	34.0 (9.3)	34.8 (7.6)	0.555[a]
Mean (SD) CGI-S score	4.8 (0.8)	5.0 (0.9)	0.259[a]
Severity of current depressive episode according to clinical judgement, *n* (%)			
Mild	6 (3.6)	2 (3.3)	0.092[c]
Moderate	115 (69.7)	33 (55.0)	
Severe	44 (26.7)	25 (41.7)	
Comorbid conditions[d]			
At least one comorbid condition, *n* (%)	58 (35.2)	13 (21.7)	0.054[b]

N values represent the number of patients who initiated treatment with vortioxetine

ADHD attention deficit hyperactivity disorder, *CGI-S* Clinical Global Impression–Severity, *MADRS* Montgomery–Åsberg Depression Rating Scale, *SD* standard deviation.

[a]Two-sample *t*-test

[b]Chi-square test

[c]Fisher's exact test

[d]The most frequently reported comorbidities (occurring in ≥1% of all 226 enrolled patients) were overweight ($n=14$), hypertension ($n=13$), diabetes mellitus ($n=7$), ADHD ($n=5$) and hypothyroidism and migraines (both $n=3$)

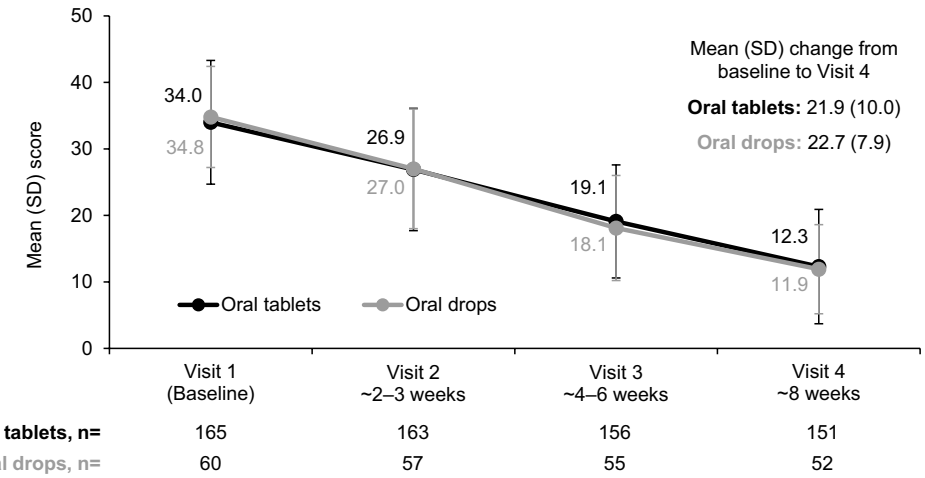

Fig. 1 Sum of the unanchored MADRS items during the observation period by formulation initiated. *SD* standard deviation

According to clinician and patient assessments at the end of observation, tablet and drop formulations of vortioxetine had comparable efficacy (Fig. S1). Clinicians rated the efficacy of vortioxetine as very good or good for 89.5% ($n=145/162$) of patients who initiated treatment with tablets, and for 93.3% ($n=56/60$) who initiated drops. Similarly, 87.7% ($n=142/162$) of patients who initiated treatment

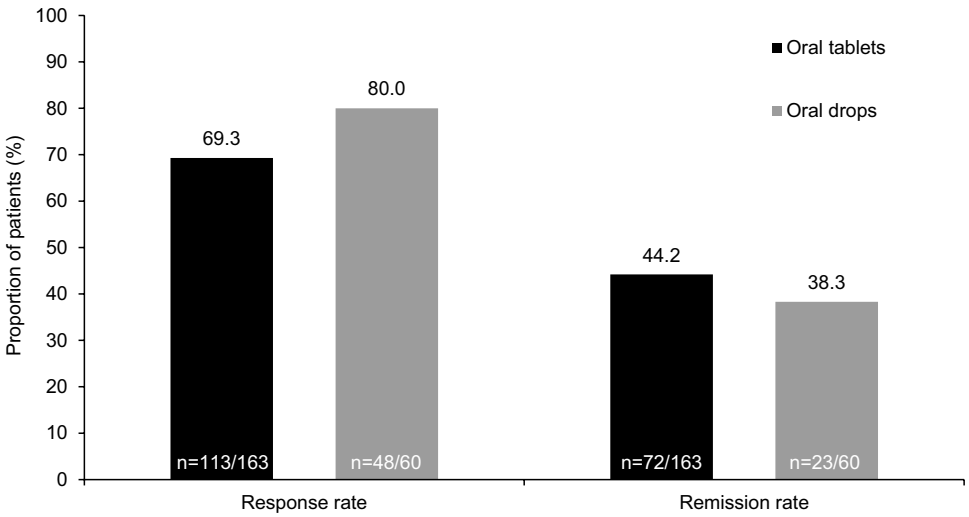

Fig. 2 Response and remission rates according to the sum of the unanchored MADRS items at Visit 4 (approximately 8 weeks), by formulation initiated. *N*-values determined using LOCF. Response was defined as a ≥ 50% reduction in the sum of the unanchored MADRS items from baseline to Visit 4 (approximately 8 weeks); remission was defined as a sum of the unanchored MADRS items ≤ 10 at Visit 4 (approximately 8 weeks). *LOCF* last observation carried forward, *MADRS* Montgomery–Åsberg Depression Rating Scale

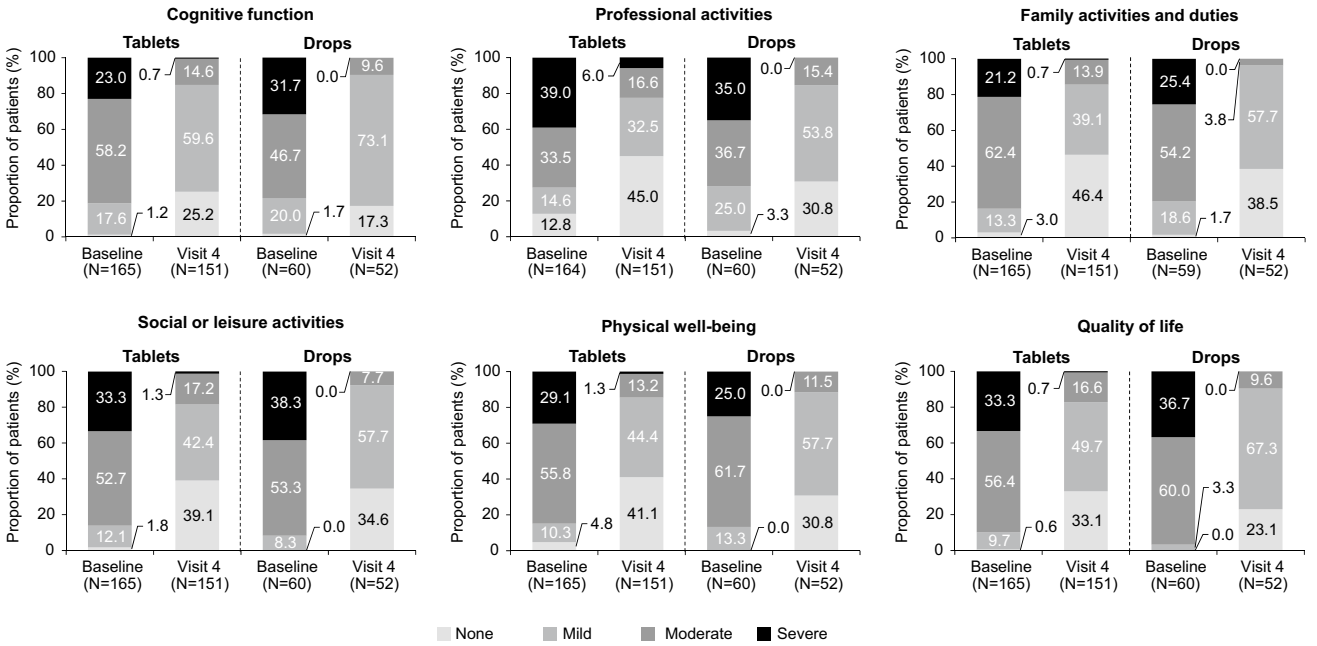

Fig. 3 Clinician-rated severity of impairment of everyday functioning at baseline and Visit 4 (approximately 8 weeks), by formulation initiated

with tablets and 91.7% ($n = 55/60$) of patients who initiated drops rated the efficacy as very good or good.

3.3 Dosing Patterns

The mean (SD) dose of vortioxetine at treatment initiation was significantly lower among patients who initiated drops (4.2 [2.2] mg/day) than those who initiated tablets (7.7 [3.2] mg/day) ($p < 0.001$). From Day 8 onwards (start of Week 2), the mean dose was similar in the two groups. At Day 57 (after 8 weeks of treatment), the mean (SD) dose of vortioxetine was 13.5 (5.2) mg/day in patients who initiated drops and 12.7 (4.5) mg/day in patients who initiated tablets. The median dose of vortioxetine remained at 10 mg/day throughout the study for patients who initiated tablets, whereas for patients who initiated drops the median dose increased from 5 mg/day at treatment initiation to 10 mg/day between Day 8 (start of Week 2) and Day 29 (start of Week 5). From Day 36 (start of Week 6) onwards, the median dose was 15 mg/day until the end of observation.

The distribution of patients across vortioxetine dose ranges varied during the observation period. A higher proportion of patients who initiated drops were receiving a dose of ≤ 5 mg/day (93.3%; $n = 56/60$), compared with patients

who initiated tablets (49.1%; $n=81/165$). However, patients who initiated treatment with drops tended to receive higher doses (> 10 mg/day) earlier in the observation period than patients who initiated treatment with tablets (Fig. 4).

From Day 8 (start of Week 2) onwards, a higher proportion of patients who initiated drops than tablets were receiving a dose > 10 mg/day. At Day 8, 4.9% ($n=8/164$) of patients who initiated tablets received a dose > 10 mg/day versus 26.7% ($n=16/60$) of patients who initiated drops (Table S2). At Day 15 (start of Week 3), 13.0% ($n=21/161$) of patients who initiated tablets were prescribed a dose > 1 mg/day versus 35.0% ($n=21/60$) of patients who initiated drops. After 8 weeks of treatment (Day 57), the proportion of patients receiving doses of > 10 mg/day had further increased with the two formulations to 32.6% ($n=42/129$) of patients who initiated tablets and 62.5% ($n=25/40$) of patients who initiated drops. Conversely, a higher proportion of patients who initiated drops were receiving a dose of ≤ 5 mg/day, after 8 weeks of treatment (12.5%; $n=5/40$) than patients who initiated tablets (3.1%; $n=4/129$).

3.4 Safety and Tolerability

The incidence of ADRs (defined as adverse events for which a causal connection with the study drug cannot be ruled out) and special notifiable cases was significantly lower among patients who initiated treatment with drops than patients who initiated tablets ($p<0.001$) (Table 2). The special notifiable case 'no or little effect' was the most common event reported during the observation period and was significantly less frequent with drops (5.0%; $n=3$) versus tablets (23.6%; $n=39$) ($p<0.001$). When analysing the incidence of ADRs without special notifiable cases, there was no difference between patients who initiated treatment with drops and patients who initiated with tablets ($p=0.602$). A total of 7 (11.7%) patients who initiated drops and 16 (9.7%) patients who initiated tablets prematurely ended treatment. The most common reasons (≥ 3%) were patient's wish ($n=3$; 5.0%), ADRs ($n=2$; 3.3%) and objective of the therapy achieved, i.e. sufficient improvement in condition, ($n=2$; 3.3%) among patients initiating drops, and ADRs ($n=7$; 4.2%) and lost to follow-up ($n=5$; 3.0%) among patients initiating tablets.

According to subjective clinician and patient assessments, the overall tolerability of vortioxetine was generally similar among patients, irrespective of whether they initiated treatment with the tablet or drop formulations (Fig. S2). Clinicians rated the tolerability of vortioxetine as very good or good for 90.8% ($n=148/163$) of patients who initiated tablets, and for 95.0% ($n=57/60$) who initiated drops. Similarly, 90.8% ($n=148/163$) of patients who initiated tablets and 93.3% ($n=56/60$) of patients who initiated drops considered the tolerability very good or good.

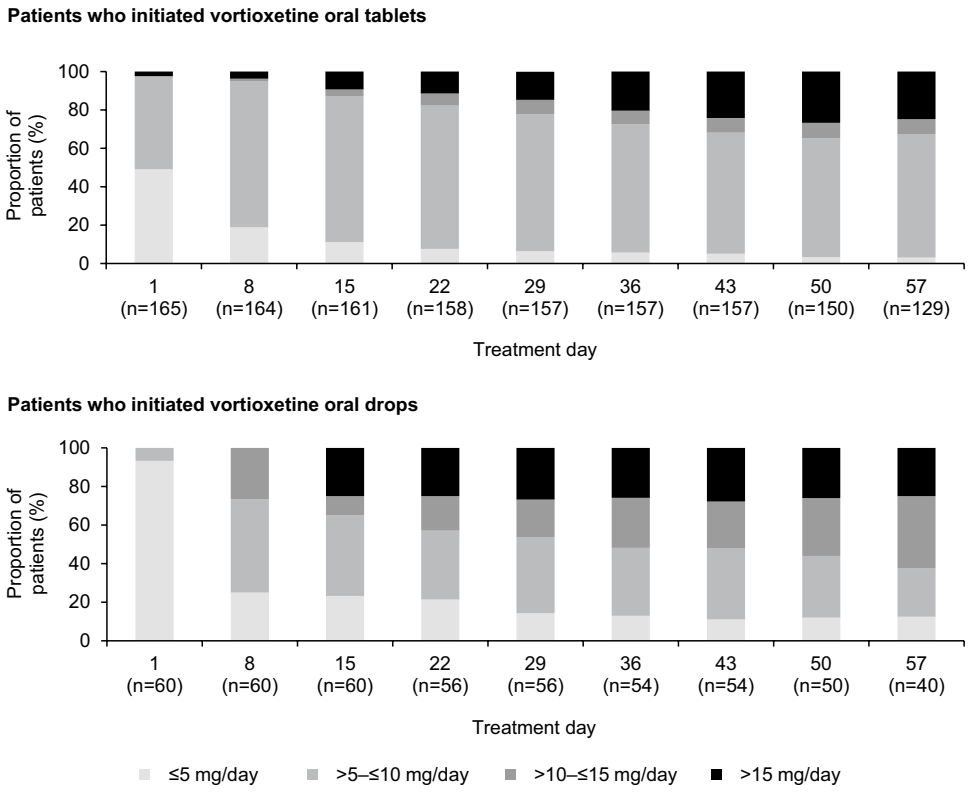

Fig. 4 Prescribed dose during the observation period by formulation initiated

Table 2 Summary of ADRs and special notifiable cases by formulation initiated

	Vortioxetine formulation at treatment initiation		*p*-value
	Oral tablets ($n=165$)	Oral drops ($n=60$)	
Patients reporting ADRs/special notifiable cases, *n* (%)	50 (30.3)	5 (8.3)	<0.001
ADRs/special notifiable cases[a] with incidence ≥2%			
No or little effect, *n* (%)	39 (23.6)	3 (5.0)	<0.001
Nausea, *n* (%)	6 (3.6)	2 (3.3)	1.000
Headache, *n* (%)	4 (2.4)	0 (0.0)	0.576

[a]Pre-defined special notifiable cases to be reported comprised: no or little effect; use in an unapproved indication (off-label use); overdose, misuse or abuse; drug interactions; use in paediatric patients; use during pregnancy/breastfeeding; incorrect use; occupational or accidental exposure; withdrawal symptoms; transmission of infectious diseases; unexpected positive effect; and transfer of the medicinal product via semen. *N*-values represent the number of patients who initiated treatment with vortioxetine.

ADR adverse drug reaction.

4 Discussion

This *post hoc* analysis is, to our knowledge, the first prospective study of the effectiveness and tolerability of the oral drop formulation of vortioxetine in patients with a major depressive episode. The effectiveness of vortioxetine on depressive symptoms was similar in patients who initiated oral drops and in patients who initiated oral tablets, with an overall reduction in the sum of the unanchored MADRS items of 22.7 and 21.9 points, respectively. Vortioxetine tablets have previously been associated with improvements in MADRS total score compared to placebo in a meta-analysis of randomised controlled trials (RCTs) [31], though clinical data for the drop formulation have not previously been available for comparison.

Response rate was numerically, but not statistically significantly, higher in patients who initiated drops (80.0%) than in those who initiated tablets (69.3%) by the end of observation (approximately 8 weeks). In both groups, response rates were higher than those in five placebo-controlled RCTs conducted outside the USA included in a previous meta-analysis, where rates of 55.0% ($n=221/402$) with 5 mg/day, to 61.6% ($n=93/151$) with 20 mg/day, were observed for 1091 patients, after 6 or 8 weeks of treatment with a fixed dose of 5–20 mg/day vortioxetine [31]. The response rate with tablets was similar to that observed (69.8%) after 12 weeks of vortioxetine treatment in a double-blind flexible-dose study in patients who previously had an inadequate response to selective serotonin reuptake inhibitor or serotonin–noradrenaline reuptake inhibitor monotherapy [30]. The flexibility of dosing with drops may contribute to higher response rates than with tablets. Although dose adjustments were allowed at any time during the observation period in the present study, the oral drop formulation, in particular, likely facilitated dose adjustments as needed for the individual patient.

At vortioxetine treatment initiation, most patients experienced moderate-to-severe impairment of everyday functioning in the areas of cognitive function, professional activities, family life, social and leisure activities, physical well-being and quality of life. After approximately 8 weeks of treatment, improvements in everyday functioning were observed, which were similar in the two formulation groups, and consistent with the results from previous controlled trials and real-world studies of vortioxetine tablets [35–38, 40, 45, 46]. Notably, after approximately 8 weeks, no patients in the drops group showed severe impairment in any functional domain, suggesting that the formulation may be particularly beneficial for patients presenting with severe impairments to everyday functioning.

While overall effectiveness appeared similar with the drop and tablet formulations of vortioxetine, differences were observed in dosing and titration patterns. The mean dose of vortioxetine drops was lower at baseline but increased more rapidly than the mean dose of tablets, ultimately resulting in mean doses after 8 weeks of treatment (Day 57) that were comparable among patients who had initiated drops or tablets. Patients who initiated drops tended to receive higher doses (> 10 mg/day) earlier in the observation period than patients who initiated tablets. This may reflect greater prescriber flexibility in titration with the oral drop formulation, allowing for more individualised treatment adjustments, and by treatment approaches implemented in routine clinical practice. Drops are typically initiated at low doses (≤5 mg/day), and then gradually increased by increments of 1–2 mg (1–2 drops) per day depending on patient tolerance, to a target dose of ≥10 mg/day. Patients who experience adverse events, such as gastrointestinal problems, may halt the incremental dose increase, while patients who tolerate the drug well may be able to increase the dose more rapidly, and exceed doses of 10 mg/day, as necessary. Consequently, drops may be a preferred option for patients who are

particularly susceptible to adverse events or are concerned about potential adverse events, to optimise their adherence to treatment and reduce anxiety. In addition, the observed early augmentation to higher doses (> 10 mg/day) increases the overall exposure to active treatment, potentially reducing the likelihood of suboptimal effectiveness during the up-titration phase. Therefore, the drop formulation may be suitable for patients who require a rapid treatment response to control symptoms.

The flexibility of dosing with the drop formulation may also be beneficial for facilitating a tapering down of the dose at treatment discontinuation instead of rapid discontinuation. In clinical studies, discontinuation symptoms following the rapid discontinuation of vortioxetine were evaluated and found to be infrequent and comparable with placebo in an analysis of 11 RCTs [14, 24]. However, cases in the post-marketing setting describing discontinuation symptoms have been reported; hence, a gradual reduction in vortioxetine dose may be considered [12, 14].

It is likely that differences in the dosing patterns of the tablet and drop formulations stem from the opportunity for greater control of dosing, within approved limits, afforded by the drops. Dose adjustments with tablets are limited to a minimum of 5 mg increments and may require a new prescription to be issued [12]. In contrast, with the drop formulation, it is possible to adjust doses in 1 mg increments, allowing for extensive variation (up to 16 possible doses) within the recommended dose range for vortioxetine (5–20 mg/day) [12]. Dose adjustments can be implemented faster and with greater flexibility with drops than with tablets. Consequently, the drop formulation allows for greater treatment personalisation than the tablet formulation. This is illustrated by the current real-world cohort study, which found that higher proportions of patients who initiated drops received a low dose (≤ 5 mg/day; 12.5%) or a high dose (> 10 mg/day; 62.5%) of vortioxetine at the end of observation, than patients who initiated tablets (3.1% and 32.6%, respectively). In the tablet group, most patients remained on a standard medium dose of > 5–≤ 10 mg/day throughout the observation period. However, it should be noted that almost half of the patients in this group started treatment with a dose ≤ 5 mg/day, lower than the starting dose of 10 mg/day recommended in the SmPC [12, 14]. Only psychiatrists who routinely used vortioxetine to treat depression were eligible to participate in the study, so this dosing pattern reflects the clinical practice of experienced psychiatrists and may explain the good tolerability observed in the group of patients who initiated tablets.

Flexibility and personalisation of treatment might be of special relevance at the beginning of treatment when the dose of vortioxetine can be gradually titrated to achieve optimal effectiveness and tolerability. Such differences in dosing control between the formulation options may account for some of the variation in baseline demographics and clinical characteristics between the drop and tablet groups. For example, compared with patients who initiated tablets, patients who initiated drops were more likely to be experiencing their first depressive episode, and tended to have more severe depression. This suggests that a drop formulation is a beneficial treatment option for patients with a first depressive episode, as well as other patient groups, such as those who are reluctant to accept antidepressant treatment, need a sense of control, are discouraged from accepting tablets due to stigma, or want to actively participate in treatment decisions. Drops may also provide an alternative for patients who have difficulty swallowing tablets [7]. In contrast to this analysis, compared with patients experiencing their first depressive episode, patients with recurrent depression have been shown to experience more severe depressive symptoms, including more comprehensive cognitive symptoms and anhedonia [47]. This suggests that patients experiencing their first depressive episode may not be the only patient group who could benefit from the drop formulation.

Importantly, once consent for pharmacological treatment is received, the patient's early experience with the medication is a crucial factor in treatment adherence and, therefore, in treatment outcome and prognosis. The process of individualised up-titration to achieve optimal efficacy and tolerability may enhance communication between patients and physicians with regards to treatment-related decision making. Shared decision making and goal setting between patients and physicians is an important consideration for the treatment of MDD [48], which could strengthen the patient–physician relationship and contribute to medication acceptance as well as concordance – that is, a mutual decision and understanding of the process.

Treatment adherence is an important factor affecting treatment outcomes [8]. The potential effects of a drop formulation on treatment adherence have been previously explored in a 6-month study of paroxetine, which is indicated for the treatment of depression and anxiety disorders [49]. The results of this study identified treatment formulation as a significant factor affecting adherence, and it was suggested that this could, partly, be the result of simpler, more controlled dosing with drops versus tablets [49]. The authors also hypothesised that a drop formulation could "maintain adequate self-perception" of quality of life [49]. Self-efficacy is defined as the expectation or experience that one's decisions and actions have an effect on an outcome and is a relevant factor in the treatment of depression and prognosis [50–52]. Strengthening self-efficacy is an important goal of cognitive behavioural therapy and enables patients to cope with stress, anxiety and depression [53, 54]. In the present analysis, a greater degree of self-efficacy may have contributed to the numerically higher response rates observed in

patients who initiated vortioxetine drops versus those who initiated tablets.

Both the tablet and drop formulations of vortioxetine were generally well-tolerated by patients and the reported ADRs are consistent with the known safety profile of vortioxetine [24–27, 30, 39]. Notably, the incidence of ADRs and special notifiable cases combined was significantly lower ($p < 0.001$) among patients who initiated treatment with drops (8.3%) than among those who initiated tablets (30.3%). While there were no significant differences in the incidence of ADRs between patients who initiated drops and patients who initiated tablets, the overall difference was driven by a significantly lower incidence of the special notifiable case 'no or little effect' among patients who initiated drops (5.0%) than among those who initiated tablets (23.6%) ($p < 0.001$). It is important to note that this apparent difference in efficacy was not reflected in subjective overall assessments of efficacy by clinicians and patients at the end of observation. It is possible that 'no or little effect' was mainly reported early in the course of treatment and was addressed during the observation period through dose adjustments. However, in placebo-controlled trials, the effect of vortioxetine has been observed as early as Week 2 of treatment [55]. The difference in the incidence of 'no or little effect' among patients who initiated drops versus tablets may also relate to the titration patterns of the two formulations. The observed early augmentation to higher doses (> 10 mg/day) in patients who initiated drops increased their overall exposure to active treatment and, potentially, reduced the likelihood of suboptimal effectiveness during the up-titration phase, compared with the tablet formulation. Furthermore, the capacity of the drop formulation for individual dose adjustment, and the subsequent empowerment of patients to control their treatment, might have ensured that patients perceived effectiveness more positively. Therefore, the flexibility of the drop formulation may be beneficial to patients who experience issues with effectiveness in the early stages of treatment.

Depression is associated with an increased risk of suicidality, and patients should therefore be closely monitored until improvement occurs. Clinical experience to date shows that the risk of suicide can increase in the early phases of improvement. Vortioxetine itself has not been associated with an increased risk of suicidal behaviour [56], and the potential for overdosing due to dose flexibility is minimal, as dose adjustments are only permitted within the approved range for vortioxetine up to 20 mg/day [12, 14]. Post-marketing experience mainly concerning vortioxetine overdoses of up to 80 mg showed that in most cases, no symptoms or only mild symptoms were reported, most frequently nausea and vomiting [12, 14]. After doses > 80 mg, several times higher than the therapeutic dose range, events of seizures and serotonin syndrome have been reported [12, 14]. Two case reports documented intentional ingestion of 250 mg vortioxetine in one case, and 1260 mg vortioxetine plus 350 mg diazepam in the other case, both with no signs of significant toxicity resulting from the exposure, suggesting good safety in the event of overdose [57, 58]. However, all patients with depression – whether receiving vortioxetine tablets or oral drops – should be monitored closely for any signs of suicidality, especially during the early phase of treatment.

In a previous pooled analysis of five open-label extension studies, vortioxetine demonstrated continued effectiveness in patients with MDD over a 52-week period [34]. Recent guidelines also recommend that flexible dose adjustments are more effective in preventing relapse than fixed doses during maintenance treatment [59]. Considering this, the oral drop formulation may also be useful for individualised dose adjustment during maintenance treatment.

The findings of this *post hoc* analysis indicate that clinicians and patients can choose the formulation of vortioxetine that best suits their needs, without compromising on efficacy or tolerability. The observed dosing patterns suggest that patients who initiated drops receive more individualised treatment. Initiating antidepressant treatment with an oral drop formulation may be suitable for various patient groups, including patients experiencing their first depressive episode. The flexible titration process associated with the drop formulation may strengthen the therapeutic alliance, enhance concordance between patients and clinicians, and encourage patient participation in treatment-related decisions. This has the potential to lead to a greater sense of control, empowerment and a higher degree of self-efficacy among patients, ultimately leading to improved medication adherence, perceived efficacy and treatment outcomes.

4.1 Limitations

This real-world cohort study has limitations. First, the observational, uncontrolled design, which did not randomise patients, limits the ability to determine how much of the improvement in depressive symptoms and functioning are related to treatment with vortioxetine tablets and drops. Second, the decision to prescribe oral drops versus tablets was made by physicians independent of study participation. This introduces the possibility of selection bias, as patient characteristics may have influenced the choice of formulation. Third, the short observation period lasting approximately 8 weeks limits the ability to explore the course of depressive symptoms, dosing patterns and tolerability of each formulation of vortioxetine over a longer period of time. Since most patients continued treatment with vortioxetine beyond the observation period, analysis of the effectiveness and tolerability of vortioxetine over a longer period may be relevant. However, the short study duration is equivalent to the treatment periods used in controlled clinical trials of

vortioxetine. Fourth, a simplified version of the MADRS, the sum of the unanchored MADRS items, was used, which may limit comparisons with previous studies. Fifth, the smaller number of patients initiating drops versus tablets may limit the statistical power of the comparisons between the two formulations. Sixth, it is not known if, or when, any patients who initiated treatment with drops converted to tablets (or vice versa) during the observation period. Finally, the reasons for choosing each of the formulations of vortioxetine were not known, which limits interpretation of the results.

5 Conclusions

In summary, the evidence from this real-world *post hoc* analysis suggests that the oral drop formulation of vortioxetine may provide comparable control of depressive symptoms to the oral tablet formulation. Oral drops could also offer additional benefits for patients owing to their greater capacity for dose individualisation, and may be an option for patients who have difficulty swallowing tablets or have anxiety related to treatment or are generally reluctant to use antidepressant medication. Both formulations of vortioxetine were tolerated by most patients, but the greater control of dosing afforded by the drops could be particularly beneficial for patients who are more susceptible to adverse events.

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Declarations

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Conflicts of Interest B.H. is a member of the Swiss Advisory Board on Brintellix, Lundbeck and speaker (Lundbeck-sponsored symposia). G.H. reports speaker/consultant fees from Janssen, Lundbeck, OM Pharma, Salon Pharma, Sanofi, Schwabe, Servier, Sunovion, and Takeda. A.B. is a member of the Swiss Advisory Board on Brintellix, Lundbeck and a speaker in Lundbeck-sponsored symposia. R.B. is a full-time employee of Lundbeck Singapore Pte Ltd. E.R. is a full-time employee of H. Lundbeck A/S. A.S. is a full-time employee of Lundbeck (Schweiz) AG. M.K. holds shares in Roche Pharma AG and Alpine Health AG and received investigator-initiated research funding from Eli Lilly Suisse SA and Pfizer Schweiz AG and speaker honoraria from Eli Lilly Suisse (SA) and Lundbeck AG.

Availability of Data and Material The datasets analysed during the current study are not publicly available due to reasons of sensitivity but are available from the corresponding author upon reasonable request.

Ethics Approval On 2 April 2017, the Ethics Committee of the Canton of Zurich confirmed that the study protocol did not require specific ethics approval due to its purely observational nature. As treating physicians had decided on treatment independently of the study and prior to inclusion, the study was not considered to fall under the definition of research in humans according to Swiss regulations. With the exception that this study was not registered (owing to its purely observational nature), this study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All patients provided written informed consent prior to enrolment in the study.

Consent to Participate Written informed consent was obtained from all participants included in the study.

Consent for Publication Not applicable.

Code Availability Not applicable.

Authors' Contributions Conceptualisation: B.H., R.B., A.S. and M.K. Methodology: B.H., R.B., A.S. and M.K. Investigation: A.B. and M.K. Writing – review and editing: B.H., G.H., A.B., R.B., E.R., A.S. and M.K. Supervision: A.S. All authors have read and approved the final version of the manuscript and agree to be accountable for the work.

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