

ORIGINAL ARTICLE

Long-term efficacy and safety of 1% glycopyrronium bromide cream in patients with severe primary axillary hyperhidrosis: Results from a Phase 3b trial

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Abstract

Background: Primary axillary hyperhidrosis (PAHH) strongly affects the patient's quality of life. To date, topical treatment options are limited. One percent glycopyrronium bromide (GPB) showed promising efficacy and safety in a pivotal 4-week Phase 3a study.

Objectives: To assess efficacy and safety of topical 1% GPB cream in patients with severe PAHH in a long-term study of 72 weeks versus baseline.

Methods: This was a long-term, open-label, Phase 3b trial for 72 weeks including 518 patients with severe PAHH. Patients were treated with 1% GPB cream once daily for 4 weeks, followed by a flexible dosing scheme (min. twice per week, max. once daily). Primary endpoint was the absolute change in sweat production from baseline to week 12. Further study endpoints included assessment of the severity of PAHH and the impact on quality of life.

Results: Total median sweat production decreased by 119.30 mg (−65.6%, both median) until week 12. Absolute change in sweat production from baseline to week 12 in logarithmic values was statistically significant ($p < 0.0001$). Patients' quality of life was improved at all study time points compared to baseline, as assessed by Hyperhidrosis Quality of Life Index and Dermatology Life Quality Index ($p < 0.0001$). Treatment was safe and locally well-tolerated with only few mild to moderate adverse drug reactions (ADRs). Dry mouth and application site erythema were the most common reported ADRs.

Conclusions: Treatment with 1% GPB cream over 72 weeks significantly reduces sweat production and improves quality of life in patients with severe PAHH. One percent GPB cream is well-tolerated and provides an effective treatment option for long-term use in patients with severe PAHH.

INTRODUCTION

Hyperhidrosis (HH) is a common disease of unknown aetiology in which a complex dysregulation of the sympathetic nervous system leads to excessive sweat production.^{1,2} Individuals with HH suffer from a highly pronounced and disproportionate increased sweating, where the actual amount of sweat can range from dampness on the skin to

the formation of droplets that can even drop off.^{1,3} Although the patient-experienced burden by uncontrollable sweating is high, patients rarely see a physician for medical help due to lack of awareness.^{4,5}

Studies on the quality of life in patients with and without HH showed that the prevalence of depression and anxiety was significantly higher in patients suffering from HH.^{6,7} These findings prove that HH, especially primary axillary HH (PAHH),

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is not only bothersome but also a serious medical issue for the affected patients and requires appropriate treatment.

Current therapeutic approaches for primary axillary HH involve topical, intradermal, systemic and device-based treatments as well as surgery procedures.^{8,9} In the EU, up to June 2022, the only topical formulations available were antiperspirants containing aluminium salts applied in high concentrations, but they commonly cause skin irritation and show limited effects, especially in severe PAHH.^{3,10,11} The use of anticholinergic substances for topical treatment of HH has been under investigation for several decades, leading to the following approvals for primary HH: glycopyrrolate as pads (also known as glycopyrronium bromide [GPB]) in South Korea, (Sweatrol® pads) glycopyrronium tosylate (GPT) wipes in the United States (Qbrexza®)¹² and Japan (Rapifort®),¹³ sofpironium bromide gel in Japan (ECCLOCK®).¹⁴ Recently a cream with GPB was approved in several EU countries (Axhidrox®), and while the systemic administration of the anticholinergic substances is regularly accompanied by adverse events, the safety profile of topical administration is favourable.^{15,16} After treatment for 2 weeks with 0.5%, 1% and 2% GPB cream (Phase 1b),¹⁶ efficacy and safety of the 1% GPB cream was recently studied in a Phase 3a randomized controlled trial for 4 weeks in patients with severe PAHH.¹⁷ Data confirmed the concept of a locally applied, locally acting product with good tolerability at the application site. Patients benefited from a significantly reduced sweat production as well as an improved quality of life in 4 weeks of treatment.¹⁷ Here, we report efficacy and safety results of the 1% GPB cream used in patients with severe PAHH in a Phase 3b trial over a study treatment period of 72 weeks.

PATIENTS AND METHODS

Study design

In this long-term, open-label Phase 3b study, efficacy and safety of a topical treatment with 1% GPB cream were assessed in a 72-week treatment period with additional 4-week follow-up (week 76). The study was conducted from June 2019 (first screened newly recruited patient) to November 2021 in compliance with the Declaration of Helsinki and International Council for Harmonisation guideline of Good Clinical Practice. The trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03658616) and was approved by responsible ethics committees and authorities.

Patients were treated once per day with 1% GPB cream applied to both axillae for the first 4 weeks. From week 5 on, 1% GPB cream could be flexibly used from a maximum of once per day to a minimum of twice per week. A dispenser was used for exact application of 0.54 g cream (an equivalent to 4.4 mg glycopyrronium) to each axilla. Dispensers were returned and weighed after the end of the study period. Patients enrolled in the study were asked to sign a written informed consent form before study entry. At the time of signing the consent, patients had to be between 18 and 65 years of age with a body mass index of 18–32 kg/m²

and suffering from severe PAHH characterized by a Hyperhidrosis Disease Severity Scale (HDSS) score of 3 or 4 and a resting axillary sweat production in one axilla above 50 mg over 5 min. Exclusion criteria included hypersensitivity against GPB, secondary HH, previous surgical treatment of HH including sympathectomy, surgical debulking of the sweat glands, subcutaneous tissue curettage and ultrasonic surgery. Patients were not included if they had botulinum toxin treatment 4 months prior to study start.

Study procedure

The initial screening visit was followed by a washout phase of 2 weeks. Sweat production was measured by gravimetric measurements at baseline, weeks 4 and 12. Patients reported outcomes, safety and efficacy outcomes were assessed throughout the study at weeks 4, 8, 12, 28, 52 and 72.

Measurements

Gravimetric measurements

Gravimetric measurements (GM) were performed at room temperature and at a humidity according to normal local climate. Patients acclimatized for at least 30 min before axillary hair was trimmed to not more than 1 cm. After both axillae were dried with an absorbent paper towel, standardized filter paper was placed on the axillae for 5 min. Weighing of filter paper before and after GM was done in a central laboratory.

Hyperhidrosis disease severity scale

To assess severity of HH, the HDSS, a disease-specific diagnostic tool, was used. This four-point (1 [lowest severity] to 4 [highest severity]) single-item scale is a measure of self-assessed disease severity and daily life interference in hyperhidrosis.¹⁸ HDSS was completed at each visit.

Hyperhidrosis quality of life index

The validated 'Hyperhidrosis Quality of Life Index' (HidroQoL©) was used as an instrument to investigate the impact of HH on the patient's quality of life.^{19,20} It consists of six questions on daily life activity and 12 questions on psychosocial life. Each question has three rating options. A summary score is calculated for each domain and overall. HidroQoL© was completed at each visit.

Dermatology life quality index

Measurement of the impact of skin disease on the quality of life was also performed using the non HH specific

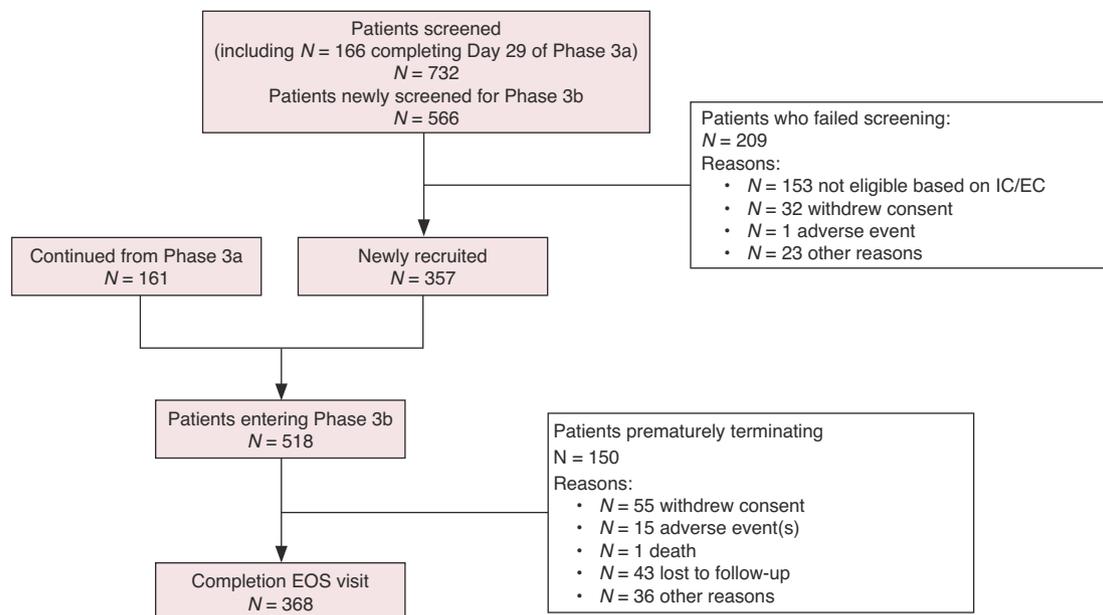


FIGURE 1 CONSORT flow diagram for the Phase 3b trial. EC, exclusion criterion; EOS, end of study; IC, inclusion criterion; N , number of patients.

TABLE 1 Patient demography and baseline characteristics

	FASb ($N = 518$)	FASnewb ($N = 357$)
Sex		
Male (N ; %)	244 (47.1%)	160 (44.8%)
Female (N ; %)	274 (52.9%)	197 (55.2%)
Age		
Mean \pm SD	35.6 \pm 11.8	34.6 \pm 11.5
Ethnicity		
White (N ; %)	494 (95.4%)	337 (94.4%)
Black (N ; %)	4 (0.8%)	3 (0.8%)
Asian (N ; %)	8 (1.5%)	6 (1.7%)
Other (N ; %)	12 (2.3%)	11 (3.1%)

'Dermatology Life Quality Index' (DLQI), a validated, well known 10-question questionnaire.²¹ Each question is answered on a 4-point scale and scored from 0 to 3. DLQI was completed at each visit.

Safety and tolerability

For safety measurement, the frequency and severity of adverse events (AEs), serious AEs (SAEs) and treatment-emergent AEs (TEAEs) were analysed. Investigators used a skin reaction score to assess local tolerability at the application sites. Treatment period was 72 weeks and safety, and tolerability follow-up were observed 4 weeks after end of treatment, that is at week 76.

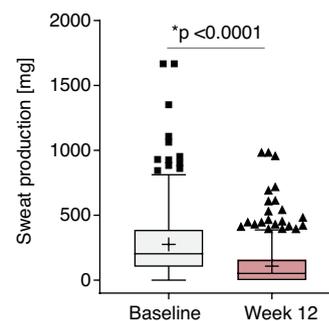


FIGURE 2 Absolute sweat production (mg) in 5 min as measured by gravimetry at baseline and week 12. Data are shown for the full analysis set of newly recruited patients (FASnewb) ($N = 357$). Boxes represent the lower and upper quartile; median values are indicated by the horizontal lines, mean values by a '+', and upper and lower whiskers indicate the maximum and minimum values (excluding outliers). Outliers are shown as black rectangles (baseline) or black triangles (week 12). *Statistically significant (p -value for treatment effect is based on the mixed model using the absolute change in logarithmic values of sweat production).

Endpoints

The primary endpoint was defined as the absolute change in sweat production from baseline to week 12. Key secondary endpoints were the percentage of responders with a ≥ 2 -point improvement from baseline at weeks 12 and 28, as assessed by HDSS, and the absolute change in HidroQoL score from baseline to week 12. Further secondary endpoints were assessed, such as: Absolute change in the HDSS, HidroQoL and DLQI from baseline to weeks 4, 8, 12, 28, 52 and 72 (if not already assessed as a key secondary endpoint).

Statistics

The primary endpoint of the Phase 3b part, change in total sweat production from baseline (day 1) to week 12, was only assessed in newly recruited patients, and was tested with a mixed effects model with mean centred logarithmic baseline values as fixed effects and centre as random effect at a significance level of 2.94% ($\alpha = 0.0294$; 2-sided).

The key secondary endpoints of Phase 3b were tested hierarchically with a 1-sample binomial test (HDSS responder) at a significance level of 1.47% ($\alpha = 0.0174$, 1-sided) or the Wilcoxon signed rank test (HidroQoL) at a significance level of 2.94% ($\alpha = 0.0294$, 2-sided). Further secondary endpoints were tested on a significance level of 5% (2-sided). The significance level for the final and the interim analysis of the long-term part of the study are split equally using the Pocock boundaries for two planned analyses to meet a global significance level of 5%.

Confirmatory hypothesis tests were performed hierarchically until the first non-significant test result was obtained

TABLE 2 Key secondary endpoints—HDSS responders at week 12 and 28 in FASb ($N = 518$)

HDSS responders (≥ 2 -point improvement from Baseline to week 12 or 28) $> 25\%$ responders	Week 12	Week 28
Responders, N (%) ^a	145 (28.0)	152 (29.3)
Proportion (CI) ^b	0.28 (0.23; 0.33)	0.29 (0.25; 0.35)
p -value ^c	0.0579	0.0112

Note: Patients with missing values were considered non responders.

Abbreviations: CI, confidence interval; FASb, full analysis set (Phase 3b); HDSS, hyperhidrosis disease severity scale; N , number of patients.

^aPercentages are based on the number of patients in each analysis set.

^bClopper–Pearson, exact 1-sided 98.53%.

^cOne-sample binomial test, one-sided, $\alpha = 0.0147$.

for the respective primary and key secondary efficacy endpoints.

RESULTS

A total of 518 patients was treated with 1% GPB cream for 72 weeks. Of these patients, 161 patients rolled over from the preceding Phase 3a trial and 357 new patients were enrolled according to the inclusion criteria (Figure 1). The population (FASb) consisted of slightly more women (53%) than men (47%). The median age was 33 years (range: 18–65 years) with a median BMI of 25.3 kg/m² and a median BSA of 1.91 m². Most patients were White (494 patients, 95%). The subgroup of newly recruited patients (FASnewb) was similar to the FASb, with 55% women and 45% men and a median age of 32 years (range: 18–65 years). The BMI and BSA were similar to those of patients in the FASb (25.4 kg/m² and 1.91 m², respectively). Demographics and baseline characteristics were well-balanced between patients from the Phase 3a trial and the newly enrolled patients (Table 1).

Median total sweat production assessed by GM was 212.4 mg at baseline and 75.8 mg after 12 weeks of treatment with 1% GPB cream. Absolute change in logarithmic values was statistically significant ($p < 0.0001$; mixed effects model) (Figure 2), thus the primary endpoint of the study was met. The proportion of responders who achieved a reduction in sweat production $\geq 50\%$ was 54.1% at week 12. Approximately every third patient achieved a reduction of $\geq 75\%$ (36%, $p < 0.0001$) and one in five achieved a reduction of $\geq 90\%$ at week 12 (22%, $p = 0.0005$).

Patients who had a ≥ 2 -point improvement in the HDSS assessment compared to baseline values were defined as responders to treatment. For the key secondary end point, percentage of responders should be greater than 25%. At week 12, although 28% of patients responded to treatment, the

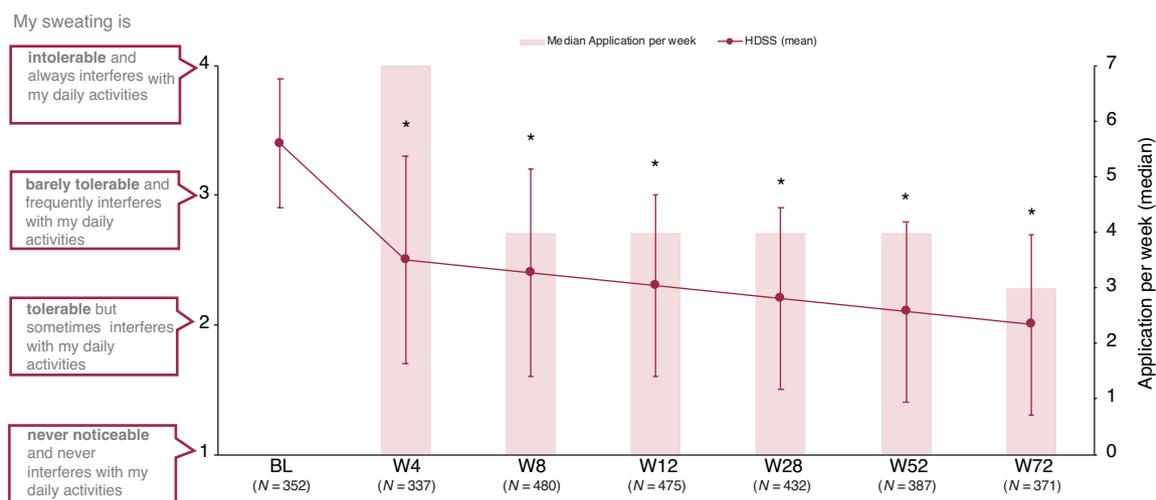


FIGURE 3 Absolute values of the hyperhidrosis disease severity scale (HDSS) from baseline to weeks 4, 8, 12, 28, 52 and 72, N , number of patients with absolute values. * $p < 0.0001$ (two-sided Wilcoxon signed rank test ($\alpha = 0.05$) for absolute change in HDSS to baseline). Data for the HDSS score (red line with red circles) are shown as mean \pm SD of absolute values and data for application per week (red bars) as median.

difference to baseline did not reach statistical significance for FAS ($p = 0.0579$). However, the proportion of responders was significant at week 28 (29%, $p = 0.0112$) and onwards (30%, $p = 0.0072$ and 32%, $p = 0.0002$ for week 52 and week 72, respectively) (Table 2, Figure 3). In addition, key secondary endpoint, at week 12 was statistically significant for the per protocol set (PPS, $N = 326$; $p = 0.003$) and week 28 (PPS, $N = 326$; $p < 0.0001$, Table S1).

The validated patient-reported outcome measure HidroQoL® total score (median change: -11.0), as well as the daily life activities (median change: -5.0) and psychosocial domains (median change: -6.0), improved from baseline to week 12 with statistical significance in the FASb ($p < 0.0001$) (Table 3) as well as in PPS (Table S1). Significant decreases in HidroQoL (Figure 4a) total scores were observed for all study time points ($p < 0.0001$).

Similar results were obtained with the DLQI which showed a decrease in median absolute change in DLQI score of 6 (week 4), 7 (week 8), 7 (week 12), 8 (week 28), 9 (week 52) and 10 (week 72) compared with baseline values ($p < 0.0001$ for all time points) (Figure 4b). Overall, significant decreases in DLQI scores were observed for all study time points ($p < 0.0001$), pointing to a considerable ongoing improvement in the patients' quality of life starting as early as 4 weeks after the first treatment with 1% GPB cream.

All changes after week 4 were seen even though the median application frequency was decreased (seven applications per week at week 4 to three applications per week at week 72).

In total, 1795 TEAEs were reported in 379 patients (73.2%) from baseline to week 72.

One patient died of unknown cause. In total, 23 patients had 28 serious TEAEs, two of which (mydriasis and unequal pupils) qualified as suspected unexpected serious adverse reactions (SUSARs). All other serious TEAEs were assessed as unlikely or not related to the IMP. Most reported TEAEs were mild or moderate.

Adverse drug reactions were assessed from baseline until week 72. Of all ADRs that occurred in more than two patients, dry mouth was the most common ADR in 62 of 518 of patients (12%) even though lower percentage of patients reported a dry mouth from week 4 to 72 (5.8%) compared to baseline to week 4 (9.8%) (Table 4). Topical application of 1% GPB cream was overall well-tolerated with erythema in 37 of 518 patients (7.1%) and pruritus in 18 of 518 patients (3.5%) being the most frequent at the application site ADRs. Other ADRs occurred in 3.3% of the patients or less and included dry eye, nasal dryness, visual impairment, and headache. All ADRs were of mild to moderate severity, were reversible after application was paused, however 14 patients discontinued the study due to ADRs (Table 4).

DISCUSSION

In two recent studies (Phases 1 and 3a), dose-finding and efficacy of a GPB cream in patients with severe PAHH was

shown.^{16,17} In the Phase 3a study, 1% GPB cream applied once daily for 4 weeks led to a significant reduction in sweat production compared with placebo ($p = 0.004$) and a significant improvement regarding quality of life (HidroQoL®). Treatment was safe with mild to moderate adverse events and an overall good local tolerability.¹⁷ The Phase 3b study was conducted to gather additional data regarding efficacy and safety of 1% GPB in a larger patient cohort and over a longer period of time. To our knowledge, compared with a 44 weeks study with GPT 2.4% wipes (Qbrexza™)²² and a 52-week study with sofpironium bromide (SB) 5% gel (ECCLOCK®),²³ this is the longest study performed in PAHH with a topical anticholinergic agent.

Over a period of 72 weeks, efficacy and safety results of the Phase 3a study could be confirmed. At week 12, total sweat production was significantly lower corresponding to a relative median reduction of about 66% (median—65.6%, $p < 0.0001$) compared to baseline values despite reduction in frequency of application after week 4. From baseline to week 44, sweat production decreased by 71.3% with Qbrexza™ wipes.²² The change in total gravimetric weight of sweat from baseline to week 52 was around—150 mg (around 70%) in study with ECCLOCK®.²³ In both studies, patients applied wipes or gel daily and according to the published results there was no reduction of the dose. The reduction of the application frequency by the individual patient is of clear benefit leading to reduced costs and adverse events.

Since the impact of HH on quality of life is comparable or even worse than in other major skin diseases,^{7,24,25} we chose to assess quality of life as an important

TABLE 3 Key secondary endpoint—change in HidroQoL at week 12 in FASb ($N = 518$)

Change in the HidroQoL from baseline to week 12	
Total score	
Baseline, median (range)	27.0 (4–36) ^c
Median change to week 12 (CI) ^a	$-11.0 (-13.0; -10.0)$ ^d
<i>p</i> -value ^b	< 0.0001
Daily life activities domain score	
Baseline, median (range)	10.0 (1–12) ^c
Median change to week 12 (CI) ^a	$-5.0 (-5.0; -4.0)$ ^d
<i>p</i> -value ^b	< 0.0001
Psychosocial domain score	
Baseline, median (range)	17.0 (0–24) ^c
Median change to week 12 (CI) ^a	$-6.0 (-7.0; -5.0)$ ^d
<i>p</i> -value ^b	< 0.0001

Note: Patients with missing values were considered non responders.

Abbreviations: CI, confidence interval; FASb, full analysis set (Phase 3b); HidroQoL, hyperhidrosis quality of life index; *N*, number of patients.

^aHahn-Meecker, 97.06%.

^bWilcoxon signed rank test, 2-sided, $\alpha = 0.0294$.

^c $N = 352$.

^d $N = 468$.

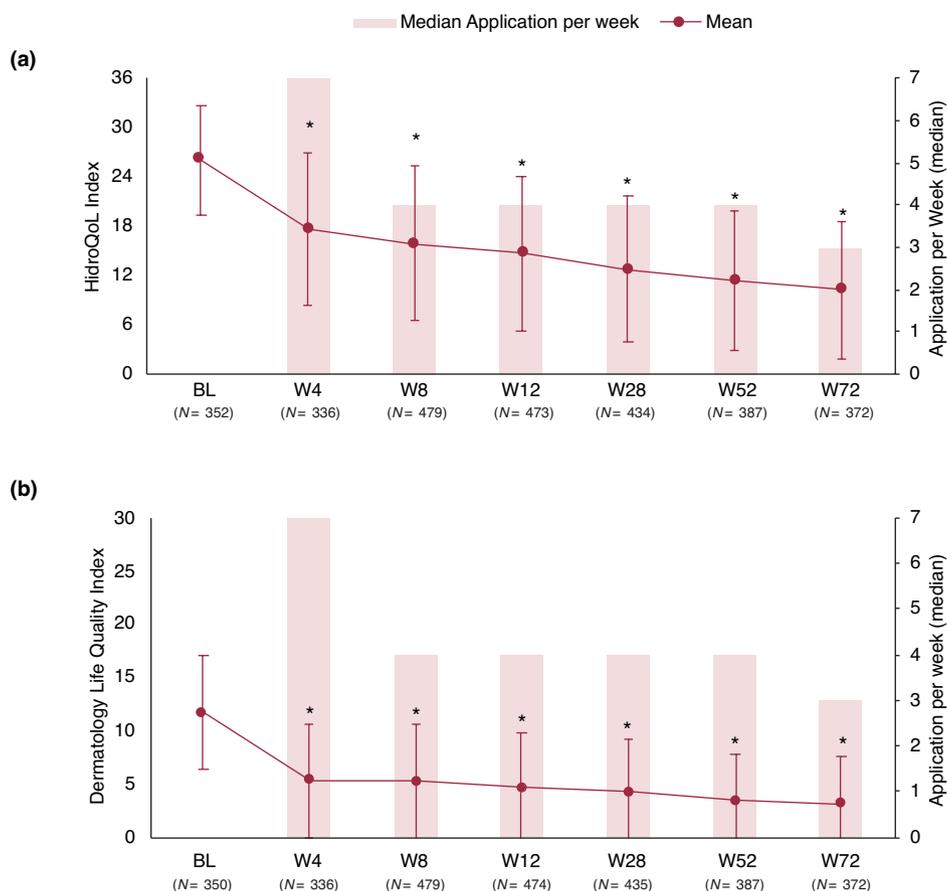


FIGURE 4 (a) Absolute values in the hyperhidrosis quality of life index (HidroQoL) from baseline to weeks 4, 8, 28, 52 and 72. (b) Absolute values in the dermatology life quality index (DLQI) from baseline to weeks 4, 8, 12, 28, 52 and 72. For both graphs N = number of patients with absolute values. $*p < 0.0001$ (two-sided Wilcoxon signed rank test ($\alpha = 0.05$) for absolute change in the HidroQoL or DLQI from baseline). Data for the HidroQoL or DLQI index (red line with red circles) are shown as mean \pm SD of absolute values and data for application per week (red bars) as median.

TABLE 4 Adverse drug reaction in $\geq 1\%$ of patients

Adverse drug reactions (ADR)	Baseline to week 4, N = patients with AE, (%)	From week 4 to 72, N = patients with AE, (%)	Baseline to week 72, N = patients with AE, (%)
	SAF ($N = 438$)	SAF ($N = 518$)	SAF ($N = 518$)
Dry mouth	43 (9.8)	30 (5.8)	62 (12)
Constipation	2 (0.5)	3 (0.6)	5 (1.0)
Dry eye	5 (1.1)	12 (2.3)	17 (3.3)
Vision blurred	1 (0.2)	4 (0.8)	5 (1.0)
Application site erythema	12 (2.7)	27 (5.2)	37 (7.1)
Application site eczema	-	6 (1.2)	6 (1.2)
Application site pruritus	4 (0.9)	14 (2.7)	18 (3.5)
Application site pain	4 (0.9)	7 (1.4)	11 (2.1)
Application site irritation	5 (1.1)	6 (1.2)	10 (1.9)
Application site papules	1 (0.2)	9 (1.7)	10 (1.9)
Application site rash	-	9 (1.7)	9 (1.7)
Application site dermatitis	1 (0.2)	5 (1.0)	6 (1.2)
Nasal dryness	5 (1.1)	2 (0.4)	7 (1.4)
Dry skin	5 (1.1)	2 (0.4)	7 (1.4)
Mean cell volume increased		5 (1.0)	5 (1.0)

patient-reported outcome measure to assess the therapeutic effect of 1% GPB cream. HDSS, HidroQoL[®] and DLQI demonstrated a significant improvement in the quality of life over the entire study period of 72 weeks compared to baseline assessment. Moreover, despite the reduction of applications, the treatment effect of the 1% GPB cream remained persistent, and the patient-reported outcomes even improved over time.

A long-term follow-up with patients using 2.4% GT wipes daily for 44 weeks showed responder rates of 63.2% at week 44 as determined by HDSS and mean score improvements of 8.7 for DLQI.²² A long-term follow-up of a 52-week once daily treatment with 5% SB gel investigated efficacy and safety of the product.²³ Results confirmed an improvement in quality of life assessed by DLQI by a mean of 8.8 and 9.7 at the end of the study.

In this Phase 3b study, flexible dosing of 1% GPB led to a HDSS responder (≥ 2 -point improvement from baseline) rate of 32% at week 72 and median DLQI score value improvements of 9 points at week 52 and 10 at week 72, respectively. As already written in a previous publication^{26,27} and also demonstrated in the Phase 3a study, HDSS proves to be not a precise tool for determining improvement in quality of life. Probably this is the reason why HDSS is not accepted by FDA as primary endpoint or PRO-tool (personal communication). HidroQoL[®] and even the HH-unspecific DLQI seem to be much better predictors for determining severity of disease and quality of life. Both DLQI and HidroQoL[®], strongly support the effective response of patients to 1% GPB. Moreover, after daily administration in the first 4 weeks, the flexible dosing scheme in our study led to as little as 3 to 4 applications per week without any negative effect on efficacy or quality of life and no discontinuation of study treatment. Overall data of the long-term-part were robust and confirmed the results obtained in the placebo-controlled 3a Part.

Only few ADRs were reported, with dry mouth being the most common and expected anticholinergic ADR. Overall, 1% GPB cream had a good safety profile and was well tolerated.

As shown in both the Phase 3a¹⁷ and 3b studies for the treatment with 1% GPB, this anticholinergic substance has a good safety profile with few ADRs. All ADRs were mild to moderate in severity and transient. The most reported ADR of treatment with GPB and also GT wipes was dry mouth, as expected for anticholinergic drugs. Overall, 20 patients (20/518; 3.9%) prematurely discontinued the study due to 33 TEAEs, 3 of which were serious and unrelated to the IMP (Crohn disease, relapsing–remitting multiple sclerosis and death) and 24 of which were classified as ADRs (leading to discontinuation of 14 patients) and constituted mainly application site conditions. GPT and SB treatment led to discontinuation in 44 (44/550 [8.0%]) and 7 (2/94 [2.1%]) and 5/91 [5.5%]) patients, respectively.^{22,23}

It should be noted that no direct comparison can be made between our data and data of the two other clinical trials because results are either presented as mean or median values. However, this long-term open-label part (Phase 3b study)

confirmed that a 1% GPB cream significantly reduces sweat production and significantly improves quality of life over 18 months even in a flexible application setting according to patient's preferences. In addition, the topical application of 1% GPB was well tolerated and indicates a safe long-term use in patients with severe PAHH. Therefore, this medicinal product was recently approved in the EU as the first topical anticholinergic for the treatment of severe primary axillary hyperhidrosis.

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CONFLICT OF INTEREST

C.M., A.K., H.R., B.B., E.SzW. and C.A. were employees of Dr. August Wolff GmbH & Co. KG Arzneimittel at the time of the study. R.-M.S. is the Principal Investigator and represents the study group. He is also the vice president of EURO-PDT; has been a member of advisory boards for Almirall, Biofrontera, Galderma, LEO Pharma, Novartis, Photonamic and Dr. August Wolff GmbH & Co. KG Arzneimittel; and has received speakers' honoraria from the aforementioned companies. C.A. is named as inventors on a patent application claiming glycopyrronium salt-containing oil-in-water emulsions. C.M. and C.A. are named as inventors on a patent application claiming a topical emulsion of an anticholinergic compound. Dr. August Wolff GmbH & Co. KG Arzneimittel is developing a topical glycopyrronium bromide formulation for the treatment of severe primary axillary hyperhidrosis. K.S., L.L. and S.H.M. do not have conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, C.M. The data are not publicly available due to restrictions, for example their containing information that could compromise the privacy of research participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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