LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Relfydess
(Clostridium botulinum type A neurotoxin)

SE/H/2438/01/DC

This module reflects the scientific discussion for the approval of Relfydess. The procedure was finalised on 2024-07-28. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Relfydess, 100 units/ml, Solution for injection.

The active substance is Clostridium botulinum type A neurotoxin. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Relfydess, 100 units/ml, Solution for injection, is an application submitted according to Article 8(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, DE, DK, ES, FI, FR, IE, IS, IT, LU, NL, NO, PL, PT as concerned member states (CMS).

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

Paediatric Regulation

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0233/2022) on the granting of a product specific waiver.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology

The primary pharmacodynamic profile of BoNT-A is well-established and based primarily on published literature. No in vitro pharmacology studies were carried out by the applicant, which is accepted. Data from two new in vivo studies are presented in the current application for the purpose of determining a theoretically effective dose range for the clinic, and correlate the potency of QM1114-DP to previously approved BoNT-A products.

No drug-drug interaction studies were carried out or identified in the literature for BoNT-A. As Botulinum toxin has anticholinergic effects, interactions may be expected with concomitant use of other anticholinergic drugs. This has been addressed in the SmPC.

Overall, data is presented to support nonclinical proof-of-concept for the mode of action of QM1114-DP as equivalent to other BoNT-A clinical products, namely dose-dependent local paralysis. It is agreed that safety pharmacological studies can be waived for QM1114-DP as the safety profile of BoNT-A is well established from its clinical use.

Pharmacokinetics

The applicant did not conduct any non-clinical PK or ADME studies of QM1114-DP, which is acceptable. The medicinal product is intended as a local treatment and, given its high potency, severe toxicity would be expected if there were systemic exposure at detectable levels.

Toxicology

A limited non-clinical toxicology package is provided for QM1114-DP; two single dose toxicity studies in Wistar rats, one single dose toxicity study in Beagle dogs, and one 6-month repeat dose toxicity study in rats. In general, findings in the toxicity studies were in line with the well-known pharmacological effects and toxicologic profile of botulinum toxin A. Repeat dose toxicity studies in a second species would have been in line with current recommendations, however, given the well-known MoA and toxicity profile, the current package may be accepted. Noteworthy findings included:

Paralysis of the injected hindlimb muscle

The expected pharmacological effect of QM1114-DP, paralysis of the injected muscle, was demonstrated in rat gastrocnemius muscle. The effect was long but reversable in line with other approved BoNT-A products. Paralysis was accompanied with atrophy of the injected muscle with reduced muscle fibres and interstitial fibrosis. Reduced bw was also observed, likely at least partly secondary to reduced mobility causing reduced food intake and dehydration.

Distended abdomen

Distended abdomen was observed at doses corresponding to ~5x and 13x the human dose per kg bw in male and female rats respectively, with increasing incidence after repeated administrations. The assessor agrees with the conclusion of the study report that spread to abdominal muscles likely reflects ipsilateral diffusion rather than spread through systemic circulation. Regardless, it is agreed with the applicant that this effect is potentially adverse, and the NOAEL and LOAEL as set by the applicant in the 6-month repeat dose study are supported.

Haematology and clinical chemistry

Haematologic findings of increased erythrocyte counts may reflect haemoconcentration secondary to dehydration but considered by the applicant to be of no toxicologic significance because of the absence of corroborative findings at the pathological examination. This can be accepted. Lower

creatinine values seen at doses ≥20 U are explained by the applicant as likely secondary to systemic PD effects of reduced injected hindlimb muscle mass. This can be agreed.

Ophthalmologic findings

Haemorrhagic discharge was observed in the ophthalmologic examination in 6/10 animals in the 32U group in the 3-month single dose i.m. toxicity study in rats. Likely, this was treatment-related and the result of systemic exposure. However, haemorrhagic discharge was not observed at clinically relevant doses and does not affect the NOAEL. No ophthalmologic pathologies were observed in the 6-month repeat dose toxicity study at lower exposure.

Fertility

The applicant proposes that the observed effects on male and female fertility observed in rats injected with other BoNT-A products are secondary to the pharmacologically induced paralysis of the hindlimb. It is agreed that this is likely. Testicular degeneration observed after injection of QM1114-DP at doses corresponding to 39x the human dose per kg bw is argued to be secondary to postural changes and open inguinal canal leading to testicular changes that are not relevant to humans.

PPDN studies were not performed for QM1114-DP. The applicant refers to the well-established impact on reproductive and developmental toxicity in animal models documented in the scientific literature, with toxicity observed at high doses causing maternal toxicity but with no selective toxicity to fetal development observed at clinically relevant exposure. The conclusion that additional reproductive and developmental toxicity studies are not needed is agreed.

Environmental Risk Assessment (ERA)

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, QM1114-DP is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

III.3.1 Pharmacokinetics

No pharmacokinetic or drug metabolism studies have been conducted with the product applied for. The product is to be administered by local intramuscular (IM) injections into the facial muscles and no systemic exposure is expected due to the small volume of these injections. Additionally, botulinum neurotoxin type A (BoNT-A) binds with high affinity at the neuronal synapses situated at the local injection site and remains localized there. Therefore, any metabolism and elimination of the product would occur at the local site of injection. This was supported when QM1114-DP was injected peri-ocularly into the eyelids of rabbits, as the free neurotoxin remained localized at the injection site and no labelled toxin spread to the eye (Tang-Liu 2003).

In the clinical program, the formulation of QM1114-DP is the same as the planned final formulation.

Discussion and overall conclusion

The absence of pharmacokinetic studies and the wording in section 5.2 of the SmPC (stating that measurable levels in the peripheral blood following intramuscular injection at the recommended dose are not expected and that PK studies therefore have not been performed) is acceptable. As the formulation used in the clinical studies is the same as the planned final formulation, no bridging between formulations is required.

III.3.2 Pharmacodynamics

Botulinum toxin (BoNT) mechanism of action is well known. It selectively inhibits the exocytotic release of acetylcholine from the presynaptic nerve terminals. When injected into a muscle, BoNT reaches the neuromuscular endplate where it inhibits the release of acetylcholine. This will cause a dose-dependent partial to total chemical denervation resulting in partial to total paresis of the muscle. As reinnervation proceeds, muscle function is slowly regained. With BoNT-A this process usually takes 3-6 months. After repeated injections, muscle atrophy has been reported, an effect for which the mechanism of action is not known.

III.3.3 Clinical efficacy

- ***Overview of the clinical development study program***

The clinical study program is comprehensive, consisting of one phase 1 study, 1 phase 2 study, 3 placebo-controlled phase 3 RCT, and an open-label uncontrolled long-term phase 3 study (please see tabular overview below).

Study ID	Design	Study Posology (QM1114-DP)	Study Objective	Subjects
302	Randomized, double-blind, PBO-controlled, 3-part dose escalation study	10–75U (GR) 30–90U (LCL) 110U or 140U (50U [GR] and 60U or 90 U [LCL]); IM inj	To evaluate the safety and efficacy	Healthy M and F subjects: 30 (Part 1); 24 (Part 2); 16 (Part 3)
313	Randomized, double-blind, PBO-controlled, parallel-group multicenter study	30 U, 45 U, or 60 U (GR); IM inj	To evaluate 3 dose levels in the treatment of moderate-to-very severe **GL**	359 healthy M and F subjects
602	Multicenter, randomized, double-blind, PBO-controlled	50 U (GR); IM inj	To evaluate efficacy and safety of QM1114-DP for the treatment of moderate-to-severe **GL**	297 healthy M and F subjects: 223 QM1114-DP, 74 PBO
901	Multicenter, randomized, double-blind, PBO-controlled	60 U (LCL); IM inj	To evaluate efficacy and safety for the treatment of moderate-to-severe **LCL**	303 healthy M and F subjects: 230 QM1114-DP, 73 PBO.
902	Multicenter, randomized, double-blind, PBO-controlled study	50 U (GR) 60 U (LCL) 110 U (50 U [GR] and 60 U [LCL]); IM inj	To evaluate efficacy and safety for treatment of moderate-to-severe **LCL and GL** alone or in combination	Healthy M and F subjects. GL: 228 QM1114-DP, 58 PBO. LCL: 241 QM1114-DP, 58 PBO
903	Multicenter, open-label; no control	110 U (50 U [GR] and 60 U [LCL]); IM inj	To assess the safety for long-term treatment of moderate-to-severe **GL and LCL**	902 healthy M and F subjects

All clinical studies in phase 2/3 were conducted in the US and Canada only, without any study site in the EU. While the efficacy and safety profile of BoNT-A in general is well-established with considerable experience also from EU-approve products, the effect can be related to ethnicity and skin type. Relevance of the results from the FLTSQ validation study and the descriptive long-term study 903 are also critically dependent on the study populations being representative for the EU target population. Transportability of study results to the EU target population has, however, been sufficiently justified by the Applicant.

Scientific advice

Scientific advice has been provided by the German agency BfArM and the Swedish MPA for the clinical development.

- ***Statistical methods - applicable for all 3 pivotal studies***

Analysis populations

Intention-to-treat (ITT) efficacy population*:* All subjects who were randomised and dispensed the study product and were analysed according to the randomisation scheme.

Modified intention-to-treat (mITT) population: All subjects who were randomised and dispensed the study product and were analysed according to the randomisation scheme. Subjects with a photographic and categorical scale Month 1 assessment via a remote visit were excluded from the mITT population. The primary efficacy analysis was based on the mITT population.

Per-protocol (PP) efficacy population: A subset of the mITT population and included subjects who had no protocol deviations that were considered to have a substantial impact on the primary efficacy outcome.

Safety population: All subjects who were administered the study product and were analysed according to as-treated principle.

Analysis methods

To evaluate the effectiveness of QM1114-DP versus placebo in the treatment, the responder rates of the QM1114-DP and placebo were compared using the Cochran-Mantel-Haenszel (CMH) test stratified by site (or region if pooled sites) at the 5% significance level (2-sided).

Since this study planned to conduct some site-level analyses, pooling of sites may have been needed to be considered for reliable and accurate results. If any site enrolled less than 5 subjects, then sites were to be pooled by the following United States geographic regions: East, North, South, and West.

The null hypothesis of no relationship between treatment and responder rate (i.e., the responder rates were the same in both groups) was tested against the alternative hypothesis that there was a relationship between treatment and responder rate (i.e., the responder rates were different in the 2 groups). For a significant result, the 2-sided p-value of the comparison of the responder rates between the QM1114-DP and placebo subjects at Month 1 using the CMH test needed to be smaller than 0.05. For consistency across strata the Breslow-Day test was used to assess the homogeneity of the odds ratios across all strata. The estimates of the responder rates in each treatment group were presented as well as the difference in responder rates (QM1114-DP responder rate – placebo responder rate). Corresponding 95% CI for the treatment group responder rates and the difference in responder rates along with the p-value for the difference were also presented. The normal approximation (Wald) method was used to calculate both the 95% CI for the individual treatment group responder rates and the 95% CI for the difference in responder rates.

The primary analysis was performed using multiple imputation as the primary imputation method and was based on the mITT population.

Sensitivity analysis

To evaluate the impact of missing data on the primary endpoint, sensitivity analyses were performed. The primary analysis was repeated using the baseline observation carried forward method, and also using the ITT observed cases. In addition, a sensitivity analysis of the primary efficacy endpoint was performed based on the PP population and the safety population to account for potential errors in randomisation.

Secondary efficacy analysis of special interest:

Facial Lines Treatment Satisfaction Questionnaire and FACE-Q™ Questionnaire

For each of these 2 questionnaires, both the individual questionnaire items, the Rasch-transformed total scores, and change from baseline in the Rasch-transformed total scores were presented descriptively at Month 1 by treatment group. The individual responses for each questionnaire were presented in frequency tables; whereas the Rasch-transformed total scores and change from baseline Rasch-transformed total scores were presented using descriptive statistics.

Missing data

The primary analysis was performed using multiple imputation as the primary imputation method and repeated using baseline observation carried forward as a sensitivity analysis for missing values.

Subgroup analysis

Subgroup analyses were performed for the primary efficacy endpoint by age, site, Fitzpatrick skin type, gender, baseline severity score of GL-ILA at maximum frown and/or LCL-ILA at maximum smile (as applicable for the study), prior BoNT use, and type of Month 1 visit, including responder rates by treatment and treatment difference from placebo in responder rates with 95% CIs.

- ***Study 43QM1602***
    - *Study population*

Male or non-pregnant females, 18 years of age or older, with moderate-to-severe glabellar lines (grade of 2 or 3 on the 4-Point Photographic Scale) at maximum frown, as assessed by the Investigator (GL-ILA) and grade of 2 or 3 on the Static 4-Point Categorical Scale at maximum frown, as assessed by subject (GL-SLA), at baseline.

    - *Treatments*

In patients randomised to QM1114-DP solution, each muscle in predefined sites across the glabellar region was injected with 10 U (0.1 mL, 100 units/mL) (one injection site per muscle) for a total dose of 50 U.

    - *Primary endpoint*

The primary efficacy endpoint reported for study 43QM1602 was the responder rate based on the GL-ILA of glabellar line severity at maximum frown at Month 1. A responder was defined as a subject who achieved a score of 0 or 1 in glabellar line severity on the GL-ILA 4-Point Photographic Scale at Month 1, according to the study report.

    - *Multiplicity*

To evaluate the effectiveness of QM1114-DP versus placebo in the treatment of moderate to severe GL, the proportion of subjects who achieve 0 or 1 on the GL-ILA at maximum frown at all post-treatment visits were compared using the CMH test stratified by site. To control the type I error rate, the fixed sequence testing procedure was used for the secondary endpoints, which required no adjustment to the level of significance. However, the comparisons were to be made in a pre-specified order as follows:

1. Primary analysis must be done first, prior to any other analysis.

Thereafter secondary analyses:
2. Month 1 responder rate
3. Day 14 responder rate
4. Month 2 responder rate
5. Month 3 responder rate
6. Month 4 responder rate
7. Month 5 responder rate
8. Month 6 responder rate
9. Day 7 responder rate.

If one of the tests in the sequence was not statistically significant ($p>0.05$), no confirmatory claims could have been made based on tests following (and including) that one. For the exploratory endpoints, no correction for multiplicity was used. P-values for these analyses were only shown for descriptive purposes.

- *Results*

A total of 300 subjects were randomised, and 297 subjects received study product. Three (1.0%) of the 300 randomised subjects did not receive study product; 2 subjects were randomised in error and 1 subject experienced presyncope and was withdrawn from the study. 92.0% randomised subjects completed the study and 8.0% subjects prematurely discontinued the study.

At Month 1, 96.3% in the QM1114-DP group compared with 4.5% in the placebo group were responders based on the GL-ILA 4-Point Photographic Scale at maximum frown (please see table below).

Table. Month 1 Responder Rate Based on the GL-ILA 4-Point Photographic Scale at Maximum Frown (Modified Intention-to-Treat Population)

Statistic	QM1114-DP (N=199)	Placebo (N=67)
Month 1, n (%)	192 (96.3)	3 (4.5)
Treatment difference, %[1,2]	--	91.8
95% confidence interval[1]	--	86.17, 97.44
P-value[3]	--	<0.001

GL-ILA: glabellar lines Investigator Live Assessment. N = number of subjects in modified intention-to-treat population; n = number of subjects in a specific category.
[1] 95% confidence interval for responder rates and difference were calculated using the normal approximation (Wald) method.
[2] Treatment difference was QM1114-DP – placebo (where difference >0 indicated a higher percentage of responders in the QM-1114-DP group).
[3] P-value was from the Cochran-Mantel-Haenszel test stratified by region. Sites were pooled based on United States geographic region (Central [3 sites], East [3 sites], and South [4 sites]), due to low enrollment at some sites.

The was used to assess treatment outcome from the subject's perspective. The mean total FLTSQ Appearance Module score at baseline (prior to treatment) was 42.6 in the QM1114-DP group and 46.8 in the placebo group. Subjects were more satisfied with their appearance following treatment at Month 1 in the QM1114-DP group (mean change from baseline: 34.5) compared with placebo (mean change from baseline: 1.8).

The mean FACE-Q psychological function Rasch-transformed total score at baseline was 71.8 in the QM1114-DP group and 70.3 in the placebo group. At Month 1, there was a mean increase from baseline of 13.5 in the QM1114-DP group and 0.6 in the placebo group.

Both the above measures are of relevance for the psychological impact both at baseline and after treatment.

Subgroup analyses

The subgroup analyses are hampered by small numbers. The major concern for effect-modification is the subgroup analysis concerning age ≥65. This cannot be reliably characterised in this study due to small numbers.

- ***Study 43QM1901***
  - *Study population*

Male or non-pregnant females, 18 years of age or older, with moderate-to-severe bilaterally symmetrical **lateral canthal lines** (grade of 2 or 3 on the 4-Point Photographic Scale) at maximum smile, as assessed by the Investigator (LCL-ILA) and graded as Level 2 or Level 3 on the 4-Point Photographic Scale at maximum smile, as assessed by subject (LCL-SLA), at baseline.

  - *Treatments*

For each treatment group (QM1114-DP solution and placebo), 0.6 mL was divided into six injections 0.1 mL per injection, 100 units/mL for a total dose of 60 U. Injection was made into 6 sites in the lateral canthal area. When lines in the lateral canthal region appeared both above and below the lateral canthus, injections were administered at sites both above and below the lateral canthus. In case lines in the lateral canthal region were mainly below the lateral canthus, injections were administered at the

sites at the level of, and below the lateral canthus. The injection site option for each subject was based on Investigator discretion and was to be consistent for the right and left treatment sides.

- *Primary endpoint*

The primary efficacy endpoint for study 43QM1901 was the responder rate based on the LCL-ILA of lateral canthal line severity at maximum smile at Month 1. A responder was defined as a subject who achieved a score of 0 or 1 in lateral canthal line severity on the LCL-ILA 4-Point Photographic Scale at Month 1 for both left and right sides.

- *Multiplicity*

To evaluate the effectiveness of QM1114-DP versus placebo in the treatment of moderate to severe LCL, the proportion of subjects who achieve 0 or 1 on the LCL-ILA at maximum smile at all post-treatment visits were compared using the CMH test, stratified by site. To control the type I error rate, the fixed sequence testing procedure was used for the secondary endpoints, which required no adjustment to the level of significance. However, the comparisons were to be made in a pre-specified order following the procedure bellow:

1. Primary analysis must be done first, prior to any other analysis.
Thereafter secondary analyses:
2. Day 14 responder rate
3. Month 2 responder rate
4. Month 3 responder rate
5. Month 4 responder rate
6. Month 5 responder rate
7. Month 6 responder rate
8. Day 7 responder rate.

If one of the tests in the sequence was not statistically significant ($p>0.05$), no confirmatory claims could have been made based on tests following (and including) that one. For the exploratory endpoints, no correction for multiplicity was used. P-values for these analyses were only shown for descriptive purposes.

- *Results*

A total of 303 subjects were randomised and received study product. A total of 290 (95.7%) randomised subjects completed the study and 13 (4.3%) subjects prematurely discontinued the study.

At Month 1, 87.2% in the QM1114-DP group compared with 11.9% in the placebo group were responders, defined as achievement of a score of 0 (none) or 1 (mild) in lateral canthal line severity for both sides (please see table below).

Table. Month 1 Responder Rate Based on the LCL-ILA 4-Point Photographic Scale at Maximum Smile (Modified Intention-to-Treat Population)

Statistic	QM1114-DP (N=204)	Placebo (N=69)
Month 1, n (%)	178 (87.2)	8 (11.9)
Treatment difference, %[1,2]	--	75.3
95% confidence interval[1]	--	66.14, 84.41
P-value[3]	--	<0.001

LCL-ILA: lateral canthal lines Investigator Live Assessment. N = number of subjects in modified intention-to-treat population; n = number of subjects who met the criteria.
[1] 95% confidence interval for responder rates and difference were calculated using the normal approximation (Wald) method.
[2] Treatment difference was QM1114-DP – placebo.
[3] P-value was from the Cochran-Mantel-Haenszel test stratified by site.

Similar results were observed using the observed cases method for the ITT, PP, safety, and mITT populations and using the baseline observation carried forward method for the mITT population.

The median number of days to treatment response based on the subject diary card was 2.0 days in the QM1114-DP group and could not be calculated for placebo, as less than 50% of subjects had a response.

The mean total FLTSQ Appearance Module score at baseline was 43.2 in the QM1114-DP group and 44.9 in the placebo group. The mean change in the QM1114-DP group was 29.0 compared with 2.0 in the placebo group.

The mean FACE-Q psychological function Rasch-transformed total score at baseline was 70.5 in the QM1114-DP group and 68.6 in the placebo group. At Month 1, the mean increase from baseline was 14.0 in the QM1114-DP group and 0.9 in the placebo group.

Subgroups

In subjects ≥65 years of age the response rate is notably lower (64.0%) compared to the younger age group (90.4%). This supports a remaining concern regarding the older age groups. The indication is therefore restricted to adult patients under 65 years of age. The difference seen in relation to severity is not considered unexpected and the magnitude of effect seen is high also in the Grade 3 group.

- ***Study 43QM1902***
    - *Study population*

Male or non-pregnant females, 18 years of age or older, with moderate-to-severe **bilaterally symmetrical lateral canthal lines** (grade of 2 or 3 on the 4-Point Photographic Scale) at maximum smile, as assessed by the Investigator (LCL-ILA) and graded as Level 2 or Level 3 on the 4-Point Photographic Scale at maximum smile, as assessed by subject (LCL-SLA) and with moderate-to-severe **glabellar lines** (grade of 2 or 3 on the 4-Point Photographic Scale) at maximum frown, as assessed by the Investigator (GL-ILA) and grade of 2 or 3 on the Static 4-Point Categorical Scale at maximum frown, as assessed by subject (GL-SLA), at baseline.

    - *Treatments*

Subjects received an injection in the lateral canthal region and/or glabellar region with QM1114-DP or placebo at baseline. The maximum total dose was 110 U (1.10 mL).

    - *Co-primary efficacy endpoints*

The co-primary efficacy endpoints for study 43QM1902 were the responder rates based on the GL-ILA of glabellar line severity at maximum frown at Month 1 and the LCL-ILA of lateral canthal line severity at maximum smile at Month 1. For the glabellar lines co-primary endpoint, a responder was defined as a subject who achieved a score of 0 or 1 on the GL-ILA scale at Month 1. For the lateral canthal lines co-primary endpoint, a responder was defined as a subject who achieved a score of 0 or 1 on the LCL-ILA scale at Month 1 for both left and right sides. However, the protocol and the SAP described the co-primary endpoints as a composite responder rate based on the GL-ILA and GL-SLA of GL severity at maximum frown at Month 1, and the composite responder rate based on the LCL-ILA and LCL-SLA of LCL severity at maximum smile at Month 1. A composite responder was to achieve a score of 0 or 1 and at least 2 grades improvement from baseline on both -ILA and -SLA scale concurrently.

The groups treated in 1 rhytid area alone (QM1114-DP in LCL/placebo in GL; placebo in LCL/QM1114-DP in GL treatment groups) and the group with concurrent lateral canthal line and glabellar line treatment (the QM1114-DP in LCL/QM1114-DP in GL treatment group) were analysed separately.

    - *Multiplicity*

To control the type I error rate among the 4 primary efficacy comparisons, the fixed sequence testing procedure was used, which required no adjustment to the level of significance. The comparisons were done in the following order:

1. Glabellar lines alone group versus placebo on the glabellar line scale (i.e., the placebo in LCL/QM1114-DP in GL group versus the placebo in LCL/placebo in GL group)

2. Glabellar lines + lateral canthal lines group versus placebo on the glabellar line scale (i.e., the QM1114-DP in LCL/QM1114-DP in GL group versus the placebo in LCL/placebo in GL group)

3. Lateral canthal lines alone group versus placebo on the lateral canthal line scale (i.e., the QM1114-DP in LCL/placebo in GL group versus the placebo in LCL/placebo in GL group)

4. Glabellar lines + lateral canthal lines group versus placebo on the lateral canthal line scale (i.e., the QM1114-DP in LCL/QM1114-DP in GL group versus the placebo in LCL/placebo in GL group).

- *Results*

A total of 413 subjects were randomised, and 412 subjects received study product. One of the 413 randomised subjects was randomised in error and did not receive study product. 93.5% randomised subjects completed the study and 6.5% prematurely discontinued the study.

At Month 1, 94.3% in the *GL QM1114-DP/LCL placebo* group and 96.3% in the *GL QM1114-DP/LCL QM1114-DP* group responded to treatment, compared to 1.8% in the *GL placebo/LCL placebo*, using the multiple imputation method for the mITT population as actually randomised (please see table below).

Table. Month 1 Responder Rate Based on the GL-ILA 4-Point Photographic Scale at Maximum Frown (Modified Intent-to-Treat Population as Actually Randomised)

Statistic	GL QM1114-DP/ LCL placebo (N=106)	GL placebo/ LCL placebo (N=55)	GL QM1114-DP/ LCL QM1114-DP (N=108)	GL placebo/ LCL placebo (N=55)
Month 1, n (%)	100 (94.3)	1 (1.8)	104 (96.3)	1 (1.8)
Treatment difference, %[1,2]	--	92.5	--	94.5
95% confidence interval[1]	--	86.88, 98.16	--	89.46, 99.49
P-value[3]	--	<0.001	--	<0.001

GL: glabellar lines; GL-ILA: glabellar lines Investigator Live Assessment; LCL: lateral canthal lines. N = number of subjects in modified intent-to-treat population; n = number of subjects who met the criterion.
[1] 95% confidence interval for responder rates and difference were calculated using the normal approximation (Wald) method.
[2] Difference = QM1114-DP responder rate – placebo responder rate (where difference >0 indicated a higher percentage of responders in the QM1114-DP group).
[3] P-value was from the Cochran-Mantel-Haenszel test stratified by site.

Using the other co-primary efficacy endpoint (based on the LCL-ILA 4-Point Photographic Scale), 78.1% in the *GL placebo/LCL QM1114-DP* group and 83.3% in the *GL QM1114-DP/LCL QM1114-DP* group responded to treatment, compared to 19.3% in the *GL placebo/LCL placebo*, using the multiple imputation method for the mITT population as actually randomised.

The mean total FLTSQ Appearance Module score at baselinewas 36.6, 37.7, 37.0, and 39.2 in the *GL QM1114-DP/LCL placebo*, *GL placebo/LCL QM1114-DP*, *GL QM1114-DP/LCL QM1114-DP*, and *GL placebo/LCL placebo* groups, respectively. The corresponding mean changes from baseline at 1 month were 9.2, 21.8, and 33.3, respective for the active treatment groups, compared to 1.1 in the placebo group.

Subgroups

In subjects ≥65 years of age in the GL placebo/LCL QM1114-DP group the response rate is notably lower (45.5%) compared to the younger age group (81.5%). Although the analysis is hampered by few subjects in the older age group, the result is consistent with study 901 and supports a remaining concern regarding the older age groups. The indication is therefore restricted to adult patients under 65 years of age.

Discussion and overall conclusion regarding statistical considerations

In Study 43QM1602, the primary endpoint was a responder rate based on the GL-ILA only. The responder was defined as a subject who achieved a score of 0 or 1 in glabellar line severity on the GL-

ILA 4-Point Photographic Scale of Glabellar Line Severity at maximum frown, at the Month 1 visit. However, according to the CSP and the SAP, the composite responder rate was to be evaluated at Month 1 using GL-ILA and GL-SLA at maximum frown; with a composite responder defined as a subject who achieves a score of 0 or 1 in glabellar line severity and at least 2 grades improvement from baseline on both the GL-ILA and GL-SLA scales concurrently.

In Study 43QM1901, the primary efficacy endpoint was the responder rate based on achievement of score 0 or 1 on the LCL-ILA of lateral canthal line severity at maximum smile at Month 1. However, according to the CSP, the primary endpoint was the composite responder rate defined as a subject who achieves grade 0 or 1 in LCL severity and at least 2 grades improvement from baseline on both the LCL-ILA and LCL-SLA scales concurrently.

In Study 43QM1902, the co-primary efficacy endpoints were the responder rates based on the GL-ILA of glabellar line severity at maximum frown at Month 1 and the LCL-ILA of lateral canthal line severity at maximum smile at Month 1. A response was defined by achievement of a score of 0 or 1 on the corresponding scale. However, the protocol and the SAP described the co-primary endpoints as a composite responder rate based on the GL-ILA and GL-SLA of GL severity at maximum frown at Month 1, and the composite responder rate based on the LCL-ILA and LCL-SLA of LCL severity at maximum smile at Month 1, where a response was defined by achievement of score of 0 or 1 and at least 2 grades improvement from baseline on both -ILA and -SLA scale concurrently.

It has been agreed in the scientific advice with MPA (2018) and BfArM (2019) to prepare separate statistical analysis plans for EU and US for the Phase 3 studies. The Applicant has clarified that different definitions of the primary endpoints were due to different requests for the submissions in US and EU. As the studies were all conducted in US, the respective protocols mainly reflect the US definition of the primary endpoint (which is a composite response based on both the Investigator and Subject assessments). However, the EU versions of the SAPs reflect the EU definition of the primary endpoint.

The primary efficacy endpoint was analysed using the Cochran-Mantel-Haenszel (CMH) test stratified by site (or region if pooled sites) at 5% significance level (2-sided). Although stratification by site was described in the SAP, analysis was stratified by region in Study 43QM1602, as the sites were pooled due to low subject enrollment counts at some sites. The pooling of study sites is acceptable.

The primary analysis was performed on the mITT population that excluded assessments via a remote visit. This is in line with the intended use of the GL-ILA as live assessment and is acceptable. In addition, primary analysis performed based on ITT population has been performed on request and the results supported the primary mITT analysis.

Missing data in the primary analysis was handled using multiple imputation with details provided in the SAP. Sensitivity analyses were performed using the baseline observation carried forward method, and also using the ITT observed cases. In addition, a sensitivity analysis of the primary efficacy endpoint was performed based on the PP population and the safety population to account for potential errors in randomisation. These sensitivity analyses as specified are not deemed to fully explore robustness of the primary efficacy results; however, may be sufficient given the obtained results. Secondary endpoints were analysed based on the observed cases in the ITT population, which may have caused bias. This is usual when missing data is not handled in the analysis.

For each study, the Type I error rate was adequately controlled at 5% using pre-specified fixed sequence testing procedure that included selected secondary endpoints (in studies 43QM1602 and 43QM1901), and the 4 co-primary comparisons in study 43QM1902, respectively.

There are two endpoints of special interest with no formal testing between the treatment groups: the Facial Lines Treatment Satisfaction Questionnaire and the FACE-Q psychological wellbeing scale. The data from these questionnaires was presented using descriptive statistics only. It was not prespecified what would constitute a meaningful change from baseline for an individual subject, or what level of between treatment difference that is clinically meaningful.

Few inconsistencies are detected in the calculations of responder rates in the primary analysis for each study. The Applicant has clarified that the responder rates were estimated using multiple imputation

procedure and that the number of responders was thereafter derived using the rates. Due to rounding of the number of responders to integer, the calculation of percentage based on the frequencies does not always equals the estimated percentage.

III.3.4 Clinical safety

The pharmacological mechanism of BoNT-A is well known, and there is substantial clinical experience from other approved BoNT-A products. The key safety concern is related to systemic exposure. There are no data indicating that the safety profile of QM1114-DP would be substantially different from other currently approved BoNT-A products.

- ***Exposure***

In total, 1847 patients have been treated with QM1114-DP and a dose ≥50U during the clinical development program. Of, these 945 were exposed in a randomised controlled trial setting. Considering the known safety profile of other BoNT-A products and the findings in these, the size of the safety populations assessed are sufficient.

- ***Adverse events***

In the pooled analysis of double-blind data, there were slightly fewer serious AEs in the QM1114-DP group than in the placebo group, but no serious AE was considered as related by the investigator.

  - *Related TEAEs*

Related TEAEs observed are consistent with known AEs of BoNT-A treatment of GLs and LCLs. Injection site pain, bruising, headache and eye disorders were the most common AEs.

  - *Remote and local toxin spread events*

There was no case with signs or symptoms of remote spread of toxin. With a dose of 50-110 U split in different injection sites, remote spread is expected to be rare.

There were subjects with clinically significant AEs suggestive of local spread of the toxin. The Applicant states that the risk of AEs occurring is reduced by using physicians who are experienced in the botulinum toxin injection technique. This should be reflected also in the SmPC 4.2.

Any eye disorder due to treatment with QM1114-DP solution is a collective term including a number of disorders. In the double-blind data of GL only and GL + LCL treatment the sum of all eye disorders had a frequency of 3.3 % and 2.12 %, respectively. The most common eye disorder was eyelid ptosis (2.56 % and 2.12 %), a known AE of BoNT-A treatment of GLs, but other eye disorders were also observed. The eye disorder part of the SmPC 4.8 section needs to reflect these findings.

  - *Hypersensitivity*

There was one case with non-serious related hypersensitivity in the placebo-controlled pool and 4 potential cases in the open-labelled study, yielding a hypersensitivity frequency of 2-3 per 1000 which is consistent with the with the SmPC of similar products. Hypersensitivity should be included in the list of undesired effects in the SmPC.

  - *Safety in special populations*

There were 866 QM1114-DP subjects <65 years in the QM1114-DP Treatment 50 U or Greater Pool and 79 QM1114-DP subjects ≥65 years. No new safety concern related to older age were identified but relatively few patients over the age of 65 have been exposed and the proportion with adverse events tends to be higher in this group.

  - *Pregnancy and lactation*

There are only limited data available from the use of BTX-A in pregnant women. Studies in animals have shown reproductive toxicity at high doses. In the absence of adequate and well controlled studies in pregnant women, the potential risk for humans is unknown. Hence, QM1114-DP solution should

not be used during pregnancy.

There is no information on whether BTX-A-HAC is excreted in human milk. The use of BTX A HAC solution during lactation cannot be recommended.

- ***Immunogenicity***

Analysis of BoNT/A immunogenicity

A standard multi-tiered approach consisting of screening, confirmation and titer was developed to evaluate anti-drug antibodies. Cutpoints were determined in healthy subjects using state of the art procedures.

The drug substance QM1114-DS was coated onto a 96 well plate, after which subject serum samples were added allowing any ADA present in the serum to bind specifically to the bound QM1114-DS. A secondary anti-human IgG/IgM/IgA antibody conjugated with Horse Radish Peroxidase (HRP) was used for detection. When adding the enzyme substrate 3,3',5,5'-Tetramethylbenzidine (TMB) a signal in form of color change, proportional to the amount of bound ADA, was included.

As for neutralisation assay, no suitable cell-based alternative was available. The applicant developed a Mouse Protection Assay (MPA) instead. This method is questionable, however given the low immunogenicity potential of BoNT/A, the nAb analysis is not considered essential. No issues are raised for the nAb method. In a worst-case scenario, it could be considered that all ADA positive samples are also nAb positive.

Immunogenicity in clinical study

Table 1. Summary of ADA confirmatory ELISA Assay Positives Across Treatment Types/Dose

Treatment type/dose	Number of Subjects with ELISA Assay Positive Sample(s)	Total Number of Samples ELISA Assay Positive
QM1114-DP 50 units or greater (N=1699)	22	24
QM1114-DP less than 50 units* (N=220)	1	3
Placebo (N=265)	1	1
Total (N=2184)	24	28

All subject samples that were found positive in the confirmatory ELISA assay were negative in the MPA.

Low immunogenicity can be concluded for BoNT/A.

Risk Management Plan

The Applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Relfydess.

Part II Safety specification

Important identified risks	• None
Important potential risks	• None
Missing information	• None

The Applicant initially proposed two important potential risks, *distant spread of toxin* and *hypersensitivity*. These have, upon request from the RMS, been removed from the summary of safety concerns.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment

The submitted Risk Management Plan, *version 3.1 received 2024-07-24 is acceptable*.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Background

QM1114-DP is a new BoNT-A product which is presented as a liquid formulation manufactured and formulated without any animal or human proteins. It is intended for the treatment of moderate-to-severe GL and LCL in in adult patients under 65 years, when the severity of these lines has an important psychological impact on the patient.

Quality

The quality part of the file is of acceptable standard. There are no outstanding issues.

Efficacy and safety

The characterisation of efficacy in the current application mainly rests on the placebo-controlled phase

III trials (studies 602, 901, and 902). All three trials demonstrate a high proportion of responders to treatment with QM1114-DP, compared to very low proportions of responders in the placebo groups. The effect is also translated into outcome measures reflecting psychological impact and patient satisfaction with treatment. The characterisation of efficacy overall demonstrate a treatment effect of relevant magnitude, in line with what is expected from BoNT-A.

All clinical studies in phase 2/3 were conducted in the US and Canada only, with no study site in the EU. While the efficacy and safety profile of BoNT-A in general is well-established with considerable experience also from EU-approve products, the effect can in theory be related to ethnicity and skin type. The Applicant has, however, provided sufficient justification for transportability of all study results and general conclusions on efficacy and safety to the EU target population.

It is agreed with the Applicant that the apparent decline in efficacy over repeated treatment cycles can mainly be related to a patient selection over time. It is in line with comparable products acceptable to present in the SmPC section 5.1 results from the subset of patients that receive repeated treatments over time. No new concern for efficacy over repeated treatments has been identified.

The pharmacological mechanism of BoNT-A is well known, and there is substantial clinical experience from other approved BoNT-A products as a basis for the characterisation of safety. The key safety concern is related to systemic exposure. There are no data indicating that the safety profile of QM1114-DP would be substantially different from other currently approved BoNT-A products.

In total, 1847 patients have been treated with QM1114-DP and a dose ≥50U during the clinical development program. Of, these 945 were exposed in a randomised controlled trial setting. No new safety concerns have been identified. The safety profile is as expected from BoNT-A products. The immunogenicity is low.

Conclusion on benefit-risk relation

The quality of the product Relfydess is found adequate. There are no objections to approval of Relfydess, from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Relfydess, 100 units/ml, Solution for injection was positively finalised on 2024-07-28.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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