LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Alluzience
(clostridium botulinum neurotoxin type A haemagglutinin complex)

SE/H/2019/01/DC
2019-1344

This module reflects the scientific discussion for the approval of Alluzience. The procedure was finalised on 2021-06-10. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Ipsen Pharma has applied for a marketing authorisation for Alluzience, 200 U/ml, Solution for injection. The active substance is Clostridium botulinum neurotoxin type A haemagglutinin complex (BTX-A-HAC). BTX A HAC is a highly potent toxin that acts selectively on the peripheral cholinergic nerve endings by targeting the synaptosomal associated protein (SNAP) and thereby inhibiting acetylcholine release, thus preventing the nerve from activating the muscles. The resulting temporary muscle denervation and relaxation has e.g. been shown to reduce the appearance of facial lines and folds by a long-lasting but reversible paralysis of injected muscle. When transmittor release from nerve endings is blocked, the neuromuscular junction responds as though it has been denervated. In response to the chemical denervation axonal sprouting occurs, in which the nerve fibre grows new nerve terminals to innervate the muscles that have lost functional input due to the blockade of nerve ending exocytosis. When the new fibres make functional contact with the underlying muscle, some or all the function is restored.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

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

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

Botulinum toxin haemagglutinin complex type A (BTX-A-HAC) is the active component in BTX-A-HAC *Solution* formulation as well as in the BTX-A-HAC lyophilised *Powder* formulation. Since the BTX-A-HAC *Powder* for reconstitution products, Dysport and Azzalure, have been marketed by Ipsen for >10 years, the pharmacological and toxicological properties of BTX-A-HAC is regarded as well established.

BTX-A-HAC is a complex of BTX-A with haemagglutinin (HA) and nontoxin nonhaemagglutinin proteins, which is isolated and purified from C. botulinum type-A bacteria. The excipients used in the manufacture of BTX A HAC *Solution* are of European Pharmacopoeia or National Formulary quality. The BTX-A-HAC *Solution* has been developed without any human or animal derived excipients (i.e. human serum albumin and lactose, which are found in the *Powder* formulation) in order to limit the potential for sensitization (the excipients are listed in section III.1 Quality aspects/ Drug product/ Table: Composition of BTX-A-HAC *Solution* drug product).

III.1 Pharmacology

BTX A HAC is a highly potent toxin that acts selectively on the peripheral cholinergic nerve endings by targeting the synaptosomal associated protein (SNAP) and thereby inhibiting acetylcholine release, thus preventing the nerve from activating the muscles. The resulting temporary muscle denervation and relaxation has e.g. been shown to reduce the appearance of facial lines and folds by a long-lasting but reversible paralysis of injected muscle. When transmittor release from nerve endings is blocked, the neuromuscular junction responds as though it has been denervated. In response to the chemical denervation axonal sprouting occurs, in which the nerve fibre grows new nerve terminals to innervate the muscles that have lost functional input due to the blockade of nerve ending exocytosis. When the new fibres make functional contact with the underlying muscle, some or all the function is restored.

In the current application, a limited non-clinical pharmacology package is presented in order to show that the pharmacology profile of the new BTX-A-HAC *Solution* formulation is essentially the same as for the approved BTX-A-HAC *Powder* formulation. The intention is to demonstrate these results are in agreement with the initial pharmacology studies conducted with the BTX A HAC *Powder* formulation and, based on the similarity of the pharmacodynamic and also toxicological profiles of the two formulations, be able to suggest that data from the *Powder* formulation can be considered supportive in the current application for the *Solution* formulation. For this purpose, three studies on the in vivo pharmacodynamic effect are presented. However, no in vitro pharmacology studies were carried out by the applicant since the general primary pharmacodynamic profile of BTX A HAC is well established and available in the literature. This is considered acceptable.

The comparison of treatments with the BTX A HAC *Solution* and the BTX A HAC *Powder* formulation was conducted in established small rodent models, a mouse grip test, the rat muscle force test and the mouse digit abduction score (DAS) test.

In the grip strength test, 2 U of either BTX A HAC *Solution* or BTX A HAC *Powder* was administered by a single injection into the left flexor carpi radialis (FCR) muscle of 7 male mice per group. Grip strength was measured before treatment (Day 1/baseline), at 5 hours, on day 1, 3, 6, 14, 21, 28 and on day 35 after injection, until recovery to baseline strength. The body weights were recorded at the same intervals. After treatment with either of the two BTX A HAC formulations, maximal reduction of grip strength occurred at median 3 days after injection (BTX A HAC *Solution* resulted in 64±2.4% reduction from baseline and BTX A HAC *Powder* 63±1.8%), with progressive recovery thereafter until the grip strength no longer was significantly different from baseline that occurred at Day 35. In the negative control groups, an increase in grip strength associated with gain in body weight was observed. Thus, both formulations of BTX A HAC (*Solution* and *Powder*) elicited

similar muscle weakening effects after i.m. injection in the mouse fore limb. Apart from symptoms of paralysis including digit abduction, the only notable clinical observation was a decrease in body weight for both BTX A HAC *Solution* and *Powder* treated groups, peaking 3 days after injection, thereafter progressively increasing, returning to baseline values on Day 14 and reaching control values on Day 35.

In the rat muscle force test, 0.1 or 1 U of either BTX A HAC *Solution* or BTX A HAC *Powder* was administered by a single injection in the gastrocnemius muscle of the left hind limb. Muscle force was measured in both the injected and the contralateral limbs prior to injection and on Day 1, 3, 5, 7, 14, 21, 35, 42, 49 and 56 post injection. The body weight and food consumption were recorded at the same intervals. Both formulations of BTX A HAC (*Powder* and *Solution*) showed similar dose dependent effects on the reduction in muscle force in the injected limb of rats. For BTX A HAC *Solution* 0.1 U resulted in ~60% and 1 U in ~80% muscle force reduction (injected limb) that were similar in all animals and remained significantly different ($p<0.05$) from control values until Day 56 in the 0.1 U group and throughout the study in the 1 U treated group. The percent of initial muscle force*days AUC (Mean±SE) for 0.1 U was 3991.9±204.6 and for 1 U, 1141.8±63.2. Treatment with BTX A HAC *Powder* resulted in the same muscle force reduction that remained significantly different ($p<0.05$) from control values until Day 35 in the 0.1 U group and throughout the study in the 1 U treated group, the AUC (Mean±SE) for 0.1 U was 3356.5±311.3 and for 1 U, 1250.4±114.8. In the contralateral hind limb, in the 1 U treated groups, a reduction in muscle force of approximately 30% was measured from Day 3 through to Day 35 for BTX A HAC *Powder* and to Day 28 for BTX A HAC *Solution*. This effect was similar for both formulations. No reduction in contralateral muscle force observed in the 0.1 U groups or after buffer treatment as negative control.

The mouse digit abduction score (DAS) test was assessed during a study which was conducted to investigate the immunogenicity of both the *Solution* and *Powder* formulations following monthly i.m. administration for 6 months. 1 U of either BTX A HAC *Solution* or BTX A HAC *Powder* was administered by repeated injections in the gastrocnemius muscle of the right rear limb. DAS was collected under blinded conditions, at pre-dose and on day 1, 3, 7, 10, 14, 18, 21, 25 and 28 after each administration. Both formulations of BTX A HAC (*Powder* and *Solution*) showed similar mean peak DAS values and DAS profiles in each dosing interval. At the end of the study, after the sixth administration, the following data were recorded for the BTX A HAC *Solution*/ *Powder* formulations, respectively: Emax (mean score±SD) 3.4±0.8 /3.4±0.7 ; Tmax (mean day± SD) 2.6 ± 3.4 / 3.0 ± 3.1; DAS AUCτ (mean±SD) value observed within each dosing interval 50.3±17.9 / 54.1±19.9.
It was noted and explained in a study report amendment, that data from a prefilled syringe (PFS) batch were presented as derived from treatment with BTX A HAC *Solution* (the two containing the same product formulation), since the liquid in vial (LIV) batch used in this study was not considered representative of the proposed clinical/ commercial product. This is considered acceptable.

In addition, four studies were reported that supported the initial BTX A HAC *Powder* formulation. In summary these showed a dose-dependent reduction in muscle force in the rat gastrocnemius muscle force model as well as a dose-related recovery and duration of effect. At higher doses (>1 U) systemic effects were observed as a decrease in body weight and reduced muscle force also in the contralateral muscle. At the higher dose levels, no clear dose-related effects on muscle force was observed. Reduction in muscle mass in adjacent muscles as well as inhibition of glycogen depletion after electrically stimulated muscle contractions indicated some spreading of toxin to adjacent muscles at doses were no systemic effects was observed. Furthermore, different independent batches of BTX A HAC bulk active substance was tested in the rat muscle force model with similar results.

III.2 Pharmacokinetics

In general, it is challenging to monitor pharmacokinetic parameters for Clostridium botulinum toxins. Due to their extremely high potency, only very low doses need to be administered, which in this case would result in samples with a BTX A HAC concentration too low for the sensitivity of most of the

existing bioanalytical methods. For this reason, the information on the PK and distribution of BTX A in the current application were restricted to data from the literature. Moreover, no formulation analyses were performed for the non-clinical studies due to the absence of a suitable analytical method.

A single new PK-related study was conducted, comparing the potential immunogenic effect of various formulation approaches of HSA-free BTX A HAC *Solution*, as compared to the initial formulation of BTX A HAC *Powder*. Male MF 1 mice were treated monthly by i.m. injections for 6 months. Putative anti-BTX A HAC antibodies in serum were then determined following a radioimmunoprecipitation assay (RIPA). Four groups (20 mice/group) were treated i.m. with saline (negative control group), BTX A HAC *Powder* (reference control group) or HSA free BTX A HAC *Solution* formulated as either a Pre-Filled Syringe (PFS) or Liquid in vial (LIV) formulation. Each animal received a total of six i.m. injections (28 days apart) into the gastrocnemius muscle of the right rear leg of saline (2 µL) or of either reference or test formulations at a dose of 1 U of BTX A HAC per animal. Blood samples were collected at predose and 14 days after each treatment administration. Data for the prefilled syringe (PFS) batch are presented herein, as the liquid in vial (LIV) batch used was not considered representative of the proposed clinical/commercial product. As the LIV and PFS presentations contained the same product formulation, data from the PFS batch were considered supportive of the immunogenicity of the BTX-A-HAC *Solution*.

The number of animals positive for BTX A HAC antibodies was not statistically significantly different between the two formulations 14 days after the sixth and final administration of treatment (0/13 and 2/13 for the BTX A HAC *Solution* and *Powder*, respectively; p=0.4841, Fisher Exact test). In the negative control group (saline), 1/14 mice had a positive response for BTX A HAC antibodies. Furthermore, at the same time point, there were no significant differences in the mean percentage of precipitation between the BTX A HAC *Solution* and the BTX A HAC *Powder* (1.45±0.09 versus 1.85±0.25; p=0.1701). The terminal blood samples were collected by heart puncture, analysed and presented in a separate report with similar results ((0/19 and 1/19 animals positive for BTX A HAC antibodies following treatment with the BTX A HAC *Solution* and *Powder* formulations, respectively. The applicant concluded that in this mouse preclinical model, the immunogenicity of the BTX A HAC *Solution* is low and comparable to that of the BTX A HAC *Powder*.
(In addition, the effect on muscle activity in these mice was also evaluated in parallel to the DAS test, as described in the non-clinical pharmacology section).

A distribution and mass balance study from the literature were reported that supported the initial BTX A HAC *Powder* formulation approval. Radioiodinated botulinum toxin A (BoNT/A),^{125}I-labelled BoNT/A, was injected into the gastrocnemius muscle of SD rats at a high dose (1.91 ng, ≈344 U) or a lower and clinically relevant dose (0.37 ng, ≈67 U). Most of the injected radioactivity in the high dose (93%) was recovered 48 hours after injection, demonstrating good mass balance. ^{125}I-labelled BoNT/A were primarily excreted in the urine. During the 0.5 to 48-hour period, ≈65% of the radioactivity recovered from the injection site was precipitable by trichloroacetic acid (TCA), indicating that it was still part of macromolecules. Recovered radioactivity at the injection site after injection of the high dose were 66.6, 39.6, 18,7, 4.8 and 1.5 % at 0.5, 2, 6, 24, and 48 hours after injection; after injection of the low dose, ~60 and ~2 % after 0.5 and 24 hours after injection. After injection of the high dose, radioactivity levels in plasma increased to a maximum of 3.9% at 6 hours, and subsequently declined thereafter. This radioactive material was predominantly associated with TCA-precipitable proteins in blood. Outside the injection site, the highest amounts of radioactivity were detected in the thyroid and in the skin. Less than 5% of the dosed radioactivity was recovered from the noninjected contralateral gastrocnemius muscle, as well as the gastrointestinal tract tissue, with <2% recovered from the liver. Minimal levels of radioactivity were detected (<1%) at any time in the sciatic nerve, brain, lungs or kidneys. Most radioactive material from the distant sites could not be precipitated with TCA.
The applicant concludes these data suggest that the majority of toxin remained localised at the site of the injection and that any radioactivity recovered from distant tissues was mainly either low molecular weight ^{125}I-containing protein/peptides or ^{125}I iodide.

III.3 Toxicology

For the current application, two new toxicity studies in rats have been carried out, one single dose with the BTX A HAC *Solution* formulation and a concurrent study with the BTX A HAC *Powder* formulation. Based on these two studies, a comparison of the safety profile of the two formulations tested under strictly the same conditions were carried out in order to demonstrate the effects after treatment with the BTX A HAC *Solution* were in agreement with the effects in the initial toxicology package conducted with the BTX A HAC *Powder* formulation. In that package, a number of initial toxicology studies, including repeat dose toxicity and a complete series of reproductive studies, had been conducted with the *Powder* formulation that formed the basis of the initial approval of BTX A HAC. These already approved studies are just briefly commented in the current assessment in order to provide an overview of the toxicology profile for BTX A HAC. The toxicology studies were conducted in rat, rabbit and dog. Overall, they were complying with current International Conference on Harmonisation (ICH) guidelines and Good Laboratory Practice (GLP) regulations. No toxicokinetic studies were warranted for this locally administered biological product.

Thus, two separate but concurrent single dose toxicology studies have been completed to support the development of the proposed liquid formulation. The studies were carried out with the proposed BTX A HAC *Solution* formulation and with the already approved BTX A HAC *Powder* formulation, respectively. These studies were designed to evaluate the histopathological changes in muscles and nerves of rats following a single i.m. administration. The reversibility of any findings following a 12-week treatment free period was also assessed.
In each study, a group of 18 male and 18 female Sprague Dawley rats received 6 U of BTX A HAC *Solution* or BTX A HAC *Powder* by injection into the left gastrocnemius muscle. A similar volume of vehicle (physiological saline; 0.9% sodium chloride) was injected into the right gastrocnemius muscle. In each study, a control group of 18 males and 18 females received placebo in the left gastrocnemius muscle and vehicle in the right muscle. Morbidity/mortality checks were performed at least twice daily and clinical observations were performed daily. A full clinical examination was performed weekly. Body weights and food consumption were recorded at least weekly. Subgroups of six males and six females were sacrificed 7, 30 or 91 days after dosing. Selected organs were weighted, and selected tissues were examined histopathologically for all animals.
There were no unscheduled deaths during either study. Body weight changes, clinical observations and organ weight changes, as well as macroscopic and microscopic observations for the same dose, were identical for both the BTX A HAC formulations. Clinically, the only test article related sign was an apparent shrinkage of the treated (left) gastrocnemius muscle in comparison with the control (right) muscle in all treated animals from 1 week after dosing, persisting until the end of the studies. Overall, these data demonstrate that single i.m. administration of BTX A HAC *Solution* to Sprague Dawley rats at a dose of 6 U was associated with histopathological findings of a reduction of fibre size in the injected and adjacent muscles, which was associated clinically with an apparent shrinkage of the injected muscle accompanied with limping until Day 49. The effects were most marked 1 month after injection and although effects were still evident at the end of the study, partial recovery was observed. No test article related findings in the nerves were observed. All effects reported for BTX A HAC *Solution* were identical to those observed following administration of BTX A HAC *Powder*.
The applicant concluded, based on the essentially identical results between the two concurrent single-dose toxicology studies with the *Solution* and *Powder* formulations, that additional repeat-dose toxicology studies with the BTX-A-HAC *Solution* were not warranted. This is agreed.

The following toxicology studies presented, were derived from the initial approval of the BTX A HAC *Powder* formulation. Since these have been part of the document for an already approved product, with the same active component, they are just briefly discussed here.

In addition to the single-dose studies carried out for the BTX A HAC *Solution* application, a single-dose toxicology study had been conducted with the *Powder* formulation with similar results as in the studies above. Moreover, a number of repeat-dose toxicity studies, including recovery periods, had

been conducted with the *Powder* formulation. In one study, five to six doses of BTX A HAC (1 U, 4 U or 12 U per animal and injection) were administered into the left and right gluteus muscles at 4-week intervals. In another study, three doses of BTX A HAC (0.1 U or 2 U per animal and injection) were administered into the left gastrocnemius muscle at 4-week intervals.
The results showed a body weight loss or reduction in body weight gain at the highest tested doses (12 U repeat dose persisting up to the end of the 4-week recovery period), associated with a reduction in the size of the injected muscle(s). Treatment was locally well tolerated, and no toxicological adverse finding was reported throughout these studies besides the known pharmacology of the drug. Histopathological effects on injected muscles (decrease in myofibre size) were also reported and were considered to be related to the pharmacological activity of BTX A HAC. Generally, these effects were partially reversible 4 weeks after injection. No evident long-term impairment of neuromuscular function was reported. At the highest tested doses, some decrease in myofibre size was noted also in the adjacent thigh muscle.

A complete series of reproductive studies (fertility, embryofoetal and pre and postnatal studies) with the BTX A HAC *Powder* were included in the package underlying the approval of the BTX A HAC *Powder* formulation. In addition to the pivotal studies described in the following, a series of dose range finding studies in nonpregnant and pregnant rats and rabbits was performed in order to ascertain the most appropriate dosing schedule (comparing daily to weekly administration regimen) and the corresponding total doses consistent with successful mating and gestation, while limiting hind limb paralysis related to the pharmacological activity of the BTX A HAC that could have impaired successful evaluation.

In a Fertility and Early Embryonic Development to Implantation study in the rat (segment I), BTX-A-HAC was administered by weekly i.m. injection to male and female rats. The males were treated with weekly injections into both gluteus muscles (25 µL in each muscle) at dose levels of 1, 2.5, 5 and 10 U/adm, respectively. They received four weekly injections before mating and a further three injections before termination on completion of the 2-week pairing period (total dose: 7, 17.5, 35 and 70 U, respectively). The females were treated weekly at dose levels of 1.5, 4, 8 and 16 U/adm, respectively, receiving two treatments before pairing and were then treated throughout mating and up to Day 7 of gestation, thus receiving at least four treatments in total (total dose; 6, 16, 32 and 64 U, respectively). A control group received the BTX-A-HAC placebo. The inseminated females were submitted to a caesarean examination on Day 13 of gestation and litter parameters were recorded. The males underwent necropsy after the end of the 14-day mating period; the testes and epididymides were weighed and used for sperm analysis. The ovaries of the females were also weighed.

No evidence of systemic toxicity was observed, besides already reported effects (i.e. a reduction in muscle size in all groups; localised muscle paralysis at the highest dose; dose related reduction in body weight gain associated with a reduction in food consumption at the two highest doses). No effects on fertility or implantation parameters at doses up to and including 8 U. The high dose level of 10 U/adm in males and 16 U/adm in females was above the maximal tolerated dose, as indicated by marked reductions in body weight, a slight reduction in food consumption, clinical signs (slight localised muscular paralysis and muscle atrophy). In addition, mating was impaired at the high dose, likely due to paresis and loss of general condition. The high intermediate dose was close to the maximal tolerated dose. The no observed adverse effect level (NOAEL) for fertility and general reproduction performance was 5 U/week for males and 8 U/week for females.

In an *Embryofoetal Development study in the rat (segment II),* BTX-A-HAC was administered by daily i.m. injection at dose levels of 0.5, 1.5 and 5 U/adm to mated female rats from Day 6–17 of gestation inclusive (corresponding to a total dose of 6, 18 and 60 U, respectively). A similar group of rats was treated with BTX-A-HAC by intermittent injection at a dose level of 10 U/adm on Day 6 and 12 of gestation only, corresponding to a total dose of 20 U. A saline control group was treated with physiological saline (0.9% NaCl) by daily injection. A second control group was treated with a placebo formulation. Each right and left gluteus muscle was injected. The females were submitted to a caesarean examination on Day 20 of gestation and litter parameters were recorded. At necropsy, the

females were examined macroscopically, and live foetuses were weighed, sexed and examined for external abnormalities. Half of the foetuses were examined internally prior to processing for skeletal examination. The remaining foetuses were preserved for fixed visceral examination.
No adverse clinical signs were observed. At the highest doses of 5 and 10 U, an increase in embryolethality, together with decreased body weight gain and food consumption, were reported. Foetal weights were comparable across all groups and there was no indication of teratogenicity. The maternal no observed effect level (NOEL) was set to 0.5 U and the developmental NOEL to 1.5 U.

In an *Embryo toxicity study in the rabbit (segment II)*, BTX-A-HAC was administered by daily i.m. injection at dose levels of 1, 10 and 20 U/adm to mated female rabbits from Days 6–19 of gestation inclusive (total dose: 14 U, 140 U and 280 U, respectively). Finally, only 11/22 rabbits were treated at 20 U/adm daily dose in view of the mortality of the initially treated rabbits. A further group of 22 rabbits was treated with BTX-A-HAC by intermittent i.m. injection at a dose level of 40 U/adm on Days 6 and 13 of gestation, corresponding to 80 U total dose. A control group was treated with physiological saline and another with placebo. The injections were performed in the right or left biceps femoris muscles (at 1, 10, 20 and 40 U/adm, respectively). All surviving females were euthanised on Day 29 of gestation for examination of their uterine contents. At necropsy, the females were examined macroscopically, and live foetuses were weighed. The foetuses were examined for external and visceral abnormalities, sexed and processed for skeletal examination. The heads of approximately half of the foetuses were examined internally by serial sectioning.
All dams treated at 20 U died or were sacrificed in a moribund condition. Premortem signs included body weight loss, decreased food consumption and muscle paralysis related to the pharmacological activity of BTX A HAC. One female treated at 40 U was sacrificed on Day 24; premortem signs were body weight reduction and abortion. No adverse clinical signs were observed up to a dose of 10 U. The doses of 10 U and 40 U resulted in decreased body weight gain and even body weight loss, which were associated with decreased food consumption*. Data from the caesarean sections indicated that there were no effects of BTX A HAC on pre and post implantation loss across the surviving treated females. Foetal survival and weights were not affected. There was no evidence of a toxin related teratogenic effect. The NOEL was considered to be 1 U for the maternal and the developmental toxicity.
* A second dose range finding (DRF) embryofoetal development study was carried out with the objective to provide information on the consequences of administration of doses ranging between 15 U and 20 U per animal in order to select appropriate dose levels for a subsequent embryofoetal development study in the rabbit. Pregnant females received daily doses of either BTX A HAC (15, 17 or 20 U per animal) or placebo from Days 6-19 of gestation into the biceps femoris muscles.
The dose levels of 15, 17 and 20 U/rabbit/day were above the maximum tolerated dose in the pregnant rabbit resulting in maternal toxicity. Based on these data, the high dose to be used in a further main embryotoxicity study in the rabbit should be lower than 15 U/rabbit/day in order to induce slight to moderate toxicity. The applicant concluded, these results corroborated the results of the previously conducted and submitted pivotal study, thereby obviating the need to conduct an additional pivotal study.

In a *Pre and Postnatal Development Study in the Rat (Segment III)*, BTX-A-HAC was administered once weekly by i.m. injection to mated female rats in both gluteus muscles at dose levels of 1, 2.5, 5 and 10 U/adm from Day 6 of gestation until weaning (Day 21 of lactation inclusive). There was a total of six injections (i.e. on Days 6, 13, 20 of gestation and on Days 6, 13 and 20 of lactation) resulting in a total dose of 6, 15, 30 and 60 U, respectively. A control group received placebo. Litter parameters were recorded up to Day 21 postpartum. One male and one female pup were selected from each litter to form the first generation (F1). The dams and unselected pups underwent necropsy at weaning. The selected F1 offspring were maintained untreated for monitoring of postweaning development, behavioural tests and mating to form a second generation. Body weights of the F1 females were recorded up to mating and during gestation. Body weights of the F1 males were monitored up to necropsy. The study was terminated with the necropsy of the F1 males after the caesarean examinations of the F1 females on Day 13 of gestation. All F0 and F1 animals were submitted to a macroscopic examination. The uterus of F1 and F0 females, the macroscopic lesions of F0 animals and

the gluteus muscles of some F0 females were preserved in formalin. The pregnancy status, number of corpora lutea, and numbers and types of uterine implantations were determined from the caesarean of the F1 females.
Apparent dose related reduction in the size of the injected muscle that developed over time (except at 1 U) was observed, attributable to the pharmacological activity of BTX A HAC. Additionally, a reduction in body weight gain occurred at doses of 5 & 10 U. No effects on in utero survival or subsequent survival and functional development were seen. No effect in the first generation (F1) on survival, body weights, sexual maturation, postweaning development or mating performance, or fertility were recorded. All offspring of the F1 generation appeared normal. The dose of 2.5 U was the NOEL for maternal toxicity and the high dose of 10 U was the NOEL for the F1 generation.

Local tolerance observations were conducted in the single- or repeat dose studies with IM injections of BTX-A-HAC *Powder* in rats and rabbits as well as in the single dose study with BTX-A-HAC *Solution* in rats. The BTX-A-HAC was well tolerated at the site of injection as no signs of irritation such as bruising, haematoma, indurations or redness were observed in any species. Microscopic evaluation of the muscle injected did not reveal any BTX-A-HAC-related signs of local toxicity, such as necrosis or inflammation. Moreover, an ocular local tolerance study had been conducted in the rabbit. A single topical administration of 20 U BTX-A-HAC *Powder* formulation in saline was applied into the inferior conjunctival sac of the right eye. No signs of ocular irritation, ptosis or effects on the ocular alignment were observed.

A study had also been conducted in dogs, where BTX A HAC *Powde*r was administered once by i.m. (approximately 200 U total dose), oral or percutaneous routes (approximately 200 U total dose) or by continuous intravenous infusion (approximately 100 U/hour/animal). No signs of local or systemic toxicity were seen after any of the treatments. The applicant concluded; the results indicated that the rat can be considered more sensitive to the effects of BTX A HAC than the dog.

No genotoxicity or carcinogenicity studies have been conducted for this biotechnology derived biologic product. In absence of genotoxicity or carcinogenicity concern, this is according to guidelines.

III.4 Ecotoxicity/environmental risk assessment

An ERA was enclosed, pointing out that the BTX A HAC product pose no risk to the environment.

III.5 Discussion on the non-clinical aspects

The primary pharmacodynamic profile of botulinum toxin haemagglutinin complex type A (BTX A HAC) is well established and is based primarily on the available literature. No in vitro pharmacology studies were carried out by the applicant, which is accepted. The present application present data from three new in vivo studies with the aim to demonstrate the new BTX A HAC *Solution* formulation result in comparable in vivo effects to the approved BTX A HAC *Powder* formulation.

The current results demonstrate that both formulations of BTX A HAC (*Solution* and *Powder*) elicited similar muscle weakening effects. The new studies comparing the two products are in agreement with the initial pharmacology studies conducted with the BTX A HAC *Powder* formulation, i.e demonstrating similar and predictable reduction in force generation in the injected muscle with a predictable time course of recovery. Thus, it is concluded that the previous studies, presented in the already approved MAA for BTX A HAC *Powder*, also apply for the current BTX A HAC *Solution* formulation and no further in vivo pharmacology studies are needed.

No secondary pharmacodynamic, safety pharmacology or drug interaction studies of BTX A HAC *Powder* or *Solution* formulations have been conducted in animals for the current application. The

absence of such studies for BTX A HAC, is accepted since the safety profile of BTX is well established from its use in the clinical setting.

The information on the pharmacokinetics and distribution of BTX A were restricted to data from the literature using radioiodinated (^{125}I) botulinum type A purified 150 kDa neurotoxin (BoNT/A). The extreme potency of BTX and the lack of sufficiently sensitive bioanalytical methods makes it difficult to conduct regular pharmacokinetic studies. Acknowledging those circumstances, the limited size of the pharmacokinetic package was previously accepted during the approval of BTX A HAC *Powder* and no additional non-clinical pharmacokinetic studies are considered to be needed for the present application.

The applicant suggested, based on the referred literature data on a distribution and mass balance study, that the majority of toxin remained localised at the site of the injection and that any radioactivity recovered from distant tissues was mainly either low molecular weight ^{125}I-containing protein/peptides or ^{125}I iodide.

A single new PK-related study was conducted, comparing the immunogenicity of BTX-A-HAC *Solution* vs the *Powder* formulation. The results from this mouse model, with several repeated i.m. administrations with sufficient time in between to develop and boost a putative immune response, showed that only a low frequency of antidrug antibodies (ADA) could be detected at a level close to what was observed also in the control group. It is acknowledged that immunogenicity data from animal models in general have limited translational value for the clinical situation and that immunogenicity have to be monitored in clinical safety.

The presented new studies were designed to confirm a similar toxicological (and pharmacological) profile between the new injectable liquid formulation of BTX A HAC *Solution* and the BTX A HAC *Powder* formulation. Based on the two new single dose toxicity studies, the toxicology profile of the proposed BTX A HAC *Solution* formulation was shown to be as expected and identical to that observed following administration of the already approved BTX A HAC *Powder* formulation under the same experimental conditions. In addition, the observed effects were consistent with the intended pharmacological action of BTX. Given these circumstances, it is agreed that no additional repeat-dose toxicology studies with the BTX-A-HAC *Solution* is needed.

Evaluation of repeated dose toxicity, genotoxicity, carcinogenic potential, reproduction and development toxicity and local tolerance have previously been performed for the already approved product BTX A HAC *Powder* formulation. These studies rise no points for concern and are considered to be valid also for the new product BTX A HAC *Solution* formulation. No additional toxicity studies are required.

In conclusion, the new studies presented confirms that data for the BTX A HAC *Powder* formulation are relevant to include in the approval of the BTX A HAC *Solution* formulation for the proposed indication based on the similarity of the toxicological as well as pharmacodynamic profiles of the two formulations. Overall, there are no objections for approval of BTX A HAC *Solution* formulation based on the non-clinical studies.

IV. CLINICAL ASPECTS

IV.1 Introduction

Botulinum toxin haemagglutinin complex type A (BTX-A-HAC) is the active component in BTX-A-HAC Solution as well as in the BTX-A-HAC lyophilised Powder formulation. Since the BTX-A-HAC Powder for reconstitution products, Dysport and Azzalure have been marketed by Ipsen for >10 years, the pharmacological and toxicological properties of BTX-A-HAC is regarded as well established. This

product is a new ready to use injectable form of BTX-A-HAC for the treatment of moderate to severe glabellar lines in adults. It is fully formulated and provided in a vial ready to inject, eliminating the need for prior reconstitution.

BTX-A-HAC is a complex of BTX-A with haemagglutinin (HA) and nontoxin nonhaemagglutinin proteins, which is isolated and purified from C. botulinum type-A bacteria. The excipients used in the manufacture of BTX A HAC Solution are of European Pharmacopoeia or National Formulary quality. The BTX-A-HAC Solution has been developed without any human or animal derived excipients (i.e. human serum albumin and lactose, which are found in the powder formulation) in order to limit the potential for sensitization (the excipients are listed in section III.1 Quality aspects/ Drug product/ Table: Composition of BTX-A-HAC solution drug product).

BTX A HAC is a highly potent toxin that acts selectively on the peripheral cholinergic nerve endings by targeting the synaptosomal associated protein (SNAP) and thereby inhibiting acetylcholine release, thus preventing the nerve from activating the muscles. The resulting temporary muscle denervation and relaxation has e.g. been shown to reduce the appearance of facial lines and folds by a long-lasting but reversible paralysis of injected muscle. When transmittor release from nerve endings is blocked, the neuromuscular junction responds as though it has been denervated. In response to the chemical denervation axonal sprouting occurs, in which the nerve fibre grows new nerve terminals to innervate the muscles that have lost functional input due to the blockade of nerve ending exocytosis. When the new fibres make functional contact with the underlying muscle, some or all the function is restored.

IV.2 Pharmacokinetics

The Applicant has not conducted formal clinical PK studies with the BTX-A-HAC due to its local administration, and the low doses which are not expected to result in measurable/detectable plasma levels. The Applicant has also referred to the scientific article by Tang-Liu et al. (Toxicon. 2003 Oct;42(5):461-9) in which the diffusion of BTX-A-HAC from the site of intramuscular injection was examined by injecting BTX-A-HAC complex radiolabelled with iodine 125 (I125) into the gastrocnemius muscle of rats. This study showed that the majority of injected radiolabelled toxin remained within the injected muscle, since no iodinated toxin was detected in the plasma.

Overall, by taking into account the mentioned aspects as well as Applicants discussion/justification, the lack of formal PK studies appears acceptable. No further data concerning systemic exposures of BTX-A-HAC are needed.

Immunogenicity
Testing of antibodies to BTX-A was performed in the pivotal Study 214. A multitiered approach was used for testing of antibodies to BTX-A-HAC solution. All serum samples collected were subjected to a screening radioimmunoprecipitation assay (RIPA) to detect the potential presence of binding antibodies. The RIPA technique used a radioactive (125I) tracer prepared from recombinant C-terminal region of the heavy chain (Hc/A) of the BTX-A toxin (rBTX-A Hc/A).

Samples positive in the screening RIPA, were then submitted to the confirmatory RIPA. A sample was considered positive for binding antibodies if it was positive in both the screening and confirmatory RIPAs. Only samples confirmed positive for the presence of binding antibodies in both the screening and confirmatory RIPAs were analysed for the presence of neutralising antibodies using the mouse protection assay (MPA).

All 595 subjects who received at least one injection of BTX-A-HAC during the study (long-term analysis population) were included in the final antibody analysis. There were no subjects tested positive for NAbs at any of timepoints assessed. Only one subject was found positive for the presence of binding antibodies at Baseline (negative for NAbs) but then tested negative for both binding and NAbs following the first treatment with BTX-A-HAC solution as well as at the end of the study (i.e.

after having received a total of five treatments with BTX-A-HAC solution).

IV.3 Pharmacodynamics

The physiological action of botulinum toxin, causing clinical weakness through chemical denervation of muscles, can be quantified by recording compound muscle action potential (CMAP) elicited with supra-maximal stimulation of the corresponding nerve. The extensor digitorum brevis (EDB) muscle on the foot has been a model for BTX pharmacodynamic studies since 1994 and was used by the Applicant in a pharmacodynamic study on BTX-A-HAC powder. The EDB CMAP was studied after supramaximal stimulation of the peroneal nerve at baseline, Day 3 Day 8, Day 29 and Day 85 after BTX injection into the muscle. Despite small groups and large variability there was a clear pharmacodynamic effect of BTX-A injected into EDB muscle, as measured with CMAP. The highest dose (20 U) had the greatest reduction of CMAP, significant compared to placebo at Day 3, peaking at Day 29 and still visible on Day 85.

Mechanism of action and pharmacodynamic effect of BTX-A-HAC solution is expected to be equivalent to BTX-A-HAC power since the active substance is the same.

IV.4 Clinical efficacy

The active substance, BTX-A-HAC, used in the newly developed BTX A HAC solution is the same as the one present in the currently approved BTX-A-HAC powder products, thus the therapeutic effect is expected to be similar based on the pharmacodynamic mechanism of action. The safety and efficacy of BTX A HAC powder formulations for the improvement in the appearance of glabellar lines is already well established; the recommended dose for this indication is 50 Units (U).

The clinical development programme for BTX-A-HAC solution consisted of one phase II dose ranging study (Study Y 52-52120 146, hereafter referred to as Study 146) and two pivotal phase III studies (Study Y-52 52120 189, hereafter referred to as Study 189 and Study Y 52 52120 214, hereafter referred to as Study 214).

Table 1 Summary of placebo-controlled and open label BTX-A-HAC solution studies in glabellar lines

Study number Start date Completion date (year)	Study population	Dose	Number of treatment cycles/duration of follow-up	Number of subjects receiving treatment
Pivotal placebo controlled studies providing substantial evidence of efficacy				
Y-52-52120-189 (Module 5.3.5.1, Study 189) 2015 2015	Moderate to severe glabellar lines	BTX-A-HAC solution 50 U or placebo	Single treatment cycle Follow-up for up to 183 days (6 months)	 BTX-A-HAC solution 50 U: 125 Placebo: 59 Total: 184
Y-52-52120-214[a] (Module 5.3.5.1, Study 214) 2015 2016	Moderate to severe glabellar lines	Double blind period: BTX-A-HAC solution 50 U or placebo Open label period: BTX-A-HAC solution 50 U	Double blind period: single treatment cycle Follow-up for at least 12 weeks Open label period: maximum of five treatment cycles[b] Follow-up for at least 12 weeks after each treatment cycle; Total: up to 15 months (~455 days)	Double blind period: BTX-A-HAC solution 50 U: 126 Placebo: 64 Total: 190 Open label period: BTX-A-HAC 50 U: 595
Supportive placebo controlled study				
Y-52-52120-146 (Module 5.3.5.4, Study 146) 2011 2011	Moderate to severe glabellar lines	BTX-A-HAC solution 20 U, 50 U, 75 U or placebo BTX-A-HAC powder 50 U	Single treatment cycle Follow-up for 113 days (4 months)	 BTX-A-HAC solution 20 U: 36 BTX-A-HAC solution 50 U: 35 BTX-A-HAC solution 75 U: 35 BTX-A-HAC powder 50 U: 35 Placebo: 35 Total: 176

BTX-A-HAC=botulinum toxin type A haemagglutinin complex, U=units.
a Study 214 consisted of a placebo controlled, double blind period followed by an open label period.
b During the open label period, de novo subjects could receive up to five treatment cycles. Eligible subjects who rolled over from the placebo controlled, double blind period could receive up to four additional treatment cycles.
Note: In all studies, BTX-A-HAC solution was injected into the glabellar region: procerus, left and right corrugator and left and right corrugator/orbicularis.

Dosefinding, supportive Study 146

Phase II Study 146 was a dose ranging study, and the first study conducted with BTX-A-HAC solution in glabellar lines. This was a double blind, placebo controlled, active comparator study that evaluated a single treatment of three doses of BTX-A-HAC solution (20 U, 50 U and 75 U) compared with placebo, as well as BTX-A-HAC powder 50 U. Eligible subjects had moderate to severe (Grade 2 or 3) glabellar lines at maximum frown and were naïve to previous treatment with any serotype of BTX. They were randomised in a ratio of 1:1:1:1:1 to receive a single treatment. For each treatment group, the total treatment volume (0.25 mL) was divided into five injections (0.05 mL per injection), each of which was to be administered into predefined sites across the glabellar region.

The Investigator's live assessment (ILA) was used to assess the appearance of glabellar lines at maximum frown and at rest by the investigator. The ILA is a validated photographic 4-point scale used for assessing the severity of glabellar lines as follows: Grade 0 (none), Grade 1 (mild), Grade 2 (moderate) or Grade 3 (severe).

The Subject's self-assessment (SSA) was used to assess the appearance of glabellar lines at maximum frown and at rest by the subject. The SSA is a validated categorical 4-point scale used for assessing the severity of glabellar lines as follows: Grade 0 (none), Grade 1 (mild), Grade 2 (moderate) or Grade 3 (severe).

The co-primary efficacy endpoint was the proportion of responders on Day 29 in the ILA and SSA of glabellar lines. A responder was defined as a subject having a severity grade of none (Grade 0) or mild (Grade 1) at maximum frown on Day 29 and a severity grade of moderate (Grade 2) or severe (Grade 3) at maximum frown at Baseline. Post-treatment assessments were performed on Days 4 (telephone assessment of AEs or concomitant medications/treatments) 8, 15, 29, 57, 85 and 113.

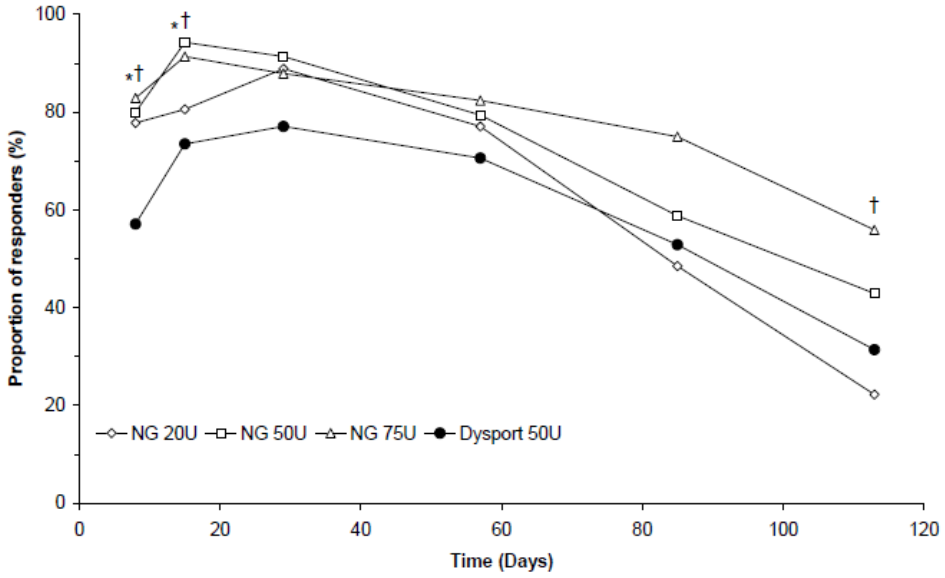
Table 2 Proportion of Responders on Day 29 by the ILA and SSA at Maximum Frown: BTX-A-HAC Solution versus BTX-A-HAC Powder and versus placebo (ITT Population)

	Treatment Group				
	BTX-A-HAC Solution 20 U (N=36)	**BTX-A-HAC Solution 50 U (N=35)**	**BTX-A-HAC Solution 75 U (N=35)**	**BTX-A-HAC Powder 50 U (N=35)**	**Placebo (N=35)**
ILA					
Responders n/N (%)	32/36 (88.9)	32/35 (91.4)	29/33 (87.9)	27/35 (77.1)	0/34
95% CI	78,99.2	82.2,100.0	76.7,99.0	63.2,91.1	-
SSA					
Responders n/N (%)	33/36 (91.7)	30/35 (85.7)	27/33 (81.8)	29/35 (82.9)	1/34 (2.9)
95% CI	82.6,100.0	74.1,97.3	68.7,95.0	70.4,95.3	0.0,8.6

BTX-A-HAC=botulinum toxin type A haemagglutinin complex, dash (-)=not applicable, CI=confidence interval, ILA=Investigator's live assessment, ITT=intent-to-treat, N=total number of subjects in group, N'=number of subjects with assessment; n=number of responders, SSA=subject's self assessment, U=units.

The proportion of early responders (i.e. at Day 8) was higher in Dysport NG 50 U group compared with the Dysport 50 U group and this difference was maintained up to Day 29. From Day 57 to Day 113, these differences are maintained but with a slightly decreased magnitude. The rate of decrease in the proportion of responders was similar in the Dysport NG 50 U and the Dysport 50 U groups. A similar, but more sustained, effect was observed with Dysport NG 75 U compared with Dysport 50 U.

Figure 1 Proportion of responders at each time point for the ILA, all active treatment groups (ITT population)



Data Source: Table 14.2.1.3

* indicates p<0.05 for Dysport NG 50 U vs. Dysport 50 U

† indicates p<0.05 for Dysport NG 75 U vs. Dysport 50 U

Safety of study 146 is presented under heading *Safety*. The Applicant concluded that the best benefit risk profile was demonstrated by BTX A HAC solution 50 U and therefore, this dose was selected for use in the pivotal confirmatory phase III studies. This is the same dose as the already approved 50 U dose of other commercialised BTX A HAC formulations for the treatment of glabellar lines.

Pivotal studies

Study 189

Study 189 was a double blind, phase III study designed to assess the efficacy and safety of a single treatment of BTX A HAC solution (50 U) compared to placebo. Study subjects were randomised in a ratio of 2:1 to receive a single treatment with either BTX-A-HAC solution (50 U) or placebo. For each treatment group, the total treatment volume (0.25 mL) was divided into five injections (0.05 mL per injection), each of which was to be administered into predefined sites across the glabellar region.

Eligible subjects were adult patients who had moderate to severe (Grade 2 or 3) vertical glabellar lines at maximum frown and were naïve to previous treatment with BTX. Post treatment assessments were performed on Days 8, 15, 29, 57, 85, 113, 148 and 183.

Inclusion Criteria

1. Subjects were eligible for participation in the study if they met all of the following criteria:
2. Provision of written informed consent prior to any study related procedures.
3. Male or female between 18 and 65 years of age, inclusive.
4. Had moderate or severe (Grade 2 or 3) vertical glabellar lines at maximum frown at Baseline (Day 1), as assessed by the ILA using a validated 4-point photographic scale.
5. Had moderate or severe (Grade 2 or 3) vertical glabellar lines at maximum frown at Baseline (Day 1), as assessed by the SSA using a validated 4-point categorical scale.
6. Were dissatisfied or very dissatisfied (Grade 2 or 3) with their glabellar lines at Baseline (Day 1), as assessed by the subject's level of satisfaction.
7. Had a negative pregnancy test (for females of childbearing potential only). Nonchildbearing potential was defined as postmenopausal for at least 1 year, surgical sterilisation at least 3 months before entering the study, or hysterectomy.
8. Had both the time and the ability to complete the study and comply with study instructions.

Exclusion Criteria

1. Previous treatment with any serotype of BTX.
2. Any prior treatment with permanent fillers in the upper face including the glabellar lines area.
3. Any prior treatment with long lasting dermal fillers in the upper face including the glabellar lines area within the past 3 years and/or skin abrasions/resurfacing (whatever the interventional technic used) within the past 5 years, or photorejuvenation or skin/vascular laser intervention within the past 12 months.
4. Any planned facial cosmetic surgery during the study.
5. A history of eyelid blepharoplasty or brow lift within the past 5 years.
6. An inability to substantially reduce glabellar lines by physically spreading them apart or lack of capacity to frown.
7. An active infection or other skin problems in the upper face including the glabellar lines area (e.g. acute acne lesions or ulcers).
8. Use of concomitant therapy which, in the investigator's opinion, would have interfered with the evaluation of the safety or efficacy of the study treatment, including medications affecting bleeding disorders (antiplatelet agents and/or anticoagulants given for treatment or prevention of cardiovascular/cerebrovascular diseases).
9. Pregnant women, nursing mothers, or women who were planning a pregnancy during the study, or believed they might be pregnant at the start of the study. Throughout the course of the study, women of childbearing potential had to use a reliable form of contraception (e.g. oral contraceptives for more than 12 consecutive weeks, or spermicide and condoms).
10. A history of drug or alcohol abuse.
11. Treatment with an experimental drug or use of any experimental device within 30 days prior to the start of the study and during the conduct of the study.
12. Known allergy or hypersensitivity to any serotype of BTX or any component of BTX-A-HAC NG.

13. Clinically diagnosed significant anxiety disorder, or any other significant psychiatric disorder (e.g. depression) that might interfere with the subject's participation in the study.
14. Use of medications that affect neuromuscular transmission, such as curare-like non-depolarising agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics, within the past 30 days.
15. A history of facial nerve palsy.
16. Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.
17. The presence of any other condition (e.g. neuromuscular disorder or other disorder that could interfere with neuromuscular function), laboratory finding or circumstance that, in the judgement of the investigator, might increase the risk to the subject or decrease the chance of obtaining satisfactory data to achieve the objectives of the study.

For each treatment group, the total treatment volume (0.25 mL) was divided into five injections (0.05 mL per injection), each of which was to be administered into predefined sites across the glabellar region (two injection into each corrugator muscle and one injection into the procerus muscle).

Primary Objective

The primary study objective was to demonstrate the efficacy of a single treatment of an injectable liquid form of Clostridium BTX-A-HAC at 50 U, used for the improvement in the appearance of moderate to severe glabellar lines at maximum frown.
The primary objective was accomplished by demonstrating the superiority of BTX-A-HAC solution 50 U over placebo assessed by the ILA of the appearance of glabellar lines at maximum frown on Day 29.

Secondary Objectives

- To compare the efficacy of a single treatment of BTX-A-HAC solution 50 U to placebo at all timepoints (except Day 29), using the ILA of the appearance of glabellar lines at maximum frown;
- To compare the efficacy of a single treatment of BTX-A-HAC solution 50 U to placebo at all timepoints, using the ILA of the appearance of glabellar lines at rest;
- To compare the efficacy of a single treatment of BTX-A-HAC solution 50 U to placebo at all timepoints, using the SSA of the appearance of glabellar lines at maximum frown;
- To compare the subject's level of satisfaction with the appearance of their glabellar lines following treatment with BTX-A-HAC solution 50 U or placebo;
- To determine the time to onset of treatment response;
- To determine the duration of treatment response;
- To compare the safety of a single treatment of BTX-A-HAC solution 50 U to placebo in the treatment of glabellar lines.

Tertiary Objectives

- To compare the subject's level of satisfaction with their facial appearance following treatment with BTX-A-HAC solution 50 U or placebo;
- To compare the subject's aging appearance appraisal, using the visual analogue scale (VAS), following treatment with BTX-A-HAC solution 50 U or placebo;
- To assess the subject's psychological well-being following treatment with BTX-A-HAC solution 50 U compared to placebo.

Efficacy variables

Investigator's Live Assessment (ILA) and Subject's Self-Assessment (SSA) are described under heading Dose finding supportive Study 146.

Assessment of Subject Satisfaction
This is a validated 4-point scale representing the level of satisfaction with the appearance of glabellar lines from very satisfied (Grade 0) to very dissatisfied (Grade 3), were used at Baseline and at each post-treatment visits, please see Table 3.

Table 3 Subject's level of satisfaction

Grade	Level of Satisfaction
0	Very satisfied
1	Satisfied
2	Dissatisfied
3	Very dissatisfied

Diary card
To assess the onset of treatment response, subjects were asked to record their assessment of study treatment response in a diary card on Days 1 through 7. They were asked to respond 'yes' or 'no' to the following question: 'Since being injected have you noticed an improvement in the appearance of your glabellar lines (lines between your eyebrows)?'

Duration of Treatment Response
The ILA and SSA assessed at maximum frown on Days 15, 29, 57, 85, 113, 148 and 183 were used for determining duration of treatment response. Duration of response was defined as the time (number of days) for a responder to re-exhibit a severity grade of 2 (moderate) or 3 (severe) following study treatment on Day 1.

FACE-Q Scale
The FACE-Q is a patient-reported outcome instrument to evaluate the experience and outcomes of aesthetic facial procedures from the subject's perspective. The FACE-Q is composed of over 40 scales, covering four domains. Each domain has one or more independently functioning scales. For the purpose of this study and given the condition treated, a subset of three scales were selected, one from the Satisfaction with Facial Appearance domain (satisfaction with facial appearance scale) and two from the Health Related Quality of Life domain (psychological well-being scale and aging appearance appraisal VAS). Subjects were asked to complete these scales at Baseline (Day 1, pre-treatment) and at each post-treatment visit to the study centre.

To describe their psychological well-being subjects have to indicate their agreement with the following statements:
(a) I feel okay about myself.
(b) I'm accepting of myself.
(c) I am comfortable with myself.
(d) I feel good about myself.
(e) I like myself.
(f) I feel positive about myself.
(g) I feel happy.
(h) I feel attractive.
(i) I feel confident.
(j) I feel great about myself.

Possible responses are 'definitely disagree' (=1), 'somewhat disagree' (=2), 'somewhat agree' (=3) and 'definitely agree' (=4).

The aging appearance appraisal VAS ranges from -15 ('I look 15 years younger' to +15 ('I look 15 years older').

Efficacy endpoints

The primary efficacy endpoint for study 189 was the proportion of responders on Day 29 in the ILA of glabellar lines at maximum frown. A responder was defined as having a severity grade of none (Grade 0) or mild (Grade 1) at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) at Baseline (Day 1, pretreatment).

The secondary efficacy endpoints for this study were:

(a) The proportion of responders at each post-treatment visit to the study centre (except Day 29) as measured by the ILA at maximum frown.
(b) The proportion of responders on Day 29 who remained responders on Days 57, 85, 113, 148 and 183 as measured by the ILA at maximum frown.
(c) The proportion of responders at each post-treatment visit to the study centre as measured by the ILA at rest.
(d) The proportion of subjects with a reduction of two or more grades in the severity of glabellar lines at each post-treatment visit to the study centre as measured by the ILA at maximum frown.
(e) The proportion of responders at each post-treatment visit to the study centre as measured by the SSA at maximum frown.
(f) The proportion of responders at each post-treatment visit to the study centre as measured by the subject's level of satisfaction with the appearance of their glabellar lines.
(g) The time to onset of treatment response based on the subject's diary card.
(h) Duration of treatment response based on the ILA and SSA at maximum frown.

A responder as measured by the SSA was defined as having a severity grade of no wrinkles (Grade 0) or mild wrinkles (Grade 1) at a given visit and a severity grade of moderate (Grade 2) or severe (Grade 3) wrinkles at Baseline (Day 1, pre-treatment).

A responder as measured by the subject's level of satisfaction was defined as having a satisfaction rating of very satisfied (Grade 0) or satisfied (Grade 1) at a given visit and a satisfaction rating of dissatisfied (Grade 2) or very dissatisfied (Grade 3) at Baseline (Day 1, pre-treatment).

For the analysis of duration of response, a responder was defined as having a severity grade of 2 or 3 at Baseline (Day 1, pre-treatment) and a severity grade of 0 or 1 at any scheduled post-treatment timepoint.

Tertiary Efficacy Endpoints

The tertiary efficacy endpoints for this study were:
(a) Mean change from Baseline to each post-treatment visit in the FACE-Q satisfaction with facial appearance scale rasch transformed score.
(b) Mean change from Baseline to each post-treatment visit in the FACE-Q psychological well-being scale rasch transformed score.
(c) Mean change from Baseline to each post-treatment visit in the FACE-Q aging appearance appraisal VAS score.
(d) Mean change from Baseline to each post-treatment visit for each item of the FACE-Q satisfaction with facial appearance scale and the FACE-Q psychological well-being scale.

Baseline data

A total of 190 male and female subjects were screened of whom 185 were enrolled and randomised into the study. One subject who did not meet the inclusion criteria was randomised into the study by mistake but did not receive study treatment. The number of subjects who completed the study was 122 (97.6%) in the BTX A HAC solution group and 51 (85.0%) in the placebo group. The main reason for withdrawal was consent withdrawal and was reported in a higher proportion of subjects in the placebo group than in the BTX-A-HAC solution group (8/60 (13.3%) versus 1/125 (0.8%), respectively).

Study subjects consisted mainly of Caucasian (99%) women (87%). Baseline assessments for ILA, SSA and Subject's level of satisfaction are shown in Table 4.

Table 4 Baseline results for ILA, SSA and Subject's level or satisfaction (mITT Population)

	Treatment group	
	BTX-A-HAC solution 50 U (N=125)	Placebo (N=59)
	n (%)	
Investigator's live assessment of glabellar lines severity at maximum frown		
None	0	0
Mild	0	0
Moderate	52 (41.6)	25 (42.4)
Severe	73 (58.4)	34 (57.6)
Investigator's live assessment of glabellar lines severity at rest		
None	10 (8.0)	3 (5.1)
Mild	62 (49.6)	24 (40.7)
Moderate	39 (31.2)	26 (44.1)
Severe	14 (11.2)	6 (10.2)
Subject's self-assessment of glabellar lines severity at maximum frown		
No wrinkles	0	0
Mild wrinkles	0	0
Moderate wrinkles	68 (54.4)	29 (49.2)
Severe wrinkles	57 (45.6)	30 (50.8)
Subject's level of satisfaction with the appearance of their glabellar lines		
Very satisfied	0	0
Satisfied	0	0
Dissatisfied	69 (55.2)	33 (55.9)
Very dissatisfied	56 (44.8)	26 (44.1)

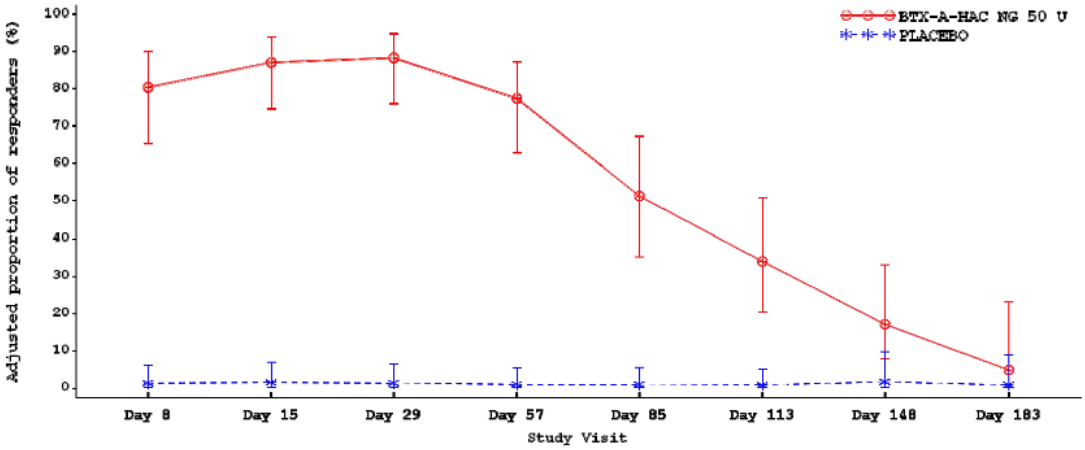
BTX-A-HAC=BTX-A Haemagglutinin Complex, mITT=modified intent to treat, N=total number of subjects in group, n=number of subjects with event, U=units.
Data Source: Table 14.1.11, Listing 16.2.6.1
Percentages are based on the number of subjects in each treatment group.

Outcomes and estimations

Primary efficacy endpoint
The proportion of responders on Day 29 for the ILA of glabellar lines at maximum frown is summarised in Table 13. The proportion of responders in the mITT population was statistically significantly higher ($p<0.0001$) in the BTX-A-HAC solution 50 U group (88.3%) than in the placebo group (1.4%). To assess the impact of missing values, a sensitivity analysis was performed, using the baseline ILA at maximum frown to impute missing assessments on Day 29. The proportions of responders were almost identical with those of the primary analysis with 88.3% responders in the BTX-A-HAC solution 50 U group and 1.3% responders in the placebo group.

Secondary efficacy endpoints
Responders at each post treatment visit are shown in Figure 2.

Figure 2 Adjusted proportion of responders (with 95% confidence interval) at each post-treatment visit in the ILA of glabellar lines at maximum frown - mITT population



Proportion of Responders on Day 29 who Remained Responders on Days 57, 85, 113, 148 and 183 as Measured by the Investigator's Live Assessment at Maximum Frown
In the BTX-A-HAC solution 50 U group the proportion of responders (ILA, maximum frown) on Day 29 who remained responders on any of the subsequent visits was 87.3% on Day 57 and then decreased gradually (61.1% on Day 85, 39.6% on Day 113, 20.1% on Day 148 and 5.3% on Day 183).

Proportion of Subjects with a Reduction of Two or More Grades in the Severity of Glabellar Lines at Each Post-treatment Visit to the Study Centre as Measured by the ILA at Maximum Frown
In the BTX-A-HAC solution 50 U group the proportion of subjects with two or more grades reduction in glabellar line severity compared with Baseline increased from Day 8 (56.2%) to a maximum on Day 15 (69.7%) and then decreased gradually up to Day 183 (3.4%). There were no subjects with two or more grades reduction in glabellar line severity in the placebo group.

Proportion of Responders at Each Post-treatment Visit to the Study Centre as Measured by the Subject's Self-Assessment at Maximum Frown
Looking at proportion of responders utilizing subject's self-assessment (SSA) at maximum frown, treatment with BTX-A-HAC solution 50 U, there were statistically significantly larger proportions of responders at maximum frown compared with placebo at each post-treatment visit (p-values ranging from <0.0001 to 0.0036). The proportion of responders in the BTX-A-HAC solution 50 U group increased from Day 8 (62.0%) to a maximum on Day 29 (76.0%) and then decreased gradually up to Day 183 (27.0%). The proportion of responders in the placebo group was within the range of 2.2 to 13.1% for the entire study duration.

Proportion of Responders at Each Post-treatment Visit to the Study Centre as Measured by the Subject's Level of Satisfaction with the Appearance of Their Glabellar Lines
Responders (defined as having a satisfaction rating of very satisfied (Grade 0) or satisfied (Grade 1) at a given visit and a satisfaction rating of dissatisfied (Grade 2) or very dissatisfied (Grade 3) at Baseline) show that treatment with BTX-A-HAC solution 50 U resulted in statistically significantly larger proportions of responders compared with placebo at all post-treatment visits (e.g. Day 29 BTX-A HAC solution 80.9% with 95% CI 68.7-89.1% and placebo 8.3% 95% CI 3.1-19.1%).

Time to Onset of Treatment Response Based on the Subject's Diary Card
The median time to onset of treatment response based on the subject's diary card was 3.0 days in the BTX-A-HAC solution 50 U group (the median could not be calculated in the placebo group due to the small number of responders).

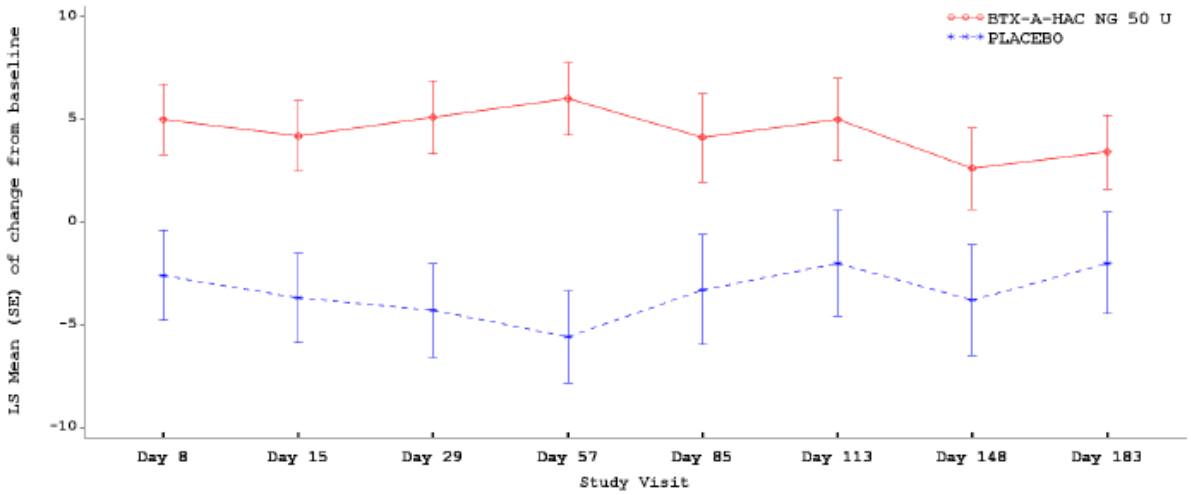
Duration of Treatment Response Based on the ILA and SSA at Maximum Frown
The median duration of treatment response based on the ILA at maximum frown was statistically significantly longer in the BTX-A-HAC solution 50 U group (137.0 days) than in the placebo group (50.0 days). The median (duration of treatment response based on the SSA was also statistically significantly longer in the BTX-A-HAC solution 50 U group (108.0 days) than in the placebo group (36.0 days).

Tertiary efficacy endpoints

Mean Change from Baseline to Each Post-treatment Visit in the FACE-Q Satisfaction with Facial Appearance Overall Scale Rasch Transformed Score
The mean value at Baseline was 40.5 score points (of 100) for the BTX-A-HAC solution 50 U group and 39.4 score points for the placebo group. The LS Mean change from Baseline ranged from 8.6 to 11.7 score points in the BTX-A-HAC solution 50 U group and from 0.8 to 6.6 score points in the placebo group. BTX-A-HAC solution 50 U resulted in statistically significantly larger improvements from Baseline on the FACE-Q satisfaction with facial appearance Overall Scale Rasch Transformed Score compared with placebo at each post-treatment visit with the exception of Day 183.

Mean Change from Baseline to Each Post-treatment Visit in the FACE-Q Psychological Well-being Scale Rasch Transformed Score
The mean value at Baseline was 55.2 score points (of 100) for the BTX-A-HAC solution 50 U group and 53.5 score points for the placebo group. The LS Mean changes from Baseline were positive for the BTX-A-HAC solution 50 U group (range +2.6 to +6.0 score points) and negative for the placebo group (range -5.6 to -2.0 score points) at all visits. The LS Mean treatment difference in change from Baseline ranged from 11.6 points on Day 57 ($p<0.0001$) to 5.4 points on Day 183 ($p=0.0279$). Treatment with BTX-A-HAC solution 50 U resulted in larger improvements in the FACE-Q Psychological well-being scale score change from Baseline compared with placebo at each post-treatment visit (Figure 3).

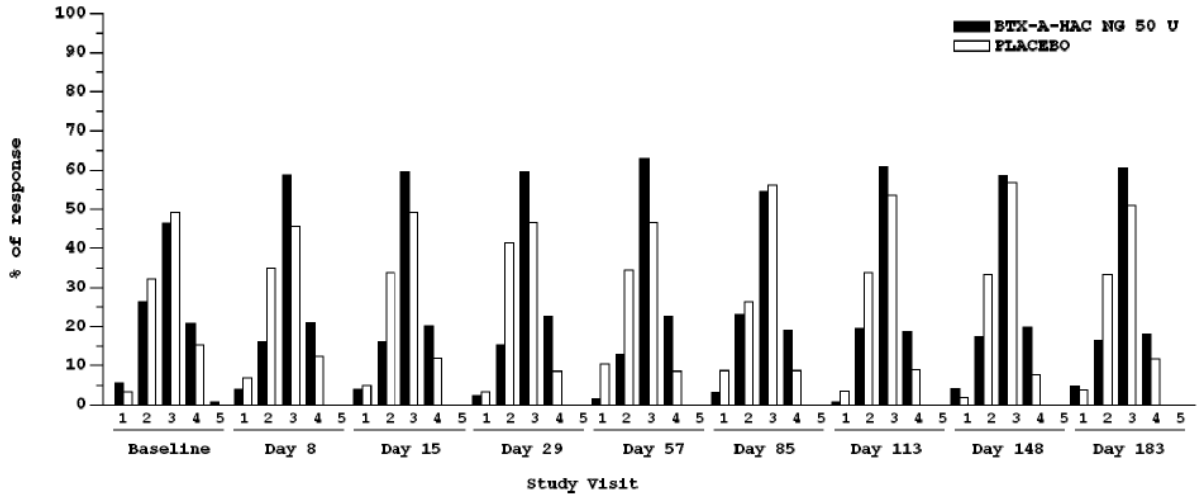
Figure 3 FACE-Q Psychological Well-being Scale - Rasch Transformed Score by Visit (mITT Population)



BTX-A-HAC NG=BTX-A-HAC solution 50 U, ILA=investigator's live assessment, LS Mean=least squares mean from general linear model, mITT=modified intent to treat, SE=standard error, U=units.
Data Source: Table 14.2.12.2
The FACE-Q psychological well-being scale rasch transformed score is calculated by adding the 10 items (scored from 1 to 4) and converting the score to a scale from 0 to 100 using a conversion table. In case of missing item less than 50%, the missing values were replaced by the mean of the completed items.
The general linear model includes mean change from Baseline as a dependent variable and treatment group, gender, centre as fixed effects and baseline severity score on ILA at maximum frown as covariate.

Mean Change from Baseline to Each Post-treatment Visit for Each Item of the FACE-Q Satisfaction with Facial Appearance Scale and the FACE-Q Psychological Well-being Scale
For most of the 10 items on each of the two scales and at most of the eight post-treatment visits, the percentages of subjects who were 'somewhat satisfied' or who 'somewhat agreed' (scale value=3) were higher in the BTX-A-HAC solution 50 U group than in the placebo group, whereas the percentages of subjects who were 'somewhat dissatisfied' or who 'somewhat disagreed' (scale value=2) were higher in the placebo group compared with the BTX-A-HAC solution 50 U group. Figure 4 shows the proportion of subjects' answers (1-4) for item e) "I like myself ", at baseline and at each visit, as an example.

Figure 4 Face-Q psychological well-being scale by item e) each visit - mITT population



A Student's t-test was used to compare the mean change from Baseline between treatment groups. The most pronounced effect of BTX-A-HAC solution 50 U compared with placebo was seen for item f ('how rested your face looks') on the satisfaction of facial appearance scale and for items a ('I feel okay about myself') and h ('I feel attractive') on the psychological well-being scale. For each of these three items a statistically significantly larger improvement from Baseline was noted in the BTX-A-HAC solution 50 U group compared with the placebo group at each of the eight visits. In addition, a statistically significant treatment difference on six or seven of the eight visits was noted for items b ('how balanced your face looks?'), d ('how your face looks at the end of day?') and e ('how fresh your face looks?') on the satisfaction of facial appearance scale and for items e ('I like myself') and j ('I feel great about myself') on the psychological well-being scale.

Mean Change from Baseline to Each Post-treatment Visit in the FACE-Q Aging Appearance Appraisal Visual Analogue Scale Score
At Baseline (before treatment) subjects in the BTX-A-HAC solution 50 U group rated themselves as looking 0.5 years younger than their true age; subjects in the placebo group rated themselves as looking 1.3 years younger. Mean change from Baseline, in the BTX -group rated themselves as looking at the most 1.4 (Day 57 and Day 85) years younger compared with Baseline, whereas subjects in the placebo group rated themselves as looking maximally 0.3 years younger (Day 57). The LS Mean treatment difference in change from Baseline ranged from 1.3 years on Day 15 and on Day 29 to 0.7 years on Day 148 (ns).

Ancillary analyses

According to the SAP an analysis of the proportion of responders on Day 29 as measured by the ILA and the SSA at maximum frown should have been performed by

• Gender and

• Baseline severity score of the ILA of glabellar lines at maximum frown,

if both treatment groups within a category contained at least 20% of subjects of the overall treatment groups. Since the percentage of male subjects was <20%, only descriptive statistics have been provided for the analysis by gender.

The proportion of responders in the BTX-A-HAC solution 50 U group was higher for female (ILA 94.4%, SSA 77.6%) than for male subjects (ILA 64.7%, SSA 58.8%), both for the ILA and for the SSA at maximum frown.

In both treatment groups a higher proportion of subjects with moderate glabellar lines responded to treatment compared with subjects with severe glabellar lines, both for the ILA and the SSA. However, the treatment by baseline severity interaction was not statistically significant.

Study 214
Study 214 was a multicentre, Phase III study conducted in two periods: a randomised DB, placebo-controlled period followed by an OL period.

Inclusion and exclusion criteria
Please see section *Study 189* above.

Treatments
For each treatment group, the total treatment volume (0.25 mL) was divided into five injections (0.05 mL per injection), each of which was to be administered into predefined sites across the glabellar region (two injection into each corrugator muscle and one injection into the procerus muscle).

Subjects entering DB Cycle 1 were randomised in a ratio of 2:1 to receive a single treatment with either BTX-A-HAC solution 50 U or placebo.

Once recruitment of the DB Cycle 1 subjects had been completed, additional subjects were enrolled. These subjects entered OL Cycle 1 (i.e. de novo subjects) and received a single treatment with OL BTX-A-HAC solution. All subjects who completed DB Cycle 1 or OL Cycle 1 and who were eligible for retreatment received OL BTX-A-HAC solution 50 U for a maximum of four additional treatment cycles (OL Cycles 2 to 5). Each cycle consisted of a single treatment. Eligibility for retreatment had to be checked after each cycle. Treatments had to be separated by at least 12 weeks. Retreatment was not allowed if the subject had been in the study for at least 12 months.

Primary objective
The primary objective was to demonstrate the superiority of BTX-A-HAC solution over placebo as measured by the ILA of the appearance of the subject's glabellar lines at maximum frown on Day 29 of the DB period.

Secondary objectives
- To compare the efficacy of a single treatment of BTX-A-HAC solution to placebo on Day 29 of the DB period as measured by the SSA of the appearance of glabellar lines at maximum frown;
- To compare the efficacy of a single treatment of BTX-A-HAC solution to placebo at all timepoints of the DB period (except on Day 29) and to assess repeat-treatments in the open-label (OL) period as measured by the ILA of the appearance of glabellar lines at maximum frown;
- To compare the efficacy of a single treatment of BTX-A-HAC solution to placebo at all timepoints of the DB period (except on Day 29) and to assess repeat-treatments in the OL period as measured by the SSA of the appearance of glabellar lines at maximum frown;

- To compare the efficacy of a single treatment of BTX-A-HAC solution to placebo at all timepoints of the DB period and to assess repeat-treatments in the OL period as measured by the ILA of the appearance of glabellar lines at rest;
- To compare the subject's level of satisfaction with the appearance of their glabellar lines following single treatment with BTX-A-HAC solution or placebo and repeat-treatments with BTX-A-HAC solution;
- To determine the time to onset of treatment response after single treatment;
- To determine the time to retreatment after single- and repeat-treatments;
- To compare the subject's level of satisfaction with their facial appearance, the subject's aging appearance appraisal using the visual analogue scale (VAS), and the subject's psychological well-being on the FACE-Q scales, following single treatment with BTX-A-HAC solution or placebo and repeat-treatments with BTX-A-HAC solution;
- To assess the short and LT safety of BTX-A-HAC solution treatment for the improvement in appearance of moderate to severe glabellar lines;
- To assess the presence of putative antibodies against BTX-A following single injection with BTX-A-HAC solution or placebo and after repeat-treatments with BTX-A-HAC solution.

Efficacy variables
Please see section on *Study 189*.

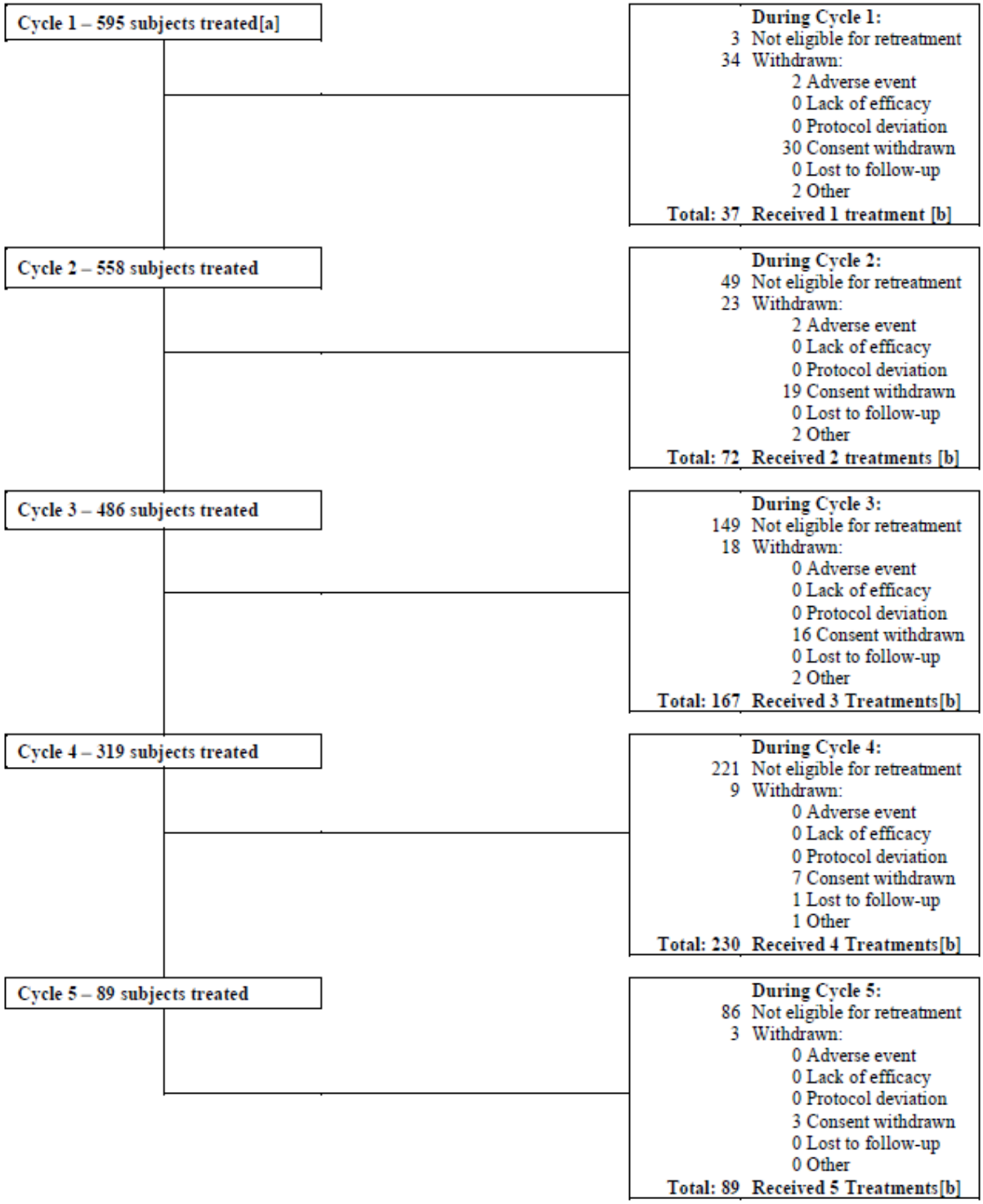
Baseline data
Of the 192 subjects screened for the DB period, two were screen failures and 190 were randomised in a 2:1 ratio to receive BTX-A-HAC solution (126 subjects) or placebo (64 subjects).

In the DB period, all randomised subjects were treated and 177 subjects completed the DB period: 118 subjects (93.7%) randomised to BTX-A-HAC solution and 59 subjects (92.2%) randomised to placebo. The percentage of subjects withdrawn during the DB period was in 7.8% the placebo group (5 subjects) and 6.3% in the BTX-A-HAC solution group (8 subjects). The reason for all withdrawals was 'consent withdrawn'.

Subjects could be retreated with BTX-A-HAC solution if pre-specified criteria were fulfilled:
1. Moderate (Grade 2) or severe (Grade 3) glabellar lines at maximum frown on both the ILA and the SSA;
2. At least 84 days (12 weeks) elapsed since the previous treatment;
3. Total follow-up duration since the first injection of study treatment (Cycle 1, Day 1) not exceeding 12 months;
4. No ongoing AEs assessed as related to treatment with BTX-A-HAC solution, which

would preclude the subject from retreatment. Figure 5 shows the number of subjects within each treatment cycle, number not eligible and number withdrawn.

Figure 5 Number of subjects in each treatment cycle with BTX-A-HAC Solution (LTA Population) - Long Term Analyses



Study subjects consisted mainly of Caucasian (99%) women (87%). ILA, SSA of glabellar lines severity and Subject's level of satisfaction at baseline are shown in Table 5 (double blind period) and Table 6 (Long term analyses).

Table 5 ILA, SSA of glabellar lines severity and Subject's level of satisfaction at baseline (mITT-population) – double-blind period

Parameter		BTX-A-HAC Solution 50 U (N=125)	Placebo (N=63)
Investigator's live assessment at maximum frown, n (%)	None	0	0
	Mild	0	0
	Moderate	58 (46.4)	29 (46.0)
	Severe	67 (53.6)	34 (54.0)
Investigator's live assessment at rest, n (%)	None	2 (1.6)	1 (1.6)
	Mild	33 (26.4)	20 (31.7)
	Moderate	70 (56.0)	32 (50.8)
	Severe	20 (16.0)	10 (15.9)
Subject's self-assessment at maximum frown, n (%)	No wrinkles	0	0
	Mild wrinkles	0	0
	Moderate wrinkles	63 (50.4)	22 (34.9)
	Severe wrinkles	62 (49.6)	41 (65.1)
Subject's level of satisfaction, n (%)	Very Satisfied	0	0
	Satisfied	0	0
	Dissatisfied	81 (64.8)	40 (63.5)
	Very Dissatisfied	44 (35.2)	23 (36.5)

BTX-A-HAC=BTX-A Haemagglutinin Complex, mITT=modified intent to treat, N=total number of subjects, n=number of subjects in category, U=units.
Data source: Table 14.1.14.1
Note: Baseline is defined as the last measurement collected before the first injection of the study. Percentages are based on the number of subjects in the mITT population.

Table 6 ILA, SSA of Glabellar lines severity and Subject's level of satisfaction at cycle baseline (LTA Population) – Long Term Analyses

Parameter		Cycle 1 (N=595)	Cycle 2 (N=558)	Cycle 3 (N=486)	Cycle 4 (N=319)	Cycle 5 (N=89)
Investigator's live assessment at maximum frown, n (%)	None	0	0	0	0	0
	Mild	0	0	1 (0.2)	1 (0.3)	0
	Moderate	260 (43.7)	413 (74.0)	395 (81.3)	263 (82.4)	74 (83.1)
	Severe	335 (56.3)	145 (26.0)	90 (18.5)	55 (17.2)	15 (16.9)
Investigator's live assessment at rest, n (%)	None	19 (3.2)	32 (5.7)	35 (7.2)	22 (6.9)	2 (2.2)
	Mild	196 (32.9)	285 (51.1)	248 (51.0)	161 (50.5)	44 (49.4)
	Moderate	311 (52.3)	218 (39.1)	180 (37.0)	128 (40.1)	40 (44.9)
	Severe	69 (11.6)	23 (4.1)	23 (4.7)	8 (2.5)	3 (3.4)
Subject's self-assessment at maximum frown, n (%)	No wrinkles	0	2 (0.4)	0	1 (0.3)	0
	Mild wrinkles	1 (0.2)	26 (4.7)	8 (1.6)	3 (0.9)	1 (1.1)
	Moderate wrinkles	277 (46.6)	398 (71.3)	383 (78.8)	260 (81.5)	69 (77.5)
	Severe wrinkles	317 (53.3)	132 (23.7)	95 (19.5)	55 (17.2)	19 (21.3)
Subject's level of satisfaction, n (%)	Very Satisfied	0	11 (2.0)	10 (2.1)	2 (0.6)	1 (1.1)
	Satisfied	0	94 (16.8)	73 (15.0)	50 (15.7)	14 (15.7)
	Dissatisfied	364 (61.2)	395 (70.8)	362 (74.5)	243 (76.2)	62 (69.7)
	Very Dissatisfied	231 (38.8)	58 (10.4)	41 (8.4)	24 (7.5)	12 (13.5)

BTX-A-HAC=BTX-A Haemagglutinin Complex, DB=double-blind, LTA=long term analysis, N=total number of subjects, n=number of subjects in category, U=units.
Data source: Table 14.1.14.2
Note: Cycle 1 includes the DB Cycle 1 of subjects treated with BTX-A-HAC solution 50 U, the Cycle 1 of de novo subjects and the Cycle 2 of subjects entered as placebo in the DB period (corresponds to the first administration of BTX-A-HAC solution 50 U). Cycles 2, 3, 4 and 5 correspond to the summary of data after the 2nd, 3rd, 4th and 5th injection of BTX-A-HAC solution 50 U. Cycle Baseline is defined as the last measurement collected before the study treatment injection of the corresponding cycle. Percentages are based on N (number of subjects in the LTA population having received the study treatment of the corresponding cycle).
The two instances of subjects who did not fulfil the retreatment criterion of mild glabellar lines according to the investigator's live assessment at maximum frown at Cycle 3 and Cycle 4 Baseline were noted as major protocol deviations;

Outcomes and estimations

Primary efficacy endpoint
The proportion of responders D29 in the mITT population was statistically significantly higher ($p<0.0001$) in the BTX-A-HAC solution group (81.6%) than in the placebo group (0.8%).

Secondary efficacy endpoints
Proportion of responders at each post-treatment visit in the ILA of glabellar lines at maximum frown for subjects treated with BTX-A-HAC solution
The proportion of responders at each post-treatment visit until Day 85 for the ILA of glabellar lines at maximum frown is shown in Figure 6 for the DB period. Treatment with BTX-A-HAC solution resulted in a larger proportion of responders at maximum frown compared with placebo at each further post-treatment visit in the DB period ($p<0.0001$ at all visits through Day 85; mITT population).

Among subjects in the LTA population, the proportion of responders for the ILA at maximum frown was highest on Day 29 (Table7). At all visits through Day 57, the proportion of responders was consistently lower in Cycle 1 than in Cycles 2, 3 and 4. This was to be expected due to the higher proportion of subjects with 'severe' glabellar lines at baseline of Cycle 1.

Figure 6 ILA of glabellar lines at maximum frown - Proportion of responders (with 95% confidence interval) at each post-treatment visit - mITT population – Double blind period

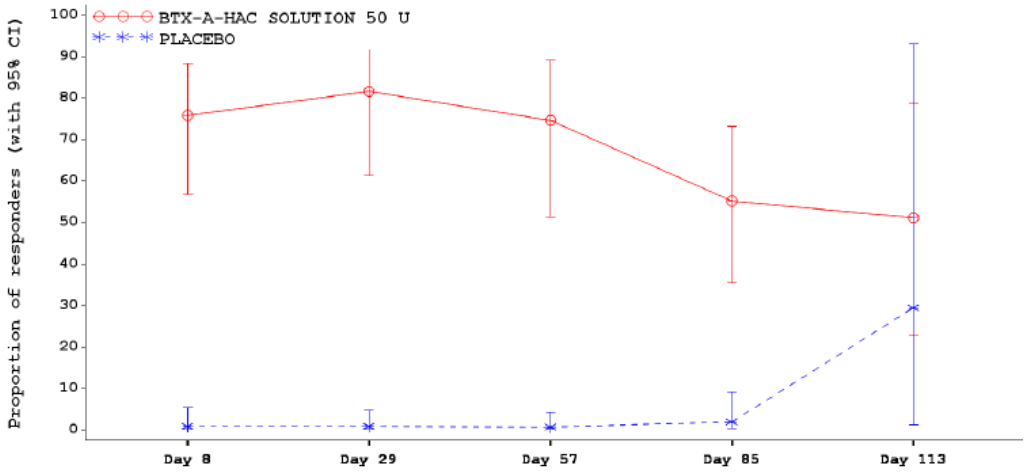


Table 7 Proportion of responders at each post-treatment visit in the ILA of glabellar lines Cycle 1-5 Long Term Analysis.

Visit	Statistic	Cycle 1 (N=595)	Cycle 2 (N=558)	Cycle 3 (N=486)	Cycle 4 (N=319)	Cycle 5 (N=89)
Day 8	n*	589	553	483	312	88
	Number of responders	446	447	418	263	74
	Proportion of responders (95% CI)	75.7 (72.3;79.2)	80.8 (77.6;84.1)	86.5 (83.5;89.6)	84.3 (80.3;88.3)	84.1 (76.4;91.7)
Day 29	n*	585	547	476	310	87
	Number of responders	481	462	418	267	72
	Proportion of responders (95% CI)	82.2 (79.1;85.3)	84.5 (81.4;87.5)	87.8 (84.9;90.8)	86.1 (82.3;90.0)	82.8 (74.8;90.7)
Day 57	n*	575	544	472	306	86
	Number of responders	402	404	371	233	48
	Proportion of responders (95% CI)	69.9 (66.2;73.7)	74.3 (70.6;77.9)	78.6 (74.9;82.3)	76.1 (71.4;80.9)	55.8 (45.3;66.3)
Day 85	n*	579	544	472	302	86
	Number of responders	307	292	268	153	39
	Proportion of responders (95% CI)	53.0 (49.0;57.1)	53.7 (49.5;57.9)	56.8 (52.3;61.2)	50.7 (45.0;56.3)	45.3 (34.8;55.9)

BTX-A-HAC=BTX-A Haemagglutinin Complex, CI=confidence interval, DB=double-blind, LTA=long term analysis, N=total number of subjects in treatment group, n*=number of subjects with an ILA of glabellar lines at maximum frown of moderate or severe at Cycle Baseline and with available data at the given visit of the corresponding cycle, U=units.
Data source: Table 14.2.2.1.6
Note: Cycle 1 includes the DB Cycle 1 of subjects treated with BTX-A-HAC solution 50 U, the Cycle 1 of de novo subjects and the Cycle 2 of subjects entered as placebo in the DB period (corresponds to the first administration of BTX-A-HAC solution 50 U). Cycles 2, 3, 4 and 5 correspond to the summary of data after the 2nd, 3rd, 4th and 5th injection of BTX-A-HAC solution 50 U. A responder is defined as having a severity grade of none or mild at a given visit and a severity grade of moderate or severe at Cycle Baseline. Cycle Baseline is defined as the last measurement collected before the study treatment injection of the corresponding cycle. Percentages are based on n*.

Proportion of responders at each post-treatment visit as measured by the ILA at rest
Treatment with BTX-A-HAC solution resulted in a larger proportion of responders at rest compared with placebo at all post-treatment visits of the DB period. Among subjects in the LTA population, the proportion of responders was highest on Day 29 (Cycle 1: 81.7%, Cycle 2: 78.4%, Cycle 3: 84.2%, Cycle 4: 81.3%). The rate of responders decreased at subsequent timepoints until Day 85 (Cycle 1: 61.1%, Cycle 2: 47.9%, Cycle 3: 58.7% and Cycle 4: 59.5%).

Proportion of responders at each post-treatment visit as measured by the SSA at maximum frown
Treatment with BTX-A-HAC solution resulted in a larger proportion of responders at maximum frown compared with placebo at each post-treatment visit of the DB period (Day 29 BTX-A-HAC 68.1%, placebo 2.3%). Among subjects in the LTA population, the proportion of responders on Day 29 was comparable among Cycles, Cycle 1: 72.5%, Cycle 2: 75.3%, Cycle 3: 80.6%, Cycle 4: 75.2%).

Proportion of responders at each post-treatment visit as measured by the Subject's level of satisfaction with the appearance of their glabellar lines
Treatment with BTX-A-HAC solution resulted in a larger proportion of responders as measured by the subject's level of satisfaction with the appearance of glabellar lines compared with placebo at each post-treatment visit of the DB period through Day 85 (mITT population).

Among subjects in the LTA population, the proportion of responders was highest on Day 29 in Cycles 1, 2 and 4 (Cycle 1: 86.0%, Cycle 2: 85.2%, Cycle 4: 87.3%). The highest proportion of responders in Cycle 3 was on Day 8 (88.3%), although this was only very slightly higher than the proportion at Day 29 (87.8%). The proportion of responders decreased in each cycle on Day 57 and Day 85, with the proportion of responders on Day 85 approximately 50% in each cycle.

Time to Retreatment
Subjects could be retreated with BTX-A-HAC solution if pre-specified criteria were fulfilled (i.e. glabellar line severity had returned to moderate or severe) and if at least 12 weeks had elapsed since the previous treatment. Time to retreatment was only calculated for subjects who were retreated; subjects who were not subsequently retreated after a given cycle were excluded from the summary of time to retreatment at that cycle.

The median time to retreatment with BTX-A-HAC solution was longer for subjects who had received BTX-A-HAC solution during the DB period than for subjects who had received placebo (BTX-A-HAC solution: 120.0 days, placebo 86.0 days; calculated for subjects from mITT population who were retreated during the OL period).

The median time to retreatment between BTX-A-HAC treatment cycles for all subjects in the LTA population was 113.0 days for Cycle 1, 114.0 days for Cycle 2, 110.0 days for Cycle 3 and 99.0 days for Cycle 4. On Day 197 of Cycle 1 and Cycle 2 and on Day 169 of Cycle 3 more than 90% of subjects in the LTA population had been retreated (Cycle 1: 93%, Cycle 2: 93%, Cycle 3: 97%, Cycle 4: 85%).

Mean change from baseline to each post-treatment visit in the FACE-Q satisfaction with facial appearance overall scale rasch transformed score
The mean value at Baseline for subjects included in the DB period was 41.1 score points (of 100) for the BTX-A-HAC solution group and 39.6 score points for the placebo group. The LS mean change from Baseline for the visits through Day 85 (the first day retreatment was allowed if glabellar line severity had returned to moderate or severe) ranged from 4.7 (Day 85) to 11.2 (Day 57) score points in the BTX-A-HAC solution group and from -5.0 (Day 85) to 0.8 (Day 8) score points in the placebo group. The LS mean treatment differences in change from Baseline through Day 85 were all statistically significant and ranged from 8.6 score points on Day 8 to 11.1 score points on Day 29.

Among subjects in the LTA population mean changes from Baseline to Day 29 were similar across the treatment cycles (Cycle 1: 10.9, Cycle 2: 9.7, Cycle 3: 9.9, Cycle 4: 9.9 score points) and comparable to the results observed following single treatment with BTX-A-HAC solution during the DB period (10.9 score points).

Mean change from baseline to each post-treatment visit in the FACE-Q Psychological well-being scale rasch transformed score

The mean value at Baseline for subjects included in the DB period was 55.2 score points (of 100) for the BTX-A-HAC solution group and 51.9 score points for the placebo group. The mean change from baseline at all post treatment visits in the DB period is shown in Table 8.

Table 8 FACE-Q - Psychological well-being scale - Summary of rasch transformed score (raw data and changes from baseline) by visit – mITT- population – Double blind period

		BTX-A-HAC SOLUTION 50 U (N=125)		PLACEBO (N=63)	
VISIT	STATISTIC	SCORE	CHANGE FROM BASELINE	SCORE	CHANGE FROM BASELINE
Baseline	n	124		62	
	Mean	55.2		51.9	
	SD	17.5		15.8	
	Median	53.5		49.0	
	Min,Max	5;100		20;100	
Day 8	n	125	124	63	62
	Mean	61.1	6.1	50.0	-1.8
	SD	18.1	15.6	16.8	11.8
	Median	58.0	4.0	47.0	0.0
	Min,Max	28;100	-35;57	17;93	-42;29
Day 29	n	124	123	61	60
	Mean	61.5	6.4	48.6	-3.1
	SD	17.1	18.6	15.3	14.0
	Median	61.0	6.0	49.0	0.0
	Min,Max	12;100	-83;95	5;83	-41;41
Day 57	n	122	121	60	59
	Mean	62.3	6.6	49.1	-3.0
	SD	17.4	18.2	16.0	14.6
	Median	61.0	5.0	49.0	0.0
	Min,Max	12;100	-88;56	5;100	-50;32
Day 85	n	123	122	60	59
	Mean	56.6	1.3	46.6	-5.2
	SD	16.9	18.0	13.9	12.5
	Median	58.0	2.5	46.0	-3.0
	Min,Max	5;100	-95;60	5;80	-43;19

Source: Listing 16.2.6.5; Data source: ADFACEQ

Note: The FACE-Q psychological well-being scale rasch transformed score is calculated by adding the 10 items (scored from 1 to 4) and converting the score to a scale from 0 to 100 using a conversion table (See Appendix 1 of the SAP). In case of missing item less than 50%, the missing values are replaced by the mean of the completed items.
Baseline is defined as the last measurement collected prior to the first injection of the study.
Days 113 to 253 correspond to additional visits.

Among subjects in the LTA population, mean changes from Baseline to Day 29 were similar across the treatment cycles (Cycle 1: 7.2, Cycle 2: 8.2, Cycle 3: 9.4, Cycle 4: 8.8 score points) and comparable to the results observed following single treatment with BTX-A-HAC solution during the DB period (6.4 score points)

Mean change from baseline to each post-treatment visit in the FACE-Q aging appearance appraisal visual analogue scale score
Subjects included in the DB period rated themselves as looking 0.9 years younger at Baseline in BTX-A-HAC solution group and as looking 0.1 years older in the placebo group.

Among subjects in the LTA population mean changes from Baseline to Day 29 were similar across the treatment cycles (subjects rating themselves 1.3, 1.0, 1.0 and 0.9 years younger following treatment in Cycles 1, 2, 3 and 4, respectively) and comparable to the results observed following single treatment with BTX-A-HAC solution during the DB period (1.0 years younger)

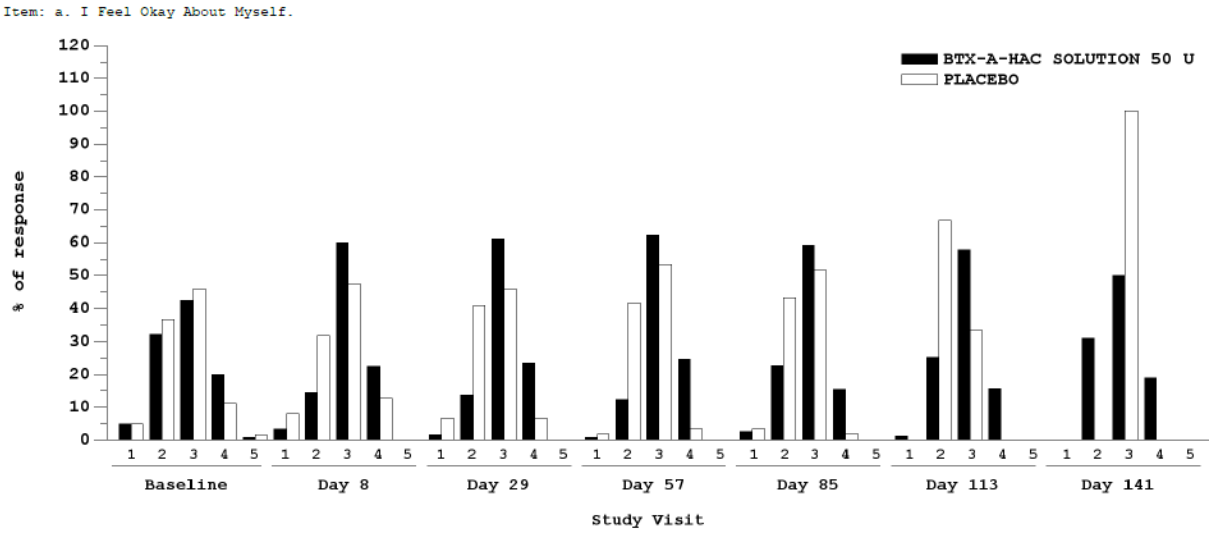
Secondary efficacy endpoints analysed for the Double-blind period

Multiple testing correction was not performed in this study.

Mean change from baseline to each post-treatment visit for each item of the FACE-Q satisfaction with facial appearance scale and the FACE-Q psychological well-being scale
The scales ranged from 1=very dissatisfied to 4=very satisfied for the FACE-Q satisfaction with facial appearance scale and from 1=definitely disagree to 4=definitely agree for the FACE-Q psychological

well-being scale. For most of the 10 items on each of the two scales and at most of the post-treatment visits during the DB period, the percentages of subjects who were ‘somewhat satisfied’ or who ‘somewhat agreed’ (scale value=3) were higher in the BTX-A-HAC solution group than in the placebo group, whereas the percentages of subjects who were ‘somewhat dissatisfied’ or who ‘somewhat disagreed’ (scale value=2) were higher in the placebo group compared with the BTX-A-HAC solution group. Figure 7 shows the first item in the FACE-Q - Psychological well-being scale, the proportion of ratings 1-4 at each study visit.

Figure 7 FACE-Q - Psychological well-being scale for item a) at each visit – mITT-population – Double blind period



Student’s t-test was used to compare the mean change from Baseline between treatment groups. Statistically significantly ($p<0.05$) larger improvements from Baseline in the BTX-A-HAC solution group compared with placebo were noted at all visits through Day 85 (the first day retreatment was allowed if glabellar line severity had returned to moderate or severe) for 8 of the 10 items on the FACE-Q satisfaction with facial appearance scale and for 4 of the 10 items on the FACE-Q psychological well-being scale.

Time to onset of treatment response based on the subject’s diary card
The median time to onset of treatment response was 2.0 days (range 2 to 3 days) in the BTX-A-HAC solution group (the median could not be calculated in the placebo group due to the small number of responders). On Day 1, 25% of subjects in the BTX-A-HAC solution group and 3% of subjects in the placebo group had recorded a treatment response. By Day 7, this was the case for 93% of subjects in the BTX-A-HAC solution group and 13% of subjects in the placebo group.

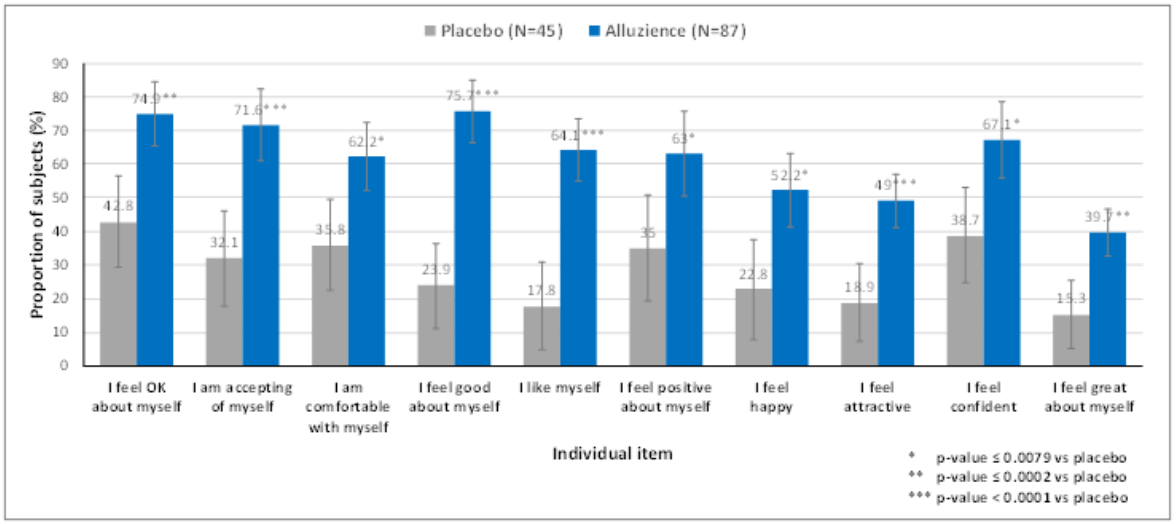
Proportion of responders on day 29 who remained responders on days 57, 85 and on additional follow-up visits as measured by the ILA at maximum frown
One patient in the placebo group was regarded as responder on day 29. This subject was still regarded as responder on Day 57, but not on day 85. In the BTX-A-HAC solution group, the proportion of responders on Day 29 who remained responders on any of the subsequent visits was 87.7% on Day 57 and 63.2% on Day 85. A total of 32 subjects continued to respond on Day 113 and 13, 8, 6 and 3 subjects were still responders on Days 141, 169, 197 and 225, respectively. The number of responders continued to decrease at each timepoint until Day 253, when there were no responders.

Ancillary analyses
Proportion of responders on day 29 by the ILA and SSA at maximum frown by gender
The proportion of responders in the BTX-A-HAC solution group was higher for female than for male subjects, both for the ILA (89.5% versus 50.0%) and for the SSA (82.5% versus 50.0%).

Proportion of responders on day 29 by the ILA and SSA at maximum frown by investigator's live assessment baseline severity score at maximum frown
In the BTX-A-HAC group a higher proportion of subjects with moderate glabellar lines at Baseline responded to treatment (97.6%) compared with subjects with severe glabellar lines (55.6%), for the ILA. For the SSA, a higher proportion of subjects with moderate GLs at baseline responded to treatment (77.7%) compared to those with severe GLs at baseline 57.3%). The effect of the Baseline severity score was statistically significant for the ILA (treatment by baseline severity interaction p=0.0318) but not for the SSA (p=0.6679).

Pooled efficacy analyses
To demonstrate the improvement in individual's well-being, the Applicant upon request calculated responder rates for the 10 items of the Psychological well-being scale. A responder was regarded as a patient who increased her/his rating by at least one grade (timepoint not specified) compared to baseline. The most interesting responders would be those with a low score at baseline (1-2) who after treatment reach a score at or above 3 (somewhat agree to positive statements about one-self). These are shown in figure 8 (pooled analysis of study 189 and study 214, mITT). Larger proportions of BTX-treated patients shifted from a low to a higher score for all items compared to placebo.

Figure 8 Proportion of subjects (± 95%CI) with Baseline score of 1 or 2 and Day 29 score of 3 or 4 per individual item in psychological well-being scale: pooled analysis of Study 189 and Study 214 (mITT population)



IV.5 Clinical safety

The sponsor has developed a new ready to use injectable form of BTX-A-HAC solution for the treatment of moderate to severe glabellar lines in adults, which is a clear colourless liquid formulation of Clostridium botulinum toxin type A (BTX-A). This BTX-A-HAC solution is fully formulated and provided in a vial ready to inject, eliminating the need for prior reconstitution. The currently approved Ipsen pharmaceutical products with BTX A HAC are freeze dried (lyophilised) powder preparations of BTX A HAC which are registered worldwide for a wide variety of indications including the treatment of glabellar lines.

This newly formulated BTX A HAC solution is expected to offer a twofold advantage: one, to simplify the injection procedure for clinicians by eliminating the need for reconstitution, thereby improving the standardisation of the desired drug concentration; and two, the replacement of the

human- and animal-derived excipients with plant and synthetic standard excipients that have shown to maintain the toxin activity in a liquid presentation with demonstrable clinical efficacy. The currently marketed Ipsen BTX-A-HAC lyophilised powder formulations are already approved for the improvement in the appearance of glabellar lines worldwide in a number of countries in the European Union (EU). The active substance, BTX-A-HAC, used in the newly-developed BTX-A-HAC solution, is the same and thus the therapeutic effect is expected to be similar based on the pharmacodynamic mechanism of action of BTX-A-HAC.

Patient exposure

The 'safety population' was defined as all randomised subjects who received at least one injection of study treatment into at least one injection site.

The presentation of safety data consists of descriptive statistics and summary tabulations. All tabular data are presented on the safety population. For any summary presentation, if a subject experienced more than one event in a category, the subject was counted only once in that category. The assessment of causality is presented based on the investigator's judgement only.

Table 9 Subject Disposition – Pooled Double-Blind Data (Randomised Population)

	BTX-A-HAC Solution 50 U	**Placebo**	**All Subjects**
Randomised subjects, N	251	124	375
Study 189	125 (49.8)	60 (48.4) [a]	185 (49.3)
Study 214	126 (50.2)	64 (51.6)	190 (50.7)
Subjects included in the safety population, N	251 (100.0)	123 (99.2)	374 (99.7)
Study 189	125 (49.8)	59 (48.0)	184 (49.2)
Study 214	126 (50.2)	64 (52.0)	190 (50.8)
Number of subjects who completed, n (%)	240 (95.6)	110 (89.4)	350 (93.6)
Number of subjects who withdrew, n (%)	11 (4.4)	13 (10.6)	24 (6.4)
Reasons for withdrawal, n (%)			
Consent withdrawn	9 (81.8)	13 (100.0)	22 (91.7)
Lost to follow-up	2 (18.2)	0	2 (8.3)

BTX-A-HAC=botulinum toxin type A haemagglutinin complex, n=number of subjects in a specific group, U=units.
Data Source: Module 5.3.5.3, Table T.DS.1; Module 5.3.5.1, Study 189, Table 14.1.4; Module 5.3.5.1, Study 214, Table 14.1.2.1.
The number of randomised subjects is the denominator used for the calculation of percentages of the number of randomised subjects for each study.
The number of subjects included in the safety population is the denominator used for the calculation of percentages of the number of subjects included in the safety population of each study, the number of subjects who completed and the number of subjects who withdrew.
The number of withdrawn subjects is the denominator used for the calculation of percentages of reasons for withdrawal.
For the study 214, only subjects enrolled in the double blind period of the study are taken into account and subjects completed are subjects who are not withdrawn during cycle 1.
a Subject 25000100003 in Study 189 was randomised but not treated.

Furthermore, the long-term safety of treatment with BTX-A-HAC solution was assessed in Study 214 where subjects could receive a maximum of five treatments with BTX-A-HAC solution with 12 months of follow-up from the first BTX-A-HAC solution treatment received. This study also provided information on the immunogenicity following long term treatment with BTX-A-HAC solution.

Table 10 Subject Disposition – Study 214 (LTA Population)

	BTX-A-HAC Solution 50 U		
	Subjects Included in the DB Period	**De Novo Subjects**	**All Subjects**
Subjects included in Study 214, N	190	410	600
Placebo subjects withdrawn during the double blind period, n (%)	5 (2.6%)	-	5 (0.8%)
Subjects included in the LTA population, N	185	410	595
Number of subjects who completed, n (%) [a]	163 (88.1)	346 (84.4)	509 (85.5)
Number of subjects who withdrew, n (%) [b]	22 (11.9)	64 (15.6)	86 (14.5)
Reason for premature withdrawal, n (%)			
Adverse event	2 (9.1)	2 (3.1)	4 (4.7)
Consent withdrawn	18 (81.8)	56 (87.5)	74 (86.0)
Lost to follow-up	0	1 (1.6)	1 (1.2)
Other reason	2 (9.1)	5 (7.8)	7 (8.1)

BTX-A-HAC=botulinum toxin type A haemagglutinin complex, DB=double blind, LTA=long term analysis, N=number of subjects having received study treatment, n=number of subjects in a specific group, U=units.
Data Source: Module 5.3.5.1, Study 214, Table 14.1.2.1 and Table 14.1.2.2.
The number of subjects randomised (included in the double blind period) is the denominator used for the calculation of percentages of completed and withdrawn subjects for the double blind period.
The number of subjects included in Study 214 is the denominator used for the calculation of percentages of placebo subjects withdrawn during the double blind period.
The number of subjects included in LTA population is the denominator used for the calculation of percentages of completed and withdrawn subjects for LTA.
The number of withdrawn subjects is the denominator used for the calculation of percentages of reasons for withdrawal.
a Subjects who completed the double blind period are the subjects who are not withdrawn during treatment cycle 1.
b Subjects included in the double blind period of the study and randomised to the placebo group who withdrew during the treatment cycle 1 with placebo are not taken into account.

In addition, the supportive clinical safety data are presented separately for the double blind, active comparator and placebo-controlled phase II Study 146. This study assessed the safety and efficacy of three doses of BTX-A-HAC solution (20 U, 50 U and 75 U) with placebo and BTX-A-HAC powder 50 U (Azzalure) administered as a single treatment in subjects with moderate to severe glabellar lines (35-36 subjects per group).

Since the active substance used in this product is the same as that used in other lyophilised powder formulations of BTX-A-HAC, the safety profile of BTX-A-HAC solution is expected to be similar (based on the clinical study data to date). Hence, the sponsor includes the postmarketing safety data for the currently approved BTX-A-HAC powder formulations from the sponsor's Global Safety Database in the indication of glabellar lines in order to provide the full context for the safety profile of BTX-A-HAC powder in this indication, and to demonstrate that there is no new safety information arising from the postmarketing data for the BTX-A-HAC powder formulation, which may need to be considered for BTX-A-HAC solution.

Adverse events

An overview of the pooled analysis of double-blind data is shown in Table 11.

Table 11 Overall Summary of Adverse Events – Pooled Double-Blind Data (Safety Population)

AE Category, n (%)	BTX-A-HAC Solution 50 U (N=251)	Placebo (N=123)	All Subjects (N=374)
Any AE	103 (41.0)	43 (35.0)	146 (39.0)
Any TEAE	101 (40.2)	42 (34.1)	143 (38.2)
Any severe TEAE	3 (1.2)	5 (4.1)	8 (2.1)
Any related TEAE	43 (17.1)	7 (5.7)	50 (13.4)
Any related and severe TEAE	0	0	0
Any TEAE leading to withdrawal	0	0	0
Any TEAE leading to death	0	0	0
Any SAE	3 (1.2)	3 (2.4)	6 (1.6)

AE=adverse event, BTX-A-HAC=botulinum toxin type A haemagglutinin complex, N=total number of subjects in in the safety population, n=number of subjects with event, SAE=serious adverse event, TEAE=treatment emergent adverse event, U=units.

The most frequently reported TEAE in ≥5% of subjects and at a frequency greater than in the placebo group was headache. Other TEAEs reported in ≥2% of subjects treated with BTX-A-HAC solution and at a frequency greater than in the placebo group were injection site pain, haematoma (mostly localised at the injection site) and tonsillitis.

Table 12 Treatment Emergent Adverse Events reported in ≥2% of subjects in any treatment group – Pooled Double-Blind Data (Safety Population)

Primary System Organ Class Preferred Term, n (%)	BTX-A-HAC Solution 50 U (N=251)	Placebo (N=123)	All Subjects (N=374)
Any TEAEs	**101 (40.2)**	**42 (34.1)**	**143 (38.2)**
Infections and infestations	**48 (19.1)**	**22 (17.9)**	**70 (18.7)**
Nasopharyngitis	23 (9.2)	13 (10.6)	36 (9.6)
Tonsillitis	5 (2.0%)	0	5 (1.3%)
Influenza	3 (1.2)	3 (2.4)	6 (1.6)
Nervous system disorders	**34 (13.5)**	**7 (5.7)**	**41 (11.0)**
Headache	30 (12.0)	6 (4.9)	36 (9.6)
General disorders and administration site conditions	**16 (6.4)**	**3 (2.4)**	**19 (5.1)**
Injection site pain	10 (4.0)	3 (2.4)	13 (3.5)
Vascular disorders	**9 (3.6)**	**2 (1.6)**	**11 (2.9)**
Haematoma	6 (2.4)	0	6 (1.6)

BTX-A-HAC=botulinum toxin type A haemagglutinin complex, N=total number of subjects in the safety population, n=number of subjects with event, TEAE=treatment emergent adverse event, U=units.

The majority of TEAEs reported were of mild (BTX: 31.9%, placebo: 22.8%) or moderate intensity (BTX: 15.9%, placebo: 13.8%). A total of 3 (1.2%) subjects treated with BTX and 5 (4.1%) subjects with placebo reported severe TEAEs; none of the severe TEAEs were considered treatment related by the investigator and all subjects recovered from the events. Severe TEAEs were most frequently reported in the SOC of infections and infestations. No severe TEAE PT was reported in more than one subject.

Severe TEAEs reported in three subjects (one treated with BTX-A-HAC solution and two with placebo) were also considered as SAEs. None of them were considered as related to treatment by the investigator.

Treatment related TEAEs reported by ≥2 subjects treated with BTX A HAC solution were headache (6.4%), injection site pain (4.0%), haematoma (2.0%; mostly localised at the site of injection from the reported verbatim terms), eyelid oedema (1.6%), and brow ptosis (1.2%); all other causally related TEAEs were reported in one subject each. All causally related TEAEs reported during the studies were mild or moderate in intensity.

Table 13 Related Treatment Emergent Adverse Events – Pooled Double Blind Data (Safety Population)

Primary System Organ Class Preferred Term, n (%)	**BTX-A-HAC Solution 50 U (N=251)**	**Placebo (N=123)**	**All Subjects (N=374)**
Any TEAEs	**43 (17.1)**	**7 (5.7)**	**50 (13.4)**
Nervous system disorders	18 (7.2)	3 (2.4)	21 (5.6)
Headache	16 (6.4)	3 (2.4)	19 (5.1)
Head discomfort	1 (0.4)	1 (0.8)	2 (0.5)
Orthostatic intolerance	1 (0.4)	0	1 (0.3)
General disorders and administration site conditions	12 (4.8)	3 (2.4)	15 (4.0)
Injection site pain	10 (4.0)	3 (2.4)	13 (3.5)
Injection site erythema	1 (0.4)	0	1 (0.3)
Injection site hypoaesthesia	1 (0.4)	0	1 (0.3)
Injection site induration	1 (0.4)	0	1 (0.3)
Eye disorders	7 (2.8)	1 (0.8)	8 (2.1)
Eyelid oedema	4 (1.6)	0	4 (1.1)
Blepharochalasis	1 (0.4)	0	1 (0.3)
Eyelid ptosis	1 (0.4)	0	1 (0.3)
Lacrimation increased	0	1 (0.8)	1 (0.3)
Ocular discomfort	1 (0.4)	0	1 (0.3)
Vascular disorders	5 (2.0)	0	5 (1.3)
Haematoma	5 (2.0)	0	5 (1.3)
Skin and subcutaneous tissue disorders	4 (1.6)	0	4 (1.1)
Brow ptosis	3 (1.2)	0	3 (0.8)
Chloasma	1 (0.4)	0	1 (0.3)
Musculoskeletal and connective tissue disorders	2 (0.8)	0	2 (0.5)
Muscle haemorrhage	1 (0.4)	0	1 (0.3)
Muscle spasms	1 (0.4)	0	1 (0.3)
Blood and lymphatic system disorders	1 (0.4)	0	1 (0.3)
Lymphatic disorder	1 (0.4)	0	1 (0.3)
Injury, poisoning and procedural complications	1 (0.4)	0	1 (0.3)
Post procedural contusion	1 (0.4)	0	1 (0.3)
Surgical and medical procedures	1 (0.4)	0	1 (0.3)
Manual lymphatic drainage	1 (0.4)	0	1 (0.3)

BTX-A-HAC=botulinum toxin type A haemagglutinin complex, N=total number of subjects in group, n=number of subjects with event, TEAE=treatment emergent adverse event, U=units.

More than 70% of the subjects in both treatment groups (76/101 in BTX A HAC solution and 31/42 in the placebo groups), who reported at least one TEAE, did so within the first 4 weeks of receiving the treatment. A similar trend was observed for the treatment related TEAEs where 41/43 subjects who reported causally related TEAEs did so within the first 4 weeks following treatment with BTX A HAC solution.

Long term adverse effects after repeat administration

Overall, there was a trend towards a decreased incidence of TEAEs with repeated cycles of BTX A HAC solution treatment (Table 14). Consistent with the pooled double-blind data, nasopharyngitis and headache were the most frequently reported TEAEs across the treatment cycles, with an overall incidence of >10% of subjects. The highest incidences for these events were reported in treatment cycles 1 (headache) or 2 (nasopharyngitis). The majority of the nasopharyngitis events following treatment with BTX-A-HAC solution showed a seasonal trend, occurring in the months of September to March. All other TEAEs were reported in <5% of the subjects.

Table 14 Overall Summary of Adverse Events in Subjects Treated with BTX A HAC Solution 50 U by Treatment Cycle – Study 214 (LTA Population)

AE Category, n (%)	TC 1 (N=595)	TC 2 (N=558)	TC 3 (N=486)	TC 4 (N=319)	TC 5 (N=89)	All TCs (N=595)
Any AE	270 (45.4)	211 (37.8)	162 (33.3)	70 (21.9)	19 (21.3)	394 (66.2)
Any TEAE	270 (45.4)	211 (37.8)	162 (33.3)	70 (21.9)	19 (21.3)	386 (64.9)
Any severe TEAE	12 (2.0)	17 (3.0)	9 (1.9)	4 (1.3)	0	37 (6.2)
Any related TEAE	75 (12.6)	34 (6.1)	22 (4.5)	8 (2.5)	4 (4.5)	110 (18.5)
Any related and severe TEAE	0	0	0	0	0	0
Any TEAE leading to withdrawal	2 (0.3)	2 (0.4)	0	0	0	4 (0.7)
Any TEAE leading to death	0	0	0	0	0	0
Any SAE	9 (1.5)	13 (2.3)	5 (1.0)	7 (2.2)	0	34 (5.7) [a]

AE=adverse event, BTX-A-HAC=botulinum toxin type A haemagglutinin complex, LTA=long term analysis, N=total number of subjects in the LTA population, n=number of subjects with event, SAE=serious adverse event, TEAE=treatment emergent adverse event, TC=treatment cycle, U=units.
Data Source: Module 5.3.5.1, Study 214, Table 14.3.1.8.
For AEs and SAEs, the column 'All TCs' includes all subjects including those with AEs which occurred before the first treatment injection with BTX-A-HAC solution.

a Two subjects reported SAEs during the double blind period while on placebo: Subject 27611100001 reported a pretreatment SAE prior to receiving the randomised placebo treatment and another SAE following placebo treatment and Subject 25010600027 reported an SAE following placebo treatment.

Causally related TEAEs were reported in 18.5% of subjects during the whole study period (with 12 months of follow-up). The majority of causally related TEAEs were reported during treatment cycle 1 (12.6%) with a decrease in incidence at the later treatment cycles (ranging from 2.5% to 6.1%) (Table 15). The most frequent causally related TEAE reported across all treatment cycles was headache with the highest incidence reported at treatment cycle 1 (ranging from 0% to 5.4% across the treatment cycles). Other causally related TEAEs reported by >2 subjects in any one treatment cycle were eyelid ptosis (range: 0% to 1.3%), eyelid oedema (range: 0.3% to 1.2%), haematoma (range: 0% to 1.2%; localised at the site of injection; glabella, above or between the eyebrows, forehead, periorbital, injection site, vessel puncture site (due to blood sampling)), brow ptosis (range: 0% to 0.7%), head discomfort (0% to 0.7%) and injection site swelling (range: 0% to 0.5%); the incidence was highest in treatment cycle 1 for all of these reported events.

Table 15 Related Treatment Emergent Adverse Events Reported in At Least Two Subjects (All TCs) Treated with BTX A HAC Solution 50 U by Treatment Cycle – Study 214 (LTA Population)

Primary System Organ Class Preferred Term, n (%)	TC 1 (N=595)	TC 2 (N=558)	TC 3 (N=486)	TC 4 (N=319)	TC 5 (N=89)	All TCs (N=595)
Any related TEAE	**75 (12.6)**	**34 (6.1)**	**22 (4.5)**	**8 (2.5)**	**4 (4.5)**	**110 (18.5)**
Nervous system disorders	**37 (6.2)**	**18 (3.2)**	**10 (2.1)**	**3 (0.9)**	**0**	**52 (8.7)**
Headache	32 (5.4)	16 (2.9)	8 (1.6)	3 (0.9)	0	46 (7.7)
Head discomfort	4 (0.7)	0	0	0	0	4 (0.7)
Paraesthesia	1 (0.2)	1 (0.2)	1 (0.2)	0	0	3 (0.5)
Eye disorders	**23 (3.9)**	**8 (1.4)**	**5 (1.0)**	**2 (0.6)**	**1 (1.1)**	**36 (6.1)**
Eyelid ptosis	8 (1.3)	4 (0.7)	2 (0.4)	1 (0.3)	0	14 (2.4)
Eyelid oedema	7 (1.2)	3 (0.5)	2 (0.4)	1 (0.3)	1 (1.1)	13 (2.2)
Blepharospasm	2 (0.3)	1 (0.2)	0	1 (0.3)	0	4 (0.7)
Dry eye	1 (0.2)	1 (0.2)	0	0	0	2 (0.3)
Lacrimation increased	2 (0.3)	0	0	0	0	2 (0.3)
General disorders and administration site conditions	**6 (1.0)**	**4 (0.7)**	**3 (0.6)**	**2 (0.6)**	**2 (2.2)**	**15 (2.5)**
Injection site swelling	3 (0.5)	1 (0.2)	2 (0.4)	0	0	5 (0.8)
Injection site haematoma	0	2 (0.4)	1 (0.2)	0	1 (1.1)	4 (0.7)
Injection site discomfort	1 (0.2)	2 (0.4)	0	0	0	2 (0.3)
Injection site pain	1 (0.2)	0	0	1 (0.3)	1 (1.1)	2 (0.3)
Vascular disorders	**7 (1.2)**	**2 (0.4)**	**5 (1.0)**	**0**	**1 (1.1)**	**14 (2.4)**
Haematoma	7 (1.2)	2 (0.4)	4 (0.8)	0	1 (1.1)	13 (2.2)
Skin and subcutaneous tissue disorders	**10 (1.7)**	**4 (0.7)**	**0**	**0**	**0**	**12 (2.0)**
Brow ptosis	4 (0.7)	1 (0.2)	0	0	0	5 (0.8)
Swelling face	2 (0.3)	1 (0.2)	0	0	0	3 (0.5)
Pruritus	2 (0.3)	0	0	0	0	2 (0.3)
Injury, poisoning and procedural complications	**2 (0.3)**	**1 (0.2)**	**0**	**1 (0.3)**	**0**	**3 (0.5)**
Periorbital haematoma	1 (0.2)	1 (0.2)	0	1 (0.3)	0	2 (0.3)
Musculoskeletal and connective tissue disorders	**2 (0.3)**	**0**	**0**	**0**	**0**	**2 (0.3)**
Muscle spasms	2 (0.3)	0	0	0	0	2 (0.3)

BTX-A-HAC=BTX-A Haemagglutinin Complex, LTA=long term analysis, N=total number of subjects in the LTA population, n=number of subjects with event, TEAE=treatment-emergent adverse event, TC=treatment cycle, U=units.
Data source: Module 5.3.5.1, Study 214, Table 14.3.1.11.

Supportive safety data – Study 146
Related TEAEs were reported in a similar proportion of subjects between the BTX A HAC solution (11.4% to 16.7%) and placebo (14.3%) groups; the incidence was lower in the BTX A HAC powder 50 U group (5.7%). The most frequently reported related TEAEs in any treatment group were injection site pain, headache and eye ptosis (frequency range from 3% to 6%); the incidence for all three events was higher in the BTX A HAC solution 75 U group. No difference was noted between the severity and the nature of related events reported in the BTX A HAC solution 50 U and BTX A HAC powder 50 U groups; all related TEAEs were reported in one subject each in both treatment groups.

Serious adverse events, deaths and other adverse events of special interest
There were no deaths reported in any of the clinical studies conducted with BTX A HAC solution.

In the pooled analysis of double-blind data, SAEs were reported in 3 (1.2%) subjects treated with BTX A HAC solution (mydriasis, joint range of motion decreased, menorrhagia) and in 3 (2.4%) subjects treated with placebo (aphthous ulcer, drug hypersensitivity, gastrointestinal infection, tendon rupture). All SAE PTs were reported for one subject each. None of the SAE was considered treatment related by the investigator. As discussed earlier, three subjects reported SAEs that were severe in intensity and

all subjects recovered from the events: one subject treated with BTX-A-HAC solution (mydriasis) and two subjects treated with placebo.

In supportive study 146, one subject experienced two serious adverse events (vertigo, headache) which were not considered as related to treatment (BTX 20 U solution) by the investigator. One subject in the BTX A HAC solution 75 U had a road traffic accident (bike accident) along with periorbital haematoma and laceration (cut right forehead) 12 days after treatment. No eye disorders (ptosis or oedema) were reported for this subject prior to the accident indicating that the accident was not due to any adverse reaction linked to treatment with BTX A HAC solution.

Serious adverse events in the long-term safety data
A total of 32 (5.4%) subjects reported 38 SAEs following treatment with BTX A HAC solution during the entire duration of Study 214. The proportion of subjects who reported SAEs was comparable amongst the treatment cycles ranging between 0% to 2.3%. With the exception of post procedural haemorrhage (verbatim terms: post-operative bleeding in one subject and bleeding after cervical conization in the other) and rotator cuff syndrome reported in two subjects each, all SAE PTs were reported for single subjects.

None of the reported SAEs were considered treatment related by the investigators. Three subjects were withdrawn from the study due to SAEs (small intestine carcinoma, Holmes-Adie pupil, and post-traumatic stress disorder).

Adverse events leading to withdrawal
In study 146 and in the pooled analysis of double-blind data, there were no TEAEs leading to withdrawals. A total of 4 (0.7%) subjects withdrew due to TEAEs during Study 214, two in treatment cycle 1 and two in treatment cycle 2 following injection with BTX A HAC solution during the open label period of the study. Of these, three subjects withdrew due to SAEs unrelated to study treatment as assessed by the investigator (small intestine carcinoma, Holmes Adie pupil and post-traumatic stress disorder) and one subject withdrew due to a treatment related AE (eyelid ptosis; also considered an adverse event of special interest).

Adverse events of special interest (AESI)
An AESI was defined as any TEAE assessed by the sponsor as possibly attributed to

1. remote spread of the effect of BTX A HAC solution or
2. hypersensitivity reaction to BTX A HAC solution or
3. any eye disorder due treatment with BTX A HAC solution.

Remote spread of toxin
No events indicative of remote spread of effect of toxin were identified in the pooled double blind, in the long-term safety data or in Study 146.

Hypersensitivity reactions
In study 146, hypersensitivity reactions are not discussed separately. There is no hypersensitivity reaction mentioned among any kind of TEADs.

In the pooled analysis of double-blind data (Studies189 and 214), of the 251 subjects treated with BTX A HAC solution, one subject reported TEAEs indicative of hypersensitivity reaction.

Of the 595 subjects (LTA population) treated at least once with BTX A HAC solution and followed-up for a minimum of 12 months, a total of 2 (0.3%) subjects experienced three TEAEs indicative of hypersensitivity reaction. One of these subjects were the same as reported above, during the double-blind phase of study 214.

Eye disorders due to treatment with BTC-A-HAC solution
In study 146, 3 subjects of 106 treated with any dose of BTX-A-HAC solution had an AE of eye disorder (2.8%). These were three subjects with mild eyelid ptosis considered related to treatment.

In the pooled analysis of double-blind data, of the 251 subjects treated with BTX A HAC solution, a total of 7 (2.8%) subjects experienced nine AESIs that qualified as eye disorders. With the exception of eyelid oedema reported in four subjects, all other events (blepharochalasis, eyelid ptosis, lacrimation increased and ocular discomfort) were experienced by one subject each. The majority of events of eyelid oedema were of mild intensity (in 3/4 subjects). In all subjects the event of eyelid oedema started ≤5 days after treatment and lasted for a maximum of 60 days.

Of the 595 subjects (LTA population) treated at least once with BTX A HAC solution and followed-up for a minimum of 12 months, a total of 40 (6.7%) subjects experienced 51 TEAEs that qualified as eye disorders. Four events in three subjects were reported during the double-blind period (hence also included under the pooled double-blind data).

Injection site reactions
In study 146, 8 of 106 subjects treated with BTA-A-HAC solution experienced Injection site reactions (7.5%). These were: Injection site pain 5 subjects, injection site haemorrhage, injection site reaction and injection site swelling one subject each.

In the pooled analysis of double-blind data (Studies189 and 214), of the 251 subjects treated with BTX A HAC solution, 13 subjects (5.2%) reported injection site reactions (placebo 3 subjects with injection site pain, 2.4%). The most common injection site reaction was injection site pain (10 subjects). The three other injection site reactions were: Injection site erythema, hypoesthesia and induration.

Of the 595 subjects (LTA population) treated at least once with BTX A HAC solution and followed-up for a minimum of 12 months, a total of 48 (8.1%) subjects experienced injection site reactions. The most common injection site reaction was hematoma which occurred in 15 subjects (2.3%). The majority of injection site reactions were reported to have occurred on the same day as the injection or the day following the injection and resolved quickly within 1 to 2 weeks.

IV.6 Risk Management Plans

The MAH 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 Dysport.

Safety specification

Important identified	Distribution of the effects of the toxin to sites remote from the site of administration
Important potential risks	None
Missing information	None

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

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection is applied using a specific adverse reaction follow up questionnaires for the important identified risk of Distribution of the effects of the toxin to sites remote from the site of administration. This is in accordance with already approved BTA-A-HAC products of the Applicant.

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

Summary of the RMP
The submitted Risk Management Plan, version 7.4 signed April 14, 2021 is considered 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.

IV.7 Discussion on the clinical aspects

This application concerns a new ready to use injectable form of BTX-A-HAC for the treatment of moderate to severe glabellar lines in adults. This BTX-A-HAC solution is fully formulated and provided in a vial ready to inject, eliminating the need for prior reconstitution. It contains plant and synthetic standard excipients that have shown to maintain the toxin activity in a liquid presentation, instead of human- and animal-derived excipients. The currently approved Ipsen pharmaceutical products with BTX-A-HAC are freeze dried (lyophilised) powder preparations of BTX-A-HAC which are registered for a variety of indications including the treatment of glabellar lines.

Posology
Because the mechanism of action (chemical denervation) and the pharmacodynamic effect is the same for BTX-A-HAC powder and solution, the dose needed for a certain effect is expected to be similar.

Of the important ADRs of botulinum toxin treatment, local muscular weakness and effects of distant spread of toxin are dose dependent. Thus, the lowest solution dose with efficacy similar to BTX-A-HAC 50 U powder, would be the logical choice of dose. In the dose-finding study the efficacy of BTX 20 U solution had nominally higher responder rates than BTX 50 U powder for approximately 2 months after injection. However, this may be due to small study groups and an imbalance in the baseline proportion of severe glabellar lines. The efficacy of 50 U BTX powder had similar responder rates in former pivotal trials as the BTX solution in this trial, supporting this theory. The Applicant chose to perform the pivotal trials with 50 U solution dose.

Efficacy
Time to efficacy onset was in the majority of cases 2-3 days based on the subjects' own self-evaluation of their appearance. Photographs for assessment by the investigator typically overestimates the effect while subjects' assessments are consistently lower than the investigators. Thus, the self-assessment can be considered as conservative even if not objective.

The primary efficacy endpoint, proportion of Investigator's live assessment (ILA) responders defined as having moderate or severe glabellar lines at maximum frown at baseline but no or mild glabellar lines at maximum frown Day 29, was the same in the two pivotal studies. Responder rates (95% CI) were 88.3% (76.1; 94.7) and 81.6% (61.3;92.5) in the BTX groups, and 1.4% (0.3;6.5) and 0.8% (0.1;4.8) in the placebo groups. No multiple testing correction was performed in this study, which affects the possibility to make claims based on secondary endpoints. However, for the ILA, there was

a consistent pattern of efficacy including a consistent temporal profile. Descriptive statistics suggest persistence of efficacy as measured by the ILA in the BTX groups for at least 3 months. Looking at the selected group of patients who were ILA responders on Day 29, efficacy was, as expected, maintained at higher responder frequencies.

Due to re-innervation, the effect of BTX injected into a muscle will decrease over time. Repeated treatment is needed, usually after 3-6 months, if continued reduction of glabellar lines after that time period is warranted. The efficacy of BTX-A-HAC after repeated treatments was studied with up to 4 re-treatments (5 treatment cycles). Responder rate at Day 29 was similar for the five cycles, 82%, 85%, 88%, 86% and 83%, respectively.

The efficacy of BTX-A-HAC 50 U solution, in terms of the temporary improvement in the appearance of moderate to severe glabellar lines seen at maximum frown, is viewed as compelling.

Subjective efficacy measurements such as Subjects' self-assessment (SSA) of their glabellar lines and Subjects´ level of satisfaction with the appearance of their glabellar lines, showed improvement compared to placebo on Day 29, at other post treatment visits, and after up to 5 re-treatments.

The proposed indication for the new BTA-A-HAC solution is for the temporary improvement in the appearance of moderate to severe glabellar lines (GLs) seen at maximum frown in adult patients under 65 years, *when the severity of these lines has an important psychological impact on the patient*. Treatment of glabellar lines as such is not a medical indication, but a cosmetic indication, for which the benefit risk would be quite different.

The study populations include subjects who by self-assessment find their GLs as moderate or severe, and who were dissatisfied or very dissatisfied with their GLs. The fact that subjects are (very) dissatisfied with their GLs need not mean that the GLs have an important psychological impact. The target population specified in the claimed indication is restricted to patients where GLs have a relevant psychological impact. All 10 items of the Psychological well-being scale had a mean baseline score below 3 (2 = somewhat disagree and 3= somewhat agree) to positive statements about one-self, which according to the Applicant indicates that the recruited population on average was below a positive psychological well-being threshold. However, 161 BTX-treated patients had a baseline score of 3-4 and 87 patients had a baseline score of 1-2 (mITT population studies 189 and 214). Thus, at baseline, the majority of patients actually scored above this positive psychological well-being threshold and it can be questioned whether the recruited population reflects the sought indication.

Patients with a greater psychological suffering may have more to gain with treatment of their glabellar lines (from a psychological perspective) and a study population restricted to patients with moderate to severe GLs at maximum frown and scores of 1or 2 for the10 items of the psychological well-being scale, might have been more adequate and more sensitive to show psychological improvement. Nevertheless, the improvement in ILA of the glabellar lines is likely not affected by the subjective suffering by the patient.

Assessment of the subject's psychological well-being following treatment with BTX-A-HAC solution 50 U compared to placebo was a secondary or tertiary objective in the two pivotal trials. The psychological well-being should preferably have been defined as a key secondary endpoint in analytical strategy.

The construction of the FACE-Q scales hampers the ability to grasp the magnitude of potential improvement in psychological well-being. The subscale of psychological well-being consists of 10 items for which the subject can rate themselves from 1-4. Worst score possible is thus 10 and best score possible is 40 (range 10-40). A rasch transformation was performed to the range 0-100. The reason for using the Rasch transformation here has not been clearly justified, but it is worth noting that the transformation is only affecting the distribution of the data, and it does not solve any potential issues in the item scorings, or in how the 10 item scores are added to form a single score. The overall single score shows improvement compared to placebo.

The ten items of FACE-Q - Psychological well-being scale are rated using an ordinal scale of four categories. Thus, mean differences for each item are not meaningful to calculate and they are not helpful in understanding the magnitude off clinical effect. The modal in the BTX group was 3 (=

“somewhat agreed”) for most items at most study visits in both pivotal studies. The modal in the placebo group was also 3 for most items, at most visits. However, in the BTX-groups, the proportion of patients answering “somewhat agree” seems to be larger on Day 29 than at baseline, and the proportion answering “somewhat disagree” smaller.

To demonstrate the improvement in individual’s well-being, the Applicant has calculated responder rates for the 10 items of the Psychological well-being scale. A responder was regarded as a patient who increased her/his rating by at least one grade (timepoint not specified) compared to baseline. Responders ranged between 23% and 37% among BTX-treated patients. This can be compared to responder rates among placebo treated patients, approximately 13% to 23%.

The most valuable responders would be those with a low score at baseline (1-2) who after treatment reach a score at or above 3 (somewhat agree to positive statements about one-self). The proportion of patients with a baseline score of 1-2 who by day 29 rated themselves as 3-4, ranged between 40% and 76% in the BTA-A group; the corresponding range in placebo treated patients was 15% to 43% Thus, in a population with moderate to severe GLs, when the severity of these lines has an important psychological impact on the patient, Alluzience seems to improve the psychological well-being to a clinically relevant extent in a sufficient part of the patients.

Safety
Safety information on the use of BTX-A-HAC solution for the treatment of glabellar lines in adult subjects was gathered from three sources:

- short term safety data from the pooled analysis of double-blind data from the two pivotal phase III Studies 189 and 214,
- long term safety data from Study 214 that allowed subjects to be retreated with a minimum follow up of 12 months, and
- data from a phase II supportive Study 146.

Additionally, the safety analyses of clinical data for BTX-A-HAC solution were supplemented by a review of the post-marketing data with the approved BTX-A-HAC powder formulation product(s) in the indication of glabellar lines.

Causally related TEAEs were reported in a higher proportion of subjects treated with BTX-A-HAC solution (17.1%) compared with subjects who received placebo (5.7%). The most frequently reported causally related TEAEs in ≥2 subjects treated with BTX-A-HAC solution were headache, injection site pain, haematoma, eyelid oedema and brow ptosis. None of the causally related TEAEs were severe in intensity. In the long-term safety data, the majority of causally related TEAEs were reported during treatment cycle 1 (12.6%) and the incidence tended to be lower at the later treatment cycles (range: 2.5% to 6.1%). Causally related TEAEs reported in >2 subjects in any one treatment cycle were headache, eyelid ptosis, eyelid oedema, haematoma, brow ptosis, head discomfort and injection site swelling. None of the severe TEAEs were considered treatment related.

Serious TEAEs were observed in similar proportion of subjects in the BTX-A-HAC solution (1.2%) and placebo (2.4%) groups in the double-blind data and varied between 0% to 2.3% across the treatment cycles in the long-term data. None of the SAEs were considered treatment related by the investigator. No deaths were reported in subjects in any of the clinical studies with BTX-A-HAC solution.

No TEAEs indicative of remote spread of effects of toxin were identified in the pooled double-blind or the long-term safety data. A total of 7 (2.8%) subjects in the pooled double-blind data and 40 (6.7%) subjects in the long-term data experienced TEAEs that qualified as eye disorders (AESIs) following treatment with BTX-A-HAC solution. The most frequently reported eye disorders were eyelid ptosis, eyelid oedema, blepharospasm (eyelid twitching) and dry eye. Events indicative of hypersensitivity reactions were reported in 2 (0.3%) subjects treated with BTX-A-HAC solution in the clinical studies: eye allergy and hypersensitivity in one subject and rash in another subject. All events reported were nonserious, mild or moderate in intensity.

As it is expected to see the same ADRs with the powder and with the solution, it was considered more informative and more complete to present ADRs collected for the same indication in one table in the SmPC. In case there was a discrepancy regarding the frequency of s certain ADR observed in the studies for the powder and the solution, the highest frequency was chosen for the table in the SmPC section 4.8.

In summary, the safety data from the studies presented by the Applicant demonstrate that treatment with BTX-A-HAC solution 50 U is well tolerated in subjects with moderate to severe glabellar lines. The safety profile in the studies is consistent with other products with the same active substance. It is therefore considered sufficient with routine pharmacovigilance and routine risk minimisation measures. For safety reasons, botulinum toxin should be administered by a physician with the right qualifications, expertise, and equipment. National deviations - for certain indications - from the general posology including information on the sovereignty of a physician to administer the injections, should be solved on a national basis.

When botulinum toxin first was introduced as a medicinal product, it was thought that the toxin would not leave the injected muscle(s). Spread to adjacent muscles was first recognised and now remote spread and even botulism are well known adverse events, however rare. Once the toxin enters the blood stream, it could possibly cross the placenta to a foetus or be excreted into milk. Pre-clinical studies have not demonstrated any teratogenic activity in either rats or rabbits and no effects were observed in a pre- and postnatal study on the F1 generation in rats. There is virtually no data in humans and as a precautionary measure Alluzience should not be used during pregnancy.

There are no pre-clinical data on the excretion of botulinumtoxin into breastmilk, but no adverse effects have been noted in suckling pups of exposed female rats. There is one case in the literature where an infant continued to be breastfed while her mother was severely affected with botulism. No toxin was found in the milk and the infant showed no adverse events. Cases in the Company’s safety database have not indicated any risks to breastfed infants. Taken together data are very limited, and even if no harmful effects have been shown, the scarce and incomplete information and the extreme potency of the toxin invoke precaution and Alluzience should not be used by breastfeeding women.

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 PIL 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

No need for conditions under Article 21a/22 of Directive 2001/83 has been identified.

The benefit/risk ratio is considered positive and Alluzience, 200 U/ml, Solution for injection is recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Alluzience, 200 U/ml, Solution for injection was positively finalised on 2021-06-10.

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se