IRISH MEDICINES BOARD

RMS FINAL VARIATION ASSESSMENT REPORT

On

BOTOX 50/100/200 Allergan Units powder for solution for injection

Type II variation: IE/H/0113/001-003/II/061

Marketing Authorisation Holder : Allergan Pharmaceuticals Ireland

Invented name of the pharmaceutical product in the Reference Member State	Botox
Pharmaceutical form and strength	50/100/200 Powder for solution for Injection
Name of the active substance	Botulinum Toxin Type A

Reference Number for the Mutual Recognition Procedure	IE/H/0113/001-002-003/II/061
Member States concerned	AT, BE, DE, DK, EL, ES, FI, IS, IT, LU, NO, PT, SE

Nature of change requested	C.I.6.a to update Section 4.1 of the SPC
Date of the assessment report	20/04/2011
Deadline for comments (Day 85)	**15/05/2011**

Marketing Authorisation Holder	Allergan Pharmaceuticals Ireland
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Marketing Authorisation number	PA 148/60/1-3

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List of Abbreviations and Definition of Terms

ACh	Acetyl choline
AHPM	Acute headache pain medication
AMPP	American Migraine Prevalence and Prevention
BASH	British Association for the Study of Headache
CDH	Chronic daily headache
CM	Chronic Migraine
CMS	Concerned Member State
CTTH	Chronic tension-type headache
DBPC	Double-blind placebo-controlled
EF	Emotional Function (domain of the MSQ)
FSFD	Fixed-site, fixed-dose (injection paradigm)
FTP	Follow-the-pain (injection paradigm)
GHC	German Headache Consortium
HIT-6	Headache Impact Test
ICHD-II	International Classification of Headache Disorders published by the Headache Classification Subcommittee of the International Headache Society, revised 2004
ICHD2R-CM	Annexe to International Classification of Headache Disorders published by the Headache Classification Subcommittee of the International Headache Society, revised 2006
IHCC	International Headache Classification Committee
HIS	International Headache Society
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
MO	Medication overuse
MOH	Medication overuse headache

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I. RECOMMENDATION

Based on the review of the new clinical data and the applicant's response to the request for supplementary information the RMS considers that the type II variation application for

is approvable following revision of the proposed indication and consequential changes to the SPC and PIL. The details of this revised text is provided in section III.4.

II. EXECUTIVE SUMMARY

II.1 Introduction

The current assessment report (FVAR) concerns the second round of the type II variation regarding an indication for use of Botox in the management of chronic migraine (revised following PVAR).

Revised indication as proposed by the Applicant:

'Prophylaxis of headaches in adults with chronic migraine (headaches on ≥15 days per month of which at least 8 days are with migraine).'

in addition, the applicant proposed to add a revised dilution and reconstitution table in 4.2, warnings in 4.4 regarding of lack of efficacy in episodic migraine and Chronic Tension Type Headache ,warnings with adverse drug reactions in 4.8 of the SPC, and two paragraphs regarding efficacy results in 5.1.

The Preliminary Variation Assessment Report of the RMS was sent out on 1 November 2010. Comments have been received from the following Concerned Member States: Denmark, Germany, Italy, Greece, Sweden, and Spain.

At this time the RMS did not consider the indication to be approvable. The PVAR was endorsed by the CMSs (DE, DK, ES, SE,EL and NO); however, Denmark, Germany Greece, Norway and Sweden had additional comments. The main comments received from the member states were related to study confounders, difficulty in defining the target group, issues with the definition of chronic migraine, the size and clinical significance of the treatment effect and lack of clarity regarding the mechanism of action of Botox in chronic migraine. The responses of the applicant to the individual items of the RMS and CMSs can be found below. For comments regarding the SPC, reference is made to annex I.

II.2 Scope of the variation

The proposed changes in the response of the applicant to the currently approved Summary of Product Characteristics (SmPC) are:

1) the addition of a new indication to section 4.1 of the SmPC

"Prophylaxis of headaches in adults with chronic migraine (headaches on ≥15 days per month *of which at least 8 days are with migraine).*"

2) the addition of a new section on pharmacodynamic properties to section 5.1 of the SmPC

Chronic migraine

BOTOX blocks the release of neurotransmitters associated with the genesis of pain. *The mechanism of action of Botox in headache prophylaxis is unclear. Pre-clinical and clinical pharmacodynamic studies suggest that Botox suppresses peripheral sensitisation, thereby possibly also inhibiting central sensitisation.* ~~The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by pre-clinical and clinical pharmacodynamic studies.~~ Chronic migraine patients without any concurrent headache prophylaxis who, during a 28-day baseline, had at least 4 episodes and ‡ 15 headache days (with at least 4 hours of continuous headache), with at least 50% being migraine/probable migraine, were studied in two Phase 3 clinical trials. Patients were allowed to use acute headache treatments 66% overused acute treatments during the baseline period. Following BOTOX injections every 12 weeks, for the 2-cycle, double –blind phase, BOTOX treatment demonstrated statistically significant improvements from baseline compared to placebo for, mean frequency of moderate/severe headache days, mean frequency of migraine/probable migraine days total cumulative hours of headache on headache days, and mean frequency of headache episodes. The percentage of patients with 50% reduction in headache days was 47% on BOTOX vs. 35% on placebo ($p<0.001$). Patient functioning and overall quality of life were significantly improved ($p<0.001$) compared to placebo as demonstrated by the Headache Impact Test (HIT-6).

3) the addition of chronic migraine specific instructions for reconstitution and administration of Botox.

4) the addition of a chronic migraine specific table of undesirable effects to section 4.8 of the SmPC (see Annex 1).

5) the addition of information relating to use in the chronic migraine indication to section 4.4 of the SmPC (see Annex 1).

III. ASSESSMENT OF THE RESPONSES TO THE MEMBER STATE(S) REQUEST FOR SUPPLEMENTARY INFORMATION

III.1 Clinical aspects

III.3.1 Questions from the RMS (Ireland)

Potential serious risk to public health

Clinical efficacy

Question 1 (RMS)

Question 1 (Insufficient data to support indication; confounding factors; clinical characteristics of responders)
There is insufficient efficacy data to support the proposed indication for use 'prophylaxis of headaches in adults with chronic migraine (headaches on ≥15 days per month)'. The key efficacy findings from the pooled analysis of Studies 079 and 080 (a 1.9 reduction in headache days against a baseline rate of 19 headache days and a reduction in frequency of headache episodes of 0.3 against a backdrop of 12 headache episodes per 28 day period) are confounded by the heterogeneity of the study population and the high level of acute headache medication overuse. Furthermore a high, sustained placebo response was seen across the entire DBPC period. Consequently pre-identification of likely "responders" within this study population is difficult, as no specific parameters (e.g. headache characteristics, duration, frequency etc.) have been show to be predictive of a true response to Botox. The applicant must identify clinical parameters that will help to select patients with chronic migraine who are likely to respond to Botox therapy.

Summary of the Applicant's Response

A. Potential Confounding Factors: Heterogeneity of the Study Population

The applicant disagrees with the RMSs assertion that the study population was heterogeneous and ultimately confounded the study outcome. In support of their position they compared the Botox phase 3 study dataset with three independent datasets to demonstrate that the Botox phase 3 studies demonstrated demographic and headache characteristics similar to those manifested by chronic migraine patients in other study populations.
They compared a population meeting ICHD-2R chronic migraine diagnostic criteria and a population meeting the IHS trial guideline criteria to the Botox phase 3 study population. This they assert provides strong evidence that the chronic migraine population evaluated in the phase 3 clinical studies is representative of the target population of chronic migraine patients who would receive Botox.

The ICHD-2R criteria specify the minimum duration of headache disorder of at least 3 months duration with greater than or equal to 15 days of headache of which 8 days include headache migraine type which had successfully been treated with a triptan or ergot. The study population had a 19.2 year mean duration of chronic migraine and at least 50% of their headache days met headache criteria for migraine or probable migraine. At baseline, the enrolled population had a mean frequency of 16.4 (± 5.76) migraine days and 19.0 (± 4.02) migraine/probable migraine days which the MAH argues exceeded the specified criteria of the ICHD-2R.
Migraine with or without aura was included on the basis that ICHD-II 1.1 migraine without aura is inclusionary for patients who meet the criteria of ICHDII1.2 Migraine with aura. This clarification was following correspondence with R.Lipton Chair of the ICHD-II migraine section.
Patients with medication overuse were included but were stratified at enrolment. The MAH outlines that inclusion of patients with MOH is in line with with guidelines for controlled trials of prophylactic treatment of chronic migraine in adults published by the Task Force of the IHS Clinical Trials Subcommittee (Silberstein et al, 2008). These recommendations were published after both phase 3 studies were initiated.

Comparison of Botox phase 3 screened population meeting ICHD-2R criteria with patients meeting Botox phase 3 study enrolment criteria.

2,736 patients enrolled into the phase 3 studies represent the dataset of potential chronic migraine sufferers. The demographic and disease characteristics of patients who met the ICHD-2R criteria for

chronic migraine from the screened population were compared with the phase 3 clinical study population. Because of ongoing clinical discussions regarding the role of MO and chronic migraine analyses were stratified according to possible medication overuse yes/no. Analyses using the ICHD-2R criteria were performed including those without possible medication overuse (denoted as ICHD-2RN=yes), and including all patients with and without possible medication overuse (denoted as ICHD-2R=yes). The demographic profiles and baseline headache disease characteristics were otherwise broadly similar across the newly analysed data regardless of whether they were classified as +/- possible medication overuse. Patients without possible medication overuse were less likely to have ever tried headache prophylaxis medications.

Table 1 Demographic Profiles by Chronic Migraine Criteria

	ICHD-2RN=yes N=673	ICHD-2R=yes N=1912	Phase 3 Study Screening Population[a] N=1383
Age, mean (SD)	38.1 (10.94)	41.9 (10.78)	41.3(10.53)
Age, median	38.1	42.0	42.0
Female (%)	85.9%	86.1%	86.4%
Caucasian (%)	84.7%	89.2%	90.1%
BMI, mean (SD)	27.9 (6.87)	27.2 (6.53)	27.0 (6.38)
Beck Score, mean (SD)	6.5 (6.00)	6.5 (6.21)	6.3 (6.09)

BMI = body mass index; SD = standard deviation

[a] Pooled data from patients enrolled into BOTOX phase 3 studies who had ≥15 headache days at baseline.

Source: Appendix 1, Tables 1-1, 1-2, 1-3

Table 2 Baseline Headache Disease Characteristic by Chronic Migraine Screening Population Criteria

	ICHD-2RN=yes N=673	ICHD-2R=yes N=1912	PREEMPT=yes (Phase 3 Study Population[a]) N=1383
Frequency Headache Days, mean (SD)	18.4 (5.08)	18.2 (5.31)	19.9 (3.67)
Frequency Headache Episodes, mean (SD)	10.0 (5.00)	11.3 (5.38)	12.6 (5.40)
Frequency Migraine Days, mean (SD)	15.6 (6.06)	15.3 (6.34)	16.4 (5.76)
Age of Onset of Chronic Migraine, mean (SD)	20.8 (11.11)	21.9 (11.61)	21.6 (11.48)
% with Medication Overuse	0.0%	64.8%	65.4%
% That Ever Tried Headache Prophylaxis Medications	50.8%	60.6%	63.5%
% Currently Using Acute Headache Medications	92.7%	97.4%	97.5%

SD = standard deviation

[a] Pooled data from enrolled patients.

Headache days and headache episodes were defined for 28-day period and had to be ≥4 hours in duration

Source: Appendix 1, Tables 1-4, 1-5, 1-6

Sensitivity and specificity analyses were conducted .Sensitivity was 68-70% between the phase 3 enrolled population and both the ICHD-2RN=yes and ICHD-2R=yes classifications .Specificity varied and was 55.0% and 94.2% when comparing phase 3 enrolled population to ICHD-2RN=yes and ICHD-2R=yes.

Further comparisons were made with data from a retrospective analysis of 557 patients seen in a headache clinic between 1990 and 2001. Within a patient population with medication overuse there was no significant difference between the proportion of those meeting criteria for ICHD-2R compared to the proportion of those meeting the phase 3 study criteria (86.9% vs. 80.9% respectively, p=NS). Similar results were demonstrated within the patient population without medication overuse (92.4% vs. 88.0% respectively, p=NS) (Bigal et al, 2007). A further comparison was made with data from a population based study comparing patients with ICHD -2R chronic migraine criteria compared with an operational phase 3 criteria. No significant differences were seen between the two groups.

RMS assessment of Applicant's response:

The applicant has demonstrated the similarity between the enrolled Phase III study population and the screened phase III study population who fitted the ICHD2R criteria in terms of headache characteristics and baseline demographics regardless of whether they were classified as +/- possible medication overuse. Similar demographic and baseline headache characteristics were also demonstrated between 2 population based studies and the Allergan definition of chronic migraine and the ICHD 2R criteria. These analyses while encouraging are limited by the fact that they are retrospective analyses. The revised IHS criteria have been field tested in a number of centres and compared to the more restrictive Allergan defined chronic migraine criteria. However the issue of MO is handled differently depending on the review. Bigal et al (2006) who field tested their criteria in patients with TM classified patients with medication overuse as probable CM with probable MOH. In a separate field test of ICHD2R criteria by Zeeberg et al (2008) patients with medication overuse were excluded if they did not undergo withdrawal from overuse. It is also apparent from these two reviews that subtle differences in inclusion criteria such as inclusion of patients whose headache fulfilled IHS criteria for migraine or probable migraine increased the numbers of CM patients significantly. The number of different definitions and the variations in inclusion criteria is an indication of the lack of clinical consensus regarding classification of CM in the clinical community. The ICHD2R criteria for CM specifically exclude medication overuse. Perhaps a classification of CM with or without medication overuse should be considered however that has not been agreed. It is unclear to what extent the current proposed ICHD-2R definition of CM fits the disease model for chronic migraine as there is no biological marker and all of the criteria have been determined by consensus rather than as evidence based criteria. The objective of the IHS in updating the appendix criteria was to classify a severely affected subgroup and to encourage research. Identification of patients with chronic migraine requires a high level of specialised clinical skill. Patients with chronic daily headache are easily misclassified. The phase three study population who don't over use medication are. Therefore in the opinion of the RMS this is the key population in this analysis.

Conclusion; This concern resolved. Ideally Botox should have been evaluated in patients who did not overuse AHPM or who withdrew AHPM prior to treatment .However by presenting the efficacy results for the medication overuse-yes (MedO-yes) and medication overuse –no (MedO-no) Subgroups the applicant has provided efficacy data for the subpopulation closest to the definition of chronic migraineurs as defined by ICHD -2R.

B. Potential Confounding Factors: Patients Overusing Acute Headache Pain Medications

Summary of Applicant's response:
Patients overusing acute medications during the 28-day baseline period were not excluded from the phase 3 studies in accordance with guidelines for controlled trials of prophylactic treatment of chronic migraine in adults published by the Task Force of the International Headache Society (IHS) Clinical Trials Subcommittee (Silberstein et al, 2008a).The applicant argues that there is new clinical evidence,
that contradicts past general beliefs that withdrawal of AHPM is necessary before initiating headache prophylaxis in all patients.(Zeeberg et al 2006; Hagen et al 2009; Trucco et al 2010; Diener et al 2007) MedO is common in patients with chronic migraine, the causal sequence is unclear and unlikely to be the same across all patients. It is possible that medication overuse precedes and is a risk factor for development of chronic migraine. Alternatively, increased frequency of headache may lead to medication overuse in response to pain. It is also possible that in patients
with frequent headache, medication overuse is an exacerbating factor (Lipton and Bigal, 2003).
Some people who overuse acute pain medications do not develop chronic migraine. For instance,
in an arthritis clinic of 103 regular users of analgesics only 8 patients (7.6%), all who had a history of migraine, had headaches on 15 or more days per month, suggesting they had chronic migraine (Bahra et al, 2003). Also, population epidemiology studies suggest that approximately 31% of patients with chronic migraine suffer from chronic pain conditions other than headache and thus may use acute pain medications for reasons other than to treat headache (Buse et al, 2010). When looking at demographic features and disease characteristics between the MedO-yes and MedO-no subgroups, there were no notable between-group differences observed for any of the parameters (other than AHPM overuse or not), suggesting that these 2 subgroups were more homogeneous than heterogeneous and MedO did not overly confounded the results of these studies.

Efficacy Results for the Medication Overuse-yes (MedO-yes) and Medication non-Overuse) Subgroup

The MAH has provided a further analysis of the efficacy data for these two subpopulations.
The key population of interest is the CM patients who do not have medication overuse as these are the patients that closest resemble the chronic migraine population as defined by the ICHD2R criteria. The subgroup of patients without acute headache pain medication overuse at baseline (i.e., MedO-No subgroup) in each individual study was too small to show a statistically significant effect of Botox on the frequency of headache days and episodes. Pooled, Botox produced a statistically significant reduction in the frequency of headache days at week 24 in the Med O-No subgroup. The between group difference was 1.5 headache days and .6 of a headache episode. The effect of Botox was significantly superior to placebo in the pooled analyses for the endpoints of migraine/probable migraine days, moderate/severe headache days, total cumulative hours of headache occurring on headache days, and proportion of patients with severe HIT-6 category scores(HIT-6 scores slightly higher than in the overall ITT population.)

In the pooled MedO-yes subgroup, the efficacy results were similar to the overall ITT population
whereby statistically significant between-group reductions from baseline favouring BOTOX treatment over placebo treatment were demonstrated for the frequency of headache days and other headache symptom measures at the week 24 primary time point. The effect of BOTOX was also significantly superior to placebo in the pooled analyses for the endpoints of migraine/probable migraine days, moderate/severe headache days, total cumulative hours of headache occurring on headache days, and proportion of patients with severe HIT-6 category scores for the MedO-yes subgroup. The only secondary headache symptom measure that was not statistically significant at the week-24 primary time point in the MedO-yes subgroup was the frequency of AHPM intakes.
This measure was significantly reduced among patients treated with BOTOX compared to placebo at week 4, but not at the primary time point. Additional analyses of the patterns of AHPM intake by medication class revealed statistically significant reductions in the frequency of triptan intakes at all visits, except week 12, in the DBPC phase, including the week 24 primary time point (-4.3 intakes BOTOX vs. -2.9 placebo, $p < 0.001$The frequency of AHPM *days* was significantly reduced among patients treated with BOTOX compared with placebo at the week 24 primary time point. Analyses of both a 3-month and 6-month persistent shift from MedO-yes to MedO-no indicate that significantly more BOTOX-treated

than placebo-treated patients had reduced use of acute medications so that they were no longer overusing symptomatic medications, starting as early as 4 weeks after treatment

For all of the endpoints except the proportion of patients with severe HIT-6 category scores, the placebo-subtracted effect of BOTOX was smaller in the MedO-No subgroup than in the MedO-Yes subgroup. However, mean baseline values were also lower in the MedO-No subgroup and this could explain at least some of the difference in the apparent effect size between the MedO-No and MedO-Yes subgroups (i.e., a lower baseline value leaves less room for improvement).Of note AHPM did not improve other than a modest reduction in triptan medication intakes.

Table 3 Headache Symptom Measures and Health Related Quality of Life Measures: LS Mean Change from Baseline at Week 24: MedO-No Subgroup (DBPC phase)

Efficacy Variable (per 28 days)	BOTOX (N=243)	Placebo (N=237)	P-value
Headache days	-8.8	-7.3	0.013
Headache episodes	-5.1	-4.5	0.146
Migraine days[a]	-8.4	-6.6	0.004
Moderate/severe headache days	-7.7	-6.1	0.005
Total cumulative hours of headache	-128.75	-99.73	0.023
Migraine episodes[a]	-4.5	-3.9	0.088
AHPM intakes	-4.6	-4.7	0.869
Triptan medication intakes	-1.1	-0.5	0.039
Multiple analgesic intakes	-1.6	-1.6	0.961
AHPM days	-3.5	-3.1	0.442
Triptan days	-1.0	-0.4	0.023
Multiple analgesic days	-1.4	-1.0	0.240
≥ 50% ↓ in headache days	49.7%	41.2%	0.101
≥ 50% ↓ in headache episodes	52.0%	50.3%	0.747
≥ 50% ↓ in moderate/severe headache days	50.8%	40.6%	0.050
≥ 50% ↓ in total cumulative hours headache	52.5%	43.3%	0.078
≥ 50% ↓ in migraine days[a]	50.3%	41.7%	0.100
Total HIT-6 scores	-5.1	-2.7	<0.001
HIT-6 'severely impacted' proportion	61.3%	70.9%	0.027
HIT-6 '5-point improvement proportion[b]	44.9%	29.1%	<0.001
MSQ RFR scores[c]	-17.2	-10.6	0.001
MSQ RFP scores[c]	-11.7	-7.7	0.032
MSQ EF scores[c]	-17.4	-11.0	0.017

AHPM = Acute Headache Pain Medication; HIT = Headache Impact Test; EF = Emotional Function; MSQ = Migraine Specific Quality of Life; RFP = Role Function – Preventative; RFR = Role Function – Restrictive

[a] ICHD-II 1.1 migraine without aura, 1.2 migraine with aura, 1.6 probable migraine

[b] Meets or exceeds established minimally important difference

[c] MSQ scores are mean values

Results in bold denote statistically significant differences favouring BOTOX

Source: Appendix 1, Tables 1-12, 1-13, 1-14, 1-15, 1-16, 1-17, 1-18, 1-19, 1-20, 1-24, 1-25, 1-27, 1-31, 1-32, 1-33,

Table 4 **Headache Symptom Measures and Health Related Quality of Life Measures: LS Mean Change from Baseline at Week 24: MedO-yes Subgroup (DBPC Phase)**

Efficacy Variable (per 28 days)	BOTOX (N=445)	Placebo (N=459)	P-value
Headache days	-8.2	-6.2	<0.001
Headache episodes	-5.6	-4.9	0.028
Migraine days[a]	-8.1	-6.0	<0.001
Moderate/severe headache days	-7.7	-5.7	<0.001
Total cumulative hours of headache	-111.91	-73.26	<0.001
Migraine episodes[a]	-5.3	-4.6	0.018
AHPM intakes	-13.2	-11.7	0.210
Triptan medication intakes	-4.3	-2.9	<0.001
Multiple analgesic intakes	-10.6	-8.9	0.151
AHPM days	-7.3	-6.4	0.033
Triptan days	-3.3	-2.4	<0.001
Multiple analgesic days	-5.8	-5.0	0.102
≥ 50%fl in headache days	45.8%	32.1%	<0.001
≥ 50%flin headache episodes	46.9%	39.4%	0.038
≥ 50%fl in moderate/severe headache days	48.6%	35.9%	<0.001
≥ 50%fl in total cumulative hours headache	49.2%	36.7%	<0.001
≥ 50%fl in migraine days[a]	47.2%	33.7%	<0.001
Total HIT-6 scores	-4.7	-2.2	<0.001
HIT-6 'severely impacted' proportion	71.0%	81.9%	<0.001
HIT-6 '5-point improvement proportion[b]	38.7%	23.3%	<0.001
MSQ RFR scores[c]	-16.9	-7.6	<0.001
MSQ RFP scores[c]	-13.9	-5.8	<0.001
MSQ EF scores[c]	-18.3	-8.7	<0.001

AHPM = Acute Headache Pain Medication; HIT = Headache Impact Test; EF = Emotional Function;
MSQ = Migraine Specific Quality of Life; RFP = Role Function – Preventative; RFR = Role Function – Restrictive

[a] ICHD-II 1.1 migraine without aura, 1.2 migraine with aura, 1.6 probable migraine

[b] Meets or exceeds established minimally important difference

[c] MSQ scores are mean values

Results in bold denote statistically significant differences favouring BOTOX

Source: Appendix 1, Tables 1-12, 1-13, 1-14, 1-15, 1-16, 1-17, 1-18, 1-20, 1-24, 1-25, 1-27, 1-31, 1-32, 1-33, 1-34, 1-35, 1-36, 1-37, 1-40, 1-47, 1-48, 1-49, 1-50

RMS Assessment of the Applicant's response :

ICHD-2R diagnosis of CM excludes medication overuse. The applicant has presented a pooled efficacy analysis of the data for the MedO-No and MedO-Yes subgroups of the ITT population. Although the MedO –No subgroup are a statistically significant subgroup the phase 3 studies were not powered to show statistically significant differences in the smaller MedO-No subgroup. The results for the Med O-Yes group are similar to those seen for the ITT population. However the results for the MedO-No group suggest that Botox is less effective in this subgroup. The absolute change from baseline is similar across both subgroups but the apparent reduced effect in the MedO-No subgroup is driven by a more pronounced placebo response in this group. Of further concern responder analyses are only statistically significantly different from placebo in one subgroup (≥50% reduction in moderate/severe headache days). This would suggest that in patients with Allergan defined chronic migraine that don't overuse acute headache pain medication the effect of Botox is even more modest than that seen in patients with a mixed chronic migraine /MOH picture. However this may represent the true level of efficacy of Botox .In the ITT

population (combined MedO-Yes and MedO-No) it is unclear to what extent the reduction in headache days is due to a true an improvement in chronic migraine or some effect on the medication overuse headache or as an effect of persistent shift from MedO-yes to MedO-no for a statistically significant proportion of the BOTOX-treated group following on from a reduction in acute medication intakes. Over the 24 week DBPC phase the proportion without medication overuse grew. A significant move to medication non-overuse in the medication overuse headache group may be part of the positive clinical response in this group. In the opinion of the RMS AHPM should have been withdrawn prior to treatment with Botox.

Conclusion: The efficacy of Botox in CM should be evaluated in the MedO-No subgroup.

C. placebo response

Summary of applicant's response:

Despite the high placebo response, statistically significant between-group differences favouring Botox vs. placebo were achieved in the Botox phase 3 studies for the key endpoint of headache days, as well as for multiple other headache symptom and health related quality of life measures.
Placebo response are found to be higher in parallel- group studies compared to crossover studies and are more commonly associated with parenteral therapies and may be effected by heightened expectations for results from an injection. A high proportion of patients in the Botox phase 3 studies in both treatment groups had AHPM overuse at baseline (68% in study 191622-079 and 63% in study 191622-080 ;), and both treatment groups in each study demonstrated a large shift in the proportion of patients not having medication overuse (MedO-no) starting as early as within the first 4 weeks of the study. Over the 24 week DBPC phase the proportion without medication overuse grew. It has been reported that with withdrawal of daily symptomatic medications that there can be a clinically significant improvement in headache symptoms in many patients (Mathew et al, 1987). Reduction in the proportion of patients with medication overuse could have contributed to some of the observed improvements from baseline in both treatment arms and may be reflected as a placebo effect. Another possible explanation of the high placebo response rate is that patients had spontaneous improvement. Although a high placebo response was observed during the DBPC phase of the Botox phase 3 studies, there was a lack of a parallel nocebo effect among placebo-treated patients. And, as noted earlier, Botox treated vs. placebo treated patients showed significant improvements across multiple headache symptom and quality of life measures.

RMS assessment of Applicant's response:

Because of the small treatment effect size for active drug over placebo the clinical significance of the difference between active and placebos is difficult to evaluate and whether the difference actually indicates specific biological effect of Botox, or various nonspecific factors have not been adequately ruled out .It is also noteworthy that the lower levels of efficacy as shown by the lack of statistical significance seen for a number of efficacy endpoints (i.e. efficacy in the Med O-No subgroup compared with MedO-yes) were driven more by a more pronounced placebo response than fluctuations in treatment effect. One of the difficulties with this application is that it is difficult to distinguish the true treatment effect from the high placebo response and possible improvement in MOH (either due to withdrawal of MO or a direct effect of Botox on the MO pain mechanism). The expectations of patients participating in the study may in part explain the strong placebo response. It is noteworthy that the placebo effect is sustained and increases for the duration of the DBPC phase of the study. In both active and placebo groups there was a reduction in AHPM days so there is no evidence that patients on the placebo took greater amounts of AHPM until their pain relief achieved the same level as the group administered Botox. However analgesic self-administration may not be an accurate reflection of pain. The high placebo response does suggest that the blind was maintained during the DBPC phase of the study.

Conclusion: The pronounced placebo effect and its role in driving efficacy should be further evaluated in future studies.

D. Predictors of Response to Botox Treatment

Summary of applicant's response:

The Botox phase 3 studies in patients with chronic migraine manifested as having ≥ 15 headache days per month have established that chronic migraine disorder is a predictor for response to Botox treatment since these studies have established efficacy whereas well controlled trials in patients with episodic migraine [headache < 15 days per month] and chronic tension type headache (Aurora et al, 2007; Relja et al, 2007; Smuts et al, 1999; Silberstein et al, 2006) have failed to establish Botox efficacy. Thus, the population of patients with chronic migraine, estimated to be 1.4% to 2.2% of the general population (Natoli et al, 2010) is a predictor of Botox response. Allergan analysed the phase 3 chronic migraine studies for possible additional predictors of response to the change from baseline in frequency of headache days such as age, gender, and body mass index and did not identify other characteristics in these patients with chronic migraine that predicted response to Botox treatment (Dodick et al, 2010). While it might be desirable to be able to predict who might respond or not-respond to a given treatment, this type of information is not commonly known for most drugs prescribed for multiple indications, including management of chronic pain disorders.

RMS assessment of Applicant's response:

The phase 3 clinical studies of patients with chronic migraine are confounded by the inclusion of patients with medication overuse. Although the applicant justifies this by referring to the 2008 IHS guidelines for controlled trials of prophylactic treatment of chronic migraine (Silberstein et al) The role of MO and the possibility that reduction in MO may have contributed to the efficacy undermines the efficacy demonstrated in the ITT population in these studies .
Because of the modest treatment effect and the sustained placebo effect and the reduced efficacy seen in the population most like a true chronic migraine population (MedO-No) the RMS is of the opinion that the Botox phase 3 studies in patients with chronic migraine in patients who are medication overuse negative (MedO-No) may be a predictor for response to Botox treatment.

Question 2 (Efficacy not demonstrated in some subgroups)

Neither the primary endpoint, headache episodes nor changes in headache days and migraine/probable migraine days was met for males or non-Caucasians. Efficacy was not demonstrated in patients who headache medication prophylaxis naive or patients who didn't overuse acute headache medication. This further limits the clinical applicability of this study findings.

Summary of applicant's response

A. Gender

In the pooled subgroup analyses of the phase 3 studies, females compromised a majority (i.e. 86.4%) of the population. the proportion of males in the phase 3 studies was consistent with the smaller proportion of males compared to females who suffer from chronic migraine (Buse et al, 2010) these studies were not powered to specifically demonstrate statistically significant differences in the subset of male patients. However, the subset of male patients showed mean improvements from baseline across a number of efficacy measures, including headache days and headache episodes and, while not reaching the level of statistical significance, these improvements were comparable to those seen in the subset of female patients and exhibited the same trend.

In study 191622-080, the efficacy response to Botox in males for headache days was the same as that observed in females, and for headache episodes was slightly better than what was observed in females. In study 191622-079, the efficacy response to Botox in males for headache days and headache episodes was not as robust as that observed in females. In both studies, the placebo response in males for both headache days and headache episodes was higher than in females. No statistically significant between-group differences were observed for either efficacy measure in males. This may have been a result of the small sample size and the higher placebo response in males vs. females.

The 188 males were further characterized 123 [65%]) also had medication overuse at baseline and 65 (35%) males without medication overuse. The placebo response in the group of males without medication overuse at baseline was higher than observed in males with medication overuse, in all females and in the overall ITT population.

The male population was analysed depending on whether they had or didn't have medication overuse. similar efficacy trends were observed whereby the Botox group versus the placebo group was numerically larger, although not statistically significant, across multiple efficacy measures. BOTOX-treated males tolerated the treatment well with no consistent pattern to suggest an influence of gender on the safety and tolerability. The female to male ratio in these studies was consistent with the population epidemiology of chronic migraine (Buse et al, 2010).

looking at other demographic features and disease characteristics between the male and female subgroups, there were no notable between-group differences observed for all parameters (except weight and BMI, as expected), suggesting that both of these 2 subgroups were similar to the overall ITT population, and that the small sample size of males likely contributed to the results in that subgroup.

BOTOX-treated males tolerated the treatment well with no consistent pattern to suggest an influence of gender on the safety and tolerability. The female to male ratio in these studies was consistent with the population epidemiology of chronic migraine (Buse et al, 2010).

Furthermore, there is currently no evidence suggesting a unique pathophysiology of chronic migraine that is influenced by gender. the small sample size of males likely contributed to the results in that subgroup

RMS assessment of Applicant's response:

The Assessor agrees with the MAH that the male/female subject ratio in the Phase III studies was representative of the chronic migraine prevalence ratio as reported in the literature. Although the studies had not enough statistical power to significantly compare the efficacy between gender stratified subjects, the raw data provided suggests that the trends in efficacy were similar in males and females. Although at this point no conclusive gender based efficacy concerns are identified this contributes to the uncertainty about the efficacy regarding Botox in this indication.

Conclusion: this point is resolved

B. Race

A total of 9.9% of the pooled ITT population (N=137) were non-Caucasians; a sample size of Non-Caucasians that is representative of the smaller proportion of non-Caucasians compared to

Caucasians who suffer from chronic migraine within the general population. According to the American Migraine Prevalence and Prevention (AMPP) study data, 9.3% of those with chronic migraine reported themselves as non-Caucasians or they did not specify race (Buse et al, 2010). No statistically significant between-group differences were demonstrated for the frequency of headache days, headache episodes, and migraine/probable migraine days at week 24 in non-Caucasians . The phase 3 studies were not powered to show statistically significant differences in the small sample size of non-Caucasian patients. When looking at other demographic features and disease characteristics between the Caucasian and non-Caucasian subgroups, there were no notable between-group differences observed for these parameters, suggesting that both of these 2 subgroups were similar to the overall ITT population. Non-Caucasians tolerated the treatment well with no consistent pattern to suggest an influence of race on the safety and tolerability.

Assessors comment.
The Assessor agrees with the MAH that the smaller proportion of non-Caucasians compared to Caucasians who suffer from chronic migraine within the general population was representative of the chronic migraine prevalence ratio in the phase III studies.
This point is considered resolved

C. History of headache prophylaxis

In January 2006, at the time that the Allergan phase 3 studies were initiated, there was no international and/or agreed upon local guidelines of 'proven effective' migraine headache prophylaxis treatments. Therefore, a guideline that identified > 100 medications and herbal supplements that may be effective as "headache prophylaxis" was proposed by the lead coordinating investigators for use by investigators as they screened patients for the phase 3 studies. Most of these treatments listed in the guideline lack evidence-based controlled data in either episodic or chronic migraine patients, but were known to be prescribed as migraine headache prophylaxis. Medication classes of drugs on this list included anticonvulsants, antidepressants, antihistamine and serotonin antagonists, antihypertensives, antipsychotics, beta blockers, calcium channel blockers, and various combination pain medications. In addition, dietary supplements (e.g., vitamins), herbs, minerals, hormonal, or combinations, ergot alkaloids, muscle relaxants, NSAIDs, and opioids were also included. Overall, approximately 64% of enrolled patients had a history of prior headache prophylaxis medication use when this broad list of possible medications was used.
An additional analysis of the 16 migraine prophylaxis treatments considered to be effective according to recommendations of the British Association for the Study of Headache (BASH) guidelines, 2007 was performed. These medications have been further sub-divided by BASH as first, second or third-line treatments. All of these medications were included on the phase 3 guideline of headache prophylaxis medications, with the exception of clonidine (third line treatment per BASH). 41.5% of enrolled patients had a history of prior BASH first line migraine headache prophylaxis medication use.

Table 5 **First-Line Pre-Study BASH Prophylactic Medication Use for Phase 3 Pooled Population**

	Pooled 191622-079 + 191622-080 Studies		
	BOTOX (N=688)	Placebo (N=696)	Total (N=1384)
Allergan Phase 3 Studies Headache Prophylaxis Medication Guideline	425 (61.8%)	454 (65.2%)	879 (63.5%)
First Line Treatment per BASH Headache Prophylaxis Medication List a	277 (40.3%)	298 (42.8%)	575 (41.5%)

Source: Module 5.3.5.3 ISE Table 1-3 and Appendix 1, Table 1-73

[a] British Association for the Study of Headache (BASH). Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 3rd edition, April 2007.N

Results

Statistically significant improvements from baseline favouring Botox over placebo were observed for headache days, for migraine/probable migraine days, moderate/severe headache days, total cumulative hours of headache on headache days, and 50% or more improvement from baseline in headache days in both subgroups. Significant results were not consistent between the two subgroups for headache episodes and migraine episodes. There were no significant differences in either subgroup for acute medication intakes and acute medication days.

There were also statistically significant improvements from baseline always favouring Botox over placebo at week 24 for all of the patient reported disability and quality of life measures including the proportion of patients with severe HIT-6 category scores, all 3 domains of the MSQ, total HIT-6 scores and the incidence of patients with ≥ 5 point improvement from baseline on total HIT-6 score.

Table 6 Week 24 Results by First-Line Pre-Study BASH Prophylactic Medication Use Subgroup for Headache Symptom Measures for Phase 3 Pooled Population

	First Line Pre-Study BASH Med Use- Yes (N=575)			First Line Pre-Study BASH Med Use- No (N=809)		
	BOTOX (N=277)	Placebo (N=298)	P-value	BOTOX (N=411)	Placebo (N=398)	P-value
Headache Episodes	-5.6	-4.6	0.009	-5.3	-4.9	0.234
Headache Days	-8.0	-5.6	<0.001	-8.7	-7.3	0.004
Migraine/Probable Migraine (MPM) Days	-7.8	-5.2	<0.001	-8.5	-6.9	<0.001
Moderate/Severe Headache Days	-7.4	-4.8	<0.001	-8.0	-6.6	0.002
Cumulative Hours of Headache on HA Days	-103.88	-60.22	<0.001	-126.38	-99.72	0.003
MPM Episodes	-5.3	-4.2	0.008	-4.9	-4.4	0.130
Acute HA Pain Med Intake	-10.3	-7.7	0.069	-10.1	-10.5	0.744
Acute HA Pain Med Days	-5.5	-4.7	0.093	-6.2	-5.7	0.168
≥50% Decrease from Baseline: HA Days	44.6%	31.6%	0.003	49.0%	38.0%	0.006

HA = headache; med = medication; MPM = migraine/probable migraine

Source: Appendix 1, Tables 1-74, 1-75, 1-76, 1-77, 1-78, 1-79, 1-80, 1-81, 1-82

RMS Assessment of applicant's response:

Approximately 40% of the phase III study population was recorded as prophylaxis naïve. With an average 20 year history of chronic migraine this seems like a considerable proportion particularly when such a broad array of medications were permitted at baseline entry raising the question of whether these patients were true chronic migraineurs in the first place. The BASH analysis is interesting as it analyses the data according to a list of medications that have been considered first line treatment on the basis of quality of the evidence of magnitude of the benefit of a particular medication and clinical experience of tolerability, and safety. The data indicates that Botox is more effective in patients who were receiving a pre study BASH specified medication compared with the combined group who never received prophylaxis or received a non-BASH specified prophylactic medication. However this does not compare patients on prestudy prophylaxis (BASH) with the true prophylaxis naive patients. Once more the main driver of the enhanced treatment effect between groups (BASH and non-BASH) is the difference in placebo response seen across the two groups.

Conclusion; this point is not considered resolved. Efficacy of Botox in patients who have never received prophylaxis has not been established. The proposed indication has been amended to reflect this fact

D. Overuse of Acute Headache Pain Medications at Baseline

RMS Assessment
See assessment of Question 1.A and 1.B

Question 3 Potential Unblinding

Unblinding to treatment was not checked for investigators or participants. The muscle relaxant effect could potentially have resulted in unblinding of treatment which may have influenced the expectation of both physicians and patients particularly as efficacy assessments were based on self reporting/assessment by patients. This could have been in a potential source of bias in the study results.

Summary of applicant's response:

Allergan conducted these DBPC trials in a manner to minimize this potential issue, including a range of methods to ensure blinding of both investigator and patient was maintained. Unblinding is attributed to robust efficacy or an unusual but characteristic adverse event. The applicant considers that unblinding is a theoretical concern and that there is no evidence to suggest that the blind was compromised in a systematic manner. This is supported by the overall very low rate of AE reporting. The injection paradigm differences between aesthetic and chronic migraine would not be expected to produce the same aesthetic effects. Allergan conducted analyses of the efficacy data on different subpopulations of patients to determine if the efficacy results were influenced by potential unblinding. Allergan conducted efficacy analyses in two subpopulations of patients that included those who reported potentially unblinding AE based on a subset of the terms that were listed in the informed consent form.

These subgroups were analyzed as patients who reported AE terms that pertained to the:

1. **Face** (diplopia, dry eye, eyelid oedema, eyelid ptosis, facial pain, facial palsy, facial paresis, hypersensitivity, hypoaesthesia [face] (e.g., hypoaesthesia eye, hypoaesthesia facial, hypoaesthesia oral), injection site [face], paraesthesia [face] (e.g., paraesthesia oral), pruritis [face], rash [face], skin tightness [face], vision blurred, visual disturbance) and

2. **Face (same as list above) or neck** (neck pain, neck tightness, neck discomfort, neck stiffness, stiff neck and neck rigidity), which was the most commonly reported AE in the Botox phase 3 studies. Analyses of the DBPC phase data demonstrated that only 10.9% (N=150) of the 1379 treated patients (Botox n = 104, placebo n = 46, $p < 0.001$). While the majority of the patients who did report such AE received Botox treatment, overall they represented only 15.1% (104/687) of all Botox -treated patients. Analyses of the DBPC phase data demonstrated that a total of 16.6% (N = 229) of the 1379 treated patients reported either a potentially unblinding AE to the face or neck (Botox n = 165, placebo n = 64, $p < 0.001$. Further efficacy analyses with and without these patients in the dataset were performed to confirm whether there was or was not an effect on the results.

Analyses of Efficacy in the Subgroup of Patients with Potentially Unblinding AE Pertaining to the Face

Results from these analyses demonstrate that the mean change from baseline in frequency of headache days and headache episodes was not different in the Botox-treated patients who reported a potentially unblinding AE that pertained to the face compared to those who did not report such AE. A difference was observed in the placebo-treated patients whereby there was a higher mean change from baseline for both frequency of headache days (-6.8 vs. -6.6) and headache episodes (-5.7 vs. -4.9) in those patients who reported a potentially unblinding AE that pertained to the face compared to those who did not report such AEs . Furthermore, when comparing the subpopulations to the ITT population, results demonstrate that there was no exaggerated efficacy response in either subgroup, and thus no significant unblinding, since the mean change from baseline in frequency of headache days in Botox-treated patients was identical across all three populations, and there was no substantial difference in the mean change from baseline in the frequency of headache episodes. These efficacy analyses demonstrate that significant improvements in the frequency of headache days and headache episodes were due to Botox effect and were not influenced by unblinding.

Table 7 Comparison of Mean Change from Baseline at Week 24 for Frequency of Headache Days and Frequency of Headache Episodes in Botox Treated Patients Between

Subpopulation of Patients Who Did and Did Not Report Potentially Unblinding AE That Pertained to the Face: Pooled Phase 3 Studies (DBPC phase)

Efficacy Variable (per 28 days)	Pooled Phase 3 191622-080 + 191622-079: Subpopulation of patients who reported potentially unblinding AE[a]	Pooled Phase 3 191622-080 + 191622-079: Subpopulation of patients who did not report potentially unblinding AE[a]	Pooled Phase 3 191622-080 + 191622-079 ITT population
	BOTOX (N = 104)	BOTOX (N = 584)	BOTOX (N=688)
Frequency of headache days	-8.4	-8.4	-8.4
Frequency of headache episodes	-5.1	-5.2	-5.2

[a] Potentially unblinding AE that pertained to the face included the following AE preferred terms: diplopia, dry eye, eyelid oedema, eyelid ptosis, facial pain, facial palsy, facial paresis, hypersensitivity, hypoaesthesia [face] (eg, hypoaesthesia eye, hypoaesthesia facial, hypoaesthesia oral), injection site [face], paraesthesia [face] (eg, paraesthesia oral), pruritis [face], rash [face], skin tightness [face], vision blurred, visual disturbance.

Results in bold denote statistically significant differences from placebo favouring BOTOX.

Source: Appendix 1, Tables 1-94, 1-95, Module 5.3.5.3 ISE Tables 2-1, 2-3

Analyses of Efficacy in the Subgroup of Patients with Potentially Unblinding AE Pertaining to the Face or Neck

There was no difference in the mean change from baseline in the frequency of headache days in the Botox-treated or the placebo-treated patients who reported potentially unblinding AE to the face or neck compared to those who did not report such AEs. The mean change from baseline in frequency of headache days is identical across all three populations. For mean change from baseline in the frequency of headache episodes the response was similar for Botox-treated patients, but there was a higher placebo response observed for those patients who reported potentially unblinding AE to the face or neck compared to those who did not report such AEs. In addition, responder analysis showed that in the subpopulation of BOTOX-treated patients who achieved ≥ 50% and ≥ 75% response across multiple headache symptom measures that only 24% and 23%, respectively, had reported a potentially unblinding AE pertaining to the face.

Responder analysis showed that in the subpopulation of BOTOX-treated patients who achieved ≥ 50% and ≥ 75% response across multiple headache symptom measures that only 24% and 23%, respectively, had reported a potentially unblinding AE pertaining to the face
These efficacy analyses performed with and without including the subgroup of patients who reported potentially unblinding AE to the 1) face or 2) face or neck demonstrated that there were no substantial efficacy differences, which provides strong evidence that the efficacy results were due to effective migraine prophylaxis due to BOTOX treatment and not driven by unblinding of patients.

Table 8 Comparison of Mean Change from Baseline at Week 24 for Frequency of Headache Days and Frequency of Headache Episodes in Botox Treated

Patients between Subpopulation of Patients who did and did not report potentially unblinding Face or Neck AE: Pooled Phase 3 Studies (DBPC phase)

Efficacy Variable (per 28 days)	Subpopulation of patients who reported potentially unblinding AE[a]	Subpopulation of patients who did not report potentially unblinding AE[a]	Pooled Phase 3 191622-080 + 191622-079 ITT population
	BOTOX (N = 165)	BOTOX (N = 523)	BOTOX (N=688)
Frequency of headache days	-8.4	-8.4	-8.4
Frequency of headache episodes	-5.5	-5.1	-5.2

[a] Potentially unblinding AE that pertained to the face or neck included the following AE preferred terms: diplopia, dry eye, eyelid oedema, eyelid ptosis, facial pain, facial palsy, facial paresis, hypersensitivity, hypoaesthesia [face] (eg, hypoaesthesia eye, hypoaesthesia facial, hypoaesthesia oral), injection site [face], paraesthesia [face] (eg, paraesthesia oral), pruritis [face], rash [face], skin tightness [face], vision blurred, visual disturbance, neck pain, neck tightness, neck discomfort, neck stiffness, stiff neck and neck rigidity.

Results in bold denote statistically significant differences from placebo favouring BOTOX.

Source: Appendix 1, Tables 1-98, 1-99; Module 5.3.5.3 ISE Tables 2-1, 2-3

RMS assessment of Applicant's response:

The validity of a study with a placebo control arm rests on the assumption of blinding. Systematic appraisal of the risk of unblinding is absent in this study. There is no independent biomarker for migraine. Self assessment by patients of pain is used as a key endpoint in the phase 3 studies submitted with this application. Blinding is particularly important when outcome measures involve some subjectivity, such as assessment of pain. End of trial evaluation of side effects is one way of assessing blinding but not the same as testing for blindness which should have been specifically evaluated at the end of these studies. The applicant has evaluated the differences in reported adverse events as a measure of maintenance of blinding in the study. It is possible that the other known effects of Botox may not have been perceived as an adverse effect. It may have been an awareness or a subtle change in physical appearance that may not have been significant enough to be identified an unwanted side effect but still could have indicated to the patient that they most likely received the active treatment. In this situation it is plausible that participants who are aware of their assignment status were more likely to report improvement, leading to biased results. However there were no group differences in visit compliance or in the intakes of AHPM therapy, or exaggerated efficacy response in either subgroup .Although over twice as many of the Botox treated group compared with the placebo treated group reported a potentially unblinding AE to the face and neck (Botox n=165 and placebo n=64) the overall total combined Botox and placebo DBPC treated patients (16.6%; 229/1379) who experienced a potentially unblinding AE was small. It is noteworthy that placebo treated patients who experienced potentially unblinding AEs had an increased efficacy response compared with those placebo treated patients who did not report such AEs. This effect was not seen in the Botox treatment arms where the treatment response was the same regardless of whether unblinding AEs were reported or not. The high levels of placebo response seen in both treatment arms and sustained across the DBPC period of the study also suggest that the blind was maintained throughout this phase of the studies. In so far as is possible the applicant has demonstrated that the overall rate of reporting of potential unblinding AEs is small and that there is no evidence of a systematic biasing of efficacy results in favour of patients who reported potentially unblinding AEs.

Conclusion: This point is considered resolved.

Reports of Possible Aesthetic Benefit Resulting in Potential Unblinding

Summary of Applicant's response:

Of the 1384 patients enrolled in the BOTOX phase 3 studies, data from the DBPC phase indicate that only 1 placebo-treated patient reported 'mild reduced forehead wrinkling' (Preferred Term: Skin Wrinkling), a potentially positive aesthetic response that could have resulted in potential unblinding of this patient. There were no potentially positive aesthetic responses noted in the case report forms for any BOTOX-treated patient during the DBPC phase of these studies.

Facial Wrinkles in Women and Men

Not all adults have wrinkles and the aesthetic effect from treatment with Botulinum toxin is dependent on the underlying cause of wrinkles. An aesthetic effect from treatment with Botulinum toxin is not expected in all patients. Facial wrinkles are more predominant in older (≥ 40 years) adults (Ernster et al, 1995). The amount and depth of facial wrinkles differ among persons and that there are certain intrinsic and extrinsic factors that are not causative, but influence the extent and rate of facial wrinkling including genetics, age, race (skin colour), gender, prior sun damage, skin thickness, amount of subcutaneous fat, alcohol consumption and smoking history**.** It has been reported that lines in the skin related to inelasticity (predominantly related to aging) or actinic damage do not respond well to Botulinum toxin. In the Botox phase 3 studies, 42% of the population was < 40 years of age. Analyses of subgroups of patients < 40 years and ≥ 40 years showed that Botox-treated patients in both subgroups had significantly greater mean change from baseline in frequency of headache days than did placebo-treated patients. The between group differences were similar. In the Botox-treated subgroup ≥ 40 years of age, the mean change from baseline in frequency of headache days was -7.9, which is less than the -9.0 mean change observed in Botox-treated patients who were < 40 years of age .The MAH reasons that if indeed there had been a Botox effect on wrinkles, one would have expected such an effect to occur in those with a greater chance of having wrinkles (i.e., the ≥ 40 year old patients), the opposite was observed in the phase 3 studies since the younger Botox-treated patients (< 40 years), who have a higher likelihood of not manifesting wrinkles, had a greater mean change from baseline in frequency of headache days than older Botox-treated patients

Table 9 Comparison of LS Mean Change from Baseline at Week 24 for Frequency of Headache Days in Patients < 40 years and ≥ 40 years: Pooled Phase 3 Studies (DBPC phase)

Efficacy Variable (per 28 days)	< 40 years			≥ 40 years			ITT population		
	BOTOX (N = 293)	Placebo (N=288)	P-Value	BOTOX (N = 395)	Placebo (N=408)	P-Value	BOTOX (N=688)	Placebo (N=696)	P-Value
Frequency of headache days	-9.0	-7.3	0.002	-7.9	-6.1	<0.001	-8.5	-6.7	<0.001

Results in **bold** denote statistically significant differences favouring BOTOX.

Source: Module 5.3.5.3, ISE Table 2-3 and Table 3-8

This subgroup analysis provides evidence that there was not an exaggerated efficacy response in patients ≥ 40 years of age, who were those most likely to have had wrinkles, compared to patients who were < 40 years of age and less likely to have wrinkles, which supports Allergan's position that the blind was adequately maintained in the BOTOX phase 3 studies.

Comparison of BOTOX Dose and Injection Paradigm for Aesthetic Treatment for the

Upper Face vs. Chronic Migraine

The Botox chronic migraine injection paradigm, although similar, does not overlap exactly with the injection paradigm for the aesthetic treatment for the upper face, which frequently includes treatment of glabellar lines, forehead lines, and/or crow's feet (Ascher et al, 2010; Frankel and Markarian, 2007). Due to differences in dose and injection site location, the chronic migraine injection paradigm is not expected to produce the same aesthetic effect as aesthetic treatments for the upper face. With aesthetic treatments patients are asked to engage their facial muscles to produce maximum wrinkle (eg, furrow brow) so that physicians can then target injections to maximize individual patient effect based on location of the wrinkles. In chronic migraine, patients do not actively engage these muscles, but are injected with facial muscles at rest into standard sites that are based on physical landmarks and not on wrinkle location. Also, the total Botox dose administered to the corrugators, procerus and frontalis muscles for chronic migraine is less than the total effective VISTABEL® dose suggested in the literature for aesthetic treatment for these same areas of the face. The chronic migraine treatment paradigm uses standardized injection sites that are determined by facial anatomical landmarks and are not dictated by position of wrinkles. The injection sites into the muscles of the face (ie,procerus, glabellar and frontalis muscles) remain unchanged regardless of where the patient's headache pain is located.

Comparison of Botox Dose and Injection Paradigm for Treatment of Glabellar Lines vs. Chronic Migraine

The injection paradigm for chronic migraine is compared to the glabellar line injection paradigm. Differences relate to the total Botox dose administered, number of injection sites, and injection site location. Total dose is 25% less that the treatment for glabellar lines and only 3 injection sites. These injection sites are higher on the forehead than the target for treatment of glabellar lines

RMS assessment of Applicant's response:

The muscle relaxant effect is an established pharmacological effect of Botox. The muscle relaxant effect of Botox and its potential effect on chronic migraine either through a direct effect on the pathogenesis of chronic migraine pain or indirectly through an aesthetic effect was not discussed by the applicant. It is acknowledged that any potential aesthetic effect is likely to be small. It is unlikely if there was an aesthetic effect that it would in practice be markedly different between participants <40 and> 40years of age.
This point is considered resolved.

Comparison of Adverse Event Profile of Botox to Migraine Drugs in Placebo-Controlled, Double-Blind Registration Clinical Trials

Potentially unblinding due to AE or other drug effects is a ubiquitous issue in clinical research, and is not unique to Botox clinical studies. Unblinding either due to robust efficacy or an unusual but characteristic AE profile is always of potential concern in a drug development program. Allergan conducted these DBPC trials in a manner to minimize this potential issue, including a range of methods to ensure blinding of both investigator and patient was maintained. While always a theoretical concern, there is certainly no evidence to suggest that this was a particular issue in these clinical trials. Indeed, the very low rate of AE overall makes this less likely to have been a confounding issue. Other drugs recently studied in the migraine field have

reported very high proportion of patients with potentially unblinding AE or other significant clinical effects. Adverse event profiles for many drugs that have been evaluated in double-blind registration studies contribute to potential unblinding, particularly when such events occur at a high frequency. Consider, for example, the class of anticonvulsant agents that are frequently used as migraine prophylaxis. Results of recent migraine prevention studies of topiramate report high AE rates that certainly could result in unblinding (Diener et al, 2007; Silberstein et al, 2007). For example, reports of paresthesia, a labeled common AE, were observed in 29% to 53% of patients treated with topiramate, but in only a few patients treated with placebo. Also, a significant reduction in body weight, which is perceived as a potential benefit to treatment by most patients, has been reported with topiramate (Diener et al, 2007). In one study, patients treated with topiramate experienced a mean weight reduction of 2.3 ± 2.9 kg during the trial, while patients on placebo gained a mean of 0.1 ± 3.1 kg (Silberstein et al, 2007).
The AE profile for Botox shows that it is well-tolerated, without an individual AE being reported in > 10% of patients in the Botox phase 3 chronic migraine studies. Only 10.9% (Botox 15.1%, placebo 6.6%;) and 16.6% (Botox 24%, placebo 9.2%;) of the 1379 patients treated in the Botox phase 3 studies during the DBPC phase reported potentially unblinding AE pertaining to the face and face or neck, respectively (as discussed above).

Table 10 Proportion of Patients That Experienced Some of the Listed "Very Common (> 10%)" and "Common (≥ 1% to < 10%)" Adverse Events for Topiramate for Migraine Prevention

	Chronic Migraine Silberstein et al, 2007a		**Chronic Migraine Diener et al, 2007b**		**Episodic Migraine Brandes et al, 2004c**	
Adverse Event	**Topiramate (N=161)**	**Placebo (N=160)**	**Topiramate (N=32)**	**Placebo (N=27)**	**Topiramate (N=119)**	**Placebo (N=113)**
Paresthesia	29%	8%	53%	7%	50%	4%
Fatigue	12%	10%	6%	0	14%	9%
Anorexia	5%	6%	6%	4%	13%	8%
Hypesthesia	9%	0	NA	NA	11%	0
Difficulty with concentration/attention	9%	3%	6%	4%	NA	NA
Difficult with memory	7%	6%	3%	4%	10%	4%
Nausea	9%	8%	9%	0	10%	8%
Dry mouth	9%	3%	NA	NA	NA	NA
Taste perversion	9%	3%	NA	NA	8%	0
Somnolence	6%	4%	3%	4%	NA	NA

RMS assessment of Applicant's response:

The rate of unblinding AE experienced with Botox is low compared with other drugs recently studied in the migraine field which have reported very high proportion of patients with potentially unblinding AEs. Although these studies may not be directly comparable this does suggest that the low rates of potentially unblinding AEs reported in the Botox studies were less likely to have been a confounding issue.

Placebo Response and Nocebo Effect During the DBPC Phase of the BOTOX Phase

Clinical Studies

Despite the high placebo response, statistical significance favouring Botox vs. placebo was achieved in the Botox phase 3 studies for the key endpoint of headache days, as well as for multiple other headache symptom and health related quality of life measures. Adverse event analysis demonstrate that of the 1379 patients treated across the two phase 3 studies, 9.2% (64/696,) of the placebo-treated patients reported a potentially unblinding AE of the face or neck during the DBPC phase of the Botox phase 3 studies. Given the high placebo response, it would be expected that placebo-treated patients would potentially report more AE associated with Botox pharmacology, but this was not the case in the Botox phase 3 clinical studies,

Efficacy Response in Open-Label Phase

If the between-treatment group difference observed in the DBPC phase was due to unblinding, then in the open label phase we would have expected the response to be identical in both treatment arms. Yet, the two treatment groups response remained different with the response in the patients who had received placebo in the DBPC phase never catching up during the course of this study to the response of the patients who received Botox in the DBPC phase.

RMS assessment of the applicant's response:

Overall the applicant has discussed the possibility of blinding in terms of the potential for unblinding adverse events, the possible aesthetic effect of Botox, the lack of a nocebo effect in the placebo arm in the DBPC phase and the enhanced treatment effect in the Botox treated group in the open label phase of the study. Although unblinding may have been a confounder the RMS agrees that it is unlikely to have been significant enough to fully explain the difference in treatment effect between the Botox treated and placebo treated patients in the phase 3 studies.

Conclusion; This point is considered resolved.

<u>Other concerns</u>

Clinical Efficacy

Question 1 (Clinical significance of pooled data)

The clinical significance of a 1.9 reduction in headache days against a baseline rate of 19 headache days and a reduction in frequency of headache episodes of 0.3 against a backdrop of 12 headache episodes per 28 day period should be justified.

Summary of the Applicant's Response:

Some efficacy measures have established minimally important between group differences (headache days, HIT-6, MSQ and responder rates), but minimally important between-group differences have not been established for all headache symptom measures, including headache episodes. The applicant then goes on to justify headache days as the preferred choice of endpoint (standardized 24 hr timeframe, minimum and maximum range over 28 days is fixed for all patients). The MAH highlights the shortcomings of headache episodes as an efficacy endpoint (variability of headache episode, variability in duration of headache

episodes at baseline, the broad range of minimum and maximum range of frequency of range of headache episodes in the phase 3 studies was 4 to 43 in study 191622-079 (median of 12 episodes) and 4 to 35 in study 191622-080). It may be difficult for a chronic migraine patient (compared to an episodic migraine patient) who typically suffers from near daily headaches to distinguish between two or three shorter headache episodes occurring back-to-back as compared to a single headache with a duration of several days since headache pain intensity may vary over a longer period of time. Treatment may reduce the hours of headache, and thereby reduce the number of
headache days and the headache-associated burden, resulting in a change in the frequency of
headache days, but not necessarily the frequency of headache episodes.
Consistent efficacy across both studies. On this basis the MAH argues it is reasonable to conclude that the number of headache days is a more sensitive endpoint compared to the number of headache episodes. Treatment may reduce the hours of headache, and thereby reduce the number of headache days and the headache-associated burden.
The applicant discusses the clinical meaningfulness of observed changes in outcome measures and refers to expert opinion that states that that clinical importance or meaningfulness of observed changes in outcome Measures cannot be based solely on the statistical significance of the primary efficacy outcome. Improvements in physical and emotional functioning are often as important to patients as the actual diminution of pain; efficacy results usually are focused on evaluating a drug's mean benefit across a population. However, of equal or greater importance is to translate mean changes in terms that better describe the effects for individual patients. The applicant summarizes the efficacy evidence of the statistically significant and clinically meaningful benefits of Botox for the pooled phase 3 studies using an adaptation of the framework suggested by Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (See tables below)

Table 11 Framework for Evaluating Clinical Meaningfulness Applied to Treatment Outcomes for the BOTOX Phase 3 Chronic Migraine Studies

Category	Content[a]
Efficacy	A. Headache symptom measures: Statistical significance vs. placebo B. Headache symptom measures: Magnitude of improvement (individual patient benefit) C. Headache symptom measures: Responder analyses D. Health-Related Quality of Life Measures E. Summary of efficacy outcomes

a Adapted from Dworkin et al, 2009

<table>
<tr><td>Category</td><td colspan="3">Content</td></tr>
<tr><td>Efficacy</td><td>A. Headache symptom measures: Statistical significance vs. placebo</td><td>Reductions from baseline in the mean frequency of headache days (Botox vs. placebo) (-8.5 vs. -6.7, p<0.001</td><td>Reductions from baseline favouring Botox over placebo were also seen in
1. frequency of migraine/probable migraine days,
2. frequency of moderate/severe headache days,
3. total cumulative hours of headache on headache days,
4. frequency of headache episodes
5. frequency of migraine/probable migraine episodes
6. AHPM days (but not AHPM days)</td></tr>
<tr><td></td><td>B. Headache symptom measures: Magnitude of improvement (individual patient benefit)</td><td colspan="2">Magnitude of Improvement (Individual Patient Benefit): LS Mean Percent Improvement from Baseline at the Week 24 Primary Time point and at Week 56[a] after BOTOX Treatment: Pooled Phase 3 Studies
<table>
<tr><th rowspan="2">Variable</th><th colspan="2">Pooled Phase 3 Studies</th></tr>
<tr><th>Week 24</th><th>Week 56</th></tr>
<tr><td>Headache Days</td><td>44.0%</td><td>60.5%</td></tr>
<tr><td>Migraine Days[b]</td><td>44.2%</td><td>60.1%</td></tr>
<tr><td>Moderate/ Severe Headache Days</td><td>41.8%</td><td>58.8%</td></tr>
<tr><td>Total Cumulative Hours of Headache on Headache Days</td><td>41.3%</td><td>58.1%</td></tr>
<tr><td>Headache Episodes</td><td>41.9%</td><td>59.4%</td></tr>
</table>
[a] Week 56 data reports the magnitude of mean percent improvement for all patients who received BOTOX, including those who received BOTOX in the 24 week double-blind, placebo controlled phase and those who first received BOTOX in the 32 week open-label phase.
[b] ICHD-II 1.1 migraine without aura, 1.2 migraine with aura, 1.6 probable migraine</td></tr>
<tr><td></td><td>C. Headache symptom measures: Responder analyses</td><td colspan="2">Headache Symptom Measures at Week 24: Proportion of Patients with ≥ 50% Responder Rates: Pooled Phase 3 Studies (DBPC Phase)
<table>
<tr><th>Efficacy Variable (per 28 days)</th><th>BOTOX (N=688)</th><th>Placebo (N=696)</th><th>P-Value</th></tr>
<tr><td>Headache days</td><td>47.1%</td><td>35.1%</td><td><0.001</td></tr>
<tr><td>Headache episodes</td><td>48.6%</td><td>43.1%</td><td>0.065</td></tr>
<tr><td>Moderate/ severe headache days</td><td>49.4%</td><td>37.5%</td><td><0.001</td></tr>
<tr><td>Total cumulative hours of headache on headache days</td><td>50.3%</td><td>38.9%</td><td><0.001</td></tr>
<tr><td>Migraine days[a]</td><td>48.2%</td><td>36.4%</td><td><0.001</td></tr>
<tr><td>Migraine episodes[a]</td><td>48.1%</td><td>43.4%</td><td>0.119</td></tr>
</table>
Results in bold denote statistically significant differences favouring BOTOX
[a] ICHD-II 1.1 migraine without aura, 1.2 migraine with aura, 1.6 probable migraine
Source: Appendix 1, Tables 1-113, 1-114, 1-115, 1-116; Module 5.3.5.3 ISE Tables 2-11, 2-12</td></tr>
<tr><td></td><td>D. Health-Related Quality of Life Measures</td><td>In the phase 3 studies, total HIT-6 score mean changes from baseline significantly favoured Botox over placebo at every time point in the DBPC phase .The between-group difference at the week 24 primary</td><td>MSQ: Week 24 Mean (±SE) Change from Baseline: Pooled Phase 3 Studies (DBPC phase)</td></tr>
</table>

		time point (2.4 in the pooled analysis) ≥ established minimally important between-group difference of 2.3 (Coeytaux et al, 2006). Stat.sig. differences favouring Botox over placebo were also observed for each of the six components of the HIT-6 assessment at the week 24 primary time point	<table><tr><th>MSQ Role Function</th><th>BOTOX (N =688)</th><th>Placebo (N =696)</th><th>Between-Group Difference</th><th>P-value</th></tr><tr><td>Role Function Restrictive (RFR)</td><td>-17.0 ± 0.90</td><td>-8.6 ± 0.81</td><td>8.4 [a]</td><td>< 0.001</td></tr><tr><td>Role Function Preventative (RFP)</td><td>-13.1 ± 0.88</td><td>-6.4 ± 0.80</td><td>6.7 [a]</td><td>< 0.001</td></tr><tr><td>Emotional Function (EF)</td><td>-17.9 ± 1.10</td><td>-9.5 ± 0.99</td><td>8.4 [a]</td><td>< 0.001</td></tr></table> Results in **bold** denote statistically significant differences favouring BOTOX [a] Between-group differences are exceeded for established MID of 3.2 for RFR. 4.6 for RFP and 7.5 for RFE (Cole et al. 2009)
	E. Summary of efficacy outcomes	The MAH concludes that the totality of evidence from all the efficacy outcomes assessed in the phase 3studies, including multiple headache symptom measures and multiple health-related quality of life measures for Botox resulted in statistically significant and clinically meaningful improvements	

In summary, for the pooled phase 3 studies, statistically significant differences for the preferred primary endpoint (headache days) and most secondary headache symptom measures favoured Botox vs. placebo at the week 24 primary timepoint, as well as at multiple other timepoints.

RMS assessment of Applicant's response:

As outlined in the IMMPACT recommendations an essential component of the interpretation of treatment effects is a determination of the clinical meaningfulness. The applicant discusses various factors to evaluate the clinical importance of group differences. The modified IMMPACT criteria discussed in this response leaves out a number of key criteria outlined in the publication by Dworkin ET al.The IMMPACT recommendations also included treatment effect size compared to available therapies, the rapidity of onset and durability of the treatment benefit, convenience and cost.

To that end the group benefit versus the individual benefit analysis is somewhat outside the scope of this evaluation. The evaluable data in this application is based on individual patient improvement. In the context of these studies as there is no comparator arm the most relevant index of clinical effect is the comparison of the magnitude of the treatment effect with placebo for the efficacy and the health related quality of life measures. As the treatment effect is small the distribution of responses as reported in the responder analyses provides important information beyond the difference in mean response. The results of the responder analyses are somewhat supportive of a clinically meaningful group effect in the pooled analyses although the magnitude of the group differences between Botox and placebo is only of the order of 10-15% across all responder analyses in the ITT population. The results are less robust in the subgroup who are closest to the true definition of chronic migraine i.e. those patients who are not overusing acute headache pain medications. In this analysis only one responder endpoint reaches statistical significance (≥ 50% reduction in moderate /severe headache days.) Use of the higher rate of ≥50% was used to estimate proportions of treatment responders which may have contributed to this result. The consistently highly significant differences seen in the health related quality of life measures for the Botox treated group suggests that patient satisfaction may not be determined only by reductions in hours of headache or

numbers of headache episodes but may perhaps be influenced by other factors such as reduction in severity of headaches.

Question 2 (Chronic Migraine definition)

One of the difficulties that has arisen in the interpretation of the dataset is the definition of chronic migraine used across the clinical development plan. The IHS classification changed during the time of the trial from chronic daily headache to chronic migraine. The final definition used in the two pivotal studies is not in line with the current ICHD II criteria (CM-R) for CM. The external validity of the efficacy findings from the two phase 3 studies is compromised by the lack of consistency between the definitions used in the clinical trials and those recommended outlined in the ICHD classification.

Summary of Applicant's response:

Based on multiple evaluations within robust datasets, the chronic migraine population evaluated in the phase 3 clinical studies is representative of the target population of patients with chronic migraine as currently defined by ICHD-2R (Olesen et al, 2006a) who would be receiving Botox for the treatment of chronic migraine as outlined in the response to question 1. However, based on feedback from the Irish Medicines Board, Allergan proposes a revision to the SPC to better define the term "chronic migraine" to ensure that the indication wording reflects the clinical trial population studied and provides treating physicians with further guidance. Therefore, Allergan proposes that the indication for the SPC reads as follows: "prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)"(see proposed SPC). Results from a 9 country population-based study, referred to as International Burden of Migraine Study (IBMS), that characterized disease burden using ICHD defined chronic migraine patients (N=499) was completed. European-specific data (N=277) from 5 of those countries shows that chronic migraine sufferers have poor health-related quality of life to a similar degree as the patients evaluated in the BOTOX chronic migraine phase 3 studies (Kawata et al, 2010, Stokes et al, 2010). The clinical trial population is representative of this heavily burdened group of migraine sufferers.

RMS assessment of Applicant's response:

The Allergan defined chronic migraine is one of a number of definitions that have been field tested against the ICHD revised criteria for CM (Bigal et al 2006 Zeeberg et all 2008). There appears to be ongoing discussion as to the merits or otherwise of including patients with MO in the definition of CM. The IHS guidelines for controlled trials of prophylactic treatment of chronic migraine in adults although recommending that the diagnostic criteria for CM should comply with those of the revised appendix ICHD2 also indicates that patients who fulfil the ICHD revised criteria for medication overuse headache should also be included. The ICHD2R criteria are consensus based rather than evidence based and require validation through clinical research. Botox should have been evaluated in patients who were medication overuse free either at entry or following withdrawal of AHPM in order to establish efficacy without the confounding effect of medication overuse. Critically the definition of CM used in these studies includes patients with MO. Role of MOH in chronification of migraine is complex and difficult to elucidate. The patients included in the ITT were more representative of a picture of probable migraine with probable medication overuse. Although this may reflect the type of clinical picture encountered in practice it remains best practice in these patients to withdraw AHPM prior to establishing a true diagnosis of chronic migraine. Efficacy of Botox should have been established in patients with chronic

migraine who were free of medication overuse. The applicant has presented efficacy analyses for the pooled phase 3 MedO-Yes and Med O-No subpopulations. As previously the med-O subpopulation is closest to the ICHD2R-CM definition and is considered to be the critical efficacy population.

Question 3 (Basis for clinically meaningful difference)

The level of difference between active and placebo that was considered a clinically meaningful difference and was used as delta in the power calculation is different across the phase 2 and 3 studies. The basis for these values should be clarified.

Summary of applicant's response:

In 2005 when the phase 3 studies were being designed there was
1) No consensus among headache specialists/clinicians or global regulatory agencies as to the choice of primary endpoint for patients with chronic migraine

2) No between group delta that established a gold standard for clinically meaningful between group differences.

3) No regulatory precedence for this group of patients

4) No guidelines for the prophylaxis of headache in patients with chronic migraine (≥ 15 headache days/month) and these patients had been systematically excluded from other headache prophylaxis registration trials.

The primary endpoints varied considerably, as did the delta between groups for a few, small exploratory, controlled studies of other headache prophylaxis treatments in patients with chronic migraine in the literature (Silvestrini et al, 2003; Spira and Beran, 2003; Saper et al, 1994; Saper et al, 2002). The sample size was estimated to detect a difference between treatment groups of ≥ 3 headache-free days, which had been suggested by clinical consultants as a meaningful change and was not validated by data, but simply their best guess. The only other information in the literature that provided any guidance on possible criterion for study design was a small, (N=133) cross-over study of gabapentin in the prophylaxis of chronic daily headache (CDH) conducted at 12 centres in Australia (Spira and Beran, 2003). The authors of this study indicated in this paper "the commonly accepted criterion of efficacy for trials of headache prophylaxis – namely, a 50% reduction in frequency of headaches" – was considered inappropriate for this highly refractory headache form. Opinion leaders were canvassed and determined that anything less than an overall mean response of 7.5% difference in headache frequency between the active and the placebo arms of the study would have no clinical relevance. This figure for the group response was accepted in light of clinical experience that many patients with CDH are refractory to all forms of intervention and their lack of response could conceal substantial therapeutic effects in others". The primary efficacy endpoint in this gabapentin study was a between-group evaluation of headache-free rate (% headache-free days per period). In this study, the between group difference was found to be 9.5%, which exceeded the clinicians overall mean response rate of 7.5%; this difference was ~ 3 headache-free days (Spira and Beran, 2003). When the Botox phase 3 studies were designed, the best available information in large, well-controlled clinical studies of any headache prophylaxis treatment were the results from the Botox phase 2 studies in CDH (Silberstein et al, 2005; Mathew et al, 2005). Clinical experts who helped design the phase 3 study were asked to comment on what they felt would be a clinically meaningful mean between group difference for the primary endpoint "frequency of headache episodes" knowing that a majority of headaches experienced by patients in the phase 2 studies were greater than 4 hours in duration. Clinicians felt that a delta of 1.5 to 2.0 for frequency of headache

episodes and/or headache days was clinically meaningful. Thus, the power calculations for the phase 3 studies estimated the power for the between group delta of 1.5, 1.75 and 2.0 as noted in the phase 3 study protocols 191622-079 and 191622-080 section 10.5.

RMS assessment of Applicant's response:

The justification for the delta of 3 days to 1.5-2 across the phase 2 and 3 studies is accepted.

Question 4 (Dose selection)

The proposed doses and treatment paradigm is not based on any clear dose finding studies a minimum effective dose and minimum number of injection sites have not been identified. Dose selection appears to have been an empirical compromise between safety and efficacy.
Justification for the lack of appropriate dose finding studies should be provided.

Summary of applicant's response;

The applicant provides an overview of doses an, five exploratory (1997 and 2000), randomized, DBPC, parallel-group design studies of episodic migraine. In these studies, each treatment arm used a fixed-site, fixed-dose (FSFD) intramuscular (IM) injection paradigm with doses ranging from 6 U to 75 U, and number of total injection sites ranging from 3 to 11, administered IM in up to four muscle groups, all in the front of the head (i.e., corrugators, procerus, frontalis and temporalis) with no posterior head or neck injections.

In 2001 two phase 2 studies (191622-038 and 191622-039) were conducted to investigate the dose and dosing paradigm in order to determine optimal efficacy and safety of BOTOX in the treatment of chronic migraine. total doses in the range of from 75 U to 260 U, dose per muscle from 5 U to 60 U, selection of muscle groups and the number of injection sites per muscle. Neither of the phase 2 studies met the primary endpoint.
The treatment paradigm for study 191622-038 was a follow the pain (FTP) approach, which included a fixed site fixed dose (FSFD) injection of 105 U in a minimum of six head/neck muscles in 23 injection sites. An additional 155 U in 35 injection sites to the same six head/neck muscles, plus they could inject the masseter (which was not a muscle injected in the FSFD paradigm), for a total dose of up to 260 U. The mean dose administered in this study was 190 U in 2 injection sites. Because most patients in this study received additional dose using the FTP approach, and the efficacy data were more robust in this study than in the second phase 2 study conducted in the same population (i.e., study 191622-039), a decision was made to further pursue a FTP dosing regimen for the BOTOX phase 3 studies.

Assessors comment:

The applicant's justification that the dosing paradigm selected for phase 3 and ultimately as a proposed posology was initially based on two phase studies Study191622-038 and 039. Both of these studies failed to meet the primary efficacy endpoint. Lowest effective dose was not established in the phase two studies.

The phase 3 dosing paradigm

Key considerations in developing the final phase 3 dosing paradigm included analysis of the phase 2 studies for the following:

• Benefit/risk assessment from injection of specific muscles and total dose per injection cycle;
• Dose per injection cycle at which best tolerability was observed;
• Dose per injection cycle at which best efficacy was observed;
• Dosing regimens and patterns that were common in the phase 2 studies

Any revisions to the injection paradigm that could improve protocol implementation and standardization that would:
• facilitate protocol training,
• ensure consistency of the injection methodology across multiple study sites,
• potentially minimize the risk of focally related adverse events by ensuring that the total dose is divided across multiple injection sites in the muscle, and
• translates easily to rigorous, practical guidance for clinicians in labelling.

The muscle groups selected for the Botox phase 3 studies targeted those muscles that align with the distribution for input to the trigeminal sensory neurons, which are believed to be the target end-organ for Botox in treating migraine. Similar muscle groups were injected across the phase 2 and 3 studies with a few notable exceptions (Masseter, Splenius capitis injected midneck , Semispinalis injected mid neck were omitted from phase 3 studies based on in-depth analyses of the safety and tolerability of the dose and dosage paradigm used in both of the Botox chronic migraine phase 2studies).
A summary of the justification of the Botox phase 3 studies dose, number and location of injection sites, and the injection paradigm as described in a recent publication (Blumenfeld et al, 2010) is presented by the MAH. A justification for the site, dose and depth of injection in the muscles in the frontal glabellar region, temporalis, cervical paraspinal muscle group and occipitalis, trapezius and massester muscle is discussed.
The phase two efficacy and safety data was used to justify the site, dose and depth of injection. Based on the data from the phase 2 studies, it was determined that the phase 3 studies would require a minimum fixed site fixed dose (FSFD) of 155 U (31 sites) divided across 7 specific head and neck muscles. The protocols also allowed treatment for a given patient to be individualized using a follow the pain (FTP)) paradigm of up to an additional 40 U divided across 3 specific muscles: temporalis, occipitalis and trapezius There was no requirement to standardize the use of FTP from one injection cycle to another.

Justification for the number of sites injected and the amount per injection

In order to support standardization in implementing the injection paradigm and to minimize AEs that the Botox phase 3 studies would require each 100 U vial of Botox to be diluted with 2.0 mL unpreserved saline so that the resulting dilution volume for each injection site could be standardized at 0.1 mL (equivalent to 5 U in Botox group). 0.1 mL per injection site was to be used as part of a muscle specific standard injection paradigm. The total number of injection sites per muscle was determined by the total dose to be given in each muscle group. The specific location of injection sites were described using anatomical landmarks. Injection sites were chosen so as to minimize potential AEs, while ensuring proper administration of the study treatment. All injectors received specific training on the injection paradigm.

Justification of Total Dose per Injection Cycle

In phase 2 study 191622-038, the minimum dose was 105 U (given as FSFD paradigm) and the

maximum dose was 260 U (given as FTP paradigm) per injection cycle. In phase 2 study 191622-039 (a dose ranging study with doses given as FSFD of 75 U, 150 U and 225 U) there were no efficacy differences between the 225 U and 150 U groups observed, suggesting that the minimum effective dose is ~150 U and that exposure to higher doses needs to be weighed against potential tolerability risk .75U group did not show statistically significant separation from placebo. Excluding patients that received the optional injection to the masseter muscle, the mean dose administered in study 191622-038 was 190 U. In order to provide optimal treatment benefit while minimizing safety risks, the Botox dose that should be confirmed in the phase 3 studies fell within the range of > 150 U and < 200 U.

All of these factors were considered when deciding that the required minimum dose of 155 U per injection cycle should be given via a FSFD paradigm divided in 31 injection sites across 7 specific head and neck muscles. The maximum dose of 195 U per injection cycle could be given using the FSFD paradigm combined with an optional FTP paradigm, which would allow for an additional 40 U across 8 injection sites in 3 specific muscle groups (temporalis, occipitalis and trapezius). Allergan concludes that provide optimal treatment benefit while minimizing safety risks is achieved with

1. a dose range of > 150 U and < 200 U
2. a standard dilution resulting in 0.1 mL = 5 U,
3. FSFD paradigm divided in 31 injection sites across 7 specific head and neck muscles.
4. FSFD paradigm combined with an optional FTP paradigm, for the maximum dose of 195 U per injection cycle could be given using allowing for an additional 40 U across 8 injection sites in 3 specific muscle groups (temporalis, occipitalis and trapezius).

RMS assessment of Applicant's response:

The injection sites are intended to adequately perfuse the trigeminal/cervical nerve endings. Anatomical variation, variability in innervation density of the facial/scalp/upper back area, injection technique could all contribute to inter and intra individual variability in response to treatment.
The treatment paradigm is still quite experimental. It is unclear whether it supports optimal efficacy.
It has however been determined using known safety data to reduce the sites and number and dose of injections and appears to be well tolerated. To that end it can be supported.

Question 5 (Definition of headache episode)

Clarification regarding the definition of a headache episode should be provided. Although duration of the episodes was recorded by patients no criteria were specified relating to the necessary interval to determine when one episode ended and the next started.

Summary of applicant's response:

A headache episode in the phase 3 studies was defined as patient-reported headache pain with a start and/or stop time recorded in the electronic diary indicating that the pain lasted at least 4 continuous hours (Module 2.7.3, Table 2.7.3.3-1). All contiguously adjacent and/or overlapping headaches were merged into one headache episode. No interval between stop and start of consecutive headaches was required.

RMS assessment of applicant's response:

This point is clarified.

Question 6 (Potential confounding effect resulting in enhanced sense of well being)

The muscle relaxant effect may have had an ancillary cosmetic effect. There is a significant psychological and psychosocial dimension to chronic migraine, which is difficult to quantify and which undoubtedly contributes to morbidity. The majority of participants were white females over 40 with slightly increased Body Mass Index (BMI). This is very similar to the populations that were studied to establish the cosmetic effect of Botox. (Mean age of patients in studies supporting indication for use glabellar lines was 46). Treatment of frown lines in adults has been linked with the psychological impact for patients (SPC Vistabel). The possibility that the group treated with Botox had an enhanced sense of wellbeing from the cosmetic effect of Botox that impacted on the clinical outcomes for chronic migraine in this study cannot be ruled out.

Summary of applicant's response:

There was an extremely low incidence of reports of possible aesthetic benefit among the 1384 total patients enrolled in the BOTOX phase 3 studies. Subgroup analyses demonstrated that there was not an exaggerated efficacy response in patients ≥ 40 years of age (i.e., those who were most likely to have had wrinkles) compared to patients who were < 40 years of age (and less likely to have wrinkles),

Differences between the injection paradigm for the chronic migraine indication to the injection paradigm for glabellar lines, relating to the total Botox dose administered, number of injection sites, and injection site location makes it unlikely that evidence that possible cosmetic effects of BOTOX impacted on the clinical outcomes for chronic migraine in the phase 3 studies. The severity of the symptoms of chronic migraine and the significant disability and overall adverse impact of the disorder on the individual, According to AMPP study data, 1 in 5 of those with chronic migraine are unable to work due to the severity of their condition (Buse et al, 2010) and nearly 40% of those with chronic migraine miss at least 5 days family activities over the previous 3 months (Bigal et al, 2008). Any aesthetic effects could not possibly override the sense of well-being in this population.

RMS assessment of Applicant's response:

The RMS fully accepts that the level of suffering and substantial burden that those with chronic migraine suffer from on a daily basis could not be fully relieved by an improved sense of wellbeing associated with an aesthetic effect. The difference in treatment effect between active and placebo is small. All potentially confounding effects of the known pharmacological action of Botox need to be considered.

This point is considered resolved.

Question 7 (Anti-nociceptive mechanism of action)

The pathophysiology of chronic migraine is not well understood. There is no clear evidence of an

anti-nociceptive effect for Botox or clear evidence of the effect of Botox in the pathophysiology of chronic migraine. This is problematic as the dosing and treatment paradigms are based on this putative mechanism of action (adequacy of dose and number of sites of injection to adequately perfuse trigeminal nerve endings). Further evidence clarifying the mechanism of action Botox in the amelioration of chronic migraine headache should be provided

Summary of Applicant's response:

The applicant disagrees that there is no clear evidence of an anti-nociceptive effect for Botox and refer the reviewer to several publications including a review of the proposed mechanism for the antinociceptive action of Botulinum toxin type A (Aoki, 2005), as well as clinical pharmacology studies that have evaluated BOTOX anti-nociceptive effects in blocking central sensitization (Gazerani et al, 2006; Gazerani et al, 2009).
It is in general accepted that with migraine there is dysfunction of the trigeminal nerve and its central connections that normally modulate sensory input (Silberstein et al, 2008b). Recent work suggests several mechanisms that could contribute to chronic migraine including "(1) increased peripheral nociceptive activation (perhaps due to chronic neurogenic inflammation) and activation of silent nociceptors; (2) peripheral sensitization; (3) altered sensory neuron excitability due to changes in ion-channel expression/phosphorylation/ accumulation in primary
afferents; (4) central sensitization of the trigeminal nucleus caudalis neurons due to posttranslational changes in ligand-and voltage-gated ion-channel kinetics, altering excitability and strength of their synaptic inputs; (5) phenotype modulation due to alternations in the expression
of receptors/transmitters/ion channels in peripheral and central neurons; (6) synaptic reorganization modification of synaptic connections caused by cell death or sprouting; (7) the clinical development program overall focused on evaluating a dose and treatment paradigm with muscles that aligned with the distribution for input to the trigeminal sensory neurons, which are believed to be the target end-organ for BOTOX in treating migraine.

However, it is important to note that the phase 3 dosing paradigm was determined after careful examination of both efficacy and safety data generated from the two phase 2 clinical studies. So while the hypothesis for ascertaining the target end-organ for treatment of chronic migraine was derived from pre-clinical and clinical pharmacology studies, the evidence supporting BOTOX effectiveness, regardless of whether the mechanism of action has been established or not, has came from clinical evidence in patients with chronic migraine

RMS assessment of Applicant's response:

The two publication s by Gazerani (2006 and 2009) referred to in the application were reported by the applicant to provide support for the anti-nociceptive effect of Botox in chronic migraine. The first study looked at the impact of i.m Botox on capsaicin-evoked pain and neurogenic vasodilatation following injection into the forehead (human model for trigeminal nerve sensitization). A significant suppressive effect of BoNT-A on pain, flare and hyperalgesia area was observed .The second study looked at the effect of subcutaneous administration of Botox on a similar model of trigeminal nerve sensitisation. This study also demonstrated a reduction in the Botox treated group in pain sensitisation. Other studies Blersch (2002) and Voller (2003) found no direct peripheral anti-nociceptive effect of Botulinum toxin in humans following intradermal injection of Dysport and Botox respectively. The analgesic effect of Botox appears to vary depending on the toxin type, the site and route of administration. The evidence in support of an anti-nociceptive effect following intramuscular administration of Botox is limited and requires further evaluation.
The mechanism of action of an effective therapeutic agent is not always known but in these situations a clear treatment effect sustained over the clinical development plan is usually apparent. Anatomical variation and variation in density of nerve endings and peripheral sites of nerve activation may result in

variability of response between treatments. From the proposed treatment model it is unclear how Botox will effectively target all possible nerve afferents. There has been no discussion of the effect of intramuscular vs. intradermal administration of Botox or the potential impact of the well-described pharmacologic effect of Botox of change in muscle tone on peripheral sites of activation. The mechanism of action has been comprehensively reviewed in the preclinical review of this application. The conclusion of the preclinical assessor based on the evaluation of the preclinical models presented by the applicant is 'that BoNT/A has not been clearly demonstrated to have the ability to prophylactically treat headaches associated with chronic migraine however it is considered reasonable to assume that BoNT/A may have a role to play in the reduction in the severity of pain perceived during headaches as well as preventing/ reducing the progression and prolongation of headaches.'

III.3.2 Questions from Denmark

Request for Supplementary Information as proposed by CMS Denmark

POINTS FOR CONSIDERATION

Question 1a (BOTOX dose)

Of particular concern is the uncertainty about the mechanism of action of Botox in chronic migraine prophylaxis. It is proposed that Botox suppresses directly the peripheral and indirectly the central sensitization involved in migraine. The results of studies with three rat models are presented in support of the hypothesis concerning involvement of Botox in peripheral sensitization. In support of Botox suppression of central sensitization, decreased Fos-like immunoreactivity in the spinal cord following treatment with Botox in another experimental model is mentioned.

1a) How do Botox doses used in experimental studies compare to the doses used in the clinical trials?

The Botox doses used in the experimental studies were 3.5, 7, and 15 U/kg. The human dose of 155 U to 195 U when normalized to a 70 kg person (which was the median weight of the patients evaluated in the Botox phase 3 chronic migraine studies) would be approximately 2.2-2.8 U/kg. However, the range of weights of the patients in these studies was broad with the minimum weight of 39.9 kg and a maximum weight of 195 kg (Module 5.3.5.3, ISE Table 1-2).Thus, the dose normalized to the minimum and maximum weight limits observed in these studies ranged from 0.8 U/kg – 4.9 U/kg of exposure. The lowest dose used in the experimental animal studies is within the range of the dose received by patients in the phase 3 studies. There have been 2 human volunteer experimental studies evaluating the effects of Botox using a capsaicin-evoked pain model (Gazerani et al, 2006; Gazerani et al, 2009). The IM dose and injection paradigm used in one of these studies is similar to the dose and injection paradigm evaluated in the phase 3 studies. The second study evaluated subcutaneous dosing of Botox, and is therefore not applicable to this program.

Table 12 Muscle Groups Injected in Gazerani Experimental Human Studies and the

Botox Phase 3 Chronic Migraine Studies 191622-079 and 191622-080

Muscle Area	Phase 3 Studies 191622-079 and 191622-080 FSFD for minimum IM dose. Variable dose and injection sites for some muscle groups as FTP		Gazerani et al, 2006 FSFD for minimum IM dose
	Total FSFD required	Total FTP dose allowed	Total FSFD required
Frontalis	20 U	0	20 U
Corrugator	10 U	0	10 U
Procerus	5 U	0	
Occipitalis	30 U	0, 5U or 10U	20 U
Temporalis	40 U	0, 5U or 10U	20 U
Trapezius	30 U	0, 5U, 10U, 15U or 20U	40 U
Cervical Paraspinal injected base of skull	20 U	0	
Semispinalis injected mid-neck	NA	NA	20 U
Splenius capitis injected mid-neck	NA	NA	20 U
Masseter	NA	NA	
Sub-Total	155 U	0 to 40 U	
TOTAL	**155 U to 195 U**		**150 U**

IM = intramuscular; NA = not applicable; U = units

Allergan agrees with the clinical reviewer's suggestion to revise the information about the mechanism of action of Botox to now read: "Botox blocks the release of neurotransmitters associated with the genesis of pain. The mechanism of action of Botox in headache prophylaxis is unclear. Pre-clinical and clinical pharmacodynamic studies suggest that Botox suppresses peripheral sensitization, thereby possibly also inhibiting central sensitization" (see the section below titled

RMS assessment of applicant's response:

The RMS agrees with the proposed changes. See RMS preclinical comments on mechanism of action.

Question 1b (Significance of neuronal reactivity in the spinal cord)

1b) What is the significance of changes in neuronal reactivity in the spinal cord for the pathophysiological mechanisms of central sensitization in the trigeminal system in migraine?

Summary of applicant's response
The changes in spinal reactivity as indexed by c-Fos protein distribution, noted in Cui et al, 2002, correlate to changes in the peripheral afferent C-nociceptor neuronal activity. Our working hypothesis of a peripheral inhibitory action of BoNT/A on C-nociceptor afferent terminals extends to chronic migraine as well.

RMS assessment
See preclinical review.

Question 2 (Explain lack of effect in episodic migraine)

Although significant analgesic effect of Botox in human volunteers was shown in a paradigm relevant to peripheral sensitization in migraine (Gazerani et al, 2006), similar studies have failed to demonstrate efficacy of Botox. No effort has been made to identify development of cutaneous allodynia in the clinical trials.
Given that peripheral and central sensitization are involved in the pathogenesis of not only chronic but also episodic migraine, how can the lack of efficacy of Botox in episodic migraine be explained in relation to these mechanisms?

Summary of applicant's response

The applicant discusses allodynia in the context of chronic migraine disorder. Primarily they hypothesise that that Botox may help to reduce allodynia that is associated with chronic migraine disorder. Allodynia was not evaluated in the clinical development plan due to the lack of a reliable easy to administer validated method of assessing allodynia other than quantitative sensory testing (QST) as it was considered to be impractical. An exploratory study in 14 patients with mostly episodic migraine concluded that there was no relationship between response to Botox and presence of allodynia. This was further explored in the phase 2 **episodic migraine** study 191622-037 Botox. Efficacy in patients with and without baseline allodynia was obtained using a simple (non-validated) questionnaire.
The conclusion of this study was that for placebo non-responders and placebo responders, there were no statistically significant differences between treatment groups in the changes from baseline in the number of migraine headaches per 30-day period (the primary efficacy measure) for patients with or without allodynia at baseline. Within the placebo non-responder and placebo responder strata, the mean changes from baseline were similar for patients with or without allodynia.
Analyses of the 2 secondary efficacy variables also were performed with and without allodynia at baseline for placebo non-responders and placebo responders. In the analyses of the proportion of patients with a decrease from baseline of 2 or more migraines per 30-day period, for the responder stratum patients with allodynia the treatment groups differed significantly favouring Botox treatment at Day 30 (Botox 85.0% [17/20], placebo 52.6% [10/19]; p = 0.029) and at Day 210 (Botox 100.0% [16/16], placebo 71.4% [10/14]; p = 0.037).

Allodynia was not explored in the phase 2 chronic migraine studies since most patients had already been enrolled into those studies at the time that the allodynia headache associated symptom questionnaire was developed; essentially it was too late to amend the protocols for those studies to collect this baseline information as there would have been an insufficient number of patients for any meaningful exploratory analysis. At the time that the phase 3 studies were designed and agreed with regulatory authorities, there still was no validated, practical, allodynia assessment tool that could be used in large, multicenter, multinational phase 3 studies and therefore no evaluation of allodynia was made in these studies.

The pathophysiology of chronic migraine is not fully understood but it is known to be a disorder of cortical hyperexcitability, brainstem pain modulating centres, and sensitisation of sensory trigeminal neurons. In contrast to episodic migraine, chronic migraine has been shown to involve persistent alterations in function including sensitisation (peripheral and central) of trigeminal pathways and enhanced excitability of the central nervous system, in addition to reversible alterations in brain structure (Aurora, 2009; Pietrobon, 2005; Goadsby, 2002; Obermann et al, 2009).The applicant outlines hypotheses for peripheral sensitisation and central sensitisation and indicates that central sensitisation is likely to play a key role in maintaining the prolonged pain of chronic migraine headache, as well as the pain referral patterns in the distribution of the first division of the trigeminal nerve and the upper cervical afferents (Dodick and Silberstein, 2006).

Presumed Mechanism of Action of Botox in Chronic Migraine

The presumed mechanism of action of Botox as described by Aoki (primary culture and animal model data) at the periphery involves the interruption of the cascade of events that results in peripheral and central sensitisation in migraine. This anti-nociceptive effect of Botulinum toxin type A is separate from its neuromuscular activity. This suppression of central sensitisation after the injection in the periorbital skin has been demonstrated in human models (Gazerani et al, 2006; Gazerani et al, 2009). A number of possible reasons why there appears to be a lack of efficacy of Botox in episodic migraine compared to chronic migraine are proposed by the applicant.

• A different underlying, but not yet fully recognized, pathophysiology that distinguishes these two disorders.
• The prevalence and severity of allodynia is significantly higher in patients with chronic migraine (≥ 15 headache days per month) compared to those with episodic migraine (< 15 headache days/month) (Bigal et al, 2008a); therefore, it makes sense that BOTOX may have greater efficacy in the population of patients with a more predominant component of allodynia.

• Allergan patient selection criteria were not optimal. Patient phase 2 studies in episodic migraine may have failed because the patients who could have had co-morbid depression were not restricted from enrolment; untreated depression may have confounded study results. In addition, in studies 191622-005, 191622-009, 191622-024, 191622-026, 191622-036 the protocols baseline frequency of migraine episodes criteria was < 8 migraine episodes, which meant that patients may not have had sufficiently frequent migraine to respond to Botox effect in blocking central sensitization.

• Phase 2 studies in episodic migraine may have failed because the dosage and treatment paradigm evaluated in these exploratory studies were not optimal. Doses evaluated In five of the seven phases 2 studies were ≤ 75 U; three studies evaluated a single treatment cycle, three studies evaluated a repeat dosing interval of 16 weeks (instead of 12 weeks, which is the recommended retreatment interval based on the phase 3 studies), five studies administered injections only into muscles in the front of the head with no posterior injections, which may not be the optimal injection paradigm. days per month), and recent data indicate that the disability associated with chronic migraine is significantly greater than disability of those with episodic migraine (Buse et al, 2010).

RMS assessment of Applicant's response;

There is scant data in the literature regarding the prevalence of allodynia in chronic migraine. However studies by Sorbino (2003) and Askenashi (2010) have indicated that 40- 60% of patients with CM report allodynia **.** As allodynia is common in CM and, unlike in EM, does not appear to be affected by the occurrence of an acute headache exacerbation it is a plausible link between chronically sensitized central trigeminovascular neurons and patients experiencing migraine headache >15 days per month. It would have been useful to measure the baseline rate of allodynia and the subsequent impact of Botox at week 24. Further clarification of the pathophysiology underpinning episodic and chronic migraine is required to clarify the lack of efficacy in episodic migraine.

Question 3 (Response characteristics)
There is evidence of different headache characteristics (imploding versus exploding headache) in responders, respectively non-responders, to Botox in migraine prophylaxis (Jakubowski et al, 2006). No effort has been made to identify such response characteristics in the clinical trials.

Summary of applicant's response

The applicant summarises the results from the Jakubowski paper that explores the imploding/exploding headache theory. It was intended to try and identify clinical features that could predict response to Botox treatment in patients with migraine. Thus, Dr. Burstein's preliminary work in a selected sample of 59 migraine patients who were selected based on their response to Botox (responders having ≥ 75% improvement from baseline and non-responders having no change from baseline) suggested that the quality of pain in these populations is different and possibly a different underlying pathophysiological mechanism exists in migraine patients who respond versus those that don't respond at the ≥ 75% level to Botox treatment. In the report by Jakubowski et al (2006), results from two small studies involving 63 migraine patients (34 with episodic migraine [mean frequency before Botox treatment of 6.2 ± 0.7 migraine days] and 29 with chronic migraine [mean frequency before Botox treatment of 23.6 ± 1.9 migraine days]) are reported.
These were patients who prospectively were evaluated and then treated with Botox and based on their response to Botox were included in the study. Data for the 63 responders/non-responders in these studies were combined. There was no significant difference in baseline characteristics or migraine symptoms between Botox responders and Botox nonresponders, with the one exception being the way that these two groups of patients described the directionality of their headache.

Table 13 Frequency of migraine days and response status for patients evaluated in the Jakubowski (2006) study

Type of Headache	N	Responders	Non-Responders
Exploding headache	27	5 (19%)	21 (81%)
Imploding headache	31	29 (94%)	2 (6%)
Ocular headache	5	5 (100%)	0

Source: Table 2 in Jakubowski et al, 2006

The Applicant tried to develop and validate a questionnaire that could be used to practically to ascertain the headache directionality for individual patients. This was not practical as it was not accurate and difficult to implement in practice .Use of the concepts introduced by this theory have not been widely adopted or explored by the clinical community.
The applicant concludes that the imploding/exploding theory is still unproven. It has been developed by evaluating patients with extreme responsiveness to a Botox dose and treatment paradigm that has not been proven to be effective. The theory was developed and the subsequent limited further testing of this hypothesis has occurred predominantly in patients with episodic migraine (< 15 headache days per month) and not in the more complex population of patients with chronic migraine (≥ 15 headache days per month).

RMS assessment of applicant's response;

The imploding /exploding theory is interesting but as discussed by the applicant remains unproven. We agree that it would be difficult to implement in practice.

Product Information (SPC section 5.1)

The uncertainty about the mechanism of action of Botox should more clearly be reflected in the text. The following section: "BOTOX blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by preclinical and clinical pharmacodynamic studies" could be replaced by:

"Botox blocks the release of neurotransmitters associated with the genesis of pain. The mechanism of action of BOTOX in headache prophylaxis is unclear. Pre-clinical and clinical pharmacodynamic studies suggest that BOTOX suppresses peripheral sensitization, thereby possibly also inhibiting central sensitization."

Summary of applicant's response:

Allergan agrees to amend the SPC as suggested.

RMS Assessment of Applicant's response:

This proposed wording is acceptable.

III.3.3 Questions from Greece

Request for Supplementary Information as proposed by CMS Greece

Assessors Comments:
The putative mechanism of pharmacological action of BOTOX supporting its prophylactic effect on a complex pathophysiology such as in CM is attributed to blockage of pain signal transmission. Following review of the product's safety profile (clinical safety) for phase II (studies 191622038 and 191622039) and pivotal phase III studies, a steadily higher incidence of distinct AEs-eyelid ptosis, muscular weakness, and less frequently dysphagia and dyspnoea- was observed in patients without pre-existing neuromuscular disorders, compared to placebo. These findings are commonly reported in myasthenic syndromes, as evidenced by scientific literature and clinical practice. In the context of BOTOX safety information/data, these events have also been recorded for most of the product's approved indications. However, the mechanism for the claimed prophylactic effect on CM employs a different pharmacological path. In light of the above, the following issues should be considered:

Question 1a (Long-term Effects-Symptom Progression)

Have patients reported with these conditions been followed up for possible long term effects -symptom progression? If this would be the case, it might be useful to include lab tests for detection of MG (Myasthenia Gravis) auto antibodies in patient sera.

Summary of applicant's response:

Patients who reported eyelid ptosis, muscular weakness, dysphagia or dyspnoea were followed until resolution of the adverse event (AE) or for the duration of the study, which in the case of the phase 3 studies was as long as 56 weeks. Beyond the study period, patients were not followed for possible AE long term effects or symptom progression. If the investigator had suspected or witnessed symptom progression suggesting an unmasking of Myasthenia Gravis, then they were obligated to follow up on the AE until resolution; there were no such instances for this development program.
While we appreciate that some symptoms may overlap with those seen in myasthenic syndrome, the symptoms of ptosis, muscular weakness, dyspnoea and dysphagia are due to local spread of toxin in or adjacent to the sites of injection. We observed that the resolution for these AEs followed a time pattern and pharmacologic effect that is consistent with the known mechanism of action of Botox in relaxing muscles. Allergan does not feel that it would be useful to systematically evaluate lab tests for detection of MG auto antibodies in patient sera. At the treating physician's discretion, it may be appropriate to order this or other lab tests if these symptoms follow a pattern that is consistent with MG since such a change in the AE manifestation would not be expected after Botox treatment due to the sustained pharmacologic effect.

RMS assessment of Applicant's response:

We agree with the conclusion of the applicant.

Question 1b (Data on parallel inhibitory effect on ACh release in pain models)

Are there any findings that correlate Botox action on CM prophylaxis with parallel inhibitory effect on ACh release. If observed, such an action would compromise Botox efficacy on CM management.

Summary of Applicant's Response:

We are not aware of any specific data that provide this correlation. However, the local muscle relaxation effect of Botox is an expected effect. Whether this local muscle relaxation contributes to clinical efficacy in chronic migraine or not remains to be fully determined. Thus, we would not expect that the inhibitory effect on ACh release would compromise Botox efficacy on management of chronic migraine.

RMS assessment of Applicant's response:

The possible contribution of local muscle relaxation effect to clinical efficacy in chronic migraine has not been discussed in this application.

Question 2 (Hypertension considered in phase 3 patient selection)

Literature data (Barbanti et al., 2010) report that Hypertension has been identified as a risk factor for migraine chronification.
Has this factor been identified in patient selection criteria during Phase III study design?

Summary of Applicant's response:

Thank you for bringing this 2010 publication to our attention. As this publication is sharing new information presented after the phase 3 studies were completed, this risk factor was not identified in patient selection criteria during the phase 3 study design. Data on patients with a medical

history of hypertension was captured and submitted in the dossier. A total of 8.8% of the patients enrolled into the phase 3 studies reported a medical history of hypertension (Module 5.3.5.3, ISS Table 1-5.1), which is lower than what has been reported in the migraine epidemiological literature whereby 33.7% of persons with chronic migraine and 27.9% of persons with episodic migraine have reported having "high blood pressure" (Buse et al, 2010).

RMS comment:

The RMS agrees with the conclusion of the Applicant. This point is considered resolved.

Question 3 (Association of females and migraine ADR)
Is there any association between overrepresentation of female population in the CM studies with the newly identified treatment-related ADR "migraine"?

Allergan Response
Allergan does not believe there is over-representation of females in the CM studies and there is no association between gender and 'migraine' as an adverse event. In the phase 3 CM studies, females comprised 86.4% of the population. This ratio correlates with the AMPP study, the largest population-based study of migraine sufferers, where approximately 79% of those with chronic migraine were female (Buse et al, 2010). In these studies, the frequency of 'migraine' as an adverse event was similar between females (3.6%) and males (4.8%), as was 'headache' (4.5% vs. 5.0%, respectively).

RMS comment
This point is considered resolved.

III.3.4 Request for Supplementary Information as proposed by CMS Norway

POINTS FOR CONSIDERATION

Assessors Comments:
The Allergan criteria for chronic migraine are **not** similar to those of the International Classification of Headache Disorders (ICHD) II1 or ICHD IIR2:
1. Both types of migraine were included and not only migraine without aura
2. The use of the term probable migraine days opens for inclusion of attacks that are "not migrainous" but will be classified as such
3. Patients with medication-overuse are not excluded

Question 1a (Efficacy in migraine without aura and migraine with aura)

The inclusion of both migraine without aura and migraine with aura is similar to many previous clinical trials on migraine. However, it would be interesting to know whether the efficacy is similar in migraine without aura and migraine with aura.

Summary of Allergan response:

Data on whether patients had migraine without aura or migraine with aura was not collected in the studies. There is no evidence to suggest that efficacy would be different in these types of migraine. Most patients with migraine have exclusively attacks without aura. Many patients who have frequent attacks with aura also have attacks without aura (Olesen et al, 2004). Typical aura consists of visual, sensory and/or speech symptoms that have a gradual development of usually less than 1 hour prior to onset of headache

symptoms that meet criteria for migraine without aura (Russell and Olesen, 1996; Olesen et al, 2004). It is Allergan's understanding from consultation with clinical experts, including Richard Lipton, MD, member of the IHS Headache Classification Committee and Chair of the ICHD-II Migraine Section, that requirement B in the revised chronic migraine diagnostic criteria whereby patients must have had at least five lifetime attacks that fulfil criteria for ICHD-II 1.1 Migraine without aura is *inclusionary* and not intended to be *exclusionary* for patients who may also meet criteria for ICHD-II 1.2 Migraine with aura (personal communication with R. Lipton, December 2010).

RMS assessment of Applicant's response:

Ashkenazi et al (2007) reported that allodynia in patients with CM was positively associated with a history of migraine aura. Evaluation of treatment response in chronic migraineurs who had migraine with aura would have been interesting in terms of exploring the link between the treatment effect of Botox and an effect on the pathophysiology of the pain process associated with chronic migraine.

Question 1b (Probable migraine days)

The second criterion above is weak and may lead to misclassification of chronic migraine, thus, increasing the patient population of "Allergan defined chronic migraine".

Summary of Applicant's response:
Allergan believes that there may be a misunderstanding as to the terminology "probable migraine". By definition in the protocol, a probable migraine day was defined as a day (00:00 to 23:59) with 4 or more continuous hours of probable migraine headache that met ICHD-2criteria 1.6 for *Probable Migraine* (an ICHD terminology, not Allergan's terminology) (Olesen et al, 2004). Previously used terms for this disorder were "Migrainous disorder". Essentially, these are headache attacks that are missing one of the features that would be needed to fulfil all of the diagnostic criteria for a migraine headache as per ICHD 1.1 and 1.2. In the definition for a migraine headache it must have at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) AND at least one of the following: nausea and/or vomiting, photophobia and phonophobia. Because patients take acute treatments to abort migraine events, the headache may not reach its' full manifestation and demonstrate ALL of the required characteristics and symptoms. For instance, if the pain intensity never reaches moderate or severe pain because the patient took an acute treatment, then this criteria is not fulfilled, even though the event was likely a migraine attack. The revised ICHD-2R criteria (Olesen et al, 2006a) included a similar aspect in that patients had to have 8 or more days per month of migraine that fulfilled the ICHD-2 1.1 criteria OR treated and relieved by triptan or ergot before the expected development of meeting two of the required characteristics, as described above. The Botox phase 3 study criteria are more restrictive than the current ICHD-2R criteria since we required at least 50% of the baseline number of headache days to fulfil criteria a "migraine" or "probable migraine" whereas the current criteria only require 8 of the baseline number of headache days to fulfil such criteria. Thus, in our studies where the baseline mean frequency of headache days was 19.9 (± 3.68), the mean frequency of migraine days was 16.4 (± 5.76) and the mean frequency of migraine/probable migraine days was 19.0 (± 4.02) (Module 5.3.5.3, ISE Table 1-3), thereby exceeding the specified criteria of only 8 migraine days or days when headache was relieved by triptan or ergot per the ICHD-2R criteria.

RMS assessment of Applicant's response:
Inclusion of patients with probable migraine potentially could increase the number of patients classified as CM. This was noted by Zeeberg et al when they field tested the ICHD revised criteria for CM and compared their results to an American study (Bigal et al) where patients with migraine or probable

migraine were allowed to fulfil the IHS criteria for headache. In the American study 94.9% of TM patients without medication overuse were classified as CM whereas only 7% of headache population at the Danish headache tertiary referral centre fulfilled the criteria for CM as per ICHD2R. All of the patients in the Danish population may not have had TM and are therefore not directly comparable to the American population but in the opinions of the authors the main reason for the discrepancy in the findings between the two studies was the inclusion of patients with migraine and probable migraine in the American study.

Question 1c (Inclusion of patients with medication overuse at baseline)
The inclusion of patients with medication-overuse is, in our opinion, a flaw of the phase 3 clinical studies. Again this deviation in relation to ICHD II and ICHD IIR increases the patient population when using the "Allergan defined chronic migraine".

Allergan Response
Patients with medication overuse were enrolled into the phase 3 studies and stratified to treatment in accordance with the IHS clinical trials subcommittee guidelines for controlled trials of prophylactic treatment of chronic migraine in adult (Silberstein 2008a). These guidelines reflect the high prevalence of acute medication use in chronic migraine patients, and recommend the inclusion of these patients in clinical studies.
When looking at demographic features and disease characteristics between the MedO-yes and MedO-no subgroups of the phase 3 studies, there were no notable between-group differences observed for any of the parameters (other than acute headache pain medication overuse or not), suggesting that these 2 subgroups were more homogeneous than heterogeneous and that medication overuse did not overly confounded the results of these studies .To validate the alignment of the phase 3 study population with patients who will be diagnosed as having chronic migraine per the ICHD-2R criteria, Allergan supported or performed analyses within 3 independent datasets to characterize and compare the population meeting ICHD-2R chronic migraine diagnostic criteria to the phase 3 clinical study population with regard to demographics and headache characteristics. Results from these analyses are discussed in Allergan Response to Question 1, Section A. Potential Confounding Factors: Heterogeneity of the Study Population. The results of these analyses demonstrate that based on multiple evaluations within robust datasets, the chronic migraine population evaluated in the phase 3 clinical studies is representative of the target population of patients with chronic migraine as currently defined by ICHD-2R who would be receiving BOTOX for the treatment of chronic migraine. Inclusion of patients with and without acute headache pain medication overuse did not confound the results from the phase 3 studies as the data consistently showed statistically significant improvements from baseline across multiple headache symptom measures in both subgroups.

See RMS comment on Allergan Response to Question 1, Section A. Potential Confounding Factors: Heterogeneity of the Study Population Efficacy .

Question 1d (Chronic Migraine definition alignment)

The Allergan studies included both types of migraine and not only migraine without aura and all types of chronic headache (≥ 15 day/month) with or without medication-overuse headache. Thus, Allergan's definition of chronic migraine deviate from the definition of chronic migraine by the ICHD as it is much broader and less well defined. Since Allergan has data on all patients participating in the trials, some are presented on page 45 in the RMS's assessment report; it should be possible to reclassify the patients according to the ICHD IIR.

Summary of Applicant's response:

To demonstrate that the Botox phase 3 study population is representative of patients who will be diagnosed with chronic migraine, we have compared the population meeting current ICHD-2R diagnostic criteria together with the IHS trial guideline criteria to the phase 3 study population with regard to demographic and headache characteristics (see Allergan Response to Question 1, Section A. Potential Confounding Factors: Heterogeneity of the Study Population). The differences between the population identified by the phase 3 study criteria and the ICHD-2R and IHS criteria are minor in our view, and the results provide strong evidence that the chronic migraine population evaluated in the phase 3 clinical studies is representative of the target population of chronic migraine patients who would be receiving Botox for the treatment of chronic migraine.

Regarding the two above mentioned deviations from the ICHD-2R, the inclusion and stratification of patients who were overusing medications at baseline is in alignment with the guidelines for controlled trials of prophylactic treatment of chronic migraine in adults published by the Task Force of the IHS for Clinical Trials Subcommittee (Silberstein et al, 2008a). The guidelines recommend that subjects meeting the revised criteria for medication overuse headache be included in prophylactic trials for chronic migraine; however, these must be stratified accordingly.

The second deviation refers to the lack of distinguishing between the number of migraine attacks without aura per ICHD-2R criterion B and C. Since a migraine is considered a migraine regardless if aura is present, the phase 3 screening period confirmed that migraine attacks met the symptoms described in ICHD-2R criterion C1 and/or C2. The ICHD-2R criterion C1 defines the exact pain and associated symptoms that must be met, and/or the headache has been treated and relived by triptan(s) or ergot before the expected development of C1 criteria. The ICHD-2R diagnostic criteria for chronic migraine were not available at the time that the Allergan phase 3 studies were initiated. Per discussions with clinical experts, Allergan did not distinguish migraine as with or without aura in the study inclusion criteria since physicians do not make decisions about whether to use headache prophylaxis treatments based on whether the patient has migraine with aura or migraine without aura, and many chronic migraine patients have some attacks with aura have other attacks without aura. From a clinical perspective if the patient is suffering from frequent migraine attacks (with or without aura) and they have significant morbidity from these attacks, clinicians will desire to prescribe prophylaxis treatment to alleviate their suffering. The assessor has requested analyses of the data for the two subgroups. As mentioned, we did not collect data pertaining to aura, and thus cannot provide the requested analyses. We did prospectively stratify patients according to medication overuse and have included a summary of those analyses herein (see Table 14 below).

Table 14 Least Square Mean Changes from Baseline, Between-Group Differences, and 95% Confidence Intervals at Week 24 for Frequency of Headache Days and Headache Episodes by Overuse of Acute Headache Pain Medications at Baseline

	Headache Days						Headache Episodes					
	Yes			No			Yes			No		
	BOTOX	Placebo	Difference [a]	BOTOX	Placebo	Difference [a]	BOTOX	Placebo	Difference [a]	BOTOX	Placebo	Difference [a]
Study 191622-079	**N = 226** **-7.8** **(-8.63, -6.96)**	**N = 235** **-6.5** **(-7.37, -5.65)**	**-1.3** **(-2.55, -0.15)**	N = 115 -7.9 (-9.13, -6.61)	N = 103 -6.2 (-7.55, -4.96)	-1.7 (-3.48, 0.16)	N = 226 -5.7 (-6.13, -4.68)	N = 235 -5.5 (-6.58, -5.13)	-0.2 (-1.09, -0.73)	N = 115 -4.7 (-5.52, -3.82)	N = 103 -3.8 (-5.05, -2.70)	-0.9 (-2.21, 0.51)
Study 191622-080	**N = 219** **-8.6** **(-9.42, -7.72)**	**N = 224** **-5.9** **(-6.73, -5.03)**	**-2.7** **(-3.89, -1.48)**	N = 128 -9.7 (-10.36, -8.54)	N = 134 -8.1 (-9.24, -6.94)	-1.6 (-3.22, 0.06)	**N = 219** **-6.5** **(-6.07, -4.62)**	**N = 224** **-4.2** **(-4.98, -3.67)**	**-1.8** **(-2.18, -0.40)**	N = 128 -5.4 (-5.98, -4.44)	N = 134 -4.9 (-5.88, -4.34)	-0.5 (-1.42, 0.46)
Pooled Phase 3 Studies	**N = 445** **-8.2** **(-8.77, -7.58)**	**N = 459** **-6.2** **(-6.81, -5.60)**	**-2.0** **(-2.84, -1.13)**	**N = 243** **-8.8** **(-9.69, -7.98)**	**N = 237** **-7.3** **(-8.16, -6.43)**	**-1.6** **(-2.78, -0.34)**	**N = 445** **-5.6** **(-5.89, -4.86)**	**N = 459** **-4.9** **(-5.60, -4.62)**	**-0.7** **(-1.35, -0.08)**	N = 243 -5.1 (-5.52, -4.38)	N = 237 -4.5 (-5.25, -3.90)	-0.6 (-1.40, 0.21)

Results in bold denote statistically significant differences (ie, $p \leq 0.05$) favouring BOTOX for between-treatment comparisons (BOTOX vs. placebo) from covariate analysis of variance. Statistical significance is based on least-squares means. Headache days and episodes are calculated over a 28-day period.

[a] The between-treatment difference is calculated for BOTOX minus Placebo groups, for least-squares means.

Source: Appendix 1, Tables 1-147, 1-148, 1-149, 1-150, 1-151, 1-152

The applicant discusses the role of MO in patients with chronic migraine referring to the number of different theories regarding the relationship between medication overuse and chronic migraine. Because MedO is common among patients with chronic migraine, patients were allowed to be enrolled into the phase 3 studies, since this population is representative of patients seen in the community. Thus, chronic migraine patients with and without medication overuse were enrolled and stratified in accordance with IHS guidelines (Silberstein et al, 2008a).The applicant provides an overview of Medication Overuse Subgroup and Medication Non-Overuse Subgroup. This data has been summarised and discussed as part of question Allergan Response to Question 1 raised by RMS, and will not be further summarized here.

See RMS comment on question III.3.1 section A and B.

Question 2 (Epidemiology of chronic migraine):

The Allergan defined prevalence of chronic migraine is up to 3-4% of the general population, while the broad ICHD IIR allowing for medication-overuse is 0.2% of the general population. The applicant should comment.

Summary of Applicant's response:
Allergan has defined the prevalence of chronic migraine as 1.3 to 2.4% of the European population .Allergan believes that the reference of 3-4% (cited in the Assessor's comment) is for the prevalence of chronic daily headache (CDH), of which chronic migraine is one type of CDH (Silberstein et al, 1996). The estimates of chronic migraine prevalence in the population vary with case definition, some which include medication overuse and others which exclude it. In our view, Natoli and colleagues' recent publication (Natoli et al, 2010) offers the most consolidated evidence for global chronic migraine prevalence rates. This systematic review of the published literature was performed to summarize population based studies reporting prevalence of chronic migraine among adults and to explore variation in definitions across studies. Among 16 publications representing 12 unique studies lower bound prevalence estimates utilized a case definition on 15 or more migraine days with no medication overuse, whereas upper bound estimates reflected a case definition of 15 or more headache days, a migraine component and made no restriction on medication overuse. The most restrictive definition for chronic

migraine was 15 or more migraine days with no medication overuse headache. The most common and perhaps broadest definition aligned with well established Silberstein and Lipton diagnostic criteria of 15 or more headache days with a link to migraine and including those with or without medication overuse (Silberstein et al, 1996). Depending on the case definition utilized in the study, the prevalence of chronic migraine ranged from 0% to 5.1%, with estimates of 1.4% to 2.2% being most typical when including those with medication overuse.

RMS assessment of Applicant's response:

Population based prevalence data need to be interpreted with caution due to the lack of public health structures in most jurisdictions to accurately record the relevant data. As expected lower prevalence estimates were associated with definitions that excluded medication overuse.

Question 3 (Different efficacy profiles)

We find the change in primary endpoint from mean change from baseline in frequency of headache episodes to change from baseline in the frequency of headache-free days to be acceptable as the duration of headache attacks varies. Headache episodes are often of long duration in patients with chronic headache and are therefore not an optimal parameter to monitor.
From a scientific point of view it is intriguing that Botox is ineffective in both episodic migraine and chronic tension-type headache, while it has a minor effect on "Allergan defined chronic migraine". Patients' selection criteria can hardly explain the difference, since patients with chronic tension-type headache are very likely to be included in the clinical trials of chronic migraine. Whether it is caused by dosage is difficult to decide, since the pharmacological effect of Botox on pain is unknown, if it exists at all. The separation of episodic and chronic migraine is an arbitrary delineation by <15 days/month *vs*. ≥ 15 days/month.
To our knowledge, different efficacy profiles for triptans have not been demonstrated in episodic and chronic migraine, as triptans continue to be effective in the treatment of migraine irrespectively of its frequency.

Summary of Applicant's response

We agree that an evaluation of headache days is a more appropriate efficacy parameter in the chronic migraine population because episodes are often of long duration. We respectfully disagree that patients with chronic tension-type headache (CTTH) were included in the phase 3 clinical trials. Based on the baseline characteristics of the headaches suffered by the enrolled population the mean frequency of headache days that met criteria for tension type headache (TTH) was 0.9 ± 1.74 (Module 5.3.5.3, ISE Table 1-3), the range of TTH days was 0 to 13 in study 191622-079 and 0 to 10 in study 191622-080, with median values of 0 in both studies (CSR 191622-079 Table 14.1-12 and CSR 191622-080 Table 14.1-12). To be classified as having CTTH, patients would have had to experience TTH on ≥ 15 days per month for an average of > 3 months with headaches that last "hours or may be continuous" (ICHD-II section 2.3 criteria in Olesen et al, 2004). Per protocol, patients with CTTH or unremitting headache were to be excluded from these studies.
We agree with the Assessor that the separation from episodic and chronic migraine using the 15 day delineation is somewhat arbitrary. We suggest 'somewhat arbitrary' because the 15 day delineation to determine if a primary headache is consider 'chronic' was first proposed to distinguish episodic and chronic tension type headache and was based on consensus of the International Headache Classification Committee (IHCC) when the headache diagnostic criteria were first developed in 1988 (Olesen et al, 1988). Over time the "chronic" terminology has evolved and in 2004 it was first applied to distinguish chronic migraine.
Regarding the distinction between chronic and episodic migraine, the unique patient and physiologic characteristics that determine whether a migraine sufferer will spontaneously remit, continue for decades

with episodic migraine, or progress to chronic migraine are not well understood. However, clinical, neurological, and functional studies of chronic migraine are increasingly suggestive of a pathophysiological state in which the brain exhibits enduring and pervasive alterations (Goadsby and Hargreaves, 2008), which are in contrast to the intermittent changes noted in episodic migraine during attacks. Chronic migraine is also associated with a greater degree of impairment in cortical processing of sensory stimuli than episodic migraine perhaps due to more pervasive or persistent cortical hyperexcitability (Aurora, 2009). The hypothetical mechanism of action of BOTOX is different than the triptans. It may be that Botox is effective in patients who have very frequent migraine attacks, such as those with chronic migraine. Also, triptans are an acute treatment generally taken to relieve an already initiated migraine whereas the premise for Botox is that it is routinely administered so as to prevent headache attacks from initiating in the first place.

Assessor's assessment of Applicant's response:

The RMS is of the opinion that both headache days and headache episodes are both clinically relevant endpoints as they are interdependent. Changes in Headache days is a convenient way of measuring headache pain but is dependent on either a reduction in the number of headache episodes or a shortening of duration headache episodes. For Botox to be convincing as a treatment a strong efficacy response in both endpoints would have been desirable. The effect of Botox on headache days and episodes (ITT population: 1.9 day reduction in headache days against a baseline rate of 19 headache days and a reduction in frequency of headache episodes of 0.3 against a backdrop of 12 headache episodes per 28 day period episodes) is limited. In the analysis of patients according to medication overuse status the results for the Med O-yes subgroup were similar to the ITT population .The reduction in headache episodes recorded for patients with Allergan defined CM not overusing acute headache pain medication was not statistically significant .The impact of Botox on duration of headache episodes was presented in response to a question raised by the German assessor. The mean duration of headache episodes increased across the full duration of each episode and across the duration of each episode truncated to 28 days although the median duration of headache episodes showed a modest reduction. It is unclear how reduction in headache days and total cumulative hours of headache was achieved without a more robust response in terms of a reduction of number of headache episodes or duration of the episodes.

Question 4 (BOTOX efficacy in chronic migraine)

Since patients with ICHD IIR *chronic migraine* did not have a statistically significant effect of Botox, ICHD IIR *chronic migraine* should not be an indication for Botox treatment.

Summary of Applicant's response:

The population studied in the BOTOX phase 3 studies is in alignment with the population as defined in the current diagnostic criteria for chronic migraine (ICHD-2R). Allergan therefore respectfully disagrees that BOTOX did not have an effect on patients with ICHD-2R chronic migraine (see Allergan Response to Question 1, Section A. Potential Confounding Factors: Heterogeneity of the Study Population). Furthermore, independent evaluation of the data by clinical experts shows that they recognize the value of Botox as a potential treatment in patients with chronic migraine (Schoenen, 2010).
Allergan proposes a revision to the Summary of Product Characteristics (SPC) to better define the term "chronic migraine" in order to ensure that the indication wording reflects the clinical trial population studied and provides treating physicians with further guidance. Allergan has proposed that the indication for the SPC reads as follows: "prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)".

Question 5 (Efficacy in subgroup of patients without history of prior prophylactic treatment)

Since patients without a history of prophylactic treatment did not have a statistically significant effect of Botox, patients with "Allergan chronic migraine" who have not tried other prophylactic treatment should not be treated with Botox.

Allergan response
See response to question 2.

Question 6 (Use in subgroup of patients with medication overuse)

Finally, patients with medication-overuse headache have a statistically significant small effect of Botox as compared to placebo. However, an almost similar effect can be reached by brief intervention, by simply advising patients to avoid medication-overuse.
This requires ethical considerations regarding whether an invasive treatment should be applied. An invasive prophylactic treatment is only appropriate if non-invasive treatments have been tried and found to be ineffective.

See RMS comment to Allergan's response to RMS Question 1 Section A and B

III.3.5 Questions from Sweden

Request for Supplementary Information as proposed by CMS Sweden

Question 1a (Headache episode results in Phase 2 studies)
The efficacy results from phase II and phase III are not consistent, e.g. in one of the phase II studies (039) placebo reduced the frequency of headache days more than Botox in two out of three Botox treatment groups, and placebo reduced the frequency of headache episodes more than Botox in all three Botox treatment groups.
Although the frequency of headache episodes was statistically significantly greater for Botox compared with placebo in the phase II study 038 this effect seems to be driven by a reduction in the placebo effect.

Summary of Applicant's response

These phase 2 studies were exploratory and therefore not likely to confirm efficacy. Rather, their purpose was to define a responsive population, dose, treatment paradigm, and endpoints that would then be taken forward into the phase 3 studies that were designed to provide the confirmatory evidence of efficacy and safety of BOTOX treatment for chronic migraine.

Consequently, it was not completely unexpected that even though Botox-treated patients showed large and significant improvements from baseline in these two phase 2 studies, neither study was able to differentiate between BOTOX and placebo in the primary endpoint, change from baseline in headache-free days/month. However, statistically significant improvements favouring Botox were seen in one or

both studies on multiple endpoints, including the change from baseline for the frequency of headache episodes, the proportion of patients with ≥ 50% improvement in the frequency of headache days, the proportion of patients with ≥ 30% or more, and ≥ 50% or more decrease in the frequency of headache episodes, frequency of migraine/probable migraine episodes, and the number of days and the number of uses of acute headache pain medication (Mathew et al, 2005; Dodick et al, 2005; Silberstein et al, 2005).
It is true that the efficacy results of phase 2 study 191622-039 were less robust than those of study 191622-038, most likely as a result of the difference in dosing and treatment paradigms between the two studies. Study 191622-038 used a follow-the-pain (FTP) approach, while study 191622-039 used only a FSFD approach. The mean dose administered in study 191622-038 was ~190 U in ~32 injection sites in 7 muscles/muscle groups, while the mean dose administered in study 191622-039 was ~150 U in ~20 injection sites in 7 muscles/muscle groups (Module 5.3.5.3,CSR 191622-038, Section 12.1 and CSR 191622-039, Section 12.1). Headache-related burden and disability in individual patients who have often suffered for decades is multifaceted, encompassing frequency, duration and severity of headaches. Therefore, a comprehensive assessment of efficacy is more meaningful than focusing on a single efficacy dimension, which may not fully reflect the clinical relevance of the outcome (Dworkin et al, 2009).
Results from both phase 3 studies, 191622-079 and 191622-080, were more robust than the phase 2 study results, and showed highly statistically significant and clinically meaningful between-group differences, always favouring Botox over placebo for headache symptoms measures including frequency of migraine/probable migraine days, frequency of moderate/severe headache days, and total cumulative hours of headache on headache days at the week 24 primary timepoint and also at multiple other timepoints. Recently published data from the study of patients treated in headache specialty clinics found that a 1-day increase in the frequency of headache was associated with a greater likelihood of headache pain significantly interfering with mood (p=<0.001), recreational activities (p=0.004) and life enjoyment (p=0.001) (Silberstein et al, 2008b), suggesting that patients' quality of life would benefit from as little as one less headache day. In addition, patient reported quality of life measures, HIT-6 and MSQ, showed statistically significant improvements with Botox treatment that were significantly greater than those seen with placebo and that met or exceeded established minimally important between group differences (Coeytaux et al, 2006).
In examining the totality of evidence from all of the efficacy outcomes assessed in the phase 3 studies, including multiple headache symptom measures and multiple health-related quality of life measures, improvements within and across multiple headache symptom measures that always favoured Botox over placebo. Both studies demonstrated the benefit of Botox prophylaxis of headache in chronic migraine through robust, consistent, and sustained improvements across multiple efficacy outcomes at the week 24 primary timepoint and at multiple other timepoints in the DBPC phase, in which patients received 2 treatments.

RMS assessment of Applicant's response:

In examining the totality of evidence from all of the efficacy outcomes assessed in the phase 3 studies, the conclusion of the applicant that Botox prophylaxis of chronic migraine resulted in statistically significant and clinically meaningful improvements is confounded by the inclusion of patients with medication overuse. The analysis of MedO-yes with MedO-no subgroups helps clarify the efficacy of Botox. The treatment effects in both subgroups were small and in a number of instances statistical significance of treatment effects were driven by fluctuations in placebo effect rather than variations in treatment effect size (see efficacy data for MED O-No versus MedO-Yes data.) That said the efficacy results for the Med-O no subgroup are in the opinion of the RMS closest to being representative of the effect of Botox in patients with chronic migraine.

Question 1b (Change in primary endpoint)

The change of primary endpoint forth and back could be questioned

The changes to the primary and secondary efficacy endpoints for study 191622-080 reflected key learning from the efficacy results of the primary analysis from study 191622-079, and were consistent with new guidelines that had been issued by the International Headache Society (IHS; Silberstein et al, 2008a), as well as being in alignment with newly available literature that provided precedent for the choice of headache days as a primary endpoint for headache prophylaxis in chronic migraine (Diener et al, 2007; Silberstein et al, 2007). The protocol and statistical analysis plan for study 191622-080 were amended prior to any treatment unblinding. Procedurally, the integrity of the blind was maintained and all steps to ensure such integrity were documented. Change from baseline in frequency of headache episodes was chosen as the primary efficacy endpoint for study 191622-079 because this seemed to be an appropriate primary endpoint based on the best available information at that time (i.e., Botox phase 2 studies in chronic daily headache).Headache days as an endpoint allows all patient to be evaluated over a standardised 24hr timeframe.

RMS assessment of Applicant's response:

There is much discussion about the suitability of headache days or frequency of headache episodes as preferred efficacy endpoints. The RMS considers that both have a clinical relevance as headache episodes and headache days are inextricably linked. It appears that Botox has a modest impact on the number of headache episodes in the Allergan defined CM population. The effect of Botox on headache episodes in the MedO-no subgroup is not statistically significant compared with placebo although numerically the change from baseline is similar to that seen in the ITT population and the MED O-No subgroup. The duration of headache episodes (≥ 4hrs) across both studies population truncated to 28 day period increased for both the placebo treated and the Botox treated groups. None of the differences in increased duration between the Botox and placebo groups were statistically significant. Only in the pooled analysis and for headache episodes of >0 hours duration was the increase in headache duration noted in the placebo group statistically significant longer compared with the increase recorded for Botox treated group. The duration of the episodes appears to increase in both Botox and placebo treated groups.

Question 1c (Placebo effect)

The placebo effect was generally much higher than the difference in effect between the active and the placebo groups

Summary of Applicant's response:
The perception of pain is a highly subjective experience that is influenced by cognitive factors such as expectation, attention, anxiety, and previous experiences. Placebo analgesia is one of the most striking examples of the cognitive modulation of pain perception (Diener et al, 2008). It is well established that placebo responses are generally robust in pain trials (Turner et al, 1994). Furthermore, larger placebo effects are generally observed in trials involving placebo injections compared to trials evaluating oral placebo (Turner et al, 1994) and in parallel group versus crossover design studies (Macedo et al, 2008; Bendtsen et al, 2003). High placebo response is also well characterized in trials evaluating acute and preventative treatments for migraine (Diener 2003). Thus, the placebo response rates observed in the BOTOX phase 3 chronic migraine trials are not unexpected due to the required injection method for drug delivery, and are consistent with high placebo response rates that have been reported in the literature for other

headache response measures evaluated in patients with chronic migraine and/or frequent headache (i.e., chronic daily headache) (Diener 2003). As noted by the reviewer, the placebo effect size observed in the BOTOX phase 3 chronic migraine studies was larger than the between treatment group difference observed at the primary endpoint. This is not necessarily an unexpected observation when there is a large placebo response. This phenomenon has been observed in other studies in patients with chronic migraine including topiramate (Silberstein et al 2007), Yet, despite the high placebo response in the phase 3 clinical program, BOTOX treatment benefit was evident across a variety of headache symptom measures (Module 2.5, Table 2.5.4-2).

See RMS assessment of Applicant's response to Question 1section C.

Question 1d (High proportion with acute medication overuse)

The high level of acute headache medication overuses (62-68%).

Allergan Response
As expected, the phase 3 clinical trial rates directly align to rates published within a clinical setting population. Bigal et al. assessed 557 individuals in a headache specialty clinic that met the Silberstein and Lipton criteria for chronic migraine and found that the majority of them were female with ages ranging from 18-75 years. Among these individuals, 62.5% were overusing medications; thus the phase 3 clinical trial population reflects the patterns of medication overuse within a headache specialty clinic population. (Bigal et al, 2007, Cephalalgia- ICHD-2R field testing). Compared to population-based estimates of acute headache medication overuse, the phase 3 clinical trials rates were higher (Katsarava et al, 2011). However, this is not unexpected as population-based studies include those who have chronic migraine, but may not recognize they have the disorder and/or may not be seeking pharmacological treatment.

RMS comment on Applicant's response:

We agree with the Swedish assessor that the baseline level of acute medication overuse was high in the phase III studies. In the Danish study (Zeeberg et al) to field test the proposed new appendix criteria for CM of the 684 patients reviewed in the study 25% overused AHPM at first visit. All of these patients did not have CM or TM but reflected an entire headache population. That said they were attending a tertiary referral centre so it is likely that a high proportion had CM.

Question 1e (Potential unblinding)

The potential of unblinding to treatment

Summary of Applicant's Response:

Unblinding either due to robust efficacy or an unusual but characteristic AE profile is always of potential concern in a drug development program. Allergan conducted these DBPC trials in a manner to minimize this potential issue, including a range of methods to ensure blinding of both investigator and patient was maintained. While always a theoretical concern, there is certainly no evidence to suggest that this was a particular issue in these clinical trials. Indeed, the very low rate of AE overall makes this less likely to have been a confounding issue. As noted in further discussions in Section V.1, Allergan's Response to Question 3, the injection paradigm differences between aesthetic and chronic migraine would not be expected to produce the same aesthetic effects; there is no evidence to suggest that the blind was compromised in a systematic manner; and even if all of the patients with potentially unblinding AEs are

removed from the dataset, the robust efficacy of BOTOX compared to placebo is maintained. Allergan is confident that the blind was sufficiently maintained during the BOTOX phase 3 studies based on the justifications provided in Section V.1, Allergan's Response to Question 3.

See RMS comment on Allergan's Response to RMS Question 3

III.3.6 Questions from Germany

Question 1: Duration of Headache Episodes

The Applicant is requested to report on the average duration of episodes in study 079 and 080 (Botox vs. placebo group).

The phase 3 protocols required subjects to have ≥ 15 headache days and 4 headache episodes (each lasting ≥ 4 continuous hours) during the baseline period. The duration of individual headache episodes for studies 191622-079 and 191622-080 were evaluated using the protocol-specified 4 hour minimum (≥ 4 hours), as well as evaluating headache episodes of any duration (> 0 hours). The cumulative duration of headache for the 28-day period of interest (e.g. which approximates the duration area under the curve for this period by summing the duration of individual episodes) was also evaluated using the protocol-specified 4 hour minimum (≥ 4 hours), as well as evaluating headache episodes of any duration (> 0 hours)

Table 15 Baseline Mean, Median, Minimum and Maximum Headache Episode Duration (hours) per Subject

Time Period	Study 191622-079			Study 191622-080			Pooled 191622-079 + 191622-080		
	BOTOX®	Placebo	P-value	BOTOX®	Placebo	P-value	BOTOX®	Placebo	P-value
Baseline Headache Episode (≥ 4 hours) Average Duration: Each episode full duration									
LS Mean	36.50	30.68	**0.010**	38.40	33.41	0.113	37.44	32.04	**0.004**
Median	25.20	20.33		23.55	22.84		24.57	20.94	
Minimum, Maximum	5, 246	4, 138		5, 205	5, 252		5, 246	4, 252	
Baseline Headache Episode (> 0 hours) Average Duration: Each episode full duration									
LS Mean	35.23	29.16	**0.005**	36.99	31.88	0.064	36.09	30.50	**0.001**
Median	23.06	19.06		21.98	20.11		22.45	19.48	
Minimum, Maximum	5, 246	4, 138		4, 205	5, 252		4, 246	4, 252	
Baseline Headache Episode (≥ 4 hours) Average Duration: Each episode truncated to 28-day period									
LS Mean	34.27	29.16	**0.012**	35.70	31.18	0.098	34.97	30.15	**0.003**
Median	23.96	19.91		23.50	22.37		23.55	20.44	
Minimum, Maximum	5, 161	4, 124		5, 157	5, 150		5,161	4, 150	
Baseline Headache Episode (> 0 hours) Average Duration: Each episode truncated to 28-day period									
LS Mean	33.05	27.69	**0.006**	34.34	29.69	0.058	33.68	28.67	**0.001**
Median	22.31	18.33		21.64	19.54		21.97	19.12	
Minimum, Maximum	5, 161	4, 124		4, 157	5, 150		4, 161	4, 150	

Average Headache Episode Duration: Week 24 Primary Efficacy Time Point

At the week 24 primary time point in both studies, the headache episode average duration in both treatment arms was similar to what was observed at baseline. This was true whether the headache episode was ≥ 4 hours or > 0 hours in duration, and whether the episode duration accounted for the full duration or was truncated per the 28-day period of interest (Appendix 1, Tables 1-1, 1-2, 1-3 and 1-4). At week 24, there were no between group differences for headache episode average duration in either study (Table 3). However, at the week 24 primary time point for the pooled analysis of headache episodes of > 0 hours duration, the placebo group had a statistically significant longer average headache duration increase from baseline compared to the Botox group for both evaluations of full headache episode duration (p=0.049, Appendix 1, Table 1-2) and when headache episode duration was truncated to the period of interest (p=0.028, Appendix 1, Table 1-4).

Table 16 Week 24 Change from Baseline Mean, Median, Minimum and Maximum Headache Episode Duration (hours) per Patient

Time Period	Study 191622-079			Study 191622-080			Pooled 191622-079 + 191622-080		
	BOTOX®	Placebo	P-value	BOTOX®	Placebo	P-value	BOTOX®	Placebo	P-value
Week 24 Headache Episode (≥ 4 hours) Average Duration: Each episode full duration									
LS Mean	10.36	15.23	0.302	10.97	11.08	0.297	10.17	12.84	0.177
Median	-0.32	0.05		-1.72	-1.26		-1.07	-0.45	
Minimum, Maximum	-172, 1523	-108, 524		-134, 2775	-163, 1358		-172, 2775	-163, 1358	
Week 24 Headache Episode (> 0 hours) Average Duration: Each episode full duration									
LS Mean	10.11	16.10	0.079	10.96	11.64	0.257	10.03	13.54	**0.049**
Median	-0.94	0.14		-1.75	-0.99		-1.45	-0.33	
Minimum, Maximum	-172, 1528	-108, 528		-134, 2775	-163, 1358		-172, 2775	-163, 1358	
Week 24 Headache Episode (≥ 4 hours) Average Duration: Each episode truncated to 28-day period									
LS Mean	4.23	9.59	0.372	-0.38	3.11	0.113	1.71	6.02	0.098
Median	-0.40	-0.30		-2.12	-1.15		-1.45	-0.72	
Minimum, Maximum	-149, 594	-94, 459		-116, 544	-120, 473		-149, 594	-120, 473	
Week 24 Headache Episode (> 0 hours) Average Duration: Each episode truncated to 28-day period									
LS Mean	4.06	10.42	0.113	-0.21	3.51	0.108	1.71	6.62	**0.028**
Median	-1.01	-0.11		-1.96	-1.03		-1.71	-0.43	
Minimum, Maximum	-149, 599	-94, 463		-116, 544	-120, 473		-149, 599	-120, 473	

Source: Appendix 1, Table 1-1, 1-2, 1-3 and 1-4

An analysis of the total cumulative hours of headache over the 28-day baseline and week 24 periods was also performed.

Total Cumulative Hours of Headache: Baseline

The baseline total cumulative hours of headache suffered by the subjects in these studies was high regardless of whether the 4-hour minimum headache duration was accounted for or not. The baseline total cumulative hours of headache had a similar range in study 191622-079 and in study 191622 080, but there was a statistically significant imbalance at baseline in study 191622-079.

Total Cumulative Hours of Headache: Week 24 Primary Time Point

At week 24, both treatment arms in both studies showed a mean reduction from baseline in the cumulative hours of headache. These differences were statistically significant favouring Botox over placebo in both individual studies and the pooled data. The between-group differences are quite large (mean ≥ 30 headache hours) and substantiate the clinical meaningfulness of the treatment effect.

Table 17 Baseline and Week 24 Change from Baseline Headache Episode Total Cumulative Duration (in hours) per Patient[a]

Time Period	Study 191622-079			Study 191622-080		
	BOTOX®	Placebo	P-value	BOTOX®	Placebo	P-value
ITT Population (ANCOVA using Observed Data; headache episodes ≥4 hours)[b]						
Baseline	300.13	279.38	0.018	299.25	290.19	0.311
Week 24	-99.79	-69.26	0.010	-138.01	-96.52	<0.001
ITT Population (ANCOVA using Observed Data; headache episodes > 0 hours)[c]						
Baseline	302.51	282.72	0.022	302.62	293.87	0.323
Week 24	-99.62	-68.87	0.010	-138.03	-95.44	<0.001

Source: Appendix 1, Tables 1-5 and 1-6

a Least Square Mean data

b Only headaches with at least 4 hours of duration were counted. A headache was only accounted for by the duration that encroached into the time period of interest.

c Cumulative daily duration is calculated for all headache days regardless of duration. Diary days without headache have cumulative duration of 0. The summary score for a patient is the average across all diary days for the patient times 28.

These results in total cumulative hours of headache may, at least in part, be explained by the effect of Botox on the frequency of headache episodes. Overall, while there was a large mean reduction from baseline in the frequency of headache episodes in both treatment groups in both studies, in study 191622-080 and the pooled analysis there was a statistically significant between-group difference favouring Botox over placebo for the frequency of headache episodes.
In conclusion, because of the broad variability in duration of individual headache episodes in this patient population, this measure is not considered the most reliable for evaluating treatment effect in subjects with chronic migraine. Cumulative duration of headache better approximates treatment effect than the average individual headache episode duration as it provides an estimation of area under the curve for a period of interest.

RMS comment on applicant's response:
The mean duration of headaches episodes increased across Botox and placebo treated groups in pooled phase three analysis of change from baseline in headache episode duration. At week 24, both treatment arms in both studies showed a mean reduction from baseline in the cumulative hours of headache. These differences were statistically significant favouring Botox over placebo in both individual studies and the pooled data. The treatment effect in terms of reduction of headache days of Botox appears to be driven by the effect on reduction in frequency of headache episodes rather than a reduction in duration of headache episodes.

Question 2: Subgroup without Medication Overuse

The complete non-response in the subgroup of subjects not showing headache medication overuse is of major concern. The role of medication overuse headache (MOH) in the pathogenesis of CM is still a matter of debate (either occurring secondary or having a contributory / causative role). In study 080 Botox worked for patients with overuse but consistently did not work for the non-overuse population. This raises the question whether Botox actually improves CM, or helps to prevent the negative (possibly algesic / headache promoting) sequelae of continuing headache medication overuse. This concern is hardened by the complete lack of a concept of a migraine-specific mode of action for Botox.

See RMS assessment of Applicant's response to RMS Question 1 section A and B

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Question 3: BOTOX® Mode of Action

The role of medication overuse headache (MOH) in the pathogenesis of CM is still a matter of debate (either occurring secondary or having a contributory / causative role). In study 080 Botox worked for patients with overuse but consistently did not work for the non-overuse population. This raises the question whether Botox actually improves CM, or helps to prevent the negative (possibly algesic / headache promoting) sequelae of continuing headache medication overuse. This concern is hardened by the complete lack of a concept of a migraine-specific mode of action for Botox.

See RMS comment on MOH and preclinical evaluation of proposed mechanism of action

Question 5: Injection Depth, Tissue Penetration and Metabolism Data

No PK data were submitted in support of the Variation. From the safety evaluation it appears that the toxin did not spread to a relevant degree in view of the fact that most AEs were local (neck pain, facial paresis, eyelid ptosis etc). However, further data on injection depth, tissue penetration (dependent upon the injected volume?), metabolism etc. are requested.

Summary of Applicant's response

Pharmacokinetic Data

The applicant justifies the lack of PK data due to the nature of the product. Its chemical complexity and extreme potency render it unsuitable for standard PK/PD studies to characterize its profile. No specific data are presented with regard to variation in injection depth and the impact on treatment effect of Botox. In relation to tissue penetration Allergan conducted a study of tissue penetration using 125I-botulinum neurotoxin A in rats and rabbits. Only approximately 40% of intact radiolabled toxin was present in the muscle 2 hours after injection, whereas at the same timepoint in plasma, only degraded proteins were found. Within 24 hours of dosing, 60% of the radioactivity was excreted in the urine .

The large protein size of the 900 kDa Botox molecule is a major determinant relevant to diffusion in muscle tissues which is consistent with Fick's law of diffusion. It is unknown if tissue penetration is dependent upon the dose or the injected volume, as the tissue target and size of the target muscle (small facial vs. large limb) are potential factors. In clinical studies where Botox has been injected into spastic muscles using different dilution volumes data have not consistently showed differences in therapeutic efficacy. Two published controlled studies failed to show differences between different dilution volumes when treating wrist and finger flexor spasticity (high dilution 100 U diluted with 2 mL and low dilution 100 U diluted with 1 mL) (Francisco et al, 2002) or gastrocnemius spasticity (high dilution 100 U diluted with 4 mL and low dilution 100 U diluted with 1 mL) (Lee et al, 2004). Another study found that after injection of the biceps brachii in patients with spastic hemiparesis, reduction in excessive muscle tone was superior when a high-volume dilution (100 U diluted with 5 mL), higher than used in the studies above, versus low-volume dilution (100 U diluted with 1 mL) (Gracies et al, 2009).

In another small study (N=20) patients were randomized to one of two Botox treatments groups (Carruthers et al, 2007b) for cosmetic treatment of "crow's feet" around the eye. Results showed that more concentrated dose of Botox (ie, 5 U per 0.05 mL) was slightly more effective in reducing orbital rhytides than the more diluted dose (5 U per 0.25 mL) at all post treatment timepoints except Day 60 post treatment. However, the differences were small and likely not clinically significant.

An additional study examined 10 subjects who received both 5 U Botox in 0.25 mL (2 U per 0.1 mL) and 5 U Botox in 0.05 mL (2 U in 0.2 mL) in the dynamic forehead lines and found a 50% greater area of effect by visual inspection with the larger volume in 9 of the 10 subjects (Hsu et al, 2004).

Neurotoxin diffusion has been evaluated in some small human studies using a model of intradermal injection to the back and forehead areas and measuring the anhidrotic area by starch-iodine (Minor's Iodine Test) (Dewland et al, 2007a; Dewland et al 2007b). In one study an average area of 1.69 cm2 of anhidrosis was found 2 weeks after injecting 4 U of BOTOX® in 0.1 ml saline solution intradermally in the middle back (Dewland et al, 2007a). A similar average area of anhidrosis of 1.7 cm2 was found 2 weeks after injecting the same dose in the skin of the forehead (Dewland et al, 2007b). A linear dose dependent relationship for Botox was found following single 0.1 ml intradermal injections of 2.5, 5, and 10 Units in a human anhydrosis model when injected in the back (Rystedt et al, 2008).

In general, it is difficult to compare pharmacodynamic effects across skeletal muscle and dermal models because of differences in target organ, muscle size and type of nerve (motor vs. autonomic). Collectively the studies suggest a dose-response at a fixed volume. However, it is not possible to draw a general conclusion regarding the effects of volume, as studies are confounded by experimental design including muscle size and location. At a fixed volume across available experimental designs, Botox exhibits a dose-response whereby there is evidence of greater penetration with higher doses, and toxin remains local to the site of injection.

RMS assessment of applicant's response:
The applicant has provided an overview of published literature evaluating the effect of volume on the efficacy of particular doses of Botox and neurotoxin diffusion. The RMSs agrees that it is not possible to draw a general conclusion regarding the effects of volume, as studies are confounded by experimental design including muscle size and location but that the overall trend in the studies suggests that a fixed volume with increasing dose (i.e. increasing concentration) is associated with a dose response .

Question 6: Dose Justification

No differential analysis between the 155 U dose patients (31 injections following the fixed-dose fixed-site paradigm) and those patients receiving 195 U (plus elective eight injections according to follow-the-pain paradigm) could be found. The Applicant is requested to justify these two dosing strategies.

See RMS comment on Allergan response to RMS Clinical Efficacy Question 4.

Question 7: Other Subgroups
Overall, essential questions regarding the possible benefit of Botox in the treatment of CM remain unclear:

1. No PK data (see above)
2. No conclusive evidence (based on preclinical data) for migraine-specific mode of action for Botulinum toxin
3. No clear information from phase II on the dose, the site of application (fixed-site vs. follow-the-pain paradigm), the treatment intervals (no evidence for the 12-week period)
4. No clarity regarding the applicability of the clinical findings (non-response in prophylaxis naïve, no response in non-overuse patients [statistically relevant sub-population], no superiority over placebo in male [about 15%] and non-Caucasian [about 10% of all participants]

RMS summary of Applicant's response Allergan response to Question 7

These issues were addressed in responses to previous questions. See RMS comment on previous answers.

Clinical Safety (RMS)
Question 1 (Headache/migraine ADR)
Worsening of headache and migraine which emerged as an ADR across all analyses should be further evaluated. The potential for evolution to an 'episodic' type clinical picture in some
patients should be discussed.

RMS summary of Applicant's response:

The applicant provides an n in depth review and clinical assessment of the data on AEs of headache/migraine in the phase III safety population. In terms of demographics, analysis of headache characteristics (overall headache burden evaluated as headache maximum severity, frequency of headache days and average headache episode duration, the data presented by the applicant does not suggest that Botox treatment results in worsening of the of severity frequency .The average duration of headache episodes increased for the patients who reported a headache migraine AE. However the incidence of migraine/headache AE declined over repeated treatment cycles and the headache /migraine AE rates by cycle were low. There was no evidence that the injection procedure itself contributed to the occurrence of headache/migraine. An overview of the six SAES reported as Migraine in the DBPC exposure and SAES related to migraine during the open label exposure have shown a similar pattern .There was no clear temporal or dose association between onset of the migraines and administration of Botox. In the open label phase all but one patient had undergone 3 or 4 cycles of active treatment before reporting Migraine as an SAE.
Both headache and migraine have been proposed as common AEs for the new Botox chronic
Migraine indication as part of the United Kingdom approval for Botox as prophylaxis of headaches in adults with chronic migraine (headaches on ≥15 days
Per month of which at least 8 days are with migraine), an observational study designed to look at
Adverse drug reactions (ADR) has been agreed with the Medicines and Healthcare Products
Regulatory Agency (MHRA). First patient enrolled in this study is anticipated for in March 2011.

RMS assessment of Applicant's response:

The RMS agrees that there is little evidence to suggest that treatment with Botox worsened symptoms of headache and migraine and that the frequency and severity of headache symptoms experienced by the subgroup reporting a headache/migraine AE is more likely to be consistent with periodic fluctuations in the frequency and intensity of headaches that occur during the natural course of chronic migraine .The outcome of the UK observational study should be provided for review.

III.4 Product information

III.4.1 Summary of Product Characteristics

4.1 Therapeutic Indications

The applicant has proposed a revision to the wording of 4.1 to further clarify the intended treatment group

‘ Prophylaxis of headaches in adults with chronic migraine (headaches on ≥15 days per month of which at least 8 days are with migraine)’ is not approvable .

The Reference Member State proposes the following wording:
‘treatment to reduce the number of headache days in patients with chronic migraine (headaches on ≥15 days per month of which at least 8 days are with migraine) who are not over using acute pain medication and who are taking or have previously taken non-acute, prophylactic migraine medications’(see section 5.1)

.
Wording is included indicating the Botox should not be used in the treatment of chronic migraine in children under 18years

Assessor’s comment on proposed wording.
This is acceptable;

4.2 Posology and Method of Administration

Detailed instructions for dilution and administration of Botox in chronic migraine are provided by the applicant.

RMS comment
This is in keeping with the dosing instructions provided for other approved indications.

4.4 Special warnings and precautions for use
The applicant has proposed the following wording

Chronic migraine
Chronic migraine

Botox should only be used in the management of chronic migraine in specialist centres by physicians who are experienced in the diagnosis and treatment of chronic migraine.
Safety and efficacy have not been established in prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month) *or chronic tension type headache*.

RMS comment on proposed wording:
The RMS has amended this wording (bold italics) to reflect the difficulty associated with diagnosis of chronic migraine in the clinical setting and the level of clinical expertise required to diagnose and manage these patients.

4.8 Undesirable effects

Warnings in ‘section a. General’ and indication specific adverse reactions for chronic migraine reflect the findings from the phase 3 clinical trials and are considered acceptable.

5.1 Pharmacodynamic properties

The proposed wording of section 5.1 is not acceptable. The wording should reflect the efficacy data in patients with chronic migraine who are not overusing acute headache pain medication.

III.4.2 Package leaflet and user test

The proposed wording of the PIL should be updated to reflect the changes to the SPC. See amended PIL Annexe 1.

See annexe 1 for proposed changes to the SPC and PIL annotated with the RMS's comments after each section.

IV Overall conclusion and Benefit-risk assessment

The Reference Member State maintains the opinion that the (adapted) indication requested for Botox,

' Prophylaxis of headaches in adults with chronic migraine (headaches on ≥15 days per month of which at least 8 days are with migraine)' is not approvable however an indication for

'treatment to reduce the number of headache days in patients with chronic migraine (headaches on ≥15 days per month of which at least 8 days are with migraine) who are not over using acute pain medication and who are taking or have previously taken non-acute, prophylactic migraine medications'(see section 5.1)

is proposed.

Benefit risk discussion:

In the opinion of the RMS the target population was not clearly identified in the original phase III studies. There appears to be ongoing debate as to what criteria best define CM. In studies field testing ICHD criteria for CM alternative proposals are tested alongside the ICHD 2R-CM criteria. None of these criteria seem to be evidence based but are based on consensus clinical opinion. The definition of CM used in these studies differs from the ICHD-2R criteria in two significant aspects. The Allergan defined CM population include patient overusing AHPM and patients with probable migraine. A relatively high proportion of participants (66%) were overusing acute pain medications at baseline. The population studied in the phase III studies is more accurately described as probable chronic migraine with probable medication overuse headache. The effect of Botox on coexisting medication overuse headache is difficult to elucidate. Analyses of both a 3-month and 6-month showed a persistent shift from MedO-yes to MedO-no indicating that significantly more Botox-treated than placebo-treated patients had reduced use of acute medications. This started as early as 4 weeks after treatment although the frequency of acute HPM intakes did not decrease significantly relative to placebo. This could suggest that some of the treatment benefit seen with Botox was due to improvement in headache following reduction in the proportion of patients overusing acute pain medication .

The first objective of the management of MOH is to achieve withdrawal from the overused medication
The second, is subsequent recovery from MOH. This is followed by review and reassessment of the underlying primary headache disorder (chronic migraine), which will probably become unmasked . . (BASH guidelines 3rd edition (1st revision) 2010). It is unclear how much of the effect of Botox is due to it's impact on chronic migraine and how much is due to the effect of Botox on recovery from MOH .
A subgroup analysis of the Med O –no subgroup has been provided by the applicant. The overall efficacy in this subgroup is less robust than the efficacy findings for the MedO-yes subgroup and the ITT population. Although change from baseline for many of the MedO-no efficacy endpoints was numerically similar to or higher than the level of response seen in the ITT population statistical significance was not achieved in a number of endpoints due mainly to the more robust placebo response seen in this subgroup. However in the opinion of the RMS the efficacy response in the MedO-no subgroup is closest to the efficacy of Botox in true chronic migraineurs.

The high proportion of patients who never had prophylaxis prior to entry to this study and the lack of efficacy in this prophylaxis naïve subgroup is puzzling possibly suggesting that patients may have been misclassified as having chronic migraine to start with. Botox has only been shown to be effective in patients who are taking or have previously taken non-acute, prophylactic migraine medications. The indication has been amended to reflect this fact.

The clinical significance of the treatment effect is difficult to evaluate. The treatment effect in terms of difference with placebo is consistently of the order of 10-15% across all statistically significant endpoints however statistical significance of many of the endpoints is driven by fluctuation in placebo response rather than by changes in treatment response. The original primary efficacy endpoint was changed from change in frequency of headache episodes to reduction in headache days. The rationale for this in the context of a clinical trial is accepted. However change in headache days requires either a reduction in the number of episodes or a shortening of episodes. The effect in terms of reduction of headache episodes is small (mean reduction of 0.3 in ITT population, 0.7 in MedO-yes group and 0.6 in Med O-no subgroups. This result was NS in the MedO-no subgroup) and the mean duration of headache episodes ($\geq$ 4hrs) across both studies population truncated to 28 day period increased for both the placebo treated and the Botox treated groups. Botox does not completely eliminate the reoccurrence of headache episodes but seems to have a modest effect on reoccurrence of some headaches and the intensity of a proportion of the headaches. This is more of pain modulatory effect rather than a prophylactic effect. The mechanistic basis as proposed by the applicant does not appear to support a prophylaxis of headache and the RMS does not support prophylaxis of headache as a proposed indication. The indication proposed refers to treatment to reduce headache days in patients with chronic migraine

Botox is well tolerated .The adverse event profile is in keeping with the known pharmacological effect. The majority of the ADRs are localised to head and neck reflecting the distribution of the treatment .There is no evidence of spread of toxin. Neck pain, headache and migraine, eyelid ptosis and musculoskeletal stiffness are the commonest ADRs. All proposed ADRs, except for migraine, have been observed with the use of Botox in other indications .There were consistently high levels of satisfaction recorded across all of the HRQoL endpoints .There is an unmet clinical need in this debilitated subpopulation of acute migraineurs.

The RMS considers that Botox should only be used in the management of chronic migraine in specialist centres by physicians who are experienced in the diagnosis and treatment of chronic migraine. Under these circumstances the RMS considers the indication for use as amended by the RMS is approvable.

Annex I: Proposed changes to the SPC ANNOTATED with THE RMS's comments AFTER EACH SECTION