Updated AR from RMS
RMS assessment of responses to List of Questions for CMD(h) Referral for IE/H/0113/001-002-003/II/061

1. This document is sent by

RMS	
Contact point project team leader Name Phone number E-mail	Cathy Hempenstall (00353 1 676 4971 Cathy.hempenstall@imb.ie
Date	24th May 2011

2. This document concerns

Name of the product in the RMS	Botox 50/100/200 Powder for solution for Injection
Name of the active substance	Botulinum Toxin Type A
Applicant	
Name	Allergan Pharmaceuticals Ireland
Contact Person	Sharon Standerwick & Robert Waters
Address	Castlebar Road, Westport, Co Mayo, Ireland
Phone	00 44 (0) 1628 494082
Fax	00 44 (0) 1628 494058
E-mail	Standerwick_Sharon@Allergan.com & Waters_Robert@Allergan.com

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)
EM	Episodic Migraine
FSFD	Fixed-site, fixed-dose (injection paradigm)
FTP	Follow-the-pain (injection paradigm)
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
IHS	International Headache Society
LoQ	List of Questions
MO	Medication overuse
MOH	Medication overuse headache
RMS	Reference Member State

1. Introduction

Background

This document refers to a type II variation application IE/H/0113/001-002-003/II/061 for Botox. In this variation application the applicant seeks approval for the indication of 'Prophylaxis of headaches in adults with chronic migraine (headaches on ≥15 days per month)'

Following initial review and circulation of the PVAR the RMS did not consider the indication proposed by the applicant to be approvable. The PVAR was endorsed by the CMSs (DE, DK, ES, SE, EL and NO); 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 queries raised by the RMS and CMSs were reviewed. The following revised indication was submitted to the RMS by the MAH as part of their response to the PVAR.

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

The RMS did not consider the MAHs proposed indication approvable but proposed the following revised restricted indication as part of the FVAR. The RMS also proposed inclusion of a statement to the effect that administration of Botox would be restricted to use in specialist centres by physicians experienced in the diagnosis and management of chronic migraine.

'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)

Following review of the FVAR responses were received from DK and EL proposing further amendments to the proposed indication. SE NO and DE indicated that they could not accept the restricted indication as proposed by the RMS for the following outstanding reasons which had not been satisfactorily addressed during the variation procedure. SE, NO and DE requested that the RMS refer the variation (IE/H/0113/001-002-003/II/061) to CMD (h). The application was referred to CMD 24th may 2011. A final List of Questions circulated to applicant 8th June 2011.

Final list of questions.

1. The clinical relevance of key efficacy findings from the pooled analysis of studies 079 and 080 has not been satisfactorily demonstrated and should be further justified. The following issues should be addressed in the justification

a) The heterogeneity of the Allergan defined chronic migraine study population due to the high level of medication overuse, high proportion of study population recorded as prophylaxis naïve and inclusion of patients with probable migraine and migraine with aura in the original study population.

b) Inconsistent outcomes in various study subpopulations (medication overuse yes/no; prophylactic treatment naïve yes/no).

c) The conflicting finding of an increased mean duration of headache episodes compared with the overall decrease in total cumulative hours of headache on headache days.

d) The potential for unblinding effects of Botox due to its muscle relaxant effect and its potential impact on the study outcome.

e) The lack of clarity regarding the potential mechanism of action of Botox in chronic migraine.

f) Lack of supporting evidence of efficacy of Botox in patients with episodic migraine (and tension headache).

g) The lack of convincing dose-finding data and a clear rationale for the proposed treatment paradigm. (fixed dose-fixed site vs. follow-the–pain),

2. RMS assessment of Response to List of Questions

Note to reviewer a summary of the main points in the applicant's response is provided. For the full text of the applicant's response please refer to original response document.

2.1 Overview

The current assessment report concerns the RMSs review of the applicants response to LoQ received on the 23rd June 2011.

2.2 Point A (Heterogeneity of the population)

The heterogeneity of the Allergan defined CM study population due to the high level of medication overuse, high proportion of study population recorded as prophylaxis naïve and inclusion of patients with probable migraine and migraine with aura in the original study population.

Summary of Allergan Response

a. Botox Phase 3 Chronic Migraine Population

Patients enrolled into the Botox phase 3 chronic migraine studies were required to have a confirmed diagnosis of migraine, medical history of frequency headaches (i.e. ≥ 15 headache days per month on average) with 50% of the headache days being migraine or probable migraine per protocol specific inclusion criteria. The frequency of headache days and the characteristics of each headache were confirmed in a 28-day prospective baseline period based on daily patient reported signs/symptoms of their headaches. The most common associated symptoms patients experienced on headache-days were: photophobia (81.2%), phonophobia (80.6%), exacerbation with physical activity (80.0%), pulsating quality (70.8%), unilateral pain (63.6%), nausea (59.8%) and to a lesser extent vomiting (13.8%). The majority of patients also had very high HIT-6 and MSQ scores, indicating how negatively their headaches were affecting their overall health related quality of life. The clinical profile of these patients aligns with headache characteristics and overall poor health related quality of life as reported by others for patients with chronic migraine.

b. Chronic Migraine Patient Population

Chronic Migraine (CM) occurs far less frequently than EM with a reported prevalence of 1.3 to 2.4% of the European population (Castillo et al., 1999; Lanteri-Minet et al., 2003). As such, the burden of this disorder, study population characteristics, accuracy of diagnosis, patterns of acute and prophylaxis treatments, and frequency of health care professional consultation, have not been extensively characterized until recently (Bigal et al., 2008; Blumenfeld et al., 2010). The population of patients evaluated in the Botox phase 3 studies has disease characteristics and patterns of acute and

prophylaxis treatment use that are highly overlapping with known population characteristics for persons with CM the characteristics of the patients enrolled into these studies align well with population based known characteristics. We agree that the best clinical setting for the diagnosis and treatment of patients with CM is the neurologist/headache specialist centre because of the complexity of the patients with regard to accurate diagnosis, co-morbid conditions and best practice for a multi-disciplinary treatment approach. The Botox phase 3 study population evaluated highly disabled patients who, on average, suffered with CM for more than two decades and experienced an average of 20 headache days per month, which is consistent with the known profile of CM in the population and in headache clinics as attested by published literature and headache experts. The vast majority of investigators for the phase 3 studies were neurologists and/or headache specialists. Indeed, most patients recruited for these studies were patients who were seeking care/treatment at a headache clinic, reflecting the fact that the patients in these studies represent patients that are being seen in the population. Many of the patients evaluated in these studies were refractory to available treatments, reporting inadequate pain relief with acute treatments, resulting in frequent intake of acute treatments (ie., acute medication overuse during the 28 days baseline period was demonstrated for 65.5% of patients) in an attempt to relieve their severe symptoms, and/or previous failure on other headache prophylactic medications due to lack of effect or intolerable side-effects, or both.

RMS comment:

Prevalence of chronic migraine and characteristics of this population seem to vary from study to study. Many of the epidemiologic studies have different methodologies and are difficult to interpret and compare (Stovner et al 2006) and it is unclear if they truly they correlate with the true prevalence of CM . The Eurolight project is the first at European Union level to assess the impact of headache disorders. The authors of this study conclude that chronic headache (i.e. on more than 15 days per month) seems to affect around 4% of the adult population, and MOH 1–2%. Other primary headaches are even rarer, and the prevalence of these has not been estimated in population-based studies. (Stovner et al 2010). Prevalence data on primary chronic headache in the general population based on clinical interviews by physicians are lacking. Difficulties with recall bias, definition of CM inclusion of patients with acute medication overuse, patients with multiple headache types confound these studies. However one population based study (Grande et al 2008) which identified patients with CDH and then subsequently invited them for interview and examination by physicians with experience of head diagnostics indentified a population prevalence of 0.01% for chronic migraine. The authors conclude that while primary chronic headache is prevalent (2.9%) CM and other primary chronic headache are rare. In the International Burden of Migraine Study (IBMS-), a web-based population based survey of 11897 eligible responders from ten countries 5.7% participants were identified as having (n = 555) chronic migraine .(Payne 2011).The Co-occurrence of migraine with CTTH and probable CTTH was frequent in the Norwegian interview based study (Grande et al 2008).

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 and/or probable migraine increased the numbers of CM patients significantly.

The number of different definitions and the variations in inclusion criteria used in various field tests is an indication of the lack of clinical consensus regarding classification of CM in the clinical community. This is reflected in the variations in prevalence for CM recorded in different epidemiological reviews. There is still a question mark over the extent to which the current 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. However

the definitons reflect the consensus opinion of the IHCC and ther do not apper to be any plans to change this wording in ICHD-3 (Olesen 2011).

References

BigalME The International Classification of Headache Disorders revised criteria for chronic migraine-field testing in a headache speciality clinic Cephalalgia 2007;27;230-234

Grande, R.B Prevalence of Primary Chronic Headache in a Population-Based Sample of 30- to 44-Year-Old Persons Neuroepidemiology 2008;30:76-83

Olesen J New plans for headache classification :ICHD-3; Third International Headache Classification Committee of the International Headache Society.Cephalalgia. 2011 Jan;31(1):4-5.

Payne KA,. The International Burden of Migraine Study (IBMS): Study design, methodology, and baseline cohort characteristics. Cephalalgia. 2011 Jun 20

StovnerL, Andree C, Prevalence of headache in Europe: a review for the Eurolight project J Headache Pain. 2010 August; 11(4): 289–299.

Stovner LJ. Headache epidemiology: how and why? J Headache Pain. 2006;7(3):141–144.

Zeeberg Medication overuse headache and chronic migraine in a specialized headache centre: field-testing proposed new appendix criteria Cephalalgia Vol 29;2;214-220

c. Acute Medication Overuse

The applicant argues that participants in the study could not have had medication overuse headache as investigators enrolling patients into the Botox phase 3 studies were experienced in the diagnosis and treatment of migraine patients suffering from frequent headache and specifically excluded other primary and secondary causes of headache. Investigators were required to confirm that patients enrolled into these studies had a primary migraine headache disorder, suffered with 15 or more headache days per 28 day period, with 50% or more of all headache days being migraine or probable migraine.The 28-day baseline period showed frequent intake of acute medications, but this does not equate to a confirmed diagnosis of MOH.

The applicant then goes on to discuss what they describe as recent advances in the understanding and classification of chronic daily headaches indicating that considerable controversy regarding classification of individual headaches, including CM and MOH remains and that revisions to the CM diagnostic criteria are currently being discussed by the ICHD3 Committee making the point that the current criteria are included in an appendix to the ICHD and were intended to support further field testing and validation of the criteria. Regionally, physicians differ in their interpretation as to whether the revised CM criteria in fact do represent "the majority" of patients seen in practice; many disagree with this perspective. It is not clear whether MOH is a cause or a consequence of CM. Epidemiology studies that have evaluated the current diagnostic criteria and other proposed criteria suggest that there is a need to consider revising the criteria based on evidence, since a large number of patients seen in specialty clinics do not meet the current criteria and yet many clinicians view such patients as those suffering from CM, frequently differentiated in current literature as CM (or transformed migraine) with or without concomitant medication overuse (eg., Grazzi et al., 2010; Fontanillas et al., 2010). What is not controversial is that affected patients suffer greatly. It has previously been demonstrated that CM is more disabling and burdensome than EM (headache on < 15 days per month) in terms of

migraine-related disability, health-related quality of life, healthcare and treatment utilization as previously discussed above (Bigal et al., 2008; Buse et al., 2010; Blumenfeld et al., 2010). These patients have high unmet needs for pain relief (Straube et al., 2010currently guidelines developed by certain country specific headache specialists now advocate for early addition of headache prophylaxis while addressing appropriate concomitant medication use for patients (eg., Spanish Society of Neurology).
Several CMS commented that the results for the MedO-Yes group are similar to those seen for the ITT population and that the findings in the MedO-Yes group appear to be more robust than results observed in the MedO-No group. Although MO was pre-defined stratification, these studies were not powered specifically to evaluate efficacy within each of the strata. In hindsight, this would have been desirable and thus represents a limitation of these studies. Regardless, statistically significant and clinically meaningful between group differences across a number of key efficacy variables were observed in both subgroups (Table 6 see company response document). Treatment response to Botox irrespective of whether the patient was assigned to the MedO-Yes or MedO-No strata, was similar and was consistently greater than placebo response for either subgroup (Table 6) for key efficacy variables. When looking closely at the subgroup data side by side, the mean change from baseline Botox-treatment response across efficacy variables (eg., headache days, migraine days, total cumulative hours of headache on headache days, etc.) was similar between the two subgroups (Table 7 see company response document); also note the consistency when the percent change from baseline is examined (Table 8 and Figure 2 see company response document). Furthermore, Botox consistently delivered high levels of satisfaction across all of the health related quality of life (HRQoL) efficacy endpoints for both MedO-Yes and MedO-No subgroups (Table 7).Clinical judgment amongst clinician's remains divided as to the optimal clinical practice with regard to addressing patients need for pain relief and suffering in the presence of CM, and the confounding use of frequent acute medications. Ultimately, Allergan believes that headache specialist managing an individual CM patient should determine the optimal course of treatment for that individual patient based on evidence. Withdrawal of AHPM prior to treatment for CM is not supported by certain headache specialists .

Conclusion by applicant
Medication Overuse: Given that there are divergent views with regard to current clinical practice across countries with regard to treatment practices in managing patients suffering from CM and medication overuse (ie. withdraw acute medications prior to or concurrent with addition of headache prophylaxis), Allergan suggests that labelling provide prescribers with appropriate guidance that recognises the national differences with regard to when detoxification from overuse of acute medication should occur (ie. before or after prescribing prophylaxis treatment). This information will allow prescribers to make robust clinical decisions about how/when to use BOTOX® as headache prophylaxis within an agreed framework.

RMS comment:

The applicant's argument the that patients were only included if they had a primary headache disorder is noted by the RMS however it is implausible that some of these patients were not suffering from MOH considering the high levels of acute pain medication used in these studies (up to 65% of patients recruited were overusing acute pain medication) and the severity and longevity of the headaches suffered by the participants. It is a concern that many of these patients may have been suffering from a secondary headache disorder .A definition for Chronic Migraine was included for the first time in ICHD in 2004 .Subsequently this definition has undergone refinement (ICHD2R 2006) but critically the key diagnostic criterion regarding absence of medication overuse has remained the same. Allergan decided to use their own definition of CM for their phase 3 clinical development program which was more in line with that suggested by Silberstein et al (Silberstein to the Classification Committee of the American Headache Society)(Bigal2006) and which was at variance with that agreed by ICHD. CM is defined as pain and symptoms associated with migraine without aura for 15 days or more per month for longer than three months without medication overuse. Withdrawal of the overused medication as soon as possible is the treatment of choice for medication overuse headache (Diener HC et al 2004,

ObermannM 2007) Currently guidance recommends withdrawal of acute pain medication to allow recovery from MOH and address the underlying primary headache disorder. (BASH 2010) to establish true clinical picture ,minimise the risk of further complications of the acute pain medications.Withdrawal of acute pain medication may result in conversion of a chronic daily headache pattern to an episodic one and increase responsiveness to previously ineffective prophylactic medications. Detoxification from acute pain medication is currently the cornerstones of management of MOH . The timing for introduction of treatment or prophylaxis of the underlying headache disorder (whether should be initiated either during or immediately following withdrawal) is unclear.. The applicant indicates that revisions to the CM diagnostic criteria are currently being discussed by the ICHD3 Committee making the point that the current criteria are included in an appendix to the ICHD and were intended to support further field testing and validation of the criteria. However an article by Olesen Chair of the ICHD indicates that the diagnostic criteria for migraine will probably not change and that CM will move from the appendix to the main body of the classification(Olesen 2011)
The RMS does not support inclusion of a recommendation regarding detoxification in relation to an indication for use for CM. Some physicians recommend starting prophylaxis at the time of withdrawal but the data supporting this are sparse. The data supporting these strategies are largely from case series, retrospective chart reviews and expert opinion. There is insufficient data available to support this proposal .It is unclear how Botox would work in this setting.

References

BASH Guidelines 2010 3rd edition (1st revision) 2010 www.bash.org.uk

BigalME The International Classification of Headache Disorders revised criteria for chronic migraine-field testing in a headache speciality clinic Cephalalgia 2007;27;230-234

Diener HC, Medication-overuse headache: a worldwide problem. Lancet Neurol. 2004;3(8):475

Obermann M, Katsarava Management of medication-overuse headache. Expert Rev Neurother. 2007;7(9):1145

Olesen J New plans for headache classification :ICHD-3; Third International Headache Classification Committee of the International Headache Society.Cephalalgia. 2011 Jan;31(1):4-5.
.

d. Prior Migraine Prophylaxis vs Prophylaxis naïve

The applicant argues that although a high proportion of patients evaluated in the phase 3 studies are naïve to first line BASH migraine prophylaxis (41.5%) this is consistent with what is with CM populations in general. In one population based study of CM, a high proportion of persons (87.6%) had sought care to discuss their headaches with a health professional. Yet, only 20.2% of those with CM received a diagnosis of CM, chronic daily headache or transformed migraine (Bigal et al., 2008; Manack et al., 2009). In this population based study 60% of persons with CM were prophylaxis naïve.
In the International Burden of Migraine Study-II (IBMS-II), a web-based population based survey of 8,726 eligible responders from nine countries (Australia, Canada, France, Germany, Italy, Spain, United Kingdom, Taiwan and United States), showed that overall 33.1% of persons with CM were prophylaxis naïve (Lipton et al., 2011).
Most (44.8%) persons with CM were not taking migraine prophylaxis at the time of the IBMS-II study (range was 40.7% to 62.0%); only 22% of these persons had previously tried a migraine preventive medication. Patients naïve to prior prophylaxis had a similar response to BOTOX® as

compared to patients who were not naïve. See Table 10 and further discussion in response to Point B below.
The Botox phase 3 studies were not powered to show statistically significant differences in a priori planned subgroups. Allergan accepts the RMS assertion that efficacy of BOTOX® in patients who are naïve to migraine prophylaxis has not been fully established**.**

Conclusion by applicant:

Prior Headache Prophylaxis vs. Prophylaxis Naïve: Given that analyses of prior prophylaxis (yes/no) were post-hoc and that the between group differences were larger for those patients who had had prior prophylaxis versus prophylaxis naïve, Allergan accepts the RMS recommendation as per the Final Variation Assessment Report that efficacy of Botox in patients who have never received migraine prophylaxis medications has not been fully established and agrees that the indication could be restricted to those patients who have previously failed prior migraine prophylaxis.

RMS Comment:

Low levels of prior prophylaxis in patients in the phase 3 studies raises the concern that patients may have had other diagnosis e.g. chronic tension type headache and were misdiagnosed and were being inadequately treated. It seems implausible that patients with true chronic migraine under the care of headache specialists/neurologists described in the studies would not have at least tried prophylaxis particularly with the longevity and with the level of disability known to be associated with the disorder. The RMS still requests that the indication should be restricted to those patients who have previously failed prior migraine prophylaxis. See proposed wording for 4.1 below.

e. Inclusion of Patients with Probable Migraine and Migraine with Aura

All patients enrolled into the Botox phase 3 studies had to have a diagnosis of ICHD-II (2004) section 1, Migraine. Thus, patients with an ICHD-II diagnosis of probable migraine were not enrolled. Data with regards to whether patients had a diagnosis of migraine without aura (ICHD-II 1.1) or migraine with aura (ICHD-II 1.2) was not collected in these studies, since either of these diagnoses met protocol requirements for a diagnosis of ICHD-II (2004) Section 1 "Migraine". As stated in the ICHD under section 1.2 Migraine with aura …" the aura is the complex of neurological symptoms that occurs just before or at the onset of migraine headache. Most patients with migraine have exclusively attacks without aura. Many patients who have frequent attacks with aura also have attacks without aura (code as 1.2 Migraine with aura and 1.1 Migraine without aura). ….The majority of migraine auras are associated with headache fulfilling criteria for 1.1 Migraine without aura." (Olesen et al., ICHD-II, 2004). A diagnosis of migraine without aura requires only that patients experience 5 attacks that fulfill criteria 1.1 in the patient's life-time

Allergan understands that the intent of the ICHD-II diagnostic criteria is to provide clinicians with specific criteria to make a clinical diagnosis. Allergan elected to additionally categorize each and every headache event as either migraine, probable migraine or tension-type by applying the criteria according to the individual symptoms recorded by the patient in the daily electronic diary as per the migraine without aura (ICHD-II section 1.1) criteria C and D. Thus, while patients may have had

accompanying aura with some of their headaches, based on the 28-day baseline characteristics of the population it appears clear that they had a very high mean frequency of migraine episodes (9.6 ± 5.32) and migraine/probable migraine episodes (11.8 ± 5.24) and thus, the vast majority of patients evaluated met diagnostic criteria for migraine without aura (ie., needing 5 life time events of migraine).

Applicants conclusion:

Probable Migraine: Patients with probable migraine were not enrolled into the study and therefore, Allergan does not believe that any revision to the proposed indication needs to address this issue.

Migraine with Aura: There is no evidence to suggest that efficacy would be different in patients who have been diagnosed as having migraine without aura and/or migraine with aura. Indeed, most patients who have been diagnosed as having migraine with aura also have a diagnosis of migraine without aura. Allergan does not believe that any revision to the proposed indication needs to address this issue.

RMS comment:

The two pivotal studies had an inclusion criterion specifying that at least 50% of baseline headache days are migraine or probable migraine days (ICHD-II 2004 sections 1.1[migraine without aura], 1.2 [migraine with aura] and 1.6 [probable migraine]) so although patients had to have a diagnosis of migraine this suggests that patients with probable migraine could also have been included in the study. The way in which the ICHD criteria are applied and which diagnoses are used impacts on the numbers who can be considered eligible for inclusion in the study. The prevalence of migraine can almost double if probable migraine (ICHD-2 1.6), i.e. cases which fulfil all but one of the criteria, is included in the definition cases that comply with all the criteria of either migraine without (ICHD-2 1.1) or with aura (ICHD-2 1.2) (Lanteri-Minet 2005). By aligning any potential indication with the approved ICHD -2R definition of CM this would exclude patients with probable migraine so the RMS does not consider that this needs to be specifically addressed in any proposed indication.
It is difficult to interpret the significance of distinguishing between migraine with or without aura in the context of CM. It is not known if the two types differ markedly in terms of the impact on the sufferer and if one group are more debilitated by their condition than the other. It does not seem to be risk factor for progression from EM to CM (Lipton et al 2009).The RMS agrees with the applicant that a revision to the proposed indication does not need to address the issue of migraine with or without aura.

References

Lanteri-Minet M, Valade D, Geraud G, Chautard MH, Lucas C. Migraine and probable migraine–results of FRAMIG 3, a French nationwide survey carried out according to the 2004 IHS classification. Cephalalgia. 2005;25(12):1146–1158.

Lipton et al. Tracing transformation Neurology 2009 ;72(Supp1);S3-S7

RMS overall conclusion : We still consider that the dataset is confounded by the inclusion of patients with acute medication overuse .

2.3 Point B (Inconsistent Outcomes)

Summary of Applicant's Response

Inconsistent outcomes for medication overuse yes/no; prophylactic treatment naïve yes/no.

Allergan respectfully disagrees with the assessor's interpretation that there are "inconsistent outcomes in various study subpopulations (medication overuse yes/no; prophylactic treatment naïve yes/no)". Subgroup analyses of the phase 3 CM studies based on overuse of acute headache pain medications at baseline (yes/no) and history of prophylactic headache medication use at baseline (yes/no) demonstrate statistically significant and clinically meaningful results for multiple headache symptom measures across each of the 4 sub-groups. Additionally, the magnitude of treatment response for patients who received Botox treatment during the DBPC phase was consistent across each of the 4 subgroups (Table 13). Please refer to Allergan's response in section 2.2 Point A (Heterogeneity of the Population) for a detailed summary and discussion of the evidence of efficacy for these 4 subgroups. In summary, the headache-related burden and disability in individual patients who have often suffered for decades is multifaceted, encompassing frequency, duration, and severity of headaches. Despite the severity, longevity, and refractory nature of their disease, these sub-groups of patients treated with Botox had statistically significant improvements from baseline in multiple headache symptom measures, irrespective of their baseline acute headache pain medication use or history of prior prophylactic headache medication use.

RMS comment:

A number of post hoc analyses were conducted to elucidate the efficacy of Botox in the following subgroups 1.Medication overuse yes/no; 2.Prophylactic treatment naïve yes/no. As previously highlighted the studies were not powered to demonstrate differences in these subgroups.
In relation to medication overuse although the magnitude of the change from baseline in Med-O No was comparable to that achieved for the Med O-yes subgroup this only reached statistical significance for one of the key endpoints (Headache days Botox -8.8 (-9.69, -7.98) placebo -7.3
(-8.16, -6.43) between group difference 1.5 (-2.78, -0.34) p value 0.013). 83% of this treatment effect can be attributed to placebo. The efficacy demonstrated in the Med O-no subgroup in the opinion of the RMS is most likely the true effect of Botox in patients this suggest only approximately 1/3 of participants included in the pivotal phase three studies had a diagnosis close to the ICHD2R diagnosis of chronic migraine. The subset defined as MedO yes is confounded by the fact that they may also be suffering from a MOH and the effect of Botox on MOH or an indirect effect of withdrawal of acute pain medications has not been elucidated. There is some evidence that merely by highlighting the possible role of medication overuse in headache chronification can result in a reduction in medication intakes and a reduction in those complaining of chronic headache.(Grande et al 2011) The RMS is of the opinion that there is a modest efficacy signal in patients who are not overusing acute pain medication and that this subpopulation most closely reflects the patient population with true chronic migraine.
Botox was ineffective in patients who prophylactic migraine treatment naïve .The reason for this is unclear .The applicant has agreed to reflect this in any agreed indication and the RMS supports this position.

References

Grande RB,. Reduction in medication-overuse headache after short information. The Akershus study of chronic headache. Eur J Neurol. 2011 Jan;18(1):129-37

2.4 Point C (Mean Duration of Headache)

The conflicting finding of an increased mean duration of headache episodes compared with the overall decrease in total cumulative hours of headache on headache days.

Summary of Applicant's Response

We appreciate the assessor's comment regarding what may appear as conflicting findings from two different analyses of the data from the phase 3 studies. Indeed, the analysis for mean duration of headache episodes shows that there was a mean increase, although minimally increased relative to the wide range and large standard deviation (see Appendix 1 Tables 1-1 to 1-4 from MRP response previously submitted). At the same time, the separate analysis of cumulative hours of headaches shows a substantial decrease. Since there is a difference in the nature of the calculations that were used to generate these two analyses, Allergan does not concur that the results are conflicting and would like to clarify. It is important to remember that the week-24 headaches are not the same headaches as those that occurred at baseline. That is, the same patients are followed throughout the study, but the headaches themselves are not the same. For example, if a patient started with 12 headaches of mean duration 25 hours and finished with 6 headaches of mean duration 30 hours, the cumulative hours would have decreased by 40%, even with an increase in the mean duration of a decreased number of headaches. The analysis of the mean duration of headaches indicates a small shift from the characteristics of the baseline headaches to the characteristics of headaches that occurred in the primary time period reported (ie. weeks 21 through 24), while the total cumulative hours of headache indicates the improvement in overall headache burden.

While the mean total cumulative hours of headache divided by the mean headache episode count would not account for the varying number of headache episodes across patients, it could give perspective to why there is no conflict in these results, especially if the division is by the mean baseline headache count. Continuing the example from above, if a patient had 12 headache episodes of mean duration 25 hours for baseline and then had 6 headache episodes of mean duration 30 hours for the primary time period ending with week 24, the overall decrease in total cumulative hours of headache would be 120 cumulative hours. This averages to a decrease of 10 hours per baseline headache, even in the presence of an apparent increase in the duration of headache episodes that occurred at week 24.

In summary, the mean duration of headache episodes for those events that occurred at week 24 (from weeks 21 through 24) was not substantially different from the mean duration of baseline headache episodes, relative to the variation observed and to the medians. The mean decrease in cumulative hours of headache is instead related to the substantial mean decreases in counts of headache episodes and headache days that occurred in these studies. Most importantly, there were significant differences favouring the Botox treated patients with regard to the overall mean reduction in burden of headache as represented by the statistically significant and clinically meaningful difference between treatment groups for the total cumulative hours of headache on headache days. Consistent with these results indicating that there was a decrease in the burden of headache, there were accompanying significant improvements from baseline favoring the Botox treated patients with regard to the overall improvements in functioning, vitality, psychological distress, and overall quality of life.

RMS comment:

As previously noted by the RMS 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 applicant has explained how the cumulative total of headache hours can reduce whilst the average episode duration can lengthen.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.

2.5 Point D (Unblinding)

The potential for unblinding effects of Botox due to its muscle relaxant effect and its potential impact on the study outcome

Summary of applicant's response

Allergan is confident that the blind was sufficiently maintained during the Botox phase 3 studies based on the justifications provided below:

- Allergan conducted these DBPC trials in a rigorous manner to minimize the potential issue of unblinding, including a range of methods to ensure blinding of both investigator and patient was maintained including 1) investigators, study site personnel, patients and sponsor staff were all blinded to the study treatment 2) study drug was prepared by an independent reconsituteur who was not involved in the conduct of the study 3) investigators were appropriately trained on how to objectively respond to patients who inferred they were unmasked.
- Only a small subgroup of patients treated during the DBPC phase of these studies reported potentially unblinding AE that pertained to the face (~11%) or the face and/or neck (~15%). Efficacy analyses performed without including these patients demonstrated that there were no substantial differences, supporting Allergan's position that efficacy results were not unduly influenced, and that the blind was adequately maintained;
- Only 1 placebo-treated patient reported „mild reduced forehead wrinkling", a potentially positive aesthetic response that could have resulted in potential unblinding of this subject. 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 wrinkling does not occur in all adults; therefore an aesthetic effect on wrinkles would not be expected to occur in all patients treated with Botox in the phase 3 studies. Facial wrinkles are more predominant in older (≥ 40 years) adults. Thus, an aesthetic effect from Botox might be more evident in older patients enrolled into these studies, which might in turn result in unblinding. If this were true, we would expect to see a larger mean change from baseline effect in older compared to younger patients. Analyses showed similar between treatment group differences in older and younger subgroups that both significantly favored BOTOX® vs. placebo. There was a smaller mean change from baseline in the frequency of headache days in older patients than younger, which suggests that patients were not unblinded due to a change in facial wrinkles;
- The dose and injection paradigm used to treat CM, although similar, does not overlap exactly with the injection paradigm for aesthetic treatment of the glabellar region (procerus and corrugators muscles), and is not expected to produce the same aesthetic effect. 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 CM, 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 and procerus muscles for CM is less than the total effective VISTABEL® dose suggested in the literature for aesthetic treatment for these same areas of the face;
- Potentially unblinding due to AE or other medicine effects is a ubiquitous issue in clinical research and is not unique to Botox. Unblinding either due to robust efficacy or an unusual but characteristic AE profile is always of potential concern in a drug development program. The very low rate of Botox related AE overall makes this less likely to have been a confounding issue in these studies. Other medicines recently studied

in the migraine field have reported very high proportion of patients with potentially unblinding AE or other significant clinical effects;

- High placebo response and lack of a nocebo effect indicate that the blind for placebo-treated subjects was maintained; Chronic Migraine Response to Referral Questions
- 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 comment :

Maintaining the blind in studies involving Botox is challenging. 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.
To evaluate any potential unblinding the applicant reviewed all potentially unblinding AEs and concludes that the absence of potentially unblinding AEs and no difference in efficacy analyses excluding these patients did not demonstrate any differences.
The lack of a nocebo effect and a high sustained placebo response are reassuring however it is unlikely patients were instructed about the motor and autonomic effects of Botox. Although 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. Participants may have been aware of 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 possibly 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. The applicant made every effort to ensure that the study blind was maintained during the conduct of the study. Furthermore there were no group differences in visit compliance or in the intakes of AHPM therapy for the placebo group, or exaggerated efficacy response in either subgroup so to that end the RMS considers that in so far as was possible the blind was maintained.

2.6 Point E (Mechanism of Action)
The lack of clarity regarding the potential mechanism of action of Botox in CM

Allergan Response:

A comprehensive response has been provided by Allergan with respect to the clinical diagnosis (differentiating the biology of episodic migraine and chronic migraine), the pathophysiology of migraine (biological basis, anatomical considerations, intra-extracranial interactions), mechanism of action (vesicular release/ recycling, neurotransmitter delivery, hyperalgesic receptor trafficking and delivery to plasma membrane). To review the data the reader is referred to the company response.

The summary review of the response focuses on the aspects considered most appropriate with respect to the issue of clarity regarding the potential mechanism of action of BOTOX as referred to in the question.

Overall the pathophysiology of chronic migraine has not been fully elucidated but it is considered that over the past two decades there has been considerable progress with respect to some biological insights into the biology of chronic migraine. Allergan has provided a review of these biological

insights and how BOTOX interferes with a number of biological components that have been associated in the literature with chronic migraine as well as confidential data, with a view to providing support for use of BOTOX in the treatment of chronic migraine.

Summary:

Individuals who suffer from chronic migraine are considered to have a CNS pathology that predisposes an individual to migraine attacks due to CNS hyperexcitability that may be related in some way to the observed electrophysiological phenomenon of cortical spreading depression (Goadsby, 2007). It is clear that the trigeminal nerve nucleus is a target, if not a primary focus of this hyperexcitability in migraine. This pain hypersensitivity may manifest as **a)** allodynia whereby pain thresholds are lowered so that normally benign stimuli become painful and **b)** hyperalgesia whereby noxious stimuli produce an exaggerated and prolonged pain. Pathological pain is a state when pain hypersensitivity persists long after an injury.

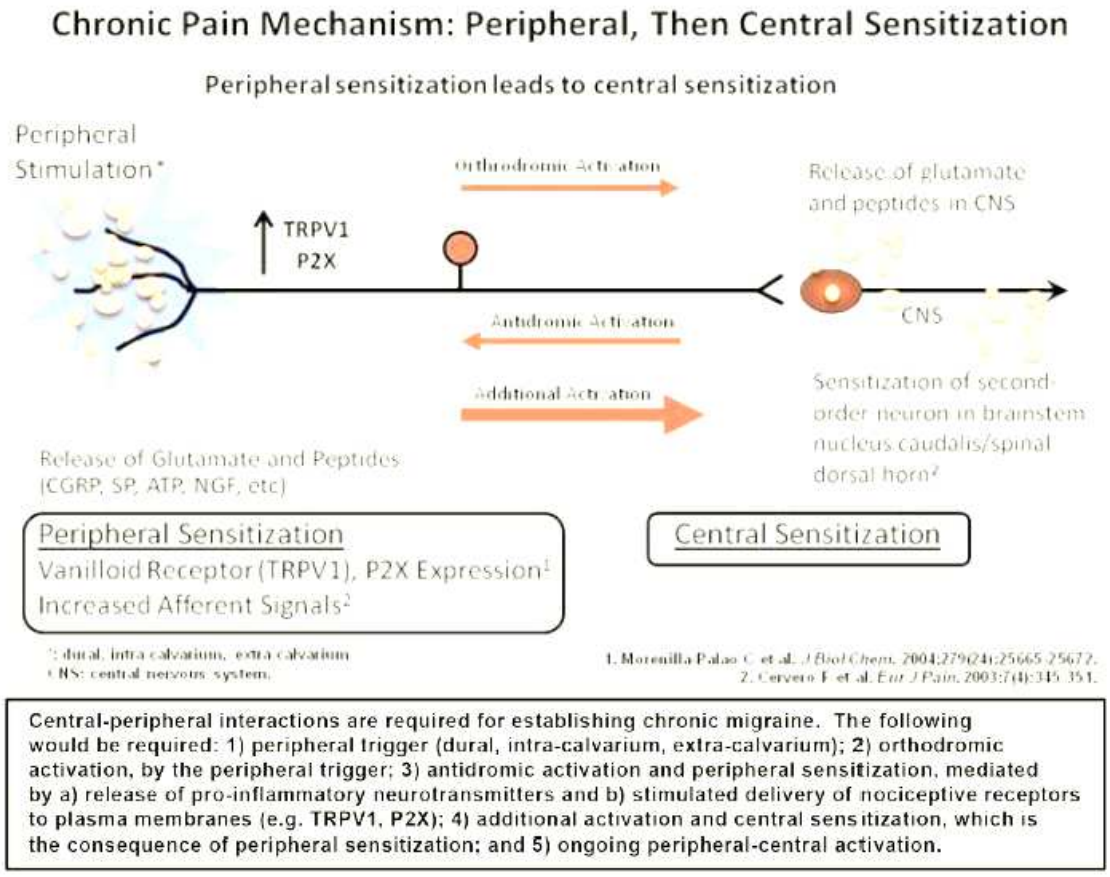
The symptoms that develop in patients as the migraine headache intensifies indicates that two well described pathophysiological processes are engaged, those of central and peripheral sensitization.

Peripheral sensitization is characterized by a reduction in the threshold for pain and increase responsiveness of the peripheral terminals of nociceptive fibers (C and A delta fibers). This increase in sensitivity is a feature of neurogenic inflammation and is a function of the effects of proinflammatory mediators, either released from the sensory neurons themselves (such as substance P and glutamate) or may be released from surrounding cells (such as kinins or histamine).

Central sensitization is increased excitability of neurons in the central nervous system whereby normal afferent activity produces abnormal responses. For instance, normally innocuous stimulation inappropriately activates neurons with heightened responses characteristic of noxious stimulation. This increased excitability is the consequence of alteration in the strength of synaptic connections – "plasticity" - between the peripheral nociceptor and the central neurons (spinal cord, brainstem) (Wolff, 2000). For the patient, the pain is mapped to the periphery even though the hyperexcitability is central in origin.

It is postulated that in biologically susceptible patients, pain may appear to arise from spontaneous stimuli that would never normally produce pain begin to do so. Upon initial peripheral activation (dural, intra-calvarium, extra-calvarium), unmyelinated C-fibers release pro-inflammatory molecules such as CGRP, glutamate and substance P (Holzer, 1988) which, in turn, trigger neurogenic inflammation (Moskowitz, 1984; Moskowitz and Macfarlane, 1993; Kosaras et al., 2009). Neurogenic inflammation includes local vasodilatation and increase in blood flow of intracranial extracerebral blood vessels, the release of vasoactive sensory neuropeptides, leakage of plasma protein from blood vessels, mast cell degranulation, and platelet aggregation. A further insult, affected nerves are subject to auto-activation where little, if any, noxious stimulus is required to sustain their activation (Figure 1, Peripheral and Central Sensitisation). Trigeminal orthodromic1 sensory afferents are stimulated with consequent release of peptides including CGRP, neurokinin A, substance P and glutamate (Goadsby, 1988; Zagami 1990). These activated orthodromic fibers also transmit information to central neurones in the trigeminal and other brainstem sensory nuclei that in turn relay the pain signal to higher cortical structures for registration and modulation of nociceptive information. The central changes regulate peripheral mechanisms, and antidromically stimulated C-fibers may have activated kinases, which increase TRPV1 and P2X receptors. These antidromically stimulated C-fibers may further release pro-inflammatory modulators, which can cause auto sensitisation of these receptors (Caterina, 1997) and result in additional orthodromic stimulation, thus establishing the peripheral - central pain cycle as depicted in Figure 1.

The proposed biology is outlined in figure 1:



Central-peripheral interactions are required for establishing chronic migraine. The following would be required: 1) peripheral trigger (dural, intra-calvarium, extra-calvarium); 2) orthodromic activation, by the peripheral trigger; 3) antidromic activation and peripheral sensitization, mediated by a) release of pro-inflammatory neurotransmitters and b) stimulated delivery of nociceptive receptors to plasma membranes (e.g. TRPV1, P2X); 4) additional activation and central sensitization, which is the consequence of peripheral sensitization; and 5) ongoing peripheral-central activation.

BOTOX acts in the periphery entering neurons and interfering with vesicular recycling and consequent exocytosis as specific delivery functions 1: interference with neurotransmitter release and 2) decreases the presentation of stimulated channel receptors, including TPRV1 and P2X to the neuronal membrane thereby inhibiting the hypersensitizatoin of the sensory afferent. Furthermore, by interfering with receptor delivery into nerve membranes, BOTOX® "*downregulates*" a sensory nerves capacity to respond to stimulating neuropeptides and transmitters that mediate propagation of pain.

This mechanism of action of BOTOX is considered to be supported within the literature and is also considered to be supported by *in vivo* studies that demonstrated the ability of BOTOX to prevent hyperalgesia in a number of animal models of peripheral sensitization which have previously been reviewed.

BOTOX can inhibit pheripheral activation at the site of injection or within close proximity to the site of injection and thereby sensitization. Allergan has provided data to support to understand and elucidate how extracanial effects can affect intracranial phenomenon experimental. This data is considered to be crucial to understanding and supporting the mechanism of action of BOTOX in the prophylactic treatement of chronic migraine.

The anatomical substrate of extracranial/ intracranial interactions was described recently in a study titled "Senory innervations of the calvarial bones of the mouse" (Kosaras et al., 2009). The authors used advanced technology that allowed entire calvaria to remain intact while being processed immunohistochemically for the presence of pain fibers. They found that calvarial sutures constituted major passageways through which peripherin-and CGRP-labeled fibers established connections between the intracranial meninges and extracranial periosteum and scalp. The mass of labeled fibers followed the very complex architectural organization of the calvarial sutures including the sagittal coronal (Figure 2), squamos and lambdoid (Figure 3).

Figure 2 CGRP-labeled fibers entering the coronal suture from the dural side (i.e. intracranially) exiting at the periosteum (i.e. extracranially)

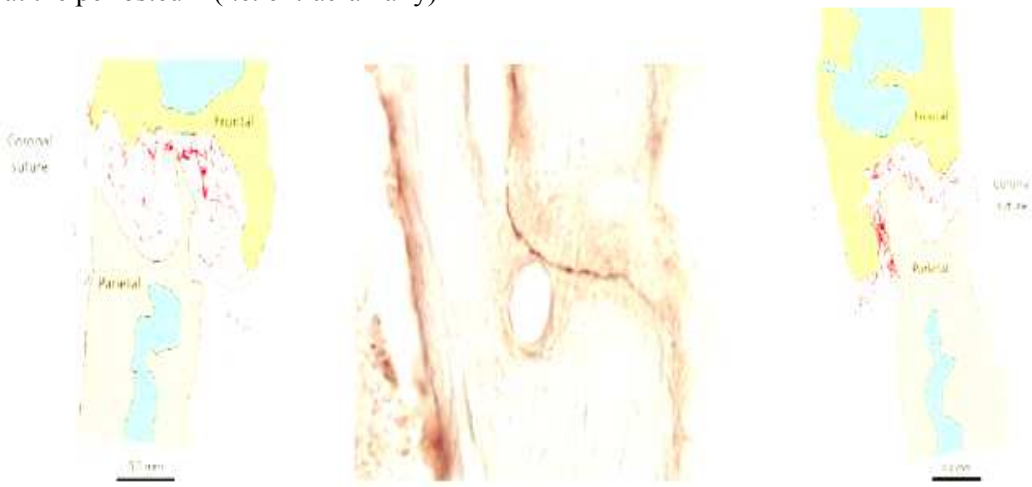
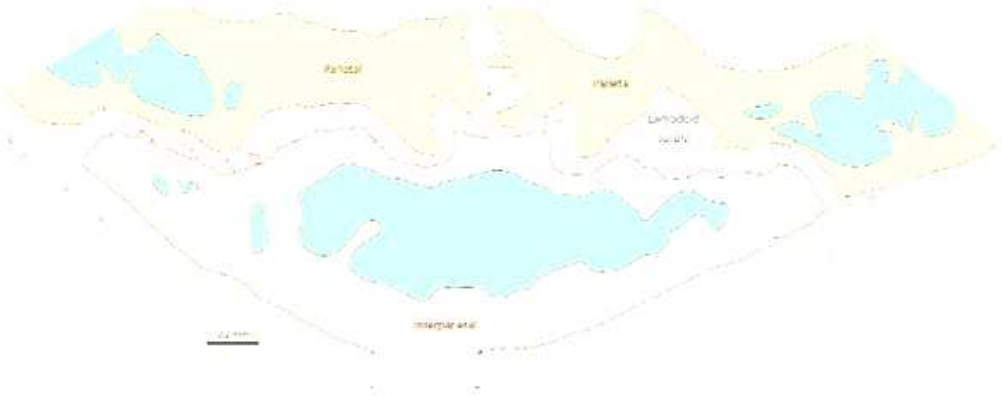


Figure 3: CGRP-labelled fibers entering the lambdoid suture from the dural side (i.e., intracranially) and exiting at the periosteum (i.e., extracranially).



Based on these findings, it was proposed that meningeal nerves that infiltrate the periosteum through the calvarial sutures may be positioned to mediate migraine headache triggered by pathophysiology of extracranial tissues, such as muscle tenderness and mild trauma to the skull. These findings, and their implications to the pathophysiology of migraine headache, are summarized in the figures below (Figure 4 and Figure 5).

Figure 4: Extracranial origin of intracranial pain. In this scenario, action potentials generated at extracranial collateral of meningeal pain fibers (1) spread antidromically to collateral that terminate inside the cranium, resulting in local release of proinflammatory neuropeptides and activation of neighboring meningeal nociceptors (2).

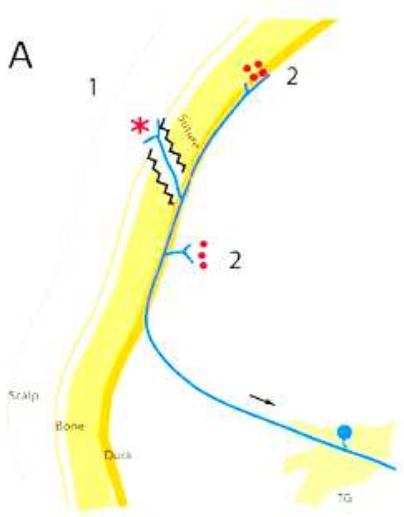
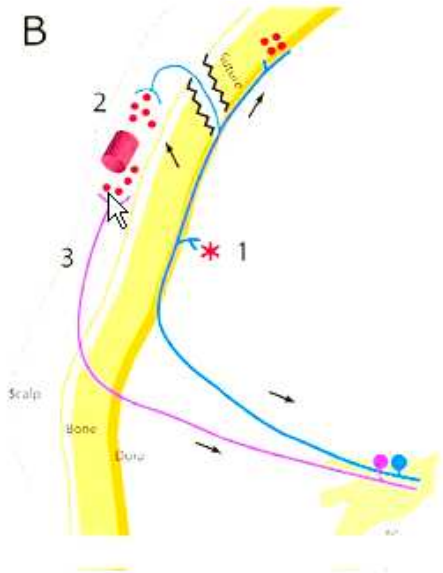


Figure 5: Intracranial origin of extracranial pain. In this scenario, action potentials generated at intracranial meningeal pain fibers (1) spread antidromically to collaterals that terminate outside the cranium (2), resulting in local release of proinflammatory neuropeptides in the scalp and activation of neighboring somatic nociceptors (3). Asterisk marks original site of activation. Red dots represent local release of inflammatory neuropeptides (e.g. CGRP, substance P). Red cylinder depicts a blood vessel (e.e. temporary artery). TG, trigeminal ganglion.



The authors also proposed that action potentials generated intracranially at the leptomeningeal pain fibers spread antidromically to collaterals that terminate outside the cranium, resulting in activation of neighbouring somatic nociceptors through local release of proinflammatroy neuropeptides in both the dura and the scalp. This concept would be consistent with extracranial perivascular edema observed in some patients undergoigng a migraine attack (Graham and Wolff, 1938; Wolf et al., 1953).
The following novel data (Figure 6, Figure 7, Figure 8, Fgure 9, Figure 10, and Figure 11) have been provided by Dr. Rami Burstein (Beth Isreal Deaconess Medical Center, Harvard Medical School). **These data are currently unpublished and should be regarded as confidential.**

Based on the above findings, it was hypothesized that extracranial injections of BoNT/A can interact with the extracranial (unmyelinated) nerve endings of intracranial meingeal nociceptors and inhibit their activation by pathophysiologies arising either extracranially (such as muscle tenderness) or

intracranially (such as aura). The experimental setup used to test this hypothesis is illustrated in Figure 6. Briefly, a recording electrode was placed in the trigeminal ganglion and 2 tiny holes were drilled into the bone in order to insert +/- (bipolar) electrodes that allow the identification of meningeal nociceptors with slow conduction (in the C-fiber range). Once identified mechanical pressure was applied on the parietal bones in an effort to squeeze branches that cross the suture. When such a response was identified, calibrated forces were then applied on and around the suture until the location where the axonal branch emerges from the suture to the periosteum was found (Figure 7).

Figure 6: Electrophysiological characterization of a meningeal nociceptor issuing a collateral branch that traverses the skull through the suture.

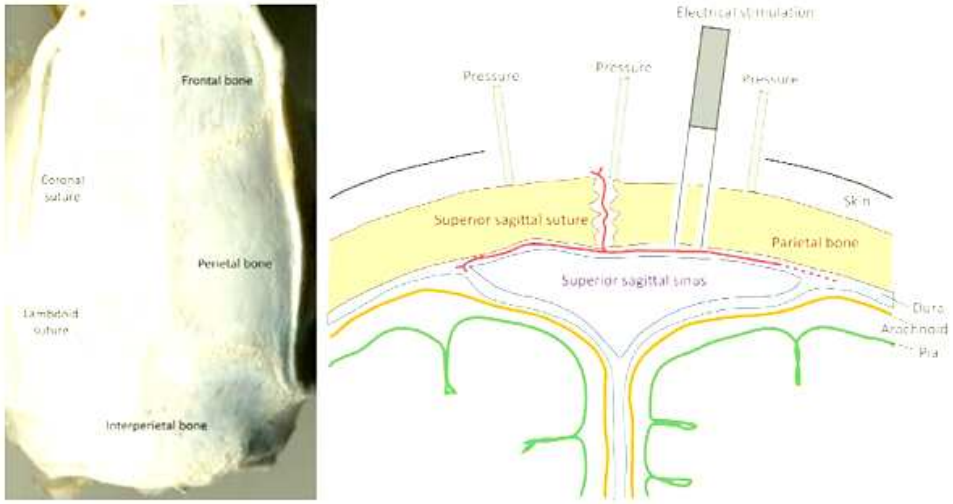
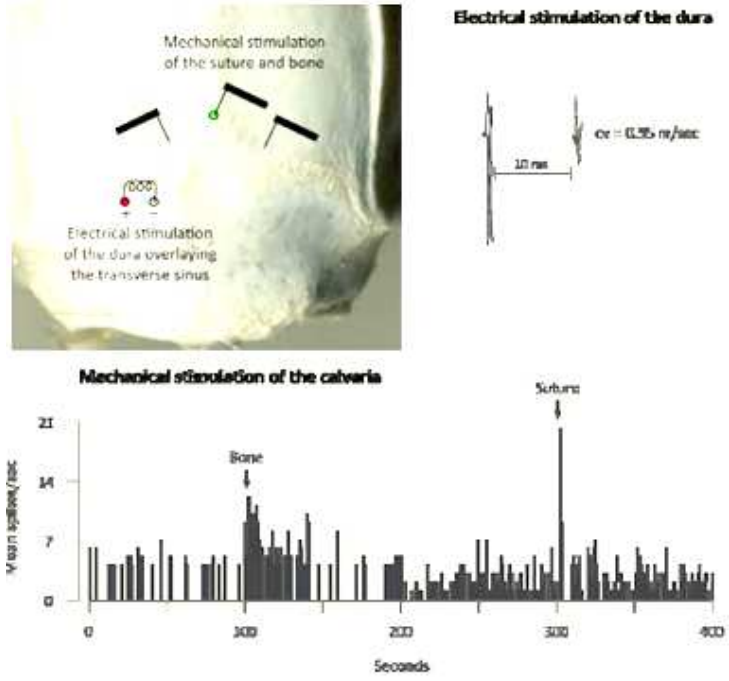


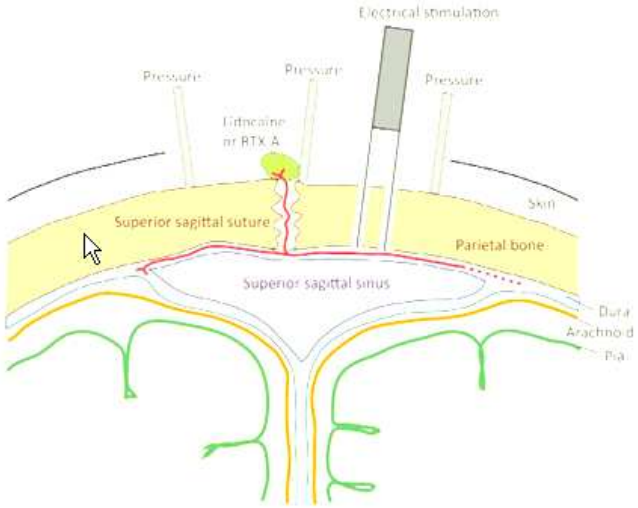
Figure 7: Identification of a suture branch of meningeal nociceptor.



After identifying meningeal nonciceptor that issues a collateral branch through the suture to the periosteum, lidocaine was applied topically and extracranially to the suture and the activity of the nociceptor and its ability to respond to mechanical stimulation of the suture was monitored. After

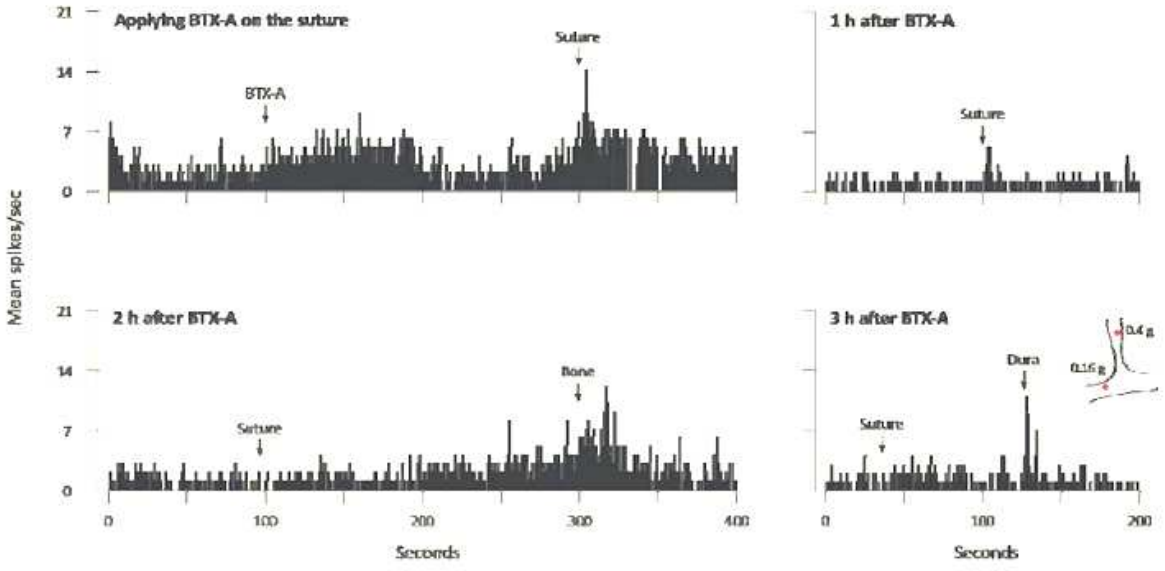
documenting that lidocaine blocked the ability to activate the nociceptor from the suture, the lidocaine-treated area was rinsed and sufficient time was allowed for functional recovery. After recovery, BoNT/A was applied topically/ extracranially to the area above and around the suture as shown in Figure 8.

Figure 8: Extracranial administration of BoNT/A to a suture/ periosteal receptive field of a meningeal nonciceptor.



Two hours after topical administration, BoNT/A blocked the ability to activate the suture branch of the meningeal nociceptor by applying pressure on the suture but not by applying pressure on the bone (Figure 9). The interpretation of these findings is that BoNT/A blocked the mechanosensitivity of the extracranial branch of the meningeal nociceptor but not the mechanosensitivity of the intracranial branches of this same nociceptor (the pressure on the bone is believed to activate the dural branch intracranially).

Figure 9: Extracranial administration of BoNT/A reduced the mechanosensitivity of the suture branch at 1 hr and blocked it completely at 2 hrs (compare neuronal response when pressure was applied to the suture immediately after, and 1, 2, and 3 hours later).

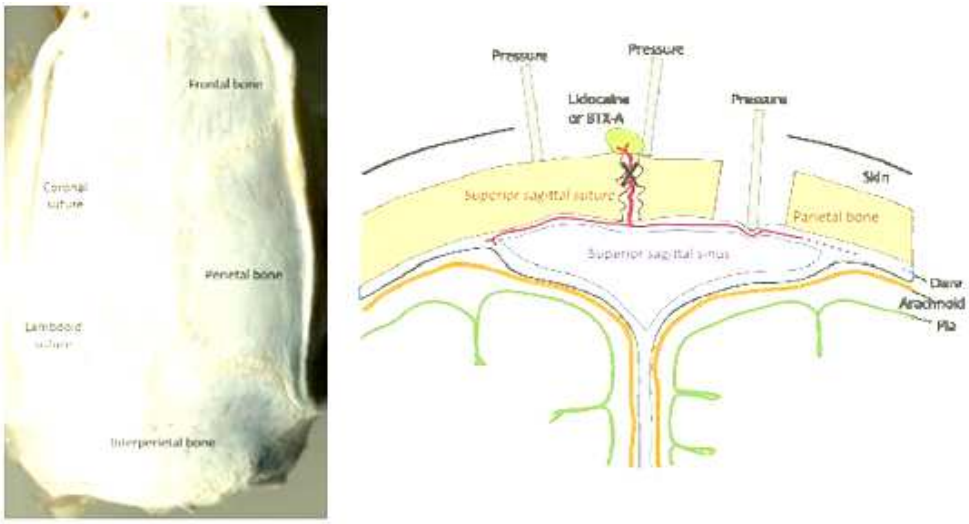


To determine more precisely the effect of extracranial administration of BoNT/A on the activity of the intracranial branch, the bone overlying the dural receptive field (as identified by the electrical

stimulation) was removed as shown in Figure 16 and the responsiveness of meningeal nociceptor to mechanical stimulation of the dura was then tested. As shown in the bottom left corner of Figure 9, mechanical indentation of the dura induced a brief burst of action potentials in the nociceptor.

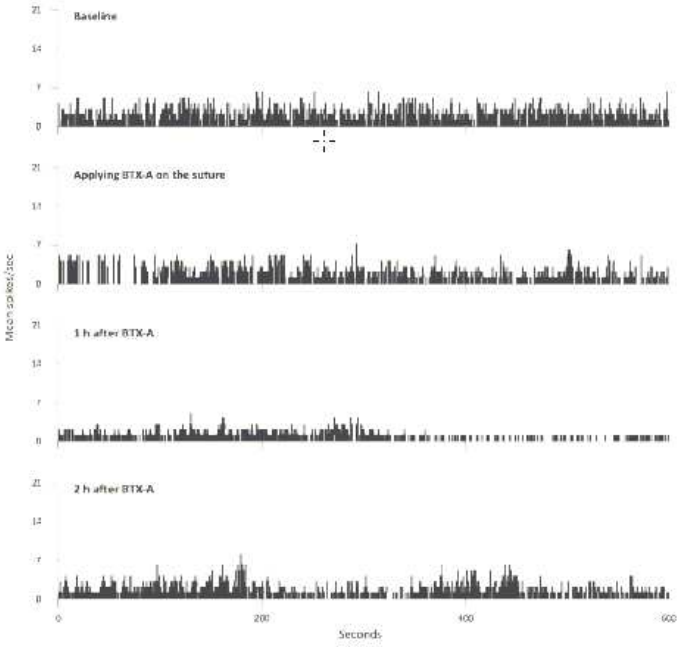
These findings correlate well with the clinical experience as BOTOX therapy does not eliminate patients ability to perceive intracranial pressure when sneezing, coughing or bending over.

Figure 10: Removal of the clavarial bone allowed stimulation of the dura mechanically after extracranial administration of BoNT/A to a suture/ periosteal receptive field of the meningeal nociceptor.



The final part of this set of experiments identifies the mechanism by which it is believed BoNT/A reduced migraine headaches. It dramatically reduced the spontaneous activity of the nociceptor (Figure 11). Current understanding of systems neurobiology suggests that the ongoing activity of the nociceptor is correlated with the ongoing pain (or headache in our case). Thus the single most important factor in judging the efficacy of a drug in an animal model (using electrophysiological recordings) is the spontaneous activity as it is the pain and its intensity that bring patients to the clinical rather than the mechanical allodynia.

Figure 11: Extracranial administration of BoNT/A inhibits the spontaneous activity of a C-fiber meningeal: Note that 1 hour after BoNT/A administration spontaneous activity dropped 60%, An hour later after the bone was removed (as shown in Fig 16.) spontaneous activity increased again in response to the massive tissue injury.



In other words Figure 11 demonstrates that the intracranial inhibitory effects of extracranially applied BoNT/A. It thus provides a reasonable answer to a question that has puzzled us for many years.

Sensory affertent mechanisms, BOTOX demonstrate an antinoceptive effect as evidenced in human models.

Gazerani has explored the anti-nociceptive effect of BoNTA by developing an experimental human model of trigeminal sensitization induced by intradermal capsaicin injection to the forehead or neighboring regions. In two studies Gazerani demonstrated that BOTOX had a significant suppressive effect on pain, flare and hyperalgesia, with the pain intensity and the mean area of hyperalgesia significantly smaller in the BOTOX group. They also showed significant differences across the trials with a significant suppression effect of BOTOX® on capsaicin-induced sensory and vasomotor reactions as early as week 1 ($P<0.001$). They concluded that BOTOX® caused suppressive effects on the trigeminal/cervical nociceptive system activated by intradermal injection of capsaicin to the forehead, and deemed these to be local peripheral effect of BOTOX® on cutaneous nociceptors. They concluded that BOTOX® preferentially targeted C-fibers and probably TRPV1-receptors, blocking neurotransmitter release and subsequently reducing pain, neurogenic inflammation and cutaneous heat pain threshold.

Assessors Comments:

The applicant acknowledges that the pathophysiology of chronic migraine has not yet been fully elucidated. A number of biological insights have been gained over the past decade with respect to the aspects of the pathophysiology and the applicant has provided a discussion with respect to these aspects and the role of BOTOX with respect to interfering with a number of these aspects and thereby having a proposed role in the treatment of chronic migraine has been discussed. It is acknowledged that BOTOX interfers with release and recycling of neruomodulators and receptor trafficking of neuropeptides/transmitters and receptors that have an important role to play in peripheral sensory neuron activation and the up-regulation of nociceptors and this is supported within the literature and by the animals and humans studies presented.

However it is more debatable as to how this relates to migraine.

The applicant had presented a model which in summary proposes that in suseptabile (hyperexcitable) individuals initial peripheral activation (dural, intra-calvaraium, extra-calvarium) of unmyelinated fibers releases proinflammatory molecules which in turn trigger neurogenic inflammation (feature of which have been associated with migraines). As a result of the inflammation the nerves are sensitized and are subject to auto-activation where little if any stimulus is required to sustain their activation. Further to the peripheral events orthodromic sensory afferents are stimulated with consequent release of peptide including CGRP, neurokinin A, substance P and glutamate (Goadsby, 1988; Zagami 1990). These activated orthodromic fibers also transmit information to central neurones in the trigeminal and other brainstem sensory nuclei that in turn relay the pain signal to higher cortical structures for registration and modulation of nociceptive information. The central changes regulate peripheral mechanisms, and antidromically stimulated C-fibers may have activated kinases, which increase TRPV1 and P2X receptors. These antidromically stimulated C-fibers may further release pro-inflammatory modulators, which can cause auto sensitisation of these receptors (Caterina, 1997) and result in additional orthodromic stimulation, thus establishing the peripheral - central pain cycle as depicted.

On the basis of the proposed biological model of migraine it is considered plausible that extracranial administration of BOTOX can interfere locally with the release of neuropeptides/ transmitters and receptor trafficking, which in the case of the proposed route of administration is extracranial. Extracranial administration of BOTOX could prevent any initial over activation (whether the signal is due to an extracranial or intracranial event) as well as preventing the feedback effect, antidromic signal from the sensitized trigeminal nucleus. By preventing the initial signal or even dampening down the initial extracranial signal BOTOX may reduce the pain intensity thereby inhibiting the antidromic signal from resulting in further exacerbation or release of further neuropeptides and transmitters thereby also reduce the intensity. Inhibition of this feedback system may inhibit further prolongation of the inappropriate detection of pain which manifests as chronic headache.

It is acknowledged that BOTOX acts locally, however ALLERGAN have provided data to support the hypothesis that extracranial injections of BOTOX can interact with the extracranial (unmyelinated) nerve endings of intracranial meningeal nociceptors and inhibit their activation by pathophysiologies arising either extracranially (such as muscle tenderness) or intracranially (such as aura). These experiments demonstrated that BOTOX blocked the mechanosensitivity of the extracranial branch of the meningeal nociceptor but not the mechanosensitivity of the intracranial branches of this same receptor. However it has been shown and is believed to be the mechanism of action by which BOTOX reduces the spontaneous activity of the nociceptor with current postulated understanding being that the ongoing activity is correlated with the ongoing pain.

In this circumstance it is acknowledged that extracranial administration of BOTOX resulted in the reduction of spontaneous activity, however it is noted that the trauma of removing the bone caused an increase in activity. In this model it has not been shown that extracranial administration of BOTOX would inhibit/ reduce the activation of intracranial neurons in response to an intracranial phenomenon or prevent the release of neuropeptide/ transmitters or interfere with the trafficking of receptors at these sites distal to the site of administration. Given that the etiology of migraine is unknown it is not clear that BOTOX would act prophylactically to prevent the initial peripheral activation (albeit electrical, chemical or mechanical) outside of the normal spontaneous activity from providing a sufficient stimulus to cause intracranical release of neurotransmitters/ peptides resulting in neurogenic inflammation. Furthermore if an intracranial phenomenon was responsible for the peripheral activation of intracranial neurons and their activation resulted in localized sensitization, it is not clear that extracranial administration of BOTOX would reduce the signalling following sensitization in a similar manner to the observed reduction in spontaneous activity.

The humans studies presented are in line with the animal models, whereby peripheral administration of BOTOX caused a significant suppressive effect on pain, flare and hyperalgesia, however unlike the animal models a recording of a reduction in the pain intensity and the mean area of hyperalgesia were also observed following intra-dermal administration of capsaicin. These studies do not address the

concern regarding the intracranial phenomenon that may be associated with the initiation of chronic migraine but are considered to demonstrate that BOTOX can prevent/ reduce extracranial signalling that may contribute to the overall perception of peripheral pain both the intensity and the duration.

2.7 Point F (Lack of supporting evidence of efficacy of Botox in patients with episodic migraine and tension headache)

Lack of supporting evidence of efficacy of Botox in patients with episodic migraine (and tension headache).

Summary of applicant's response

CM and EM may exist along a clinical spectrum with remission and progression between the two, yet, these disorders are distinct and differ in severity and overall burden (Lipton et al., 2009; Manack et al., 2010). The migraine attacks that occur with EM and CM share many characteristics; however, sufficient differences exist such that different clinical and epidemiological profiles between the two are apparent (Manack et al., 2010). While the populations overlap (as evidenced by some people with EM who progress to CM and vice versa), there is believed to be a different pathophysiology, primarily influenced by the contribution of peripheral and central sensitization in susceptible persons, which appears to be different in EM and CM (Dodick and Silberstein, 2006; Aurora et al. 2011). In CM there is a constant peripheral sensitization due to the frequency and intensity of headache in these patients, which likely gives arise to a near constant central sensitization. In contrast, with EM there are long periods, sometime weeks to months, between headache attacks and thus, in EM there is not the constant peripheral and central sensitization that is seen with CM. Given the recent gains in the understanding of differences between CM and EM, which are further discussed below, it not surprising that differences in clinical response to preventive therapy can vary between the two patient populations. Indeed, the recognition of the two disease states within the ICHD-2 guidelines is designed to facilitate the optimal treatment paradigm and the development of therapies specifically targeted at either CM and/or EM.

Key Elements from Migraine Development Program

CM is a distinct disorder with a clinical profile, epidemiological profile and proposed pathophysiology different from that of EM; thus, it is not likely the treatment response to Botox would be identical between the two patient populations.

Allergans clinical development program evaluating the use of Botox in migraine patients included 7 exploratory, randomized, double-blind, parallel group studies in 1,640 adult patients with EM (studies 191622-005, 191622-009, 191622-024, 191622-026, 191622-036, 191622-037, and 191622-509). Botox treatment was found to be well tolerated at doses ranging from 6 U to 260 U and thus support the safety of the product. Overall, the EM studies failed to demonstrate statistically significant efficacy differences between Botox and placebo. While it is possible that Botox is not effective in this patient population, perhaps because the underlying disease pathophysiology is different than that of CM, it is also possible that patient selection criteria and/or the dosage and treatment paradigm evaluated in these exploratory studies were not optimal. Regardless, Allergan has ceased pursuing clinical development activities in patients with EM, for which there are other preventive therapies that have demonstrated efficacy in EM. Instead, Allergan has focused efforts towards the development program for CM patients, who have the most substantial headache-related burden and highest unmet medical need. Safety data, but not efficacy data, from these EM studies were summarized in the CTD as these data are relevant to the evaluation of the overall safety of Botox for CM prophylaxis (see Module 5.3.5.3, ISS Text and Module 2.7.4).

Differentiation between Chronic and Episodic Migraine

Current epidemiological research continues to improve the understanding of CM and EM. Recently published data supports the concept that the two disorders differ with regard to clinical definitions,

prevalence, symptom profiles, functional consequences and disabilities, indirect and direct costs, patterns of consultation and treatment, rates of co-morbidities, and risk factors (Manack et al., 2010). In addition and given that the disorders separate on multiple levels, it has been hypothesized that there are also pathophysiological differences, which in turn suggests that treatment response may vary between the two populations (Aurora et al, 2011).

Cortical excitability is more prominent in CM vs. EM (Lipton 2009). Comparing the performances of normal subjects to those with EM and also to those with CM, those with CM have the highest baseline level of cortical excitability as seen by their failure to visually suppress stimuli (Aurora et al., 2007). Those with CM have also been show to have significantly lower phosphene thresholds in transcranial magnetic stimulation (TMS) (Aurora et al., 2005). Additionally, trigeminovascular sensitisation occurs in CM. Evidence increasingly suggests that the progression from peripheral to central sensitisation of trigeminal neurons may contribute to the "chronification" of migraine (Dodick and Silberstein, 2006). Repetitive activation of the trigeminovascular neurons and consequent repetitive activation of modulatory pain pathways in the PAG may lead to structural changes of functional impairment within those with CM (Lipton et al., 2009). There is also evidence that brainstem pain center dysmodulation may be occurring in CM. It is known that rostral brainstem nuclei such as the periaqueductal gray matter (PAG) play a role in modulating sensory information changes in those with CM (Bigal et al., 2008) (Aurora et al., 2007). Brain imaging such as PET, functional MRI (fMRI) and volumetric MRI has enabled researchers to see structural changes, including reduction of grey and white matter, in the brainstem and in both lateral and medial pain pathways in individuals with CM (Chiapparini et al., 2010). Furthermore, iron homeostasis, an indicator of brain function, is impaired in the PAG of migraineurs in a progressive fashion that positively correlates to duration of illness (Welch et al., 2001).

CM differs from EM with regard to clinical profile, epidemiological profile and proposed pathophysiology. It is not likely that patterns of treatment or treatment responses to acute or preventive therapies would be identical between the two patient groups. Indeed, the recognition of the two disease states within the ICHD-2 guidelines is designed to facilitate the optimal treatment paradigm and the development of therapies specifically targeted at either EM or CM. Additionally, to ensure utilization in the appropriate migraine population, the proposed SPC includes wording that Botox is not recommended in those with EM.

With regard to the use of Botox in patients with tension headache, we acknowledge the lack of supporting evidence for efficacy. Allergan has not comprehensively evaluated Botox efficacy in chronic or episodic tension type headache (TTH). A single phase 2, double-blind, placebo-controlled, 6 dose group, exploratory study was performed to evaluate the efficacy and safety of Botox as prophylaxis for chronic tension-type headache (Silberstein et al, 2006). The primary efficacy endpoint, mean change from baseline in number of TTH-free days per month at Day 60, was not met in this study. There was no statistically significant difference between placebo and four Botox groups for the primary efficacy endpoint, but a significant difference favouring placebo vs. Botox 150 U was observed (4.5 vs. 2.8 tension headache-free days/month; $P = 0.007$). All treatment groups showed mean improvements from baseline at day 60. Although efficacy was not demonstrated for the primary endpoint, more patients in three Botox groups had $\geq 50\%$ decrease in TTH headache days than did placebo ($P \leq 0.024$) at Day 90. Other reports of results from small, double-blind, placebo-controlled studies with botulinum toxin type A in patients with chronic TTH have also failed to separate from placebo (Gobel et al., 1999; Rollinick et al., 2006). However, there are several positive open-label studies reported in the literature (Jost and Gobel, 2003).

Thus, there is insufficient evidence to demonstrate efficacy of Botox in treating tension headache. However, the mechanism by which we believe Botox prevents headache in CM does not clearly apply to tension headache. In CM there is peripheral and central sensitization; Botox intervenes in this process (as describe in section 2.6 above). This mechanism is not known to be as relevant in tension headache. Whether or not a different mechanism (such as neuromuscular relaxation) could be relevant to treatment of tension headache is not known. However, to our knowledge, headache experts have not found utility of Botox in this condition in clinical practice and this is not an area that has been systematically evaluated. The dose paradigm for CM was specifically developed to follow the distribution of the trigeminal nerve, known to be important in the pathophysiology of CM.

As outlined above with EM, those suffering from tension headache represent a different patient population with different patterns of treatment and treatment responses from those with CM. We presume that the assumption that Botox would be effective within those with tension headache is based on the known mechanism of action which is specific to muscle relaxation. However, this premise is not aligned with our current understanding of the mechanism of action for Botox in CM. [See Allergan response to Point E, section 2.6 above, for an overview of the current understanding of the pathophysiology of CM and the mechanism of action for Botox in CM.]

RMS Comment:

The applicant discusses episodic migraine and chronic migraine as two distinct clinical entities with different epidemiological profiles and a different pathophysiological basis. They support this argument by referring to various publications that outline various hypotheses for the underlying pathophysiological process for EM and CM (levels of cortical hyperexcitability, trigeminal sensitisation(progressive central sensitisation) with structural changes to the PAG ,changes in iron homeostasis etc) These are all combined to form complex hypotheses that underpin much of the current clinical research but it remains unclear where chronic or acute migraine for that matter fits into these current theories of migraine pathogenesis . Lipton et al (2009) state that headache experts conceptualize the transformation from acute migraine to chronic migraine with a model that envisions transition into and out of four distinct states: no migraine, low-frequency episodic migraine (<10 headaches per month), high-frequency episodic migraine (10-14 headaches per month), and chronic migraine (CM, >or=15 headaches per month) and that this transition may be in the direction of increasing or decreasing headache frequency and is influenced by specific risk factors. Some commentators argue that the rigid 15 day cut-off makes no sense and question whether frequency of headache has any bearing on tractability (Goadsby et al 2008) Overall 2.5% of the low-frequency episodic migraine or high-frequency episodic migraine population studies will transition to CM per year. In a population based study conducted by Allergan 26% of respondents who had CM had remitted after 2yrs.(Manack A .2011) This suggests that the transition between EM and CM can be both ways and that over the lifetime of somebody suffering with CM the natural history of the disorder will result in periods of remission. In this context EM and CM seem to part of a continuum rather than two distinct clinical entities. It is clear that there is a lack of clinical consensus regarding the clinical profile of CM and that the relationship between EM and CM requires further investigation and clarification.
Regarding patients with TTH these represent a different patient population with different patterns of treatment and treatment responses from those with CM. TTH was not evaluated as part of the dossier so no further discussion is warranted.

References

Lipton RB. Tracing transformation: chronic migraine classification, progression, and epidemiology. Neurology. 2009 Feb 3;72(5 Suppl):S3-7

Goadsby P Refractory Migraine headache 2008;48-799-804 2008

Manack A., Rates, predictors, and consequences of remission from chronic migraine to episodic migraine Neurology 2011;76:1–1.

2.8 Point G (Dose-finding data and treatment paradigm rationale)
The lack of convincing dose-finding data and a clear rationale for the proposed treatment paradigm (fixed dose-fixed site vs. follow-the-pain).

Summary of Applicant's Response

As is true for any therapeutic treatment, the lowest effective dose is recommended. Allergan believes that sufficient exploration of a safe and well-tolerated, and effective B**otox** dose has been determined over the course of the Botox headache clinical development program. Furthermore, patients evaluated in the phase 3 studies responded to 155 to 195 U of Botox using the fixed dose-fixed site and follow the pain treatment with significant, consistent, and sustained improvements over placebo treatment across multiple headache symptom measures and health related quality of life measures.
As discussed above, the trigeminal nerve is the target end organ for Botox treatment of CM. Because of the unique delivery method required for this locally acting agent, a delivery paradigm was developed targeting the trigeminal nerve distribution in order to ensure that the protein reaches the nerve terminal. See further discussion of Botox mechanism of action in Allergan response to Point F.
See further information related to dose-finding data and a rationale for the proposed treatment paradigm fixed dose-fixed site vs. follow-the-pain in Appendix 4.

RMS comment:

The doses, sites of application and treatment intervals used in the phase three studies were justified on the basis of the findings of the two phase 2 studies in CDH that did not have positive outcomes for the primary endpoints. Due to the lack of proper dose finding studies a minimum effective dose has not been identified so it is unclear if an optimal dosing strategy has been developed. 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. No direct comparative studies exist evaluating different injection sites or routes of injection (intradermal vs. intramuscular. Further studies to define the optimal dose ,site ,depth and number of injections are warranted.
However on the basis that a treatment effect has been demonstrated and the safety profile reported in the phase 3 studies is in keeping with the known safety profile for comparable indications the proposed treatment paradigm can be accepted.

3. RMS overall conclusion on applicant's response to CMD referral list of questions.

The study population presented in this application had suffered on average with CM for more than 20 years was highly disabled, and experienced an average of 20 headache days per month. Patients were inadequately treated by available medical therapies, even though surprisingly approx one third had never been treated with headache prophylactic medications and approximately two-thirds had previously failed to respond to headache prophylactic medications. Two thirds of the patients with Allergan defined chronic migraine were overusing acute pain medication at baseline even though this does not necessarily indicate that all of the patients were experiencing MOH it is implausible that a significant number of these patients were not experiencing MOH. Diagnosis of other primary or

secondary headache disorders was included as an exclusion criterion in the Phase 3 studies however medication overuse headache was not specifically referenced in the exclusion criteria. The decision not to exclude patients overusing acute medication appears to have been made made following consultation with members of the Task Force of the International Headache Society Clinical Trials Subcommittee, and is consistent with guidelines for controlled trials of prophylactic treatment of CM in adults (Aurora et 2010). However these guidelines were published in 2008. The Botox CM phase 3 clinical trial program was started in 2006 and completed in 2008. The ICHD-2 diagnostic criteria for CM (CM was included for the first time and specifically excluded medication overuse) and MOH were published in 2004. These were revised in 2006 (ICHD 2R) however the ICHD diagnostic criteria for CM continued to exclude MO. It was clear in 2004 and subsequently in 2006 from these ICHD publications that MO is excluded from the diagnostic criteria for CM (see criterion D. of the revised International Headache Society criteria for Chronic Migraine). Allergan chose an alternative definition for chronic migraine in line with a proposal by Silberstein et al (presented to Classification Committee of the American Headache Society 2005) where chronic migraine is diagnosed if a patient had 15 or more days of headache a month with at least 50% of headaches being migraine or probable migraine.(Sun-Edelstein 2006).
Although the applicant argues that participants with secondary headaches were excluded MOH is not referenced in the exclusion criteria for either phase 3 study. It is unclear how MOH was handled in the phase 3 population.
The Allergan Criteria for medication overuse ((MO-yes) subgroup) included subjects who during the 28-day baseline had taken AHPM ≥2 days/week, and had taken simple analgesics on ≥15 days/month and/or other AHPM types ≥10 days/month (e.g. triptans). It is implausible that this level of overuse did not persist in such a disabled group of patients for a period of > three months bearing in mind the average duration of chronic migraine was greater than 20 years so by virtue of the fact that these patients were overusing acute pain medication to this extent it is reasonable to argue that they never fulfilled the criteria for CM as defined by ICHD in the first place and that a significant proportion were likely to have been suffering from MOH. The Botox CM data has already been published highlighting it's efficacy in patients with CM who are overusing acute pain medication (Silberstein 2010).

The RMS is of the opinion that inclusion of patients overusing acute pain medication in the Allergan CM clinical trials confounded the outcome of the studies. We do not support the Applicants proposal to include advice on withdrawing AHPM in the SPC. We could find no recognised guidelines on management of MOH that did not recommend withdrawal of AHPM as the first line treatment of MOH. The applicant has recommended concomitant withdrawal of AHPM treatment with prophylactic treatment however this is only supported by clinical opinion . No clinical study data has been provided in support of this suggestion.

The treatment of effect of Botox in patients with CM is modest but for patients who have failed other treatments and who are true chronic migraineurs (ie. not overusing acute pain medication) with all of the physical, social and psychological disability associated with this condition we are of the opinion that there is a role for Botox in the management of these patients. This should be under the care of neurologists who are expert in the management of headache.

The following wording for 4.1 was proposed by the RMS at the time the FVAR was circulated

Proposed wording for section 4.1 circulated by RMS with original FVAR

'*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) in patients 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)*

Further amendments to this wording were received from DK and EL. The RMS has incorporated these proposals into a revised proposed wording for section 4.1.

Proposed new wording for 4.1 incorporating comments from DK and EL received following review of the FVAR.

'Symptom relief in adults fulfilling all criteria for definite chronic migraine (headaches on ≥15 days per month of which at least 8 days with migraine and with no medication overuse headache), in patients who have responded inadequately or are intolerant of prophylactic migraine medications'.

'Treatment should be exclusively administered at headache clinics under the supervision of physicians who are experts in the treatment of migraine (see section 4.4).'

References

Bigal ME. The International Classification of Headache Disorders revised criteria for chronic migraine-field testing in a headache speciality clinic Cephalalgia 2007;27;230-234

Silberstein S. OnabotulinumtoxinA for treatment of chronic migraine: 56-week analysis of the PREEMPT chronic migraine subgroup with baseline acute headache medication overuse. Neurology 2010;74(9 Suppl 2)

Sun-Edelstein C. Chronic migraine and medication overuse headache: clarifying the current International Headache Society classification criteria. Cephalalgia. 2009 Apr;29(4):445-52. Review.

Aurora,S Reply: Clinical trials on onabotulinumtoxinA for the treatment of chronic migraine
J Headache Pain. 2011 April; 12(2): 137–138