ERG response to manufacturers Pro-forma comments on ERG report

07 January 2012

Botulinum toxin type A for the prophylaxis of headaches associated with chronic migraine

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **5pm, Thursday 22 December 2011** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Note from ERG.

The timelines for STAs are very tight. The ERG had significant, unexpected, staffing problems during this STA. We were faced with a choice of trying to adhere to the original timelines, or of asking NICE to postpone the appraisal. With considerable effort, we kept to the original timelines. We accept that there were some points of detail in the ERG report that we did not get entirely correct, listed below, but most were inconsequential, and none affected the results.

Issue 1 Source of Healthcare Resource Use Data

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Pages 10,12, 13, 82, and 96 express uncertainty or incorrect assertions about the population from which healthcare resource use was gathered. Although the relevant publication is titled *Health Resource Utilization and Costs for Migraineurs in Scotland,* the healthcare resource estimates are taken from the entire International Burden of Migraine (IBMS) sample. To calculate costs for migraineurs in Scotland, Scottish costs were applied to the international estimates. A Scottish or UK subgroup of patients was not chosen due to limitations in sample size, hence	<u>Page 10:</u> *"The IBMS also provides the data for the additional resource use associated with the individual health states, though this appears to rely upon a probably small subset of Scottish patients' data."* This sentence should be modified as: *"The IBMS also provides the data for the additional resource use associated with the individual health states"* <u>Page 12:</u> *"The resource use data may have relied upon a very small sample size for chronic migraine based upon the Scottish subset of the UK data*	The ERG cites the use of a Scottish subgroup of the IBMS to populate healthcare resource use as a major limitation to the model. However, this is incorrect, the entire IBMS sample was used and thus this concern should be eliminated. A copy of the ISPOR 2011 poster describing the overall resource use is attached for your information.	This is the first time we have been sent a copy of the Bloudek poster from ISPOR, despite it having been presented in May 2011. The poster (second bullet in Objectives) states that the objective is "to apply healthcare resource utilisation and associated costs for adult Scottish migraineurs…". This implies that the analysis is based only on Scottish patients from the IBMS, who must be small in number, especially distributed across six health states. Nowhere are we told

any reference to a reliance on a Scottish population is incorrect.	*within the IBMS."* This sentence should be deleted. <u>Page 13:</u> *"The resource use of the overall International Burden of Migraine Study (IBMS) rather than the poorly reported Scottish subset"* This sentence should be deleted or modified to explain the source of the overall International Burden of Migraine Study (IBMS) data. It is unclear, but likely that the ERG used pooled EM and CM estimates presented in the Blumenfeld publication. <u>Page 82:</u> *"The health states are also associated with resource use in terms of GP visits, A&E visits and hospital admissions, reported to be drawn from Scottish data within the IBMS study."* This sentence should be modified as: *"The health states are also associated with resource use in terms of GP visits, A&E visits and hospital admissions, reported to be drawn*		the number of patients in each health state. The lack of data on numbers means that the analysis lacks essential detail. If the analysis is based only on the Scottish patients, we think numbers will be too small. If the analysis was based on all patients in IBMS, then the use of resources will reflect experiences in a variety of different health care systems, so may not be applicable to the UK. For example, out of hours care will be from NHS Direct not ER departments The manufacturer states that a Scottish or UK subgroup was not selected for the Bloudek analysis of the IBMS study. Table 3 of the Bloudek poster on resource use corresponds with the parameter estimates as summarised within table 38 of the ERG report. The fuller description of results for the

	from the IBMS study." Page 96: *The 12 weekly rate of GP visits, A&E visits, hospital admissions and triptan use is drawn from the IBMS, and is apparently based upon the Scottish subset of the UK data as summarised in Bloudek et al 83 and as clarified within the manufacturer response to ERG clarification question. A.1.* This sentence should be modified as: *The 12 weekly rate of GP visits, A&E visits, hospital admissions and triptan use is drawn from the IBMS, as summarised in Bloudek et al 83 and as clarified within the manufacturer response to ERG clarification question. A.1.* Page 96 *"Further restricting this sample to only Scottish patients, as appears to be the case from the Bloudek and colleagues abstract may result in very small patient numbers and quite unreliable estimates."* This sentence should be removed, as the overall sample of IBMS was used for the Bloudek and colleagues publication rather than a Scottish subset of IBMS patients and thus sample size is not a relevant issue.		IBMS as presented by Blumenfeld et al at and as also summarised in table 38 of the ERG report is noticeably different from those of Bloudek et al. The reasons for the discrepancies warrant further explanation. No changes made. This seems to contradict what is said in the Bloudek poster.

Issue 2 Use of 1-prior group to represent 3-prior group

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 11 of the report describes the focus on the 1-prior group as "surprising".	Page 11 *"Given the NICE scope, concentrating upon the 1-prior group is surprising. It may have been better to concentrate upon the 3-prior group, and present the 1-prior group as a sensitivity analysis."* This sentence should be modified as: *"The submission concentrates upon the 1-prior group. The effect of Botox relative to placebo remains directionally similar, regardless of the number of previous treatments patients have experienced. Therefore for reasons of power, the dataset of patients who have received at least 1 previous oral prophylactic treatment is used to represent the population specified in the NICE scope. Extensive sensitivity analyses demonstrated the model was not sensitive to the number of prior treatments received."*	The manufacturer submission explains the reasons for using the 1-prior group to represent the 3-prior group, on page 126. The ERG appear to accept the pragmatics of this assumption and approach in the ERG Report, section 5.2.3 (p83).	The ERG accepts the pragmatic decision not to restrict the patient population to those overusing acute headache pain medication at baseline in order to preserve patient numbers. But using the 3-prior patient population for the baseline modelling would have retained reasonable patient numbers while remaining more in line with the NICE scope. It would also have eliminated possible concerns around the utility estimates which are applied to this group within the manufacturer sensitivity analyses; i.e. to have forced the

			estimation of utilities specific to this subgroup.

Issue 3 Botox administration time

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pages 12 and 114 of the report describe the proposed 30 minute consultant appointment as 'optimistic.' Clinical practice indicates that a 30 minute consultation is ample.	Page 12 *"The cost of a Botox administration based upon 30 minutes of consultant time may be too optimistic."* This sentence should be removed. Page 114 *"The Botox administration time assumed by the manufacturer may be towards the optimistic end of the spectrum."* This sentence should be removed.	Botox administration uses a series of small clusters of injections. We have made available a video demonstrating how quick administration is. On page 90, the ERG report states "As regards time cost for Botox administration, the ERG notes the submission to NICE from Dr Andrew Dowson, a very experienced user, in which he states that 15 minutes would be sufficient time."	The video was not provided to the ERG. The time required for injections remains uncertain and might be longer for inexperienced staff. If a time cost is used (rather than using a standard neurology outpatient tariff) then varying the time has some impact on the ICER, though not great. The base case assumed admin costs was £73 giving an ICER of £6,341. Other times give ICERs roughly as follow; 15 minutes, £37 cost, ICER £5,160. Admin cost £110, ICER £7,538

			In the base case admin makes up about 20% of total botox cost. If we assume the OP reference costs is used, admin comprises about 30%. Neurologists in OP departments are supported by other staff, and a simple cost per minute calculation omits their costs. The OP tariff reflects the other staff costs, and other costs such as "hotel" costs. We would expect the tariff price to be used.

Issue 4 Unblinding in previous and different design Botox studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 9, *In previous Botox trials, 70% of participants receiving Botox correctly guessed what they had received, because of changes in muscle tone, such as reduced forehead wrinkles*. This statement does not identify the significant differences in study design between the exploratory Phase II and the pivotal Phase III PREEMPT trials.	Please replace: *"In previous Botox trials, 70% of participants receiving Botox correctly guessed what they had received, because of changes in muscle tone, such as reduced forehead wrinkles"* With the following: *"In previous exploratory Phase II trials for*	There are significant differences in study design between the exploratory phase II study and the PREEMPT studies, including unit dose injected, selection of target muscles and numbers of injections, that make any extrapolation of the ability of patients to correctly guess treatment assignment inappropriate between the two studies. For example, the exploratory phase	We do not know how any patients in the PREEMPT trials guessed whether they had received Botox or not, because (contrary to what the guidelines for trials say) they were not asked at study end what they thought they had had. We accept that there were

This is potentially misleading, as the reader might assume similar designs and therefore that as many as 70% of the BOTOX treated patients in the PREEMPT studies may also have been un-blinded due to Botox side effects. It is incorrect to state that changes in muscle tone were reported as reduced forehead wrinkles.	*Botox, 70% of participants receiving Botox correctly guessed what they had received after the first cycle of injections, however, there were significant differences in study design versus the Phase III PREEMPT studies. The previous Botox trials involved a single-blind placebo run-in phase and a different treatment schedule to PREEMPT in terms of dose, target muscles and number of injections per muscle. The percentage of participants receiving Botox, who correctly guessed what they had received, reduced to 60% at the primary endpoint of day 180. The most common adverse event reported by those patients treated with Botox was muscular weakness".*	II study involved a single blind placebo run-in phase, following which patients were randomly assigned to Botox or placebo. It is not surprising that 70% of patients subsequently randomised to Botox correctly guessed this allocation, as it is conceivable that patients who correctly guessed that they had received placebo during the run-in phase (78%) would be more likely to detect differences in subsequent active Botox treatment cycles. The PREEMPT study did not involve a placebo run-in phase. Having completed the placebo run-in phase, patients in the phase II study underwent a treatment schedule that was distinctly different from that of the PREEMPT studies. Differences between the Phase II and PREEMPT studies include; number of muscle areas injected (minimum of 6 versus 7), number of injection sites (23 to 58 versus 31 to 39) and the number of units of Botox injected (105-260U versus 155-195U). Finally, although 70% correctly guessed their treatment after the first treatment, this dropped to 65 and then 60% after the third treatment. Sixty percent correctly guessing their treatment does not differ significantly from the 50%,	differences amongst the trials.

		which would be expected by chance. Furthermore, although the most commonly reported adverse event in the Phase II studies was muscle weakness, it is incorrect to imply these were specifically reported as reduced forehead wrinkles. Reduced forehead wrinkles was not reported by any patients in this study as a preferred term. Indeed no data were collected from patients to determine the reasons for their guess.	

Issue 5 BASH guidelines reporting incomplete

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 26 of the report describes the BASH guidelines, but omits to include 1. The reference to Botox (OnabotulinumtoxinA) as a licensed treatment for the prophylaxis of headache in chronic migraine and 2. An updated BASH statement regarding Botox.	Page 26 *Onabotulinumtoxin A is licensed for prophylaxis of patients with more than 15 headache days per month, of which at least eight days are with migraine. The difference between active and placebo treatments was small in reported clinical trials, although statistically significant."* *"The British Association for the Study of Headaches (BASH) produced guidance on the*	The ERG report has included the BASH guidelines for management of CM including other prophylactics. The guidance on Botox ought therefore to be also included.	This is not relevant, and there is no factual inaccuracy. We accept that the BASH guidelines include Botox as a treatment option. The key point here is the sequence of treatments – i.e. what people should have been tried on before progressing to Botox.

	management of migraine in 2010.25 Although chronic migraine is not mentioned as a specific subtype, the most severe end of the stepwise ladder of management described is applicable to migraines which are chronic. The guidance is summarised in some detail below." This paragraph should be expanded to include. "*The British Association for the Study of Headache (BASH) recommends that all licensed treatments for Migraine should be made available to patients on the National Health Service (NHS) including Botox in CM."*		

Issue 6 Chronic Migraine Follow-up consultations

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 30 of the report notes that follow-up consultations would not allow sufficient time for Botox injections, but this has not been suggested by the manufacturer.	<u>Page 30</u> *"Note that the follow-up consultations would not allow sufficient time for Botox injections."* This sentence should be removed.	The follow-up times presented in Table 1 on page 30 show **current** clinical practice, and are unrelated to Botox administration. 15 minute follow-up appointments are not used in assessing the cost-effectiveness of Botox. Our cost-effectiveness model assumes that administration requires 30 minutes of consultant time – an additional 15 minutes on top of the existing consultations, in line with Issue 3.	Explanation accepted, though as noted above, the exact amount of time required for botox injections remains uncertain, and may vary amongst those administering it. One option is that there could be a shared care system, with initial assessment, diagnosis and treatment given by specialist services, but with responders then receiving

			treatment in primary care, but seen again in specialist care at say one year to decide on continuation or not. If that happened, the cost in primary care might be that of an enhanced service payment. The ERG is aware that courses on how to give Botox are being provided for GPs.

Issue 7 History of Chronic Migraine (CM) in PREEMPT

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 31 of the report states that Allergan did not consider that definition of CM requires a 3-month duration of headaches of the defined frequency and type. However, PREEMPT patients had a mean CM duration of 18 years, and by default this definition is addressed.	Page 31 *"Firstly, a minor point - the Allergan account of the decision problem does not mention that the definition of CM requires a 3-month duration of headaches of the defined frequency and type."* This sentence should be removed.	Section 1.4 on page 14 of the submission reads "No criterion was formally mentioned about the duration of CM at study entry (more than 6 months is recommended) but the description of the patients actually enrolled showed that this must have been the case in the great majority of patients (mean duration of about 18 years)."	We accept that the patients in these trials had had migraine for a very long time, but this issue was about the headaches of the defined frequency and type. However as we said, this is a minor point.

Issue 8 Medication overuse

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 31 of the report states that medication overuse had not been managed in the trial. This is incorrect. Patients were stratified at baseline for medication overuse, and a review highlighted that the high rate of medication overuse is representative of real-world patients.	Page 31 *"Secondly, as discussed later, the main evidence comes from the PREEMPT trials which recruited a much broader patient group, in which medication over-use had often not been managed."* This sentence should be changed to: *"Secondly, as discussed later, the main evidence comes from the PREEMPT trials which recruited a much broader patient group, in which medication over-use had often not been managed. However patients were stratified at baseline for medication overuse, and the high rate of medication overuse is representative of real-world patients."*	Page 113 of the Allergan submission states "Because in the Botox phase 3 studies patients were stratified at baseline for medication overuse" Page 116 of the Allergan submission states "In a recent review, it is described that the high rate of medication overuse in the PREEMPT trials is representative of real-world patients with this condition (Schoenen et al. 2010)."	We accept that randomisation was stratified for medication over-use. However, the issue was about whether medication over-use had been managed, in the sense of whether it had been assessed and treated, not whether it had been used for stratified randomization. We agree that the inclusion of patients in whom MO had not been managed could make the patients more representative.

Issue 9 Incorrect description of the PREEMPT trial design

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 33 of the report states refers to an "extension" of the	Page 31 *"They included a 4-week screening/baseline*	The manufacturer stated in response to the ERG question A.21 (submitted to NICE in November	We are happy to accept "phase" rather than

trial. This is incorrect.	*phase (week -4 to day 0), followed by a 24-week, double-blind, randomised, placebo-controlled, parallel-group phase, which was then followed by a 32-week open-label extension"* This sentence should be changed to: *"They included a 4-week screening/baseline phase (week -4 to day 0), followed by a 24-week, double-blind, randomised, placebo-controlled, parallel-group phase, followed by a 32-week open-label phase."*	2011) that : "Each of the two phase 3 studies were designed to include both a randomised, double-blind, placebo-controlled (DBPC) phase and an open-label (OL) phase; thus, there was no separate extension study. As such subjects received two double blind placebo controlled injections and 3 open label injections. All patients were informed of the study design, including the open-label phase, at the time of recruitment"	"extension".

Issue 10 Blinding of patients to Botox treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG
P35 & 36 (Tables 2 & 3) describe the blinding of participants as *uncertain*. It is incorrect that unblinding may have occurred due the side-effects of Botox.	Blinding of participants adequate? Yes	See Appendix 1	The data in appendix 1 have not been submitted before, and could not have been considered in the ERG report. No change to report – AC can consider the appendix if NICE accepts late submission of data. But see comments just above appendix 1.

Issue 11 Acute rescue medications

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 46 of the report describes the use of acute rescue medications as not different between the two groups at any time. The use of acute recue medications was different at all time points, but not statistically significant.	Page 46 *"Curiously, the use of acute rescue medications was not different between the groups at any time, which seems at odds with improvements in other outcomes."* This sentence should be changed to *"Curiously, the difference in the use of acute rescue medications between the groups was not statistically significant at any time, which seems at odds with improvements in other outcomes."*	Correction of description of acute rescue medication use outcome of PREEMPT	Accepted – differences were observed but were not statistically significant.

Issue 12 Incorrect endpoint, use of absolute risks, and the word "only"

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 70 of the report refers to a reduction in "migraines" of "only 11%" • These results are for headache days	Page 70 *"As noted at the start of this section, the difference in the reduction in migraines was only 11%."* This sentence should be changed to	The endpoint should be described accurately. The risks given are absolute. For consistency with other parts of the review, relative differences	No change required. Absolute differences are more important than relative ones..

• This risk is absolute. • The world “only” is not justified.	*“As noted at the start of this section, the absolute difference in the reduction in headache days was 11%, a 30% relative difference (-8.4 vs -6.6 headache days per month).”*	should also be given. There is inappropriate use of the word “only.”	

Issue 13 Inappropriate speculative “wonderings”

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 73 of the report contains a speculative unjustified statement.	<u>Page 73</u> *“The ERG wonders if it would take only a small percentage in the Botox group to be unblinded and report a better response, and a small percentage in the placebo group to be unblinded, disappointed and report more headaches, to cause the small difference in self-reported headache days.”* This sentence should be removed.	This is speculative and unjustified, and not appropriate in an evidence-based assessment report.	In view of the small difference between Botox and placebo groups, and the possibility that there could be different sizes of placebo effect, this speculation seem justified. No change.

Issue 14 Wording – inappropriate and inaccurate

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 76 of the report contains inappropriate and inaccurate	<u>Page 73</u> “*If we accepted the costs in table 6.17, there*	Botox does ‘work’ – as evidenced by PREEMPT and the regulatory	What if the difference observed in the PREEMPT trials is due to differences in the size of the

wording.	*would be a large drop in costs of care if Botox worked. The alleged savings would help to make Botox cost-effective. "* This sentence should be modified as: "*If we accepted the costs in table 6.17, there would be a drop in costs of care. The estimated savings would help to make Botox more cost-effective. "*	approvals system. The savings are estimated, not 'alleged'. The resource use savings make Botox more cost-effective, not cost-effective. If no resource use is assumed in each state (0 physician visits, 0 hospitalisations, 0 ER visits, no triptan usage), treatment with Botox has an ICER of £9,160 compared to placebo – an ICER which would be considered to be cost effective by all standard thresholds.	placebo effect due to unblinding? Or due to the effects of being in a trial? As stated above, the ERG does not find the Bloudek poster provides sufficient detail to make it convincing. We accept this additional point.

Issue 15 1 cycle stopping rule

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 85 of the report incorrectly describes the 1 cycle stopping rule in the model.	Page 73 "Within the electronic copy of the model is referred to as "*Patients discontinue if they did not improve at least 1 health state within 1 cycle*", which could be interpreted as not improving by one health state between baseline	This stopping rule is not considered in the original submission itself, but was provided in response to initial ERG questions (November 2011) and so we have provided clarification here.	Proposed revision accepted

	and week 12 weeks or between week 12 and week 24." This sentence should be modified as: "Within the electronic copy of the model is referred to as "*Patients discontinue if they did not improve at least 1 health state within 1 cycle*", which means not improving by one health state between baseline and week 12."		

Issue 16 Clarification of the source of productivity data

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 95 of the report speculates that the values may be drawn from the IBMS study, but the manufacturer has previously stated this.	<u>Page 73</u> *"It appears likely that these values were also drawn from the IBMS study."* This sentence should be modified as: *"These values were also drawn from the IBMS study."*	The manufacturer submission states in section 6.5.8 page 161 that these values were drawn from the IBMS study.	Proposed revision accepted

Issue 17 Typographical error in the manufacturer submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 97 of the report refers to a typo in the submission.	Page 73 *"Slightly bizarrely, the model apparently "estimates" a small proportion being within HS1 at baseline in the placebo arm though this may be a typo."* This sentence should be modified as: *"The model apparently "estimates" a small proportion being within HS1 at baseline in the placebo arm though this is a typo."*	Appropriate wording	Proposed revision accepted

Issue 18 Date of receipt of the ERG model

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 104 of the report states that the NICE ERG model was sent on 2nd December. The manufacturer did not receive it until 16th December.	Page 104 *"In the light of this and the general spirit of openness and transparency, the ERG model rebuild cross check was sent to NICE for forwarding to the manufacturer for checking on 2nd December."*	The ERG model rebuild was received by the manufacturer on 16th December.	No change required. What is said in the ERG report is correct.

	This sentence should be modified as: *"In the light of this and the general spirit of openness and transparency, the ERG model rebuild cross check was sent to NICE for forwarding to the manufacturer for checking on 2nd December. The manufacturer received the model on 16th December."*		

Issue 19 Typographical Errors in Describing Migraine Classification Criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 74 of the report incorrectly cites "ICDG02" criteria for migraine rather than ICHD-II.	Page 74 *"Participants had to have an email address. Recruits had to meet the ICDG02 criteria for migraine."* This sentence should be modified as: *"Participants had to have an email address. Recruits had to meet the ICHD-II criteria for migraine."*	The inclusion criteria relied on well known and accepted international criteria for migraine diagnosis. "ICDG02" does not exist and mischaracterizes the included population.	Accepted – we should have used Roman numerals II instead of 2.

Issue 20 Typographical Error in Describing the International Burden of Migraine Study

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 77 of the ERG report cites the "IMBMS"	Page 77 *"Furthermore, they contradict the published data from the IMBMS study with hospital admissions being rare in Canada and the USA."* This sentence should be modified as: *"Furthermore, they contradict the published data from the IBMS study with hospital admissions being rare in Canada and the USA."*	Consistency should be maintained throughout the document as to the source of model inputs.	Minor typo accepted.

Issue 21 Error in Describing the American Migraine Prevalence and Prevention Study

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 78 of the ERG report has a factual error in describing the population in Munkata et al. Those with 15 and above days per month were classified as "transformed migraine", thus this level of healthcare resource use applies to the average 15 and	Page 78 *"Note however that these are averages across all patients with CM, and the 15 and above days per month groups might require more health care.*[78]*"* This sentence should be modified as: *"Note however that these are averages across*	No impact is made on the analysis presented in the report, but the sentence does not make sense as-is.	Accepted.

above days per month group.	*all patients with transformed migraine (i.e. CM).*[78]*"*		

Issue 22 Benefit Valuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 80 incorrectly states that the benefit valuation was based on time trade off for the IBMS EQ-5D data.	Page 80: *"Time trade off for the IBMS EQ-5D data."* This sentence should be modified as: *""Time trade off for the PREEMPT EQ-5D data (estimated)."*	The mapping algorithms were developed in IBMS and then applied to the PREEMPT data.	It would read better as; "EQ-5D data collected within the IBMS study was transformed to utilities using the UK social tariff; i.e. time trade off. These were then used to inform the mapping exercise summarized above"

Issue 23 Summary of Mapping Algorithm Development

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 81 incorrectly summarizes the development of the mapping algorithms.	Page 81: *"They examined Spearman correlation coefficients between paired EQ-5D utility values and both Headache Impact Test (HIT-6) scores and Migraine Specific Quality of Life Questionnaire version 2.1 (MSQ) domain*	The first part of the sentence is accurate, however "...to construct an algorithm for the validation of the sample" is very confusing and inaccurate. The modified sentence accurately reflects the development of the mapping algorithms as	Accepted, but has no effect on report.

	scores. Regression models were constructed to estimate EQ-5D utility values from the HIT-6 score or the MSQ domain scores to construct an algorithm for the validation of the sample." This sentence should be modified as: *"Regression models were constructed to estimate EQ-5D utility values from the HIT-6 score or the MSQ domain scores. Preferred mapping algorithms for the HIT-6 and MSQ were selected based on RMSE in view of variable coefficient significance, variable impact on RMSE, and model simplicity. Preferred algorithms were validated through a split-sample confirmatory analysis"*	described in Gillard et al. (2011).	

Issue 24 Description of Bivariate Analysis from Gillard, 2011

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 81 does not accurately describe the bivariate analysis conducted in Gillard et al. (2011).	Page 81: *In the bivariate analysis, Chi-square test for categorical variables and the two-sample t-test for continuous variables were used.* This sentence should be modified as: *"Bivariate analysis of demographic and clinical characteristics between individuals with episodic and chronic migraine was conducted*	The modification accurately describes the bivariate analysis.	No change required

	using the Chi-square test for categorical variables and the two-sample t-test for continuous variables."		

Issue 25 Statistics Used to Assess Mapping Algorithm Performance

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Pages 81 and 88 do not accurately describe the statistics used to determine the preferred mapping algorithms.	Page 81: *"The coefficient of determination (R^2) was used to assess the goodness-of-fit of the regression models."* This sentence should be modified as: *"The size of the prediction error of the models was assessed using root mean square error (RMSE). The coefficient of determination (R^2) was used to assess the goodness-of-fit of the regression models."* Page 88: *"OLS modelling explored the relationships between the HIT-6 elements, the MSQ dimensions and the EQ-5D utilities, valued using the standard UK tariff. Non-linearities were apparently explored through quadratic functions, with an F-test being used to determine whether additional covariates significantly improved the overall fit of the*	RMSE was the statistic used to assess mapping algorithms in Gillard et al. (2011). If this is omitted, it will inaccurately assumed that R^2 was the statistic used to assess performance. In other words, it is OK for the ERG to report R-squared but it is inaccurate to do so without reporting RMSE.	These are points of detail and do not affect anything.

	model." This sentence should be modified as: *"OLS modelling explored the relationships between the HIT-6 elements, the MSQ dimensions and the EQ-5D utilities, valued using the standard UK tariff. Non-linearities were apparently explored through quadratic functions, with an F-test being used to determine whether additional covariates significantly improved the predictive accuracy and the overall fit of the model. Preferred mapping algorithms for the HIT-6 and MSQ were selected based on RMSE in view of variable coefficient significance, variable impact on RMSE, and model simplicity."* <u>Page 88:</u> *"For the preferred model based upon the HIT-6, 22% of the variation in the estimation sample for episodic migraine and 36% of the variation in the estimation sample for chronic migraine was explained. The corresponding percentages for the preferred MSQ model were 25% and 45%."* This sentence should be modified as: *"The preferred HIT-6 algorithm explained 22% of the variance in the episodic migraine training sample and 36% in the chronic migraine training sample. The RMSE of the preferred*		

	HIT-6 model was 0.30 in episodic migraine and 0.31 in chronic migraine. *The preferred MSQ algorithm explained 25% of the variance in the episodic migraine training sample and 45% in the chronic migraine training sample. The RMSE of the preferred MSQ model was 0.30 in episodic migraine and 0.29 in chronic migraine."*		

Issue 26 Utility Base Case Description

Description of problem	Description of proposed amendment	Justification for amendment
Page 81 incorrectly summarizes the development of the mapping algorithms used to estimate utilities in the base case scenario.	Page 81: *"For the base case, each of these health states is associated with a treatment specific HRQoL estimated from an MSQ to EQ-5D utility mapping exercise estimated using data from the International Burden of Migraine Study (IBMS).* This sentence should be modified as: *"For the base case, each of the six health states is associated with a treatment specific HRQoL value estimated from preferred MSQ mapping algorithms developed in the International Burden of Migraine Study (IBMS)."*	The use of "these" and "HRQoL" in the original sentence was ambiguous. The mapping study (Gillard, 2011) was conducted independent to the NICE submission, and by different researchers.

Issue 27 Rationale for Mapping Algorithms

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 91 incorrectly states that it is not obvious why the mapping algorithms were developed in two migraine populations (episodic and chronic migraine).	Page 91: *"It is not immediately obvious why separate models were estimated for episodic migraine and chronic migraine."* This sentence should be deleted. Page 91: *"A pooled analysis with dummy variables could have explored the requirement for this, with possible benefits of an increased sample size for estimation of some of the coefficients for chronic migraine, the MSQ model for this having only one statistically significant MSQ coefficient."* This sentence should be deleted.	Separate mapping models for chronic and episodic migraine are appropriate given the differences observed between the two populations in Gillard et al. (2011) and Blumenfeld et al. (2011). In other words, these two patient populations are distinct, therefore mapping algorithms need to be developed in both populations. Any benefits of pooling the populations are not relevant given the populations are clinically distinct (and therefore should not be pooled). This could be loosely akin to describing cancer utilities as being more robust if taking all patients from a trial. However this would disregard the impact of progression, a clinical event known to impact HRQL.	Revision rejected. The cancer analogy would be better if it suggested a dummy also be included for progression (possibly on the intercept term also), which as the manufacturer suggests would be anticipated to be significant.

Issue 28 IBMS is the source of mapping algorithms – not utility mapping data

Description of problem	Description of proposed amendment	Justification for amendment	
Page 91 incorrectly describes how the mapping algorithms relate to the treatment populations.	Page 91: *"As the IBMS is the source of the utility mapping data there may be no particular reason to anticipate that it will capture any difference in adverse events between the Botox arm and the placebo arm, though these may be picked up by the elements of the MSQ."* This sentence should be modified as: *"As the IBMS is the source of the utility mapping algorithms, the models were not specifically developed in the treatment populations (Botox and the placebo arms). Although the difference in adverse events between the Botox arm and placebo arm may be picked up by elements of the MSQ. "*	IBMS is the source of the mapping algorithms (not utility mapping data). Moreover, the modified sentence eliminates the contradictory elements of the original sentence.	Revision rejected, but the offending sentence can have the highlighted "data" deleted from it.

Issue 29 3 health state model

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 105 of the report suggests that the 3 health state model in the submission is incorrect.	Page 104 *"But this condensed model appears to be the same as the full model, with only the utility*	The resource use for 4-9 and 10-14 HA days per month is the same. The resource use for 15-19, 20-23,	The manufacturer does not suggest a factual error.

	values for the different health states being changed. The net costs do not change between the two arms." This sentence should be modified as: *"The condensed model appears to be the same as the full model, with only the utility values for the different health states being changed. The net costs do not change between the two arm, because the resource use for episodic and chronic health states does not change."*	and 24+ HA days is the same. Therefore, the costs should not change when a 3HS model is used, as the resource use definitions are already built around the 'episodic' and 'chronic' health states. Resource use is presented in Table 6.17 on page 160 of the original manufacturer submission.	

Issue 30 Not all episodic migraineurs will cease treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG
Page 107 of the report questions the use of the positive stopping rule for stopping the treatment of episodic patients.	Page 107 *"These patients will definitely not want to stop their treatment, and it is apparently difficult to argue against the fear of relapse. Another issue is that this rule would be entirely dependent upon patients' reported symptoms. Those not wishing to stop will just report whatever is required in order to remain on treatment."* This sentence should be modified as:	The model has been designed to allow the user to select the proportion of episodic patients who continue, or discontinue treatment. If 80% of episodic patients are assumed to discontinue treatment, and 20% continue to receive treatment, Botox has an ICER of £7,131 compared to placebo. If 50% of episodic patients are assumed to discontinue treatment, and 50% continue to receive	The point about the modelling is accepted (and useful), but there is no factual error here.

	"These patients may not wish to stop their treatment, and it is apparently difficult to argue against the fear of relapse. Another issue is that this rule would be entirely dependent upon patients' reported symptoms. Those not wishing to stop will just report whatever is required in order to remain on treatment. However, Botox is still cost-effective when only 50% of episodic migraineurs cease treatment, with an ICER of £9,112."	treatment, Botox has an ICER of £9,112 compared to placebo.	

ERG comments.

This appendix examines whether adverse events could lead to unblinding. These are events significant enough to be reported. However much lesser side-effects, including some that are not harmful, might be enough to let patients know they had received Botox.

Appendix 1

Summary

Unblinding either due to robust efficacy or an unusual but characteristic adverse event (AE) profile is always of potential concern in a drug development program. Allergan conducted these DBPC trials in a manner to minimize this potential issue, including a range of methods to ensure blinding of both investigator and patient was maintained. While always a theoretical concern, there is no evidence to suggest that this was a particular issue in these clinical trials. Indeed, the very low rate of AE overall makes this less likely to have been a confounding issue. The injection paradigm differences between aesthetic and chronic migraine are distinct, and therefore the chronic migraine injection paradigm would not be expected to produce the same aesthetic effects; there is no evidence to suggest that the blind was compromised in a systematic manner; and even if all of the patients with potentially unblinding AEs are removed from the dataset, the robust efficacy of BOTOX® compared to placebo is maintained. Allergan is confident that the blind was sufficiently maintained during the BOTOX® phase 3 studies based on the justifications provided below:

1. Reports of Adverse Effects That Could Have Resulted in Potential Unblinding

The ERG has commented that blinding of study participants was uncertain, due to the side effects of BOTOX®. Allergan has conducted analyses of the efficacy data on different subpopulations of patients, who reported potentially unblinding AEs pertaining to the face and face or neck, to determine if the efficacy results were influenced.

At the time of study entry, all patients in the PREEMPT studies were made aware of possible risks or discomforts that may result from BOTOX® administration based on adverse effects that have been reported after exposure to BOTOX® in prior Allergan sponsored studies, or observations received through post-marketing reports. Therefore, patients could have potentially been unblinded to the study treatment based on their expectations and/or experiences of such adverse effects. Allergan conducted efficacy analyses in two subpopulations of patients that included those who reported potentially unblinding AEs based on a subset of the terms that were listed in the informed consent form.

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

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

- Face (same as list above) or Neck (neck pain, neck tightness, neck discomfort, neck stiffness, stiff neck and neck rigidity), which was the most commonly reported AE in the BOTOX® phase 3 studies.

Face: Analyses of the DBPC phase data demonstrated that only 10.9% (N=150) of the 1379 treated patients (BOTOX® n = 104, placebo n = 46, $p < 0.001$) reported potentially unblinding AEs that pertained to the face. While the majority of the patients who did report such AE received BOTOX® treatment, overall they represented only 15.1% (104/687) of all BOTOX®-treated patients.

Face or Neck: Analyses of the DBPC phase data demonstrated that a total of 16.6% (N = 229) of the 1379 treated patients reported either a potentially unblinding AE to the face or neck (BOTOX® n = 165, placebo n = 64, $p < 0.001$).

Although it may be speculated that the efficacy response in the BOTOX® phase 3 studies was potentially influenced by patients knowledge that they had received BOTOX® instead of placebo, as discussed above the apparent absence of an excessive reporting of potentially unblinding AE (< 25%; 165/687) in the BOTOX®-treated patients during the DBPC phase provides confidence that the blind was maintained. Nevertheless, efficacy analyses with and without these patients in the dataset were performed to confirm whether there was or was not an effect on the results.

2. A) Analyses of Efficacy in the Subgroup of Patients with Potentially Unblinding AE Pertaining to the Face

Results from this analysis demonstrate that the mean change from baseline in frequency of headache days and headache episodes was not different in the BOTOX®-treated patients who reported a potentially unblinding AE that pertained to the face compared to those who did not report such AE (Table 1). A difference was observed in the placebo-treated patients whereby there was a higher mean change from baseline for both frequency of headache days (-6.8 vs. -6.6) and headache episodes (-5.7 vs. -4.9) in those patients who reported a potentially unblinding AE that pertained to the face compared to those who did not report such AEs (source tables available upon request). Furthermore, when comparing the subpopulations to the ITT population, results demonstrate that there was no exaggerated efficacy response in either subgroup, and thus no significant unblinding, since the mean change from baseline in frequency of headache days in BOTOX®-treated patients was identical across all three populations, and there was no substantial difference in the mean change from baseline in the frequency of headache episodes. These efficacy analyses demonstrate that significant improvements in the frequency of headache days and headache episodes were due to BOTOX® effect and were not influenced by unblinding.

Table 1 **Comparison of Mean Change from Baseline at Week 24 for Frequency of Headache Days and Frequency of Headache Episodes in BOTOX® Treated Patients Between Subpopulation of Patients Who Did and Did Not Report Potentially Unblinding AE That Pertained to the Face: Pooled Phase 3 Studies (DBPC phase)**

Efficacy Variable (per 28 days)	**Pooled Phase 3 191622-080 + 191622-079: Subpopulation of patients who reported potentially unblinding AE[a]**	**Pooled Phase 3 191622-080 + 191622-079: Subpopulation of patients who did not report potentially unblinding AE[a]**	**Pooled Phase 3191622-080 + 191622-079 ITT population**
	BOTOX® (N = 104)	**BOTOX® (N = 584)**	**BOTOX® (N=688)**
Frequency of headache days	**-8.4**	**-8.4**	**-8.4**
Frequency of headache episodes	-5.1	**-5.2**	**-5.2**

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

Results in bold denote statistically significant differences from placebo favoring BOTOX®.

Source: Module 5.3.5.3 ISE Tables 2-1, 2-3; additional source tables available upon request

In addition, responder analysis showed that in the subpopulation of BOTOX®-treated patients who achieved ≥ 50% and ≥ 75% response across multiple headache symptom measures that only 16% had reported a potentially unblinding AE pertaining to the face (source tables available upon request), thus supporting Allergan's position that efficacy results were not unduly influenced, and that the blind was adequately maintained.

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

There was no difference in the mean change from baseline in the frequency of headache days in the BOTOX®-treated or the placebo-treated patients who reported potentially unblinding AE to the face or neck compared to those who did not report such AEs (Table 2). Furthermore, when comparing both of these subpopulations to the ITT population, results demonstrate that the mean change from baseline in frequency of headache days is identical across all three populations, further supporting that there was no unblinding among the BOTOX®-treated patients that resulted in an exaggerated efficacy response. For mean change from baseline in the frequency of headache episodes the response was similar for BOTOX®-treated patients, but there was a higher placebo response observed for those patients who reported potentially unblinding AE to the face or neck compared to those who did not report such AEs (Table 2).

Table 2 **Comparison of Mean Change from Baseline at Week 24 for Frequency of Headache Days and Frequency of Headache Episodes in BOTOX® Treated Patients Between Subpopulation of Patients Who Did and Did Not Report Potentially Unblinding Face or Neck AE: Pooled Phase 3 Studies (DBPC phase)**

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

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

Results in bold denote statistically significant differences from placebo favoring BOTOX®.

Source: Module 5.3.5.3 ISE Tables 2-1, 2-3 ; additional source tables available upon request)

In addition, responder analysis showed that in the subpopulation of BOTOX®-treated patients who achieved ≥ 50% and ≥ 75% response across multiple headache symptom measures that only 24% and 23%, respectively, had reported a potentially unblinding AE pertaining to the face (source tables available upon request), thus supporting Allergan's position that efficacy results were not unduly influenced, and that the blind was adequately maintained.

Conclusions

These efficacy analyses performed with and without including the subgroup of patients who reported potentially unblinding AE to the 1) face or 2) face or neck demonstrated that there were no substantial efficacy differences, which provides strong evidence that the efficacy results were due to effective migraine prophylaxis due to BOTOX® treatment and not driven by unblinding of patients.

3. Reports of Possible Aesthetic Benefit Resulting in Potential Unblinding

Of the 1384 patients enrolled in the BOTOX® phase 3 studies, data from the DBPC phase indicate that only 1 placebo-treated patient reported 'mild reduced forehead wrinkling' (Preferred Term: Skin Wrinkling), a potentially positive aesthetic response that could have resulted in potential unblinding of this patient. This event was reported as starting 37 days after receiving the first placebo treatment. The event resolved 21 days later. 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. Only 1 BOTOX®-treated patient reported a similar event in the open-label phase. This extremely low incidence of reports of possible aesthetic benefit among the 1384 total patients enrolled in the BOTOX® phase 3

studies provides robust evidence that patients were not unblinded due to possible aesthetic benefits.

4. Facial Wrinkles in Women and Men

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. To the best of our knowledge no population based study has been done to evaluate the prevalence of facial wrinkles. However, clinical literature indicates that the amount and depth of facial wrinkles differ among persons and that there are certain intrinsic and extrinsic factors that are not causative, but influence the extent and rate of facial wrinkling including genetics, age, race (skin color), gender, prior sun damage, skin thickness, amount of subcutaneous fat, alcohol consumption and smoking history (Kligman et al, 1985; Martires et al, 2009; Hillebrand et al, 2010). Facial wrinkles are more predominant in older (≥ 40 years) adults (Ernster et al, 1995). It has been reported that lines in the skin related to inelasticity (predominantly related to aging) or actinic damage do not respond well to botulinum toxin. Thus, an aesthetic effect from treatment with botulinum toxin is not expected or achieved in all patients (Frankel and Markarian, 2007).

Based on this information, patients < 40 years of age would be less likely to have the potential to become unblinded following facial muscle injections than patients ≥ 40 years. In the BOTOX® phase 3 studies, 42% of the population was < 40 years of age. Analyses of subgroups of patients < 40 years and ≥ 40 years showed that BOTOX®-treated patients in both subgroups had significantly greater mean change from baseline in frequency of headache days than did placebo-treated patients (Table 3). The between group differences were similar. In the BOTOX®-treated subgroup ≥ 40 years of age, the mean change from baseline in frequency of headache days was -7.9, which is less than the -9.0 mean change observed in BOTOX®-treated patients who were < 40 years of age (Table 3). If indeed there had been a BOTOX® effect on wrinkles, if would seem to reason that one would have expected such an effect to occur in those with a greater chance of having wrinkles (ie, the ≥ 40 year old patients), and thus those that might have a greater chance for possible unblinding due to a aesthetic effect on their wrinkles. Indeed, the opposite was observed in the phase 3 studies since the younger BOTOX® treated patients (< 40 years), who have a higher likelihood of not manifesting wrinkles, had a greater mean change from baseline in frequency of headache days than older BOTOX® treated patients (Table 3).

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

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

Results in bold denote statistically significant differences favoring BOTOX®.

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

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

5. Comparison of Adverse Event Profile of BOTOX® to Migraine Drugs in Placebo-Controlled, Double-Blind Registration Clinical Trials

Potentially unblinding due to AE or other drug effects is a ubiquitous issue in clinical research, and is not unique to BOTOX® clinical studies. Unblinding either due to robust efficacy or an unusual but characteristic AE profile is always of potential concern in a drug development program. Allergan conducted these DBPC trials in a manner to minimize this potential issue, including a range of methods to ensure blinding of both investigator and patient was maintained. While always a theoretical concern, there is certainly no evidence to suggest that this was a particular issue in these clinical trials. Indeed, the very low rate of AE overall makes this less likely to have been a confounding issue. Other drugs recently studied in the migraine field have reported very high proportion of patients with potentially unblinding AE or other significant clinical effects (Table 4). Adverse event profiles for many drugs that have been evaluated in double-blind registration studies contribute to potential unblinding, particularly when such events occur at a high frequency. Consider, for example, the class of anticonvulsant agents that are frequently used as migraine prophylaxis. Results of recent migraine prevention studies of topiramate report high AE rates that certainly could result in unblinding (Diener et al, 2007; Silberstein et al, 2007). For example, reports of paresthesia, a labeled common AE, were observed in 29% to 53% of patients treated with topiramate, but in only a few patients treated with placebo. Also, a significant reduction in body weight, which is perceived as a potential benefit to treatment by most patients, has been reported with topiramate (Diener et al, 2007). In one study, patients treated with topiramate experienced a mean weight reduction of 2.3 ± 2.9 kg during the trial, while patients on placebo gained a mean of 0.1 ± 3.1 kg (Silberstein et al, 2007). The AE profile for BOTOX® shows that it is well-tolerated, without an individual AE being reported in > 10% of patients in the BOTOX® phase 3 chronic migraine studies. Only 10.9% (BOTOX® 15.1%, placebo 6.6%; source table available upon request) and 16.6% (BOTOX® 24%, placebo 9.2%; source table available upon request) of the 1379 patients treated in the BOTOX® phase 3 studies during the DBPC phase reported potentially unblinding AE pertaining to the face and face or neck, respectively (as discussed above).

Table 4 **Proportion of Patients That Experienced Some of the Listed "Very Common (> 10%)" and "Common (≥ 1% to < 10%)" Adverse Events for Topiramate for Migraine Prevention**

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

[a] This study evaluated 100 mg/day versus placebo

[b] This study evaluated doses up to 200 mg/day; average dose was 100 mg/day

[c] This study evaluated 3 dose groups: 50 mg/day (N=117), 100 mg/day (N=119) and 200 mg/day (N=117) versus placebo. For illustration purposes results for the 100 mg/day group are shown

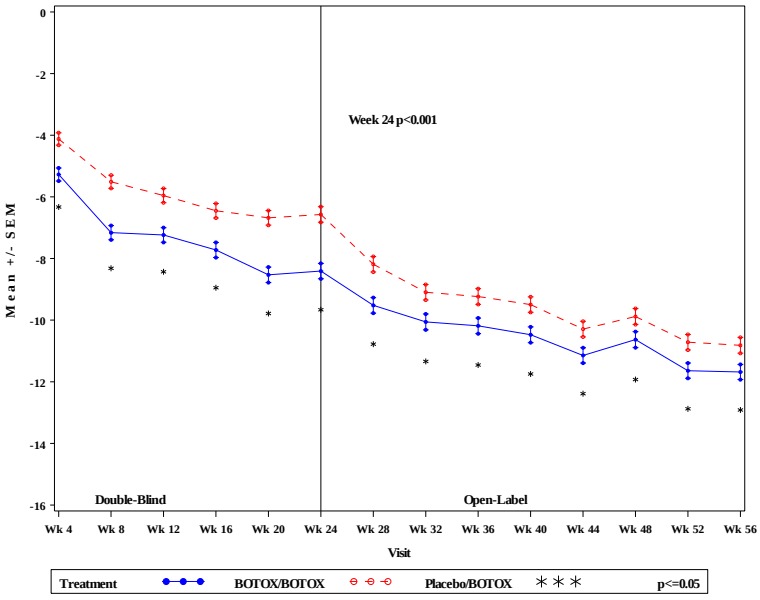
6. Placebo Response and Nocebo Effect During the DBPC Phase of the BOTOX® Phase Clinical Studies

Although a high placebo response was observed during the DBPC phase of the BOTOX® phase 3 studies, there was a lack of a parallel nocebo effect among placebo-treated patients. Adverse event analysis demonstrate that of the 1379 patients treated across the two phase 3 studies, 9.2% (64/696, source table available upon request) of the placebo-treated patients reported a potentially unblinding AE of the face or neck during the DBPC phase of the BOTOX® phase 3 studies. Given the high placebo response, it would be expected that placebo-treated patients would potentially report more AE associated with BOTOX® pharmacology, but this was not the case in the BOTOX® phase 3 clinical studies, further supporting that the blind was maintained. Despite the high placebo response, statistical significance favoring BOTOX® vs. placebo was achieved in the BOTOX® phase 3 studies for the key endpoint of headache days, as well as for multiple other headache symptom and health related quality of life measures.

7. Efficacy Response in Open-Label Phase

If the between-treatment group difference observed in the DBPC phase was due to unblinding, then in the open label phase one 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 as demonstrated in Figure 1. This response pattern was observed across multiple headache symptom measures.

Figure 1 **Mean Change from Baseline in the Frequency of Headache Days per 28 day Period: Pooled Analysis of Phase 3 Studies**



Source: Module 5.3.5.3 ISE Figure 2-2.2

P-values from statistical comparisons are for changes from baseline. Missing values were estimated using mLOCF.

8. A) Comparison of BOTOX® Dose and Injection Paradigm for Aesthetic Treatment for the Upper Face vs. Chronic Migraine

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