Botox (Botulinum toxin type A) for the prophylaxis of headaches associated with Chronic Migraine

Additional Analyses requested following receipt of the Appraisal Consultation Document

Allergan, 24 February 2012

Introduction

Botox® (Botulinum toxin type A) is currently undergoing a NICE Single Technology Appraisal examining clinical and cost effectiveness in the prevention of headaches in adults with chronic migraine. Following an Appraisal Committee (AC) meeting held on 24 January 2012 an Appraisal Consultation Document (ACD) was issued requesting that Allergan provides further information on the clinical and cost effectiveness of Botox® in advance of the next AC meeting, scheduled for 22 March 2012.

The ACD formally requests the following (sections 1.3 to 1.5 in the ACD):

> The information should include full deterministic and probabilistic economic analyses of botulinum toxin type A compared with placebo in adults whose chronic migraine has failed to respond to at least three prior preventive medications and whose medication overuse has been appropriately managed, and which incorporates the following assumptions:
>
> - A neurologist outpatient follow-up cost of £140 for botulinum toxin type A and placebo administration and follow-up.
> - Applying the routine care costs used in the placebo arm to people stopping treatment due to inadequate response with botulinum toxin type A.
> - Resource use estimates specified in Blumenfeld et al. (2010).
> - An average accident and emergency cost of £77.33.
> - Transition probability matrices from the three or more prior preventive medications subgroup.
> - Positive stopping rule applied to 24% of people who move from health states of chronic migraine to episodic migraine.
> - A range of negative stopping rules (up to and including a 50% response rate and also a stopping rule for people whose migraine does not respond) based on the reduction in the number of headache days per 28 days applied to people with chronic migraine after two cycles of treatment.
>
> Alternative scenario analyses were also requested which explore the following:
>
> - The impact of using different and the same utilities (within each health state) in the botulinum toxin type A and placebo arms on the revised base-case incremental cost-effectiveness ratios (ICERs).

- Removing the anomaly that for the botulinum toxin type A arm the utility in health state 5 (20–23 headache days per month[i]) is lower than the utility in health state 6 (24–28 headache days per month).

The Committee also required further clarification of the following:

- Why the utilities have been calculated in the way they have in terms of the choice of disease-specific outcome measure, the selection of the final regression models and the ability to differentiate between the model health states and between treatments.
- The cause of the lack of monotonic (defined as consistently increasing or decreasing) utilities in the botulinum toxin type A arm, the impact this has on the ICER and whether alternative methods for calculating utilities or defining health states could avoid this issue.
- Why different utilities were used in the botulinum toxin type A and placebo arm (including the evidence to support the size of the difference).
- Why there is a large difference between the deterministic and probabilistic ICERs.
- The costs incurred by only the UK group in the International Burden of Migraine Study (IBMS). Data should include the numbers and ages of patients, sites, resource use (in terms of contacts with outpatients, accident and emergency departments and NHS Direct), the reasons for contacts and the associated costs

Provided herein are responses to each of the requests noted above. Revisions to the model have been made and are provided for review by the evidence review group. A revised economic model has been submitted to NICE (loaded to Basecamp) in parallel with submission of this document.

Finally, Allergan confirms that no material in the original or revised manufacturer model or submission needs to be classed as commercial in confidence. The recent patient survey data referred to (see later) may be developed for peer review publication.

[i] Where one month = 28 days throughout the document and analyses

Modification of model base case to match the ERG preferred model

Following receipt of the ACD for Botox® for the prophylaxis of headaches associated with chronic migraine, Allergan has revised the modelling assumptions (to adopt the ERG base case) and methodology (to address errors highlighted in the AC meeting, and ACD.

An issue raised for further discussion in the ACD pertained to the application of different utilities where Botox® patients exhibit a higher utility than placebo patients per health state (defined as number of headache days per month). Therefore, the model was run with i) different and ii) the same utilities applied per heath state and the impact on the ICER was noted (see Table 1). The different utilities (which are generally higher on Botox® than placebo in most health states) arise from a combination of factors, that are reflected in differences in the Headache Impact Test 6 (HIT-6), Migraine-specific quality of life questionnaire (MSQ), number of moderate and severe headache days, as well as other metrics, and are discussed fully in Appendix 1.

Table 1 lists the revisions made to the model in order to reach the base case preferred by the AC. Each change is additive – the first change is made, and then the second is added without undoing the first change. Thus, the result of these changes to the originally submitted model is an ICER of £15,270 with different utilities, and £24,540 using the same utilities per health state. In both cases in Table 1 the negative stopping rule requiring patients to improve 2 health states in 2 cycles to remain on treatment was from the original submission.

Table 1: Changes made to the original model, ICERs given with different and the same utilities per health state

Change made sequentially to address ERG requirements	**ICER with different utilities per health state**	**ICER with same utilities per health state**
1. Model adapted to more closely match ERG model, including applying placebo cost to discontinuers.	£7,170	£13,110
2. Positive stopping rule changed such that 24% of episodic patients cease treatment after 1 year.	£12,355	£22,572
3. Blumenfeld resource use (Appendix 3)	£13,776	£25,168
4. Administration as neurology outpatient cost (£140)	£11,997	£21,917
5. A&E visit cost of £77.33	£12,047	£22,008
6. Utility values from ≥3 prior treatments	£16,243	£23,624
7. Pooling the bottom two health state utility values*	£14,876	£23,975
8. Transition probabilities from the ≥3 prior patients (2 HS in 2 cycle Botox® stopping rule)	£15,270	£24,540

*Further detail given in Appendix 1 on removal of non-linear utilities, and on the rationale for patients exhibiting better utility when on Botox® treatment

In the absence of any other evidence, and per NICE requirements, all the revised analyses in this document include the 24% positive stopping rule. This is based on one US abstract (Rothrock et al 2011). This single arm observation study comprised 100 patients, the vast majority of whom were

insured by Blue Cross Blue Shield. Allergan consider that the US derived data in terms of positive stopping rules is not reflective of what would happen in the NHS in England and Wales. Rather Allergan consider (based on input from clinical experts) that an NHS positive stopping rule is more likely to be that once the patient has Episodic Migraine (namely <15 headache days per 28 days) they would discontinue Botox®.

Were this to be the case, this influences the ICER down from the values seen in Table 1 and elsewhere in this response, making the use of Botox® in the NHS more cost effective still.

Negative stopping rule

In the AC meeting, the clinical experts did not relate their experience of negative stopping rules to the improvement in health states. Rather they stated a preference for the use of patient diaries, and 'responder rates' – an endpoint in the original clinical trials.

In order to better reflect NHS context as discussed by the experts present at the AC meeting, the ACD requested that Allergan perform additional analyses using stopping rules based on 'responder rate' criteria. Thus the negative stopping rule defined non-responders as patients whose number of headache days per month decreases by less than the specified criteria in Table 2 at week 24 compared with baseline.

Table 2: ICERs and percentage of patients ceasing treatment, using different 'negative' stopping rules

Negative Stopping rule	% of Botox® patients discontinuing	% Botox® patients discontinuing due to stopping rule	ICER with different utilities per health state	ICER with same utilities per health state
No negative stopping rule (e.g. patient data shows discontinued for other reasons, such as AEs)	10.9%	0	£19,508	£35,637
Negative stopping rule – 1 HS in 1 cycle	37.0%	26.1%	£14,198	£23,849
Negative stopping rule – 1 HS in 2 cycles	31.7%	20.8%	£15,433	£26,823
Negative stopping rule – 2 HS in 2 cycles	54.1%	43.2%	£15,270	£24,540
Negative stopping rule – 0% response rate required (i.e. discontinue if their headaches become worse)	21.6%	10.7%	£17,174	£30,755
Negative stopping rule – 10% response rate required	31.2%	20.3%	£15,565	£27,080
Negative stopping rule – 20% response rate required	37.7%	26.8	£14,743	£24,995
Negative stopping rule – 25% response rate required	41.2%	30.3%	£14,921	£25,313
Negative stopping rule – 30% response rate required	47.7%	36.8%	£14,999	£24,939
Negative stopping rule – 40% response rate required	55.0%	44.1%	£15,289	£24,806
Negative stopping rule – 50% response rate required	63.6%	52.7%	£15,686	£24,392

Experts recommend that responder rates should be defined as either ≥30% or ≥50% reduction; responder rates have been traditionally defined in episodic migraine (< 15 headache days per 28 days) as ≥50% reduction, but in a CM population, a ≥30% responder rate is considered to be clinically meaningful (Silberstein et al 2008). In the new base case, a ≥30% response rate has therefore been selected in order for CM patients to remain on treatment.

In absolute change, a ≥30% reduction in the number of headache days requires 5 to 9 fewer headache days per month at week 24 compared to baseline. This suggested base case is associated with an ICER of £14,999 per QALY gained (with different utilities) and £24,939 (with the same utilities), respectively (Table 2). All other elements of the ERG base case remain unaltered and utilities have been pooled in the bottom health states.

Patients who do not exhibit at least a 30% reduction in number of headache days per month within two cycles are discontinued. Clinicians in the NHS will not treat CM patients who do not respond; at the AC meeting clinicians advised that a 30% to 50% reduction in the number of headache days per month would be required to continue treatment. In clinical practice patients differ in their baseline disease burden and speed of response to prophylaxis. If a higher threshold for response were to be chosen, this could disadvantage patients with a greater burden of disease at baseline as they would have to obtain a larger absolute change to be considered responders. A ≥50% reduction could therefore be deemed to be too aggressive, as almost 2/3 of patients would discontinue treatment under this scenario. In the case of CM, responder rates is in itself a limited endpoint, capturing only frequency of headache days and does not capture the holistic benefit of prophylactic treatment itself.

The ICER decreases as the negative stopping rule percentage response rate increases from 0 to ≥25%. This is because the patients in the worst health state who did not improve are discontinued and do not incur Botox® costs. The ICER increases again by a small amount as the percentage reduction required increases from ≥25% to ≥50%. This is because more patients in the better health states who have seen some improvement are also discontinued.

The number of patients discontinuing in each health state for each stopping rule is shown in Table 3, with there being a close correlation between health state and response rate

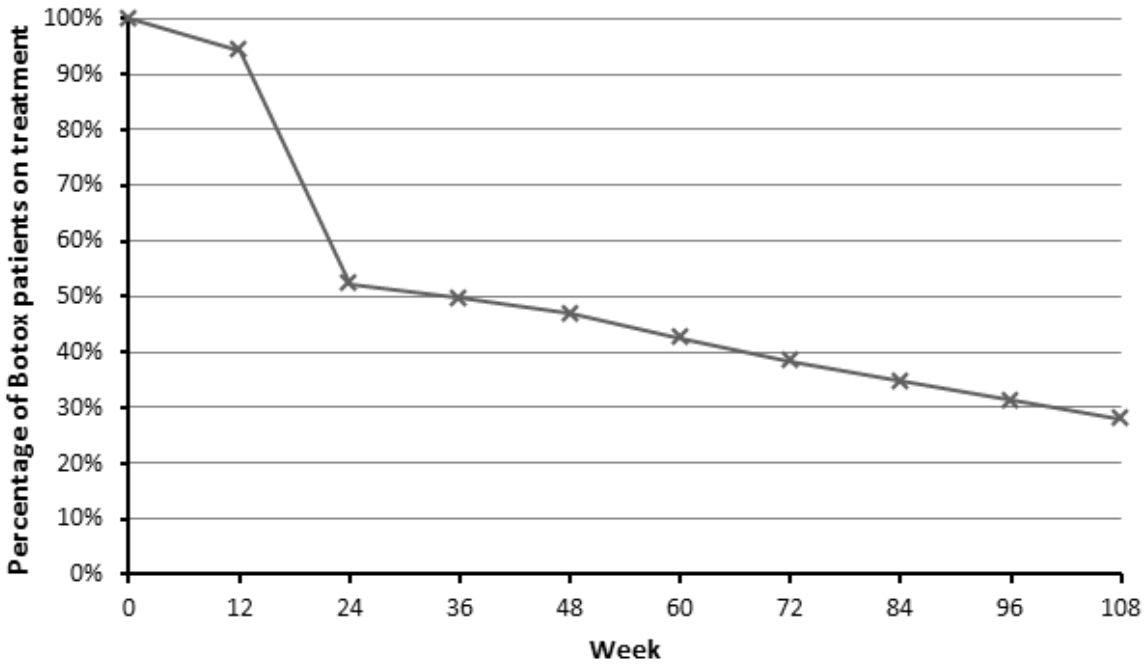
Table 3: Health states of patients discontinued at 24 weeks due to responder based stopping rules

Negative Stopping rule	0-3 HA Days per month	4-9 HA Days per month	10-14 HA Days per month	15-19 HA Days per month	20-23 HA Days per month	24+ HA Days per month
No stopping rule	0	0	0	0	0	0
0%	0	2	0	2	8	12
10%	0	2	2	11	13	18
20%	0	4	6	14	17	20
30%	0	6	12	23	20	23
40%	0	12	15	26	24	24
50%	0	19	21	28	29	24

NB: Some patients discontinue treatment not due to the stopping rule (shown in the 0% row); these patients are **included** in the numbers ceasing treatment on all rows. HA=Headache

The numbers of patients on treatment in the model assuming the 30% negative stopping rule and 24% positive stopping rule is seen in Figure 1.

Figure 1: Number of patients on Botox® treatment over the 2 years (with a 30% negative stopping rule and 24% positive stopping rule):



Probabilistic Sensitivity Analysis

In the manufacturers' submission, there was a discrepancy between the deterministic estimate of the ICER, and the probabilistic estimate. This led to the probabilistic ICER being higher (at £12,275), compared to the deterministic ICER of £5,828.

Allergan suggested that using monotonic utility values brought the probabilistic ICER much closer to the deterministic ICER for the original base case results. Using the original probabilistic sensitivity analysis (PSA) methodology, but pooling the bottom two health state utility values, the probabilistic mean ICER for the revised base case is £19,595. Allergan established that the lack of monotonic utility values was not the sole cause of the discrepancy, and therefore investigated the PSA to understand the cause of the discrepancy. On further examination it was apparent that the difference was due to the transition probabilities; when these were not varied, the probabilistic ICER was much closer to the deterministic ICER.

The original methodology, using Bayesian techniques and complex Dirichlet distribution calculations, was incorrectly applied. A continuity correction was not applied, and this generated bizarre results in transitions where very few patients had moved between two health states.

We appreciate the AC bringing this issue to our attention. The probabilistic values for the transition probabilities have been recalculated using a beta tree distribution with a continuity correction (see Appendix 2).

The new probabilistic mean ICER for 10,000 results in the base case is £13,067 (compared to a deterministic estimate of £14,999). Results are presented in Table 4andFigure 2. The difference in the probabilistic mean ICER and the deterministic ICER is driven by the difference in QALY gain (0.088 compared to 0.074). This QALY gain is influenced by extreme values generated in the PSA.

The probabilistic median ICER is £13,807 (Figure 2), with an incremental QALY of 0.078 and incremental cost of £1,131. In the probabilistic median results, the incremental QALY gain and incremental costs are very similar to the deterministic mean results.

Since the incremental costs between Botox® and placebo are relatively low (£1,114 in the deterministic base case), a small difference in incremental QALYs can make a large difference to the ICER. As the ICER is a ratio, the mean is therefore skewed by the extreme values that can be produced, which results in the PSA value not exactly matching the deterministic value. However, that the median value matches closely the deterministic value shows that the PSA is a good reflection of the uncertainty around the model inputs.

Using this revised methodology, Botox® is cost-effective at a threshold of £20,000 per QALY on 77% of occasions, and on 86% of occasions at a threshold of £30,000 per QALY (Figure 3).

Table 4: Probabilistic mean results using a 30% responder rate negative stopping rule (and different utilities)

Treatment Arm	Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs			
Placebo	£ 2,330	1.15			
Botox®	£ 3,478	1.24	£ 1,144	0.09	£ 13,067

Figure 2: Scatterplot of revised probabilistic sensitivity analysis results, 10,000 simulations

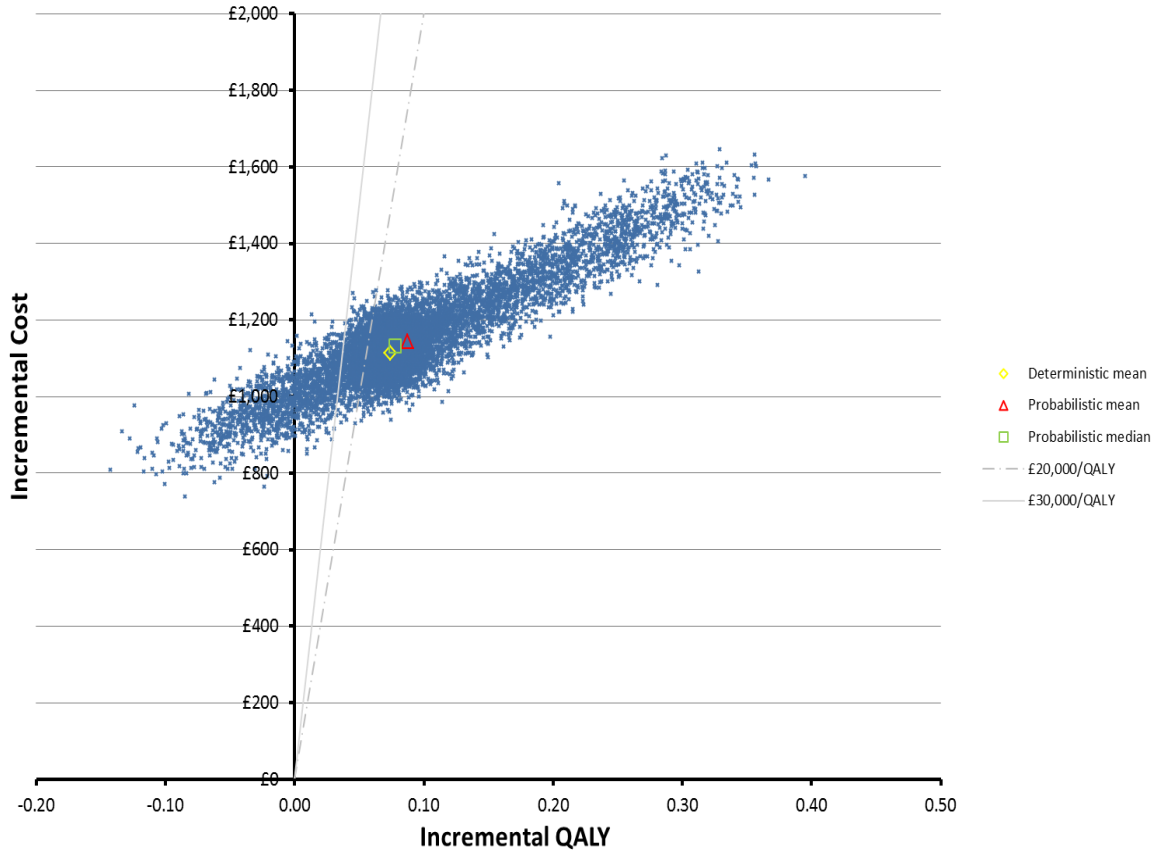
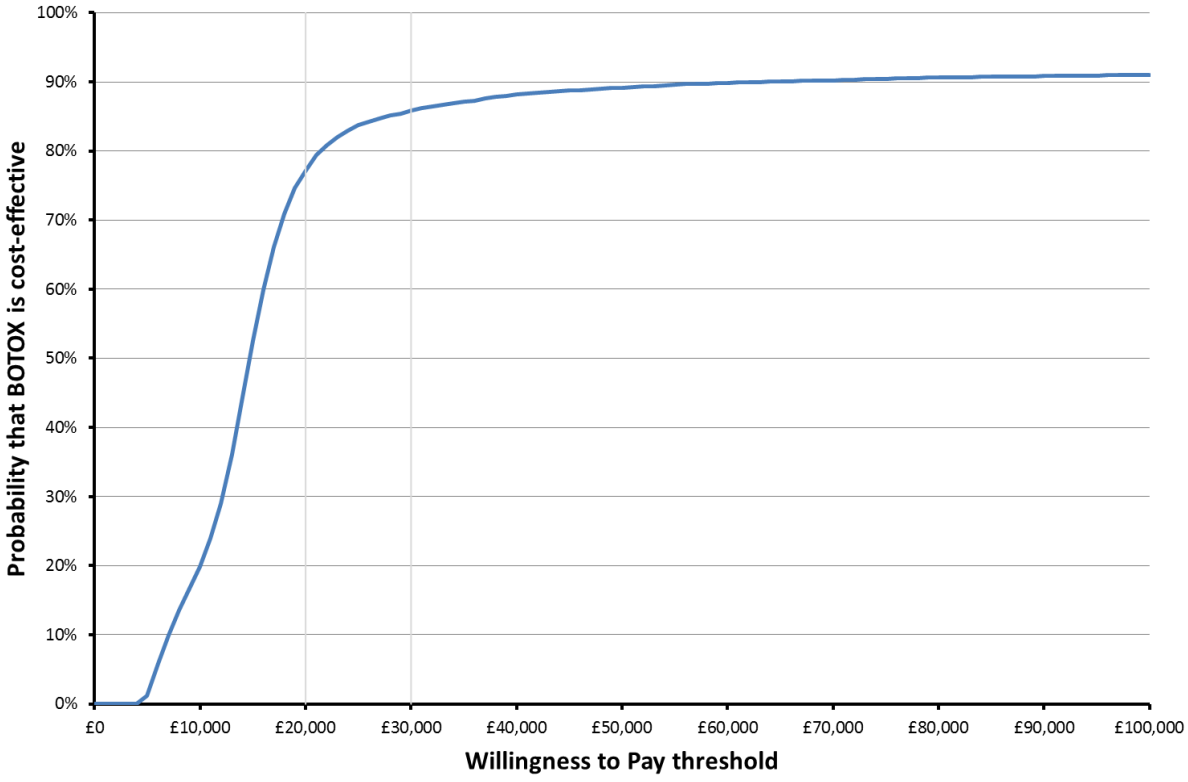


Figure 3: Cost-effectiveness acceptability curve, 10,000 simulations



Predictive accuracy of the model

In both the ERG report, and the AC meeting, the predictive accuracy of the model was questioned, largely based on Table 6.22 of the original manufacturers' submission (Page 167). In reviewing the model, we realised there were mistakes in the original table. We appreciate the AC bringing this issue to our attention. The previously submitted Table 6.22 compared the results of the clinical trial with the outcomes of the model. In that table, the ERG highlighted that in some metrics there were predictive errors. However, in revisiting this table, we realised the model results were for the ≥1 prior treatment subpopulation, not the entire clinical trial population. Further they included negative stopping rules. The sheet 'Table 6.22' in the economic model contains this table, with instructions for recreation.

When the correct results are generated (Table 5), the predictive accuracy of the model was demonstrated by the close alignment of model predictions to the original clinical data for both Botox® and placebo (Table 5).

Table 5: Clinical trial results compared to economic model results (Revised Table 6.22 from original manufacturer submission)

Outcome	**Clinical trial result**	**Model result** *(original incorrect values)*
Mean headache days at baseline (Botox®)	19.9	19.8 *(20.0)*
Mean headache days at baseline (Placebo)	19.8	19.9 *(20.1)*
Mean change from baseline in frequency of headache days (Botox®)	-8.4	-8.2 *(-9.5)*
Mean change from baseline in frequency of headache days (Placebo)	-6.6	-6.5 *(-6.9)*
Mean intergroup difference in change in frequency of headache days	-1.8	-1.7 *(-2.6)*

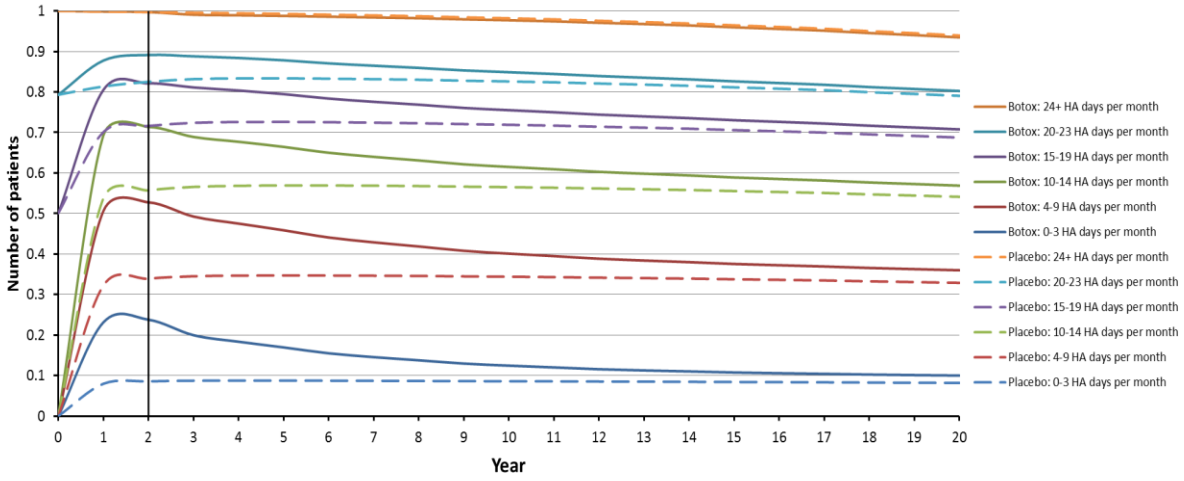
Appropriateness of the time horizon used

The AC queried whether the 2 year time horizon used in the original submission was sufficient for a chronic condition. Following receipt of the ACD, Allergan has investigated the 'end states' of patients in the economic model.

Using a 2 year horizon in the model shows that at the end of the 2 years, Botox® patients are generally in better health states, with fewer headache days than placebo patients. Although the majority of Botox® patients have discontinued (only 38.6% remain on treatment at 2 years in the ERG/AC's base case), Botox® patients have discontinued in better health states, having an average of 12.7 headache days per month, compared to 14.1 headache days on placebo.

Following discontinuation, both placebo and Botox® patients follow transition probabilities taken from the placebo arm of the clinical trial (receiving placebo utilities). However, as Botox® patients discontinue treatment in better health states, they take several years to reach the 'steady state' transitions seen in the long term with placebo. Figure 4 shows the different ending states of patients graphically.

Figure 4: Patient distribution over 20 year time horizon, Botox® and placebo



As a consequence, the impact of the longer time horizon is to reduce the ICER for Botox®, as the lingering benefit is captured, whilst relatively few additional costs are incurred. This reduction in the ICER is shown in Table 6, for both different and the same utilities applied per health state.

Results at 20 years are presented in Table 7, at which point patients are in approximately equal health states, with Botox® patients experiencing approximately 12.4 headache days a month, comparable to the 13.0 experienced by placebo patients. As highlighted in the ERG report, this may

also represent a more appropriate time horizon for a chronic disease model. The ICER at this time point is £8,825 per QALY gained [using different utilities].

Table 6: ICERs at different time horizons

Time horizon	ICER with different utilities per health state	ICER with the same utilities per health state
2 year	£14,999	£24,939
5 year	£11,355	£16,664
10 year	£9,885	£13,711
15 year	£9,241	£12,476
20 year	£8,825	£11,700

Table 7: Economic model results, 20 year time horizon

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Placebo	£ 21,437	11.25	£ 15,638	8.18			
Botox®	£ 23,474	11.50	£ 17,527	8.40	£ 1,888	0.21	£ 8,825

In longer time horizons episodic migraine patients (fewer than 15 days of headache a month) who discontinue treatment after 1 year due to the positive stopping rule (24%), are assumed to maintain the benefit only until the end of year 2, after which they have placebo efficacy and utility values (i.e. the success of Botox® treatment is maintained in these patients for only 1 year).

Effectiveness of placebo as a treatment

During the AC meeting, the marked placebo response in PREEMPT was discussed (an observation common to migraine and headache RCTs (Silberstein et al 2008)), prompting the question of use of placebo as a prophylactic treatment for this population of CM in the NHS. Per the criteria for well controlled clinical trials in CM in adults (Silberstein et al 2008), the new treatment (Botox®) should be compared with sham treatment when relevant. The comparison presented in the submission looks at the added value of Botox® over placebo. However, in clinical practice patients would not receive sham injections every 12 weeks, and the placebo effect would not be expected to exist, particularly in a population of patients who must have tried and failed at least three prior headache prophylaxis treatments.

As a sensitivity analysis, a scenario is presented in Table 8, where placebo patients are assumed to remain in their original health states. This assumes that placebo treatment has no effect on the number of headache days per month. This is applied in the model using an identity matrix – with this patients may not transition to any other health state. For example, if a patient is in the 15-19 headache days per month health state, their probability of moving to the 15-19 headache days per month health state is 1, and the probability of moving to any other health state is 0.

In this scenario analysis, the ICER for Botox® reduces from £14,999 to £5,677 (assuming different utilities). Treatment with Botox® remains highly cost-effective, regardless of the use of different or the same utilities per health state (Table 8, Table 9, Table 10).

Table 8: Economic model results with placebo efficacy set to zero

	ICER with different utilities per health state	**ICER with the same utilities per health state**
Identity matrix for placebo efficacy	£5,677	£6,008

Table 9: Economic model results with placebo efficacy set to zero - different utilities per health state

Treatment Arm	**Totals**		**Discounted Totals**		**Incremental Costs**	**Incremental QALYs**	**Cost per QALY**
	Costs	**QALYs**	**Costs**	**QALYs**			
Placebo	£ 2,806	1.09	£ 2,719	1.06			
Botox®	£ 3,568	1.23	£ 3,471	1.19	£ 751	0.13	£ 5,677

Table 10: Economic model results with placebo efficacy set to zero - the same utilities per health state

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Placebo	£ 2,806	1.09	£ 2,719	1.05			
Botox®	£ 3,568	1.22	£ 3,471	1.18	£ 751	0.13	£ 6,008

UK IBMS resource use data.

The resource use data for the UK subgroup of IBMS has been used in place of the Blumenfeld resource use estimates as a sensitivity analysis in the model (full details presented in Appendix 3), as requested in the ACD.

This results in an ICER of £12,624 (down from £14,999 in the base case which uses a ≥30% response rate as the negative stopping rule) using different utility values per health state (Table 11), and £20,989 (down from £24,939) when using the same utility values per health state (Table 12). This is a reduction of approximately £2,500 per QALY in the ICER, which is largely due to the higher than average number of hospitalisations seen in the UK subgroup of IBMS (0.39 compared to 0.09) (see Appendix 3).

Table 11: Results for UK IBMS resource use – different utility values per health state

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Placebo	£ 3,146	1.17	£ 3,054	1.13			
Botox®	£ 4,099	1.24	£ 3,991	1.21	£ 937	0.07	£ 12,624

Table 12: Results for UK IBMS resource use – the same utility values per health state

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Placebo	£ 3,146	1.19	£ 3,054	1.15			
Botox®	£ 4,099	1.24	£ 3,991	1.20	£ 937	0.04	£ 20,989

Appendix 1: Utility Values

Lack of monotonic utilities in the Botox® and placebo arms and methods to overcome this observation

In the AC meeting and ACD, it was noted that the provided utility values used in the submission, and shown in Table 13, contained a discrepancy between the bottom two health states, where Botox® patients with 20-23 headache days have a lower utility than those with 24+ (while patients on placebo have a higher utility). This is likely a result of random chance, in combination with low patient numbers (n=18 and n= 21 in the 20-23 headache day groups for Botox and placebo, respectively). In the original submission, in the 1-prior population, lack of monotonic utility was only observed in the Botox® arm.

Table 13: Utility values used in the original manufacturer submission for the ≥3 prior treatment group (utility correction letter)

Health State	Botox®			Placebo		
	n	Mean	SE	n	Mean	SE
0 - 3	24	0.691	0.028	13	0.669	0.053
4 – 9	45	0.699	0.018	40	0.638	0.022
10 – 14	36	0.635	0.024	44	0.565	0.024
15 – 19	26	0.561	0.028	36	0.55	0.037
20 – 23	18	0.462	0.054	21	0.597	0.039
24 +	15	0.501	0.055	41	0.461	0.035

In order to resolve this issue, the bottom two health states (20-23 and 24+ headache days per month) within each treatment arm (Botox® and placebo) have been pooled. In performing this pooling, the patient numbers increase, (n=33, n=62, respectively), and monotonicity is restored – generating a negative correlation between the number of headache days per month, and health related quality of life.

The pooled utilities used in the revised model are presented in**Table 14**. In the worst two health states Botox® patients exhibit a lower quality of life (0.480) than placebo (0.507) patients. As this data is taken from patient responses from a clinical trial, it has not been altered other than the pooling as described above. These values have been used in the revised analyses in the ACD response.

Table 14: Utility values used in ACD response analysis, pooling utilities for health states 20-23 and 24+ headache days per month, ≥3 prior treatment subgroup

Health State	Botox®			Placebo		
	n	Mean	SE	n	Mean	SE
0 - 3	24	0.691	0.028	13	0.669	0.053
4 – 9	45	0.699	0.018	40	0.638	0.022
10 – 14	36	0.635	0.024	44	0.565	0.024
15 – 19	26	0.561	0.028	36	0.55	0.037
20 – 23	33	0.480	0.054	62	0.507	0.036
24 +	33	0.480	0.054	62	0.507	0.036

Calculation of utilities, and justification of differentiated utilities for Botox® and placebo treated patients

A mapping algorithm (Gillard et al 2012) was employed to estimate health utility of CM patients across the spectrum of headache frequency and by health states defined in the economic model.

Additionally, the mapping algorithm was applied separately to patients treated with Botox® and placebo to detect differences in health related quality of life in addition to improvements in the number of headache days (e.g. reduction in headache severity and duration of headache on headache days). The rationale for applying different utility to treatment arms comes from the Phase III data, which showed clinical and health related quality of life improvements for those receiving Botox® that went beyond the reduction in the number of headache days.

The Headache Impact Test (HIT-6™) measures the adverse impact of headache on social functioning, role functioning, vitality, cognitive functioning and psychological distress. The score range is 36 to 78 with higher scores indicating greater headache impact: that is, lower health-related quality of life. The Migraine Specific Quality of Life Questionnaire Version 2.1 (MSQ) uses a 14 item measure to yield results for 3 factorally-derived subscales: the role-restrictive dimension that assesses the degree to which migraine affects the performance in normal activity; the role-preventive dimension that assesses the degree to which migraine interrupts an individual's performance of normal activities; and the emotional function dimension that measures the emotional impact of migraine. Items are captured on a standard six-point ordered-categorical scale with choices ranging from none of the time to all of the time.

Botox®-treated patients experienced significant improvement from baseline in both the HIT-6 and all three MSQ subscales that met or exceeded established minimally important differences for these measures. Botox®-treated patients also reported statistically significantly greater reductions in the frequency of migraine days, of moderate/severe headache days, and cumulative hours of headache on headache days (some of which is captured within the health state modelling, some of which is not). The mean difference in cumulative hours of headache on headache days between Botox® and placebo groups after 2 treatment cycles Botox® was 39.2 hours (approximately 120 vs. 80 hours).

Headache days per 28 days, HIT-6 and MSQ subscale scores by health state for ≥3 prior prophylactic use at week 24 (after 2 treatment cycles) are presented in Table 15. When assessed cross-sectionally by headache-day frequency health states, patients treated with Botox® tend to report better health-related quality of life (Table 15) than those treated with placebo. These results explain firstly the differences seen between treatments, but secondly the differences seen within treatments *in the*

same health state, supporting the hypothesis that Botox® reduces not only the number of headache days, but also improves other factors affecting quality of life.

A variety of variables influence someone's quality of life, in terms of their health. They include, for example, the level of pain the person is in, any comorbidity, the person's ability to operate in society, disability, access to health services, the persons' subjective perception of general well-being, as well as their general mood. While the subjective nature of headache is well known (Silberstein et al 2008), across the variety of appropriate outcome measures collected in the PREEMPT trial (presented in the original submission and in this response), there is a reassuring consistency of statistically significant and clinically relevant benefit of Botox® over placebo .

Allergan Australia has recently undertaken qualitative research in CM patients treated with Botox® to provide insight into what a successful response to treatment looks like for them (see Appendix 4). In brief, the following aspects of patients lives were explored in a series of patient interviews (n=10):

- What was the patient's life like prior to treatment? What was the impact of chronic migraines on their lives and livelihoods?
- What response have they had to Botox® treatment? In what way do they consider this response successful?
- What change has Botox® treatment brought in their lives? What does this successful patient outcome look like?
- What are the different manifestations of a successful outcome? How does this vary amongst different patients

Patients in this study reported three main types of **clinical** responses to Botox® treatment, as follows.

- Reduced frequency of migraine and headache days
- Reduced severity of migraine
- Reduced length/ duration of migraine symptoms

Patients also identified additional benefits of their Botox treatment which impacted their lives:

- Reduced reliance on other pharmaceutical treatments
- Reduced reliance on other pharmaceutical treatments
- When they occur, migraines responded to simple over the counter (OTC) medications
- Ability to work through and/or function better during the migraine
- Less unpaid and sick leave from employment
- Ability to continue tertiary education

- Reduced hospitalisations and/or doctor visits

Such treatment benefits impacted positively on patients lives, and hence overall wellbeing, and these are summarised in Appendix 4.

Allergan believes the use of the utility - as an attempt to combine the value of these attributes into a single index number – does indeed reflect the overall impact of prophylactic treatment in chronic migraine on the person. Given the information provided, the application of differential utilities is appropriate, and allows indirect capture of the multidimensional improvement of patients receiving Botox®. The impact of Botox® beyond improvements in the number of headache days is demonstrated by the mapped utilities that captures these improvements in a way which can be incorporated into the decision problem.

Table 15: Outcome characteristics at week 24 by health state for ≥3 prior prophylactics

		Botox®			**Placebo**		
Outcome Characteristic	Health State at Week 24	N	Mean	SD	N	Mean	SD
Headache days per 28 days[1]	0 - 3	30	1.8	1.19	15	1.7	1.18
	4 – 9	55	6.6	1.51	48	7.4	1.51
	10 – 14	56	11.9	1.45	60	12.2	1.42
	15 – 19	44	16.9	1.48	44	16.8	1.40
	20 – 23	23	21.3	1.19	32	21.3	1.14
	24 +	23	26.6	1.73	49	26.9	1.23
HIT-6™[1]	0 - 3	30	56.9	8.53	15	57.1	11.80
	4 – 9	55	58.8	6.28	48	61.5	6.43
	10 – 14	56	63.1	5.24	60	64.7	5.59
	15 – 19	44	63.8	5.52	44	63.8	4.83
	20 – 23	23	65.8	7.51	32	64.7	4.53
	24 +	23	66.2	3.66	49	66.7	6.03
MSQ Role Function – Restrictive[2]	0 - 3	29	27.7	20.12	14	40.2	29.00
	4 – 9	54	38.9	18.26	45	46.4	20.28
	10 – 14	47	55.3	17.94	51	60.1	19.73
	15 – 19	39	55.8	18.40	42	55.9	19.95
	20 – 23	20	63.4	23.55	28	60.7	20.05
	24 +	20	61.7	18.03	47	66.9	23.14
MSQ Role Function – Preventive[2]	0 - 3	29	19.5	16.44	14	27.5	29.79
	4 – 9	54	25.5	19.28	45	28.7	17.37
	10 – 14	47	40.4	19.61	51	43.9	22.46
	15 – 19	39	42.6	23.05	42	41.9	24.47
	20 – 23	20	51.0	26.64	28	39.6	20.45
	24 +	20	46.3	24.65	47	48.0	25.08
MSQ Emotional Function[2]	0 - 3	28	25.0	29.12	14	39.5	35.90
	4 – 9	54	33.2	26.90	45	41.3	29.94
	10 – 14	47	48.2	25.94	51	52.4	24.62
	15 – 19	39	49.7	24.61	42	54.6	25.30
	20 – 23	20	59.7	34.09	28	59.3	25.94
	24 +	20	62.3	25.53	47	55.2	27.34

[1]Missing values were estimated using modified last observation carried forward

[2]observed data only, lower scores denote better HRQL

Appendix 2: Probabilistic Sensitivity Analysis – revised method

The population of patients beginning in a given health state at the start of a cycle are divided into mutually exclusive and exhaustive groups – the health states into which they transition. This can be divided into a number of beta distributions, which is represented with a "beta tree" distribution.

For example, in the placebo arm, between baseline at week 12, the patient transitions from the 15-19 headache days per month health state are shown below:

Table 16: patient transitions from the 15-19 headache days per month health state – baseline to week 12

	0-3 HA Days per month	4-9 HA Days per month	10-14 HA Days per month	15-19 HA Days per month	20-23 HA Days per month	24+ HA Days per month	Discontinued Treatment
15-19 HA days per month	8	25	44	26	6	7	8

HA = headache

The probability of a patient transitioning from 15-19 headache days per month to 0-3 headache days per month can be represented as a beta distribution with 8 successes, and 116 failures (25+44+26+6+7+8). A random number between 0 and 1 is then used to sample from the beta(8,116) distribution, producing a value *p* between 0 and 1. The probability that a patient transitions to any of the other states is then *1-p.* The probability of a patient transitioning from 15-19 headache days per month to 4-9 headache days per month can be represented as a beta distribution with 25 successes, and 91 failures (44+26+6+7+8) (excluding transitions to 0-3 headache days per month). A random number is then used to sample from the beta (25,91) distribution, producing a value *q* between 0 and 1. Since this value *q* is the probability of transitioning from 15-19 headache days per month to 4-9 headache days per month, given that they do not transition from 15-19 headache days per month to 0-3 headache days per month, the probability of transiting from 15-19 headache days per month to 4-9 headache days per month is *q*(1-p).* Similarly, the transition from 15-19 headache days per month to 10-14 headache days per month can be represented with a beta(44,47) distribution (excluding transitions to 0-3 headache days per month and excluding transitions to 4-9 headache days per month), to give a value *r.* The probability of transiting from 15-19 headache days per month to 10-14 headache days per month is *r*(1-p-q).*

The probabilistic values for the transition probabilities are therefore:

Table 17: Transition probability calculations

	0-3 HA Days per month	4-9 HA Days per month	10-14 HA Days per month	15-19 HA Days per month	20-23 HA Days per month	24+ HA Days per month	Discontinued Treatment
15-19 HA days per month	p	q*(1-p)	r*(1-p-q)	s*(1-p-q-r)	t*(1-p-q-r-s)	u*(1-p-q-r-s)	(1-u)*(1-p-q-r-s)

HA=Headache

Where p is a random sample from the beta (8, 116) distribution, q is a random sample from the beta (25, 91) distribution, r is a random sample from the beta(44,47) distribution, s is a random sample from the beta (26, 21) distribution, t is a random sample from the beta (6, 15) distribution, u is a random sample from the beta (7, 8) distribution.

Where the number of patients transitioning from one health state to another is below 5, a continuity correction is applied. This continuity correction divides an additional observation equally amongst the health states. For example, in the Botox® arm, between baseline at week 12, the patient transitions from the 15-19 headache days per month health state are shown below:

Table 18: probabilistic patient transitions from the 15-19 headache days per month health state – baseline to week 12

	0-3 HA Days per month	4-9 HA Days per month	10-14 HA Days per month	15-19 HA Days per month	20-23 HA Days per month	24+ HA Days per month	Discontinued Treatment
15-19 HA days per month	15	34	33	16	10	1	6

HA=Headache

Since only 1 patient moved from 15-19 headache days per month to 24+ headache days per month, a continuity correction of 1/7 has been applied to every transition, giving the values shown below:

Table 19: probabilistic patient transitions from the 15-19 headache days per month health state – baseline to week 12, including continuity correction

	0-3 HA Days per month	4-9 HA Days per month	10-14 HA Days per month	15-19 HA Days per month	20-23 HA Days per month	24+ HA Days per month	Discontinued Treatment
15-19 HA days per month	15.14	34.14	33.14	16.14	10.14	1.14	6.14

HA=Headache

Appendix 3: Resource use estimates

Table 21 details the healthcare resource used incurred by the UK group in the IBMS (Allergan data on file). Mean resource use is reported for patients reporting 1 or more visit, so the mean resource use for all patients has been calculated. Blumenfeld (2010) reported the healthcare resource use for all patients within the IBMS study.

Healthcare resource utilization from Bloudek (2011) from the submission and published paper are presented in Table 18. Both the submission and published manuscript are based on the International Burden of Illness Study. Because the published results from Blumenfeld 2010 do not stratify based on model health states, the additional Bloudek 2011 analyses were conducted in order to populate the model with more granularity. It was noted that there was a discrepancy in healthcare resource utilization figures provided in the Allergan submission compared to a recent manuscript published by Blumenfeld (2010). Because of the relatively small sample size in chronic migraine health states, an additional exercise was completed to pool healthcare resource utilization across the chronic migraine health states (15-19, 20-23, 24+). This approach was taken for the NICE submission. When these groups were pooled, it was noted by the ERG that a discrepancy existed between the pooled chronic migraine health states in the submission and the published manuscript. The primary reason for this discrepancy is the inclusion of the Brazilian cohort of the IBMS survey in the figures of Bloudek (2011), but exclusion from the Blumenfeld publication as the Brazilian data was not ready at the time of publication. In addition, Blumenfeld (2010) combined nurse practitioner visits and physician assistant visits with primary care whereas Bloudek (2011) did not. The Blumenfeld (2010) figures provide insufficient detail to populate all health states of the economic model, however due to the superior transparency of the published manuscript, the model base-case has been revised to use the Blumenfeld (2010) healthcare resource utilization.

Table 20: Resource use comparison between the original model values (Bloudek), the values from Blumenfeld (new base case), and the UK IBMS subset (sensitivity analysis)

	Health states	Bloudek resource use (original model values)	Blumenfeld resource use (revised model values)	UK IBMS subset (sensitivity analysis)
Physician visits per 12 weeks	0-3 HA days per month	0.10	0.69†	0.72
	4-14 HA days per month	0.30		0.72
	15+ days per month	0.58	2.07†	1.44
Hospitalisations per 12 weeks	0-3 HA days per month	0.03	0.03	0.03
	4-14 HA days per month	0.08		0.03
	15+ days per month	0.32	0.09	0.39
ER visits per 12 weeks	0-3 HA days per month	0.12	0.10	0.07
	4-14 HA days per month	0.28		0.07
	15+ days per month	0.63	0.41	0.51

†Includes primary care physician, physician assistant and nurse practitioner visits

Table 21: Healthcare resource use incurred by only the UK group in the IBMS (Allergan data on file)

Study Measure[1]	Chronic Migraine (n=57)	Episodic Migraine (n=1013)
Age, mean(SD)	42.9(12.7)	44.3(11.2)
Primary care physician visits, %	56.10%	28.3%**
Mean (SD)[2]	2.57(1.55)	2.54(3.43)
Min-Max	1 – 6	1 – 35
Neurologist/headache specialist visits, %	28.10%	6.0%**
Mean (SD)	1.53(1.06)	1.73(1.10)
Min-Max	1 – 5	1 – 5
Nurse practitioner/physician assistant visits, %	3.50%	3.30%
Mean (SD)	3.00(2.83)	3.28(5.24)
Min-Max	1 – 5	1 – 29
Other specialist visits[3], %	14.00%	6.70%
Mean (SD)	2.14(1.46)	3.83(5.89)
Min-Max	1 – 5	1 – 30
Emergency room visits, %	12.30%	3.5%*
Mean (SD)	4.14(5.05)	1.86(2.17)
Min-Max	1 – 15	1 – 10
Hospitalizations, %	8.80%	1.5%*
Mean LOS (SD)	4.40(6.27)	2.13(1.88)
Min-Max	0 – 15	0 – 8
Diagnostic testing[4], %	14.00%	4.6%*
Mean (SD)	3.13(2.90)	3.30(7.37)
Min-Max	1 – 10	1 – 48
Blood Tests, %	12.30%	4.0%*
Mean (SD)	3.57(3.82)	2.22(1.90)
Min-Max	1 – 12	1 – 9
Botulinum toxin A injections, %	3.50%	0.60%
Mean (SD)	3.00(†)	2.00(2.00)
Min-Max	3 – 3	1 – 5
Transcutaneous nerve stimulator procedures, %	5.30%	3.80%
Mean (SD)	20.50(27.58)	6.87(6.43)
Min-Max	1 – 40	1 – 30
Acupuncture, %	7.00%	3.50%
Mean (SD)	1.00(0.00)	3.00(2.36)
Min-Max	1 – 1	1 – 8
Occipital nerve block procedures, %	12.30%	0.9%**
Mean (SD)	6.67(6.62)	5.50(3.46)
Min-Max	1 – 15	1 – 12

Appendix 4: Narratives from chronic migraine patients whohave responded to BOTOX treatment

The Appendix 4 .pdf document attached in the Allergan covering email with this document summarises a recent (February 2012) patient survey in Australia. It details the impact of Botox® in the lives of ten CM patients who were treated with Botox®. This qualitative research gives an insight into the broader overall beneficial impact of treatment with Botox® in order to understand and illustrate what a successful 'response' to Botox® treatment means for different patients.

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