Botox® (Botulinum toxin type A) in the prophylaxis of headaches in chronic migraine

Manufacturer responses to clarification questions from the Evidence Review Group

November 2011

Clarification on manufacturer's submission: clinical and cost effectiveness

A.1 *Page 160, section 6.5.6 states that "..quantities of resources are taken from the International Burden of Migraine Study (Section 6.4.6, page 148)...." , however section 6.4.6 (on pages 149-150) refers to Blumenfeld 2011 (Cephalgia) but does not give any data on resource use by frequency of headache bands.*

a) Please explain where the data on resource use by health states, used in table 6.17, come from (if from the IBMS, should the data be labelled as academic in confidence)?

b) The Blumenfeld 2010 paper from the IBMS refers to hospital visits (in addition to neurologist visits) in table 6, but refers to hospitalisations in the text on page 10. Please clarify whether the table is really referring to admissions, and similarly, in tables such as 6.17 and 6.18, whether the term hospitalisations refers to hospital admissions.

Manufacturer response to Q A.1:

a) The Blumenfeld et al. Study was referenced to provide a description of the study methods and patient population surveyed in the International Burden of Migraine Study. The resource use by health states has been presented in poster form as the Health Resource Use and Costs for Migraineurs in Scotland and thus is not considered AIC. The full reference for this poster presentation is shown below.

Bloudek LM, Hansen RN, Liu L, Batty AJ, Varon SF, Lipton RB, Sullivan SD. Health Resource Utilization and Costs for Migraneurs in Scotland. International Society for Pharmacoeconomics and Outcomes Research 16th Annual Conference, May 21-25, 2011, Baltimore, MD [PND32]

b) Throughout the submission, data from IBMS has been defined as hospitalisations with the appropriate NHS reference costs used in calculation.

Hospital visits i.e. specialist visits are captured in the model in the administration of either Botox or costs associated with placebo care (e.g. management of acute medications, specialist reviews).

Despite the use of the term "visits", both the Blumenfeld 2010 paper and the model refer to hospital admissions. As part of IBMS, participants were asked to record the total number of headache related admissions in the past 3 months. The exact wording of the question asked of participants related to hospital admissions is included below:

During the past 3 months, were you admitted to a hospital for your headache? (Please select one answer)		Yes		No
Programming Logic Rules If "Yes", go to questions #3a and 3b. If "No", go to question #4.				

3a. Record the total number of headache related admissions to the hospital in the past 3 months. Please type in a number	
Hospital **Admissions**	# of headache related admissions during the past 3 months

A.2 *It is stated that at present only 17% of people with chronic migraine are seen in specialist care. Please provide data on this, including how often patients are seen and how long each visit lasts.*

Manufacturer response to Q A.2:

Unfortunately the market research source cited did not capture adequate information to address the ERGs questions around the frequency and duration of visits.

In order to provide further information, we conducted a brief email survey of UK Neurologists treating chronic migraine patients. 6 responses were received and these are summarised below:

This survey demonstrates that assumptions made for the placebo arm of the economic model, in terms of frequency of follow up are potentially conservative.

Question	A1	A2	A3	A4	A5	A6
Thinking about patients presenting with a diagnosis of chronic migraine to your specialist clinics, how long would an initial consultation last?	30 mins	20-30 mins	30 mins	30 mins	30 mins	30 mins
How long might a follow up consultation last?	15 mins	10-15 mins	15 mins	15 mins	15 mins	15 mins
Following an initial assessment and perhaps initiation of oral prophylaxis or advice regarding acute medications, when would a patient be followed up?	3-6 months	2-6 months	3 months	3-6 months	3 months	No routine f/u*
How many times might a patient with chronic migraine be seen in your clinical before being discharged? (average, recognising wide variation)	4	3	4	4	4-10	*Can have multiple attendances

Advisers responding represented a good geographical spread across England and Scotland and both secondary and tertiary settings

A.3 *Please provide the justification for why the number of injections has been set at between 31 to 39, and in 7 areas.*

Manufacturer response to Q A.3:

Botox has been found to be effective and well-tolerated for the prophylaxis of headache in adults with chronic migraine, when injected in accordance with the treatment paradigm evaluated in the phase 3 studies: a minimum dose of 155 U per injection cycle given via a Fixed-Site-Fixed-Dose (FSFD) paradigm divided in 31 injection sites across 7 specific head and neck muscles, with the option of a further 8 injection sites in 3 specific muscle groups (temporalis, occipitalis and trapezius) as part of the follow-the pain (FTP) paradigm (Blumenfeld et al, 2010).
The number of injections and sites of administration in the phase 3 paradigm were determined after careful analysis of the efficacy and safety data generated from Allergan's phase 2 studies, in addition to expert advice from the two headache specialists (lead coordinating investigators for the phase 3 studies), who were experienced in injecting Botox for migraine prophylaxis. The key considerations in developing the final phase 3 dosing paradigm included analysis of the phase 2 studies for the following:

- Benefit/risk assessment from injection of specific muscles and total dose per injection cycle:
    - dose per injection cycle at which best tolerability was observed
    - dose per injection cycle at which best efficacy was observed
- Dosing regimens and patterns that were common in the phase 2 studies
- Any revisions to the injection paradigm that could improve protocol implementation and standardization that would:
    - facilitate protocol training
    - ensure consistency of the injection methodology across multiple study sites
    - potentially minimize the risk of focally related adverse events by ensuring that the total dose is divided across multiple injection sites in the muscle, and
    - translate easily to rigorous, practical guidance for clinicians in labeling

Justification of the muscle groups injected

Botox blocks the release of neurotransmitters that are known to be associated with the genesis of pain. The presumed mechanism for Botox in chronic migraine headache prophylaxis is that by blocking peripheral signals to the central nervous system, central sensitization is disrupted and/or inhibited, as confirmed by pre-clinical (Aoki 2005) and clinical studies (Gazerani et al, 2006; Gazerani et al, 2009) Thus, the muscle groups selected for the Botox phase 3 studies targeted those muscles that align with the distribution for input to the trigeminal sensory neurons, which are believed to be the target end-organ for Botox in the prevention of headache in chronic migraine. Details for the justification of the Botox phase 3 studies dose, number and location of injection sites, and the injection paradigm have been described in a recent publication (Blumenfeld et al, 2010). A brief summary is provided below:

Frontalis, Corrugator and Procerus (Frontal/Glabellar Region)

In the Botox phase 2 studies (Mathew 2003, Silberstein 2005), patients reported that the frontal/glabellar region was the most frequent location where their head pain started and ended. In the first study, only a total dose was specified for the overall frontal region, which was administered at the investigator's discretion across the frontalis, corrugators and procerus muscles. In the second study the protocol specified that only the frontalis and corrugator muscles were to be injected. Overall, the first study demonstrated better signals for efficacy. Thus, to ensure the best chance for confirming efficacy, as well as ensuring consistency and standardization of the treatment paradigm, the Botox phase 3 studies required treatment to the frontalis, corrugator and procerus muscles.

To reduce the potential for focal AEs such as eyelid ptosis, a slightly lower total dose (35 U) was designated for the Botox phase 3 studies with specified number and location for injection to the Frontalis, Corrugator and Procerus muscles. In addition, injection training to ensure optimal tolerability was required. Indeed, the injection method in these muscles appears to have achieved this goal since the Botox phase 3 studies had statistically significant separation from placebo across multiple headache symptom measures with an overall eyelid ptosis rate for Botox-treated patients in the double-blind placebo-controlled phase of the Botox phase 3 pooled studies of 3.6%.

Temporalis

In the phase 2 trials, the temporalis area was the second most frequent location of head pain. The FSFD for this muscle in the phase 3 trials was determined based on the fact that the mean dose administered to the temporalis muscle in the first trial was ~40 U (~20 U per side) and the maximum dose was 50 U. There were no

emerging tolerability issues from injecting this muscle at these doses in the phase 2 trials. As this muscle was a very common location of predominant pain for many patients in the phase 2 trials, it was decided that for the phase 3 treatment paradigm the total dose of 40 U (20 U per side) would be required as a minimum dose, and an allowance for an additional 10 U to this muscle area could be given using the FTP regimen

Occipitalis

In the phase 2 trials, patients reported that occipitalis was the third most frequent location where their head pain started and ended. The phase 2 data were also evaluated to ascertain the frequency of FTP paradigm actually used by clinicians in the first trial, because variation in the dosage was allowed for all muscle groups in that protocol except for the occipitalis. The mean and median doses for each muscle group showed that the dosages for the temporalis and trapezius muscles were the muscle groups with the most variation across patients, which indicated FTP was most frequently used for these muscle groups. Most patients have predominant pain on one side of the head, or in the back of the head, or in the shoulders that may warrant additional treatment to those areas. Because a decision had been made to reduce the overall dose administered to the neck and to not allow FTP regimen in the neck muscles, there was concern that there would be insufficient “back of the head” dose to ensure efficacy, especially since so many patients complain of pain in that area. Thus, the minimum dose administered to the occipitalis was increased from the phase 2 dose, and, to reduce risk of neck weakness, the sites for injection into the occipitalis were located primarily above the occipital ridge. Furthermore, if patients had a complaint of predominant pain in the back of the head, additional FTP dosing would be allowed in this muscle

Cervical Paraspinal Muscle Group (Neck Muscles)

In the phase 2 trials, patients indicated that their headache pain frequently started and/or stopped in the back of the head (either in the occipitalis and/or the neck). The splenius capitis and semispinalis muscles were the neck muscles injected in both phase 2 trials. The phase 2 protocols allowed investigators some discretion as to specific injection location in these muscles, and many of the investigators administered the treatment to the mid-neck region and often injected these muscles using longer needles to ensure that they reached the semispinalis muscle.

Upon review of the tolerability data from these phase 2 studies, the phase 3 injection paradigm for the neck was revised. The injection instructions specified that injections were to be given to the upper neck (cervical paraspinal muscles) at the base of the skull, rather than to the mid-neck region, and only FSFD paradigm would be allowed

in the neck region. Also, injections were to be more superficial rather than deep into the neck muscles. Hence, the injection needle length and gauge were standardized to 0.5 inch and 30 gauge, respectively, which is a shorter and smaller bevel than what had been allowed in the phase 2 studies. The total dose injected to the neck region was reduced to 20 U (10 U to each side of the head) using a FSFD paradigm.

Trapezius

In the phase 2 trials, approximately 20-30% of patients reported that their headache pain started and/or ended in the trapezius muscles. In the second trial, the total doses administered to the trapezius muscles were 20 U, 40 U, and 60 U in the 75 U, 150 U, and 225 U dose groups, respectively. The incidence of arm (shoulder) pain, which was felt to be related to injections into the trapezius muscle due to the close location and the thinness of the muscle at the proximal location near the shoulder muscle, was higher for the 2 higher dose groups: 8.2% in the 225 U group and 8.9% in the 150 U group compared with 6.3% in the 75 U group. In the first trial, the mean dose administered to the trapezius was ~48 U and the incidence of arm (shoulder) pain was 5.8%, which is lower than that observed in the second trial. The incidence of arm (shoulder) pain in the patients who received the maximum 60 U dose was not felt to be a general safety concern, but at the same time there was a desire to minimize patient discomfort while ensuring optimum efficacy from this treatment. Thus, Allergan and the headache experts proposed that the dosage regimen for the trapezius muscle in the Botox phase 3 studies be standardized to a minimum dose of 30 U (15 U on each side), with the option for additional FTP treatment to a maximum dose of 60 U (30 U on each side).

Thus, based on the phase 2 studies summarized above, it was determined that the phase 3 studies would require a minimum FSFD of 155 U (31 sites) divided across 7 specific head and neck muscles. The protocols also allowed treatment for a given patient to be individualized using a FTP paradigm of up to an additional 40 U divided across 3 specific muscles: temporalis, occipitalis and trapezius. Directions to the injecting physician with regard to when to implement the FTP paradigm were noted in the protocols. There was no requirement to standardize the use of FTP from one injection cycle to another.

Number of injection sites per muscle

The physician injectors for the phase 3 studies were required to adhere to the muscle-specific standard injection paradigm and administer only 0.1 mL (5 U) per injection site. This would result in multiple injection sites per muscle being required when the total dose per muscle exceeded 5 U. Thus, the total number of injection

sites per muscle was determined by the total dose to be given in each muscle group. The specific location of injection sites were described using anatomical landmarks. Injection sites were chosen so as to minimize potential AEs, while ensuring proper administration of the study treatment. All injectors received specific training on the injection paradigm.

Conclusion

Based upon the issues discussed above and considering the desire to provide optimal treatment benefit while minimizing safety risks, Allergan and the headache specialists determined that the required minimum dose of 155 U per injection cycle should be given via a FSFD paradigm divided in 31 injection sites across 7 specific head and neck muscles. The maximum dose of 195 U per injection cycle could be given using the FSFD paradigm combined with an optional FTP paradigm, which would allow for an additional 40 U across 8 injection sites in 3 specific muscle groups (temporalis, occipitalis and trapezius). In practice and in accordance with the Botox Summary of Product Characteristics, standardized recommendations for dilution and injection are provided in order to implement the phase 3 injection paradigm. Each 200 U vial of Botox should be diluted with 4.0 mL sterile sodium chloride 9 mg/ml (0.9%) solution for injection, so that the resulting volume for each injection site is standardized at 0.1 mL (equivalent to 5 U per 0.1ml).

A.4 *Please explain whether Botox therapy for chronic migraine is an evolving technology?*

Manufacturer response to Q A.4:

Botox is a licensed therapy for the prophylaxis of headache in chronic migraine across many countries worldwide. It has been extensively studied in the largest phase 3 study of chronic migraineurs ever undertaken and has been proven to be effective and well tolerated in providing meaningful benefits to patients. Consequently, it would not be considered an evolving technology.

A.5 *Please provide a graph of the observed (from mapping from MSQ) and predicted EQ-5D scores in the pooled data for the population in the decision problem.*

Manufacturer response to Q A.5:

The International Burden of Migraine Study (IBMS) dataset does not allow for the population described in the decision problem to be defined (i.e. the variables needed to group individuals into the decision problem population are not available from the IBMS). Thus, we are not able to provide a graph of the observed and predicted EQ-5D scores for this population.

A.6 *Please clarify why the MSQ was not used in conjunction with the HIT in the pooled analysis to derive utilities for the economic model.*

Manufacturer response to Q A.6:

The mapping algorithms used to estimate utilities for the economic model were not exclusively developed for use in PREEMPT. If the MSQ and HIT-6 were used concurrently in the mapping algorithms, only studies that contain both instruments could make use of the algorithms. Therefore, in order to not limit the use of the algorithms, it was chosen to develop algorithms using either the MSQ or the HIT-6 but not algorithms that include both.

However, recognizing that PREEMPT included the MSQ and HIT-6, algorithms containing both instruments were initially explored. The models included the HIT-6 total score, the MSQ domain scores, and the other covariates reported in the preferred algorithms (Gillard, 2010). Interaction terms between the HIT-6 and MSQ were also investigated. The performance of these algorithms did not significantly improve relative to the preferred algorithms that only contain the MSQ or HIT-6. These results further supported the decision to develop algorithms that contain the MSQ or HIT-6 but not algorithms that include both.

Although not preferred, the utilities generated using the algorithm with HIT6 and MSQ are tabulated below, along with cost-effectiveness results in the ≥1 prior prophylactic population and ≥3 prior prophylactic population. The ICER changes only marginally when compared to the original modelling (i.e. the preferred mapping algorithms), with a decrease in the ICER of approximately £70 in the population who have received ≥1 prior prophylactic, and an increase in the ICER of approximately £2 in the those who have received ≥3 prior prophylactics.

To note, more complex models in the mapping literature have generally not improved the predictive accuracy of mapping algorithms (Brazier, 2009).

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[redacted]

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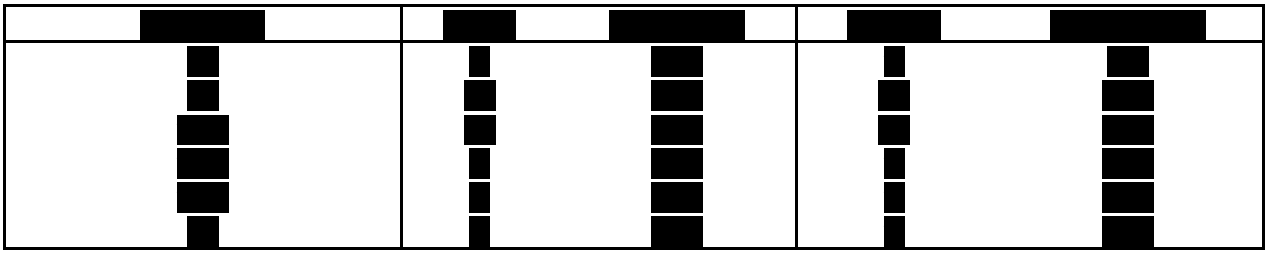

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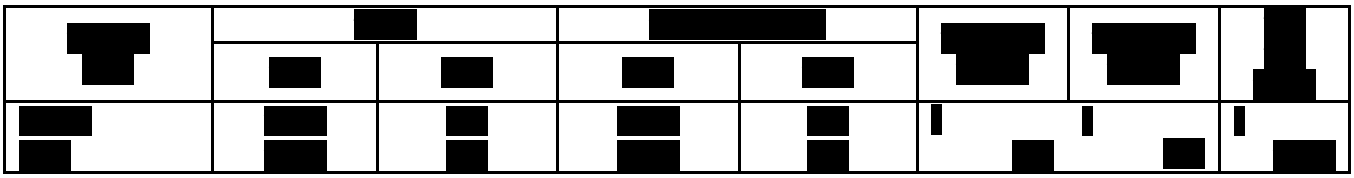

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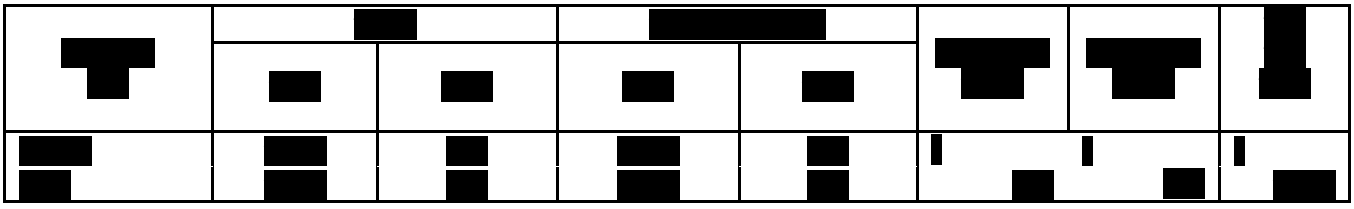
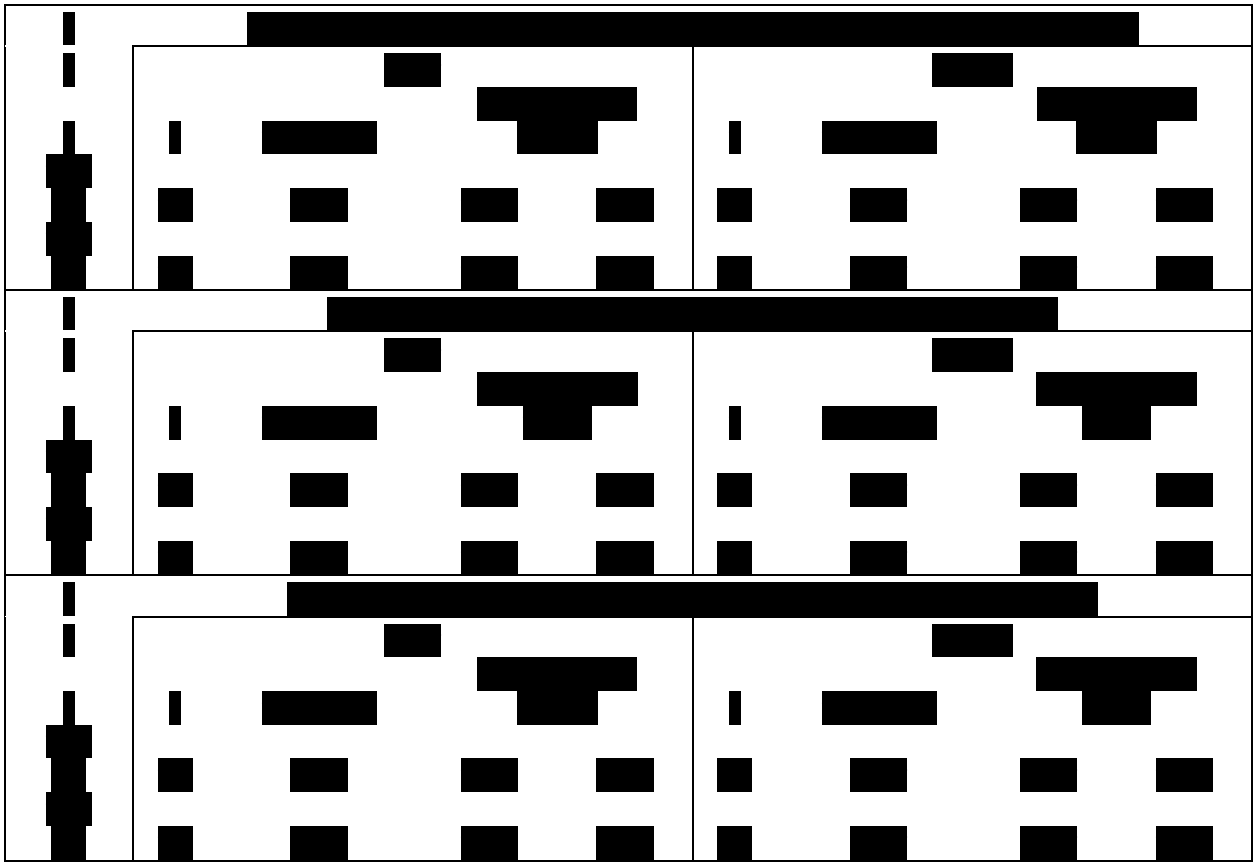


A.7 *Please provide the percentages of people having clinically meaningful (taken to be 10.9 for RR; 8.3 for RD and 12.2 for EF) MSQ responses for each of the three domains as done for the HIT results in figure 5.12 of the submission, and a graph as per figure 2a (for HIT 6) of the paper by Lipton et al (Neurology 2011;77:1465-72) showing the percentages of patients with clinically meaningful MSQ results for the same time periods.*

Manufacturer response to Q A.7:

Results have been tabulated below, and presented in graphical form



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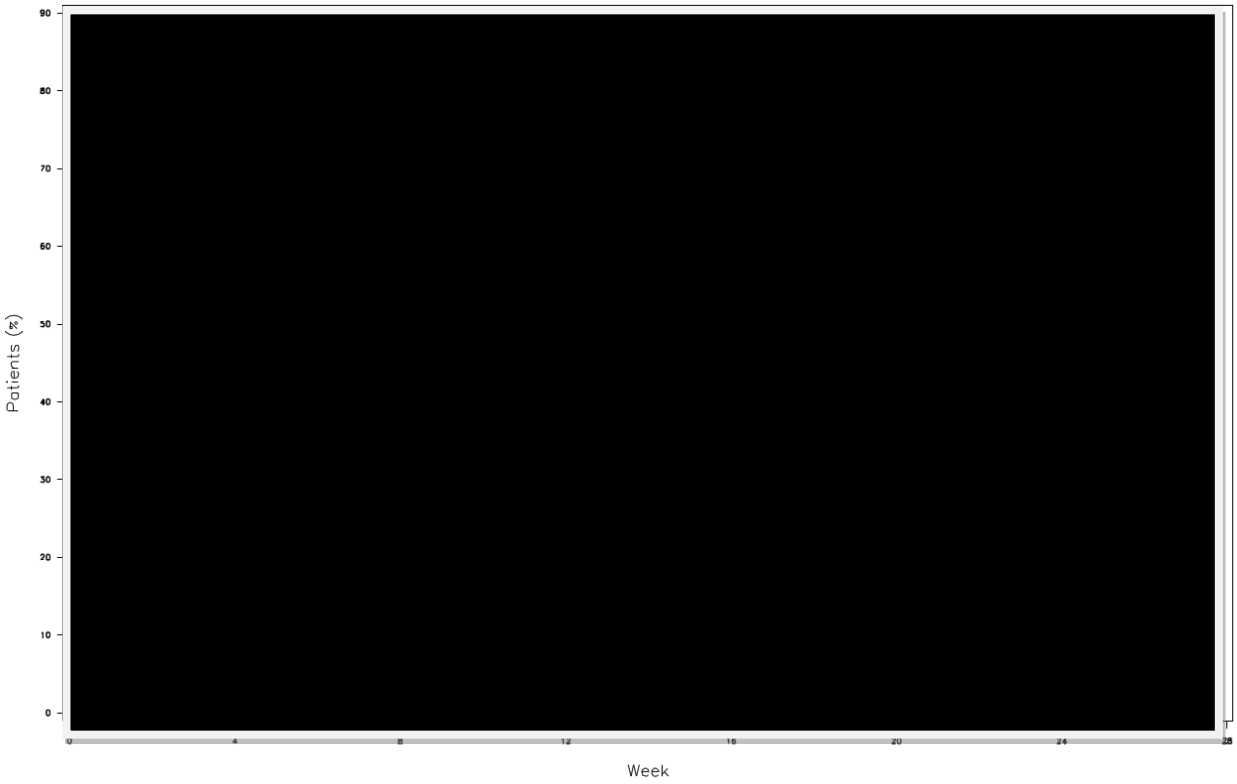

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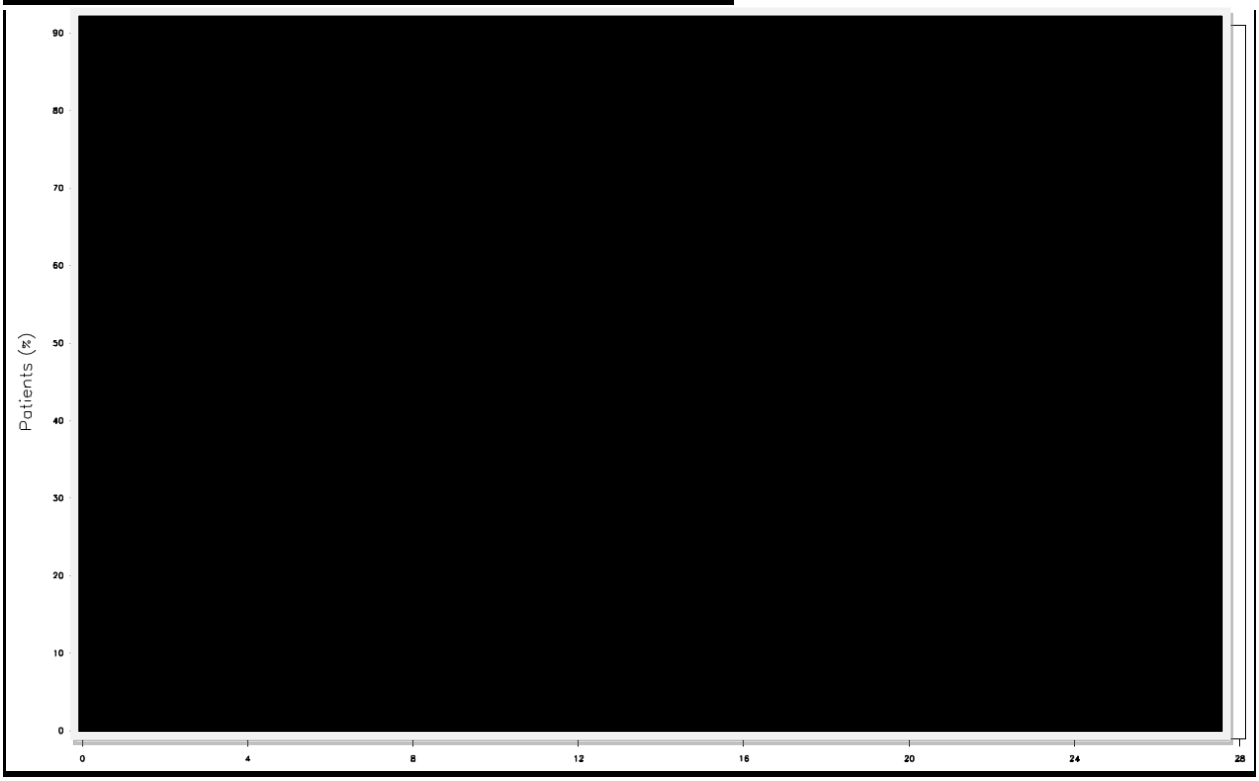

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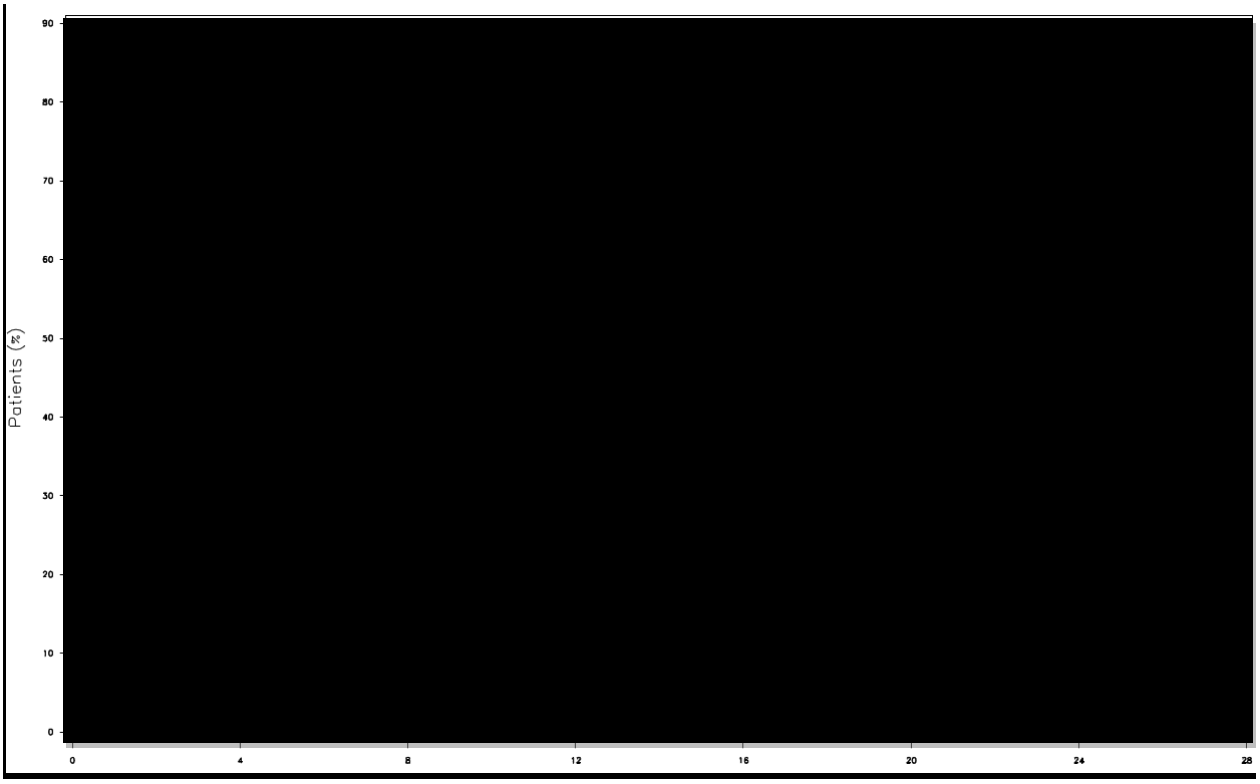


A.8 *Please check table 6.24. Life years should be the same.*

Manufacturer response to Q A.8

A corrected version of Table 6.24 is provided below, while Table 6.25 is also recognised to have been produced incorrectly. Both of these errors have been rectified in the revised submission provided along with this response.

Corrected version of table 6.24

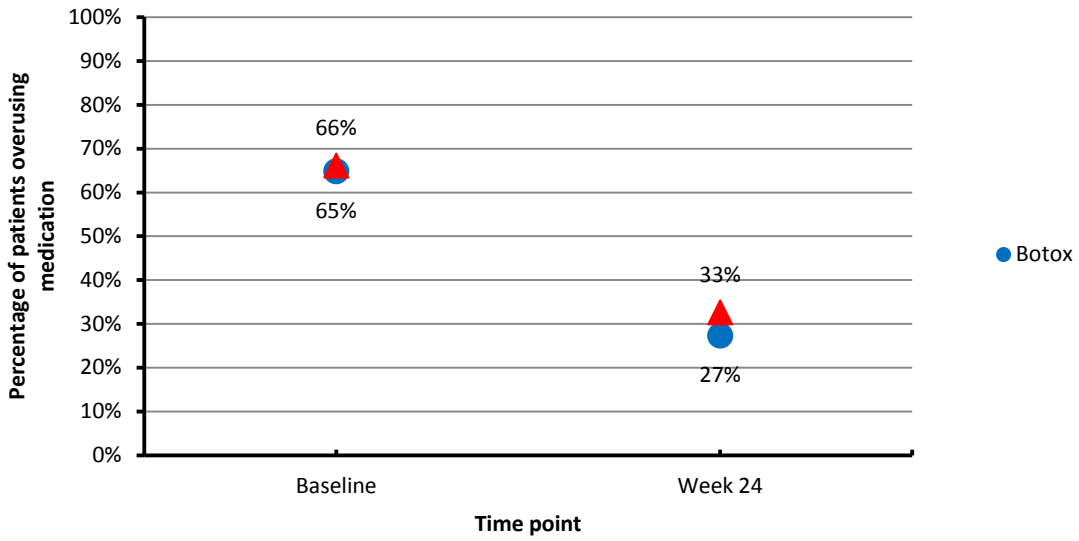
Health state	LY intervention (Botox)	LY comparator (Placebo)	QALY intervention (Botox)	QALY comparator (Placebo)	Cost intervention (Botox)			Cost comparator (Placebo)		
					Treatment cost	Other costs	Total	Treatment cost	Other costs	Total
0-3 HA Days per 28 days Health State	0.389	0.150	0.290	0.109	261.996	63.925	£326	£24	£25	£48
4-9 HA Days per 28 days Health State	0.358	0.378	0.254	0.249	326.497	153.018	£480	£60	£162	£222
10-14 HA Days per 28 days Health State	0.149	0.341	0.097	0.212	157.161	63.812	£221	£54	£146	£200
15-19 HA Days per 28 days Health State	0.065	0.284	0.039	0.162	98.275	80.735	£179	£45	£354	£399
20-23 HA Days per 28 days Health State	0.033	0.184	0.017	0.102	50.227	41.262	£91	£29	£228	£257
24+ HA Days per 28 days Health State	0.024	0.274	0.015	0.131	36.544	30.021	£67	£43	£341	£385
Treatment discontinued patients*	1.010	0.416	0.598	0.252	199.290	815.500	£1,015	£12	£305	£317
Total	**2.028**	**2.028**	**1.310**	**1.216**	**£1,130**	**£1,248**	**£2,378**	**£267**	**£1,561**	**£1,828**

*treatment discontinued patients continue to follow placebo transition probabilities through the 6 health states, but do not incur costs of treatment or administration

A.9 *Are there data on medicines overuse in the trial by arm? If so, please provide these data.*

Manufacturer response to Q A.9:

Data are available examining acute medication overuse in the trial by arm. These are presented below for the RCT phase of the trial.



A.10 *In table 6.27, there is an administration cost of £267 for placebo: the administration costs are greater for the non-Botox arm than for Botox. Please explain this.*

Manufacturer response to Q A.10

The administration cost for Botox is £73 per cycle The "administration cost" for placebo is £36.50 which relates to six-monthly follow up appointments with a specialist to review patient status and optimise acute medication management. The patient flow sheets calculate the cost of each arm of the model, including the costs of Botox and associated administration, or the cost of six-monthly appointments for the management of placebo patients. In producing the breakdown of results, the cost of Botox alone was calculated using the formula

cost of Botox and administration from patient flow (cost of Botox/(cost of Botox + cost of administration))*

However, this formula was incorrectly copied into the cells for patients following the positive stopping rule. Patients who had ceased treatment with Botox were assumed to receive placebo appointment (administration) costs. Applying the formula to this meant that costs were incorrectly assigned to the drug costs of Botox and insufficient costs were assigned to administration. The overall cost is correct, but the breakdown is incorrect as highlighted. Results were not impacted by this error.

Table 6.27 should appear as below (corrected in revised submission supplied)

Item	Cost intervention (Botox)	Cost comparator (Placebo)	Increment	Absolute increment	% absolute increment
Drug cost	£849	£0	£894	£894	52%
Admin cost	£281	£267	-£31	£31	2%
Triptan medication	£95	£170	-£75	£75	4%
Non-triptan medication	£0	£0	£0	£0	0%
Physician visits	£60	£115	-£55	£55	3%
Emergency department visits	£176	£339	-£163	£163	9%
Hospitalisations	£440	£948	-£507	£507	29%
Total	**£1,902**	**£1,839**	**£63**	**£1,725**	**100%**

The administration costs for Botox are lower than may be expected due to the application of response orientated stopping rules – patients who discontinue treatment change to placebo transition probabilities, and no longer receive Botox (or associated administration costs). When no stopping rules are applied, the administration cost of Botox increases to £522.

A.11 *In PREEMPT 1, there were significant differences in the baseline variables (table 5.7) with p values of 0.023 for mean headaches episodes; 0.006 for mean migraine episodes; and 0.022 for headache hours.*

a) What is the likely explanation for these p values?

b) In the pooled data (table 5.9) the p values for some variables are smaller than in tables 5.7 and 5.8. Please explain this since pooling would be expected to dilute the significance seen in table 5.7, not increase it.

Manufacturer response to Q A. 11

a) In PREEMPT 1 there were significant differences in the baseline variables for mean headache episodes, mean migraine episodes and headache hours. This imbalance was an outcome of the randomization process. By chance alone, patients in the placebo group had more headache and migraine episodes and fewer cumulative hours, but similar numbers of headache days, migraine days and moderate/severe days than patients randomized to placebo. The study design did not control for baseline headache characteristics.

b) The variation of the data as noted by the standard deviation was similar for by-study and pooled study results, both within and across treatments. However, the pooled data has a larger sample size compared to each separate study, providing more power to detect differences. Furthermore, the pooled data standard error (SE) and 95% confidence interval (CI) bands around the treatment means were narrower compared to the SE and 95% CI results for the separate study results. The differences between treatment means are indeed diluted by the pooling (treatment difference of -2.0), but the narrowing of the confidence bands is more than sufficient for those smaller differences to have a smaller p-value. In summary, there is more power for the larger sample size to detect the diluted difference.

A.12 *Please provide details of the observed distributions of baseline variables in the UK sample in the CM subgroups in the PREEMPT 1 and 2 trials (tables like 5.7 and 5.8 for the UK sample only would be helpful).*

Manufacturer response to Q A.12

Unfortunately there is insufficient data available to allow this analysis to be conducted. Only PREEMPT 2 included UK sites and the total patient numbers recruited across 3 UK sites are insufficient to permit meaningful analysis.

A.13 *Please provide a table similar to table 5.9 for participants relevant to the decision problem – that is, only CM patients who have been unsuccessfully treated with 3 or more oral prophylactics.*

Manufacturer response to Q A.13

A table of baseline characteristics for the 3 or more prior prophylactic treatments population is provided below.

Characteristics	Pooled sample (n=479)	Range	P value
Mean age (yrs)	42.5	18, 65	0.599[a]
Mean time since onset of chronic migraine (yrs)	20.4	0, 57	0.608[a]
Women (%)	86.4		0.090[b]
Caucasian (%)	94.2		0.846[b]
Mean body mass index (kg/m2)	26.4	17.1, 53.9	0.096[a]
Mean headache episodes during baseline (SD)	13.6 (5.56)		0.068[a]
Mean headache days during baseline (SD)	20.1 (3.71)		0.775[a]
Mean migraine episodes during baseline (SD)	10.6 (5.64)		0.131[a]
Mean migraine days during baseline (SD)	16.8 (5.72)		0.534[a]
Mean moderate/severe headache days during baseline (SD)	18.3 (4.28)	4, 28	0.720[a]
Cumulative headache hours occurring on headache days during baseline (SD)	281.9 (117.16)	5.5, 634.21	0.461[a]
Patients who overused acute headache pain medications during baseline (%)	71.6		0.774[b]
Patients with severe (≥60) HIT-6 score	93.5		0.273[b]
Mean HIT-6 score	65.7	50, 78	0.559[a]

P-values: [a] if based on the Wilcoxon rank-sum test, [b] if based on Pearson's chi-squared test.

A.14 *Please justify the time horizon of 2 years (which is contrary to the NICE methods guide which requests a lifetime horizon for the economic model). On page 70 it was noted that the population in PREEMPT 1 had been "severely impacted by their headaches with means of >20 years of frequent headaches". Would that not suggest that a 20 year time horizon should be used as one of the scenarios?*

Manufacturer response to Q A.14

The question of time horizon is very relevant in this case, with this in mind analyses are presented below for time horizons of 2, 5, 10, 15 and 20 years.

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
2 year time horizon, positive and negative stopping rules applied							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,419	1.34	£2,388	1.31	£549	0.09	£5,828
5 year time horizon, positive and negative stopping rules applied							
Placebo	£4,332	3.05	£4,036	2.83			
Botox	£4,336	3.29	£4,104	3.06	£68	0.23	£300
10 year time horizon, positive and negative stopping rules applied							
Placebo	£8,226	6.08	£7,074	5.20			
Botox	£7,497	6.57	£6,570	5.62	-£504	0.42	Dominant
15 year time horizon, positive and negative stopping rules applied							
Placebo	£11,952	9.08	£9,514	7.16			
Botox	£10,588	9.80	£8,593	7.73	-£921	0.57	Dominant
20 year time horizon, positive and negative stopping rules applied							
Placebo	£15,396	11.87	£11,418	8.70			
Botox	£13,463	12.82	£10,182	9.40	-£1,236	0.70	Dominant

However these results are potentially confounded by the use of the positive stopping rule, which may not be appropriate for long term extrapolation (as patients remain in the same health state for the remainder of the modelled period). Performing the same analysis without the positive stopping rule also shows Botox to be increasingly cost-effective over longer time horizons, however not to the same degree.

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
2 year time horizon, negative stopping rules applied, positive stopping rule not applied							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£3,039	1.34	£2,983	1.31	£1,144	0.09	£12,486
5 year time horizon, negative stopping rules applied, positive stopping rule not applied							
Placebo	£4,332	3.05	£4,036	2.83			
Botox	£6,219	3.25	£5,833	3.02	£1,797	0.19	£9,467
10 year time horizon, negative stopping rules applied, positive stopping rule not applied							
Placebo	£8,226	6.08	£7,074	5.20			
Botox	£10,812	6.39	£9,423	5.47	£2,349	0.27	£8,662
15 year time horizon, negative stopping rules applied, positive stopping rule not applied							
Placebo	£11,952	9.08	£9,514	7.16			
Botox	£14,876	9.43	£12,086	7.46	£2,572	0.30	£8,508
20 year time horizon, negative stopping rules applied, positive stopping rule not applied							
Placebo	£15,396	11.87	£11,418	8.70			
Botox	£18,474	12.24	£14,075	9.01	£2,658	0.31	£8,470

An alternative to the approach taken to the original analysis is to use placebo efficacy (transition probabilities) for patients who cease treatment due to the 'positive stopping rule'. The results of this approach are shown below:

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
2 year time horizon, negative stopping rules applied, positive stopping rule applied with placebo efficacy and utility values							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,495	1.31	£2,460	1.28	£621	0.07	£9,503
5 year time horizon, negative stopping rules applied, positive stopping rule applied with placebo efficacy and utility values							
Placebo	£4,332	3.05	£4,036	2.83			
Botox	£4,833	3.13	£4,553	2.91	£517	0.08	£6,519
10 year time horizon, negative stopping rules applied, positive stopping rule applied with placebo efficacy and utility values							
Placebo	£8,226	6.08	£7,074	5.20			
Botox	£8,682	6.17	£7,556	5.28	£482	0.08	£5,740
15 year time horizon, negative stopping rules applied, positive stopping rule applied with placebo efficacy and utility values							
Placebo	£11,952	9.08	£9,514	7.16			
Botox	£12,400	9.17	£9,990	7.24	£476	0.09	£5,562
20 year time horizon, negative stopping rules applied, positive stopping rule applied with placebo efficacy and utility values							
Placebo	£15,396	11.87	£11,418	8.70			
Botox	£15,843	11.96	£11,893	8.79	£476	0.09	£5,519

The decreasing ICER observed with an increasing time horizon is driven by the assumption that in the long term, patients with Botox will all have discontinued, and will be following the same (placebo) transition probabilities as placebo patients (who

will also discontinue). Over a sufficient time horizon therefore, all will eventually settle into a similar ‘steady state’ from the end of the 2 year modelled period where Botox patients are in better health states, with the difference in treatments being not only the difference while on treatment, but also an element of ‘durable benefit’ as patients move to the placebo ‘steady state’. It should be cautioned however there is substantial uncertainty around long term outcomes, and it would be expected that a proportion of patients who are withdrawn from treatment in the event of a positive response might later require further cycles of treatment.

The philosophy of the ‘lifetime’ time horizon however relates to the issue that at the end of modelling, patients on all arms should be in identical health states – met by the criteria in death in most cases. This criteria however is clearly broken in the Allergan model (as described above), as Botox treated patients are in better health states at the end of the basecase 2 year analysis.

The ERG are correct therefore that one way to solve this issue it to use a longer time horizon - over the 20 year time (99% of Botox patients still alive at year 20) have discontinued treatment, with a mean of 4 cycles of treatment each.

A.15 *There was a statistically significant reduction of secondary efficacy end points favouring Botox (a reduction of 1.5 migraine days) in the PREEMPT 1 trial. Please clarify the exact statistical test undertaken in the pooled data and explain why it is expected that this difference is clinically significant.*

Manufacturer response to Q A.15:

The statistical test used for the individual study data and for the pooled data was a covariate analysis of variance (ANCOVA), with baseline migraine days as a covariate and main effects of treatment and medication-overuse strata, using type III sum of squares. This test is based on normal-distribution theory and is aligned with the protocol-specified power calculations for headache days in study 2, which indicated 81% power to detect a between treatment difference in headache days of 1.5, which was based on a similar SD estimate as was observed for migraine days.
A previous study demonstrated that a 1-day difference in headache days correlated with significant improvements in health related quality of life measures and can be considered clinically meaningful (Silberstein et al, 2010).

A.16 *In the Markov Model standard of care, the cycle probability of death is the same from week 0 to week 48 over 365 days. Please clarify why it is expected that there is the same cycle risk of death in the placebo arm from 0 to 48 weeks and why this assumption was not made over the 2 year time horizon?*

Manufacturer response to Q A.16:

Assumptions made around the risk of death within the economic model result solely from the application of age adjusted background mortality. Neither Botox nor placebo treatment are associated with any altered risk of disease specific mortality. As such, the cycle probability of death is calculated from ONS life tables 2008-10.

The probability of dying in one year depends on age. Patients are assumed to enter the model with a starting age of 42 years. The probability of dying between the ages of 42 and 43 is 0.001156. this is adjusted to give a 12-weekly probability of dying – 0.000266. The probability of dying between the ages of 43 and 44 is 0.001286. As such, the cycle probability of dying increases.

Between week 0 and week 48, patients are aged 42 years. Between week 60 and week 96, patients are aged 43 years. Between week 96 and week 108, patients are aged 44 years. The cycle probability of dying increases as age increases, therefore the cycle probability of death is not constant over the 2 year time horizon, however this is not an error as age has been used as an integer (i.e. 42/43) rather than a marginally increased risk of death per cycle.

A.17 *a) The model applies the negative stopping rule after 2 cycles, i.e. Botox injections at baseline and 12 weeks. Given that most benefits occur after the first injection, please explain what would be the impact of applying the stopping rule after one injection?*

Manufacturer response to Q A.17a:

A negative stopping rule can be applied after 1 cycle. This rule assumes that patients discontinue treatment if they did not improve by at least 1 health state in 1 cycle – that is, after the first injection. Using this stopping rule, the ICER is £5,694, a small increase from the base case ICER.

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,497	1.36	£2,464	1.33	£625	0.11	£5,694

b) In figure 5.12, reproduced below, there is a marked improvement in the former placebo group after their first injection of Botox. This is similar to the former Botox group after their first injection. However there is also a marked improvement in the former Botox group. What is the likely explanation for this?

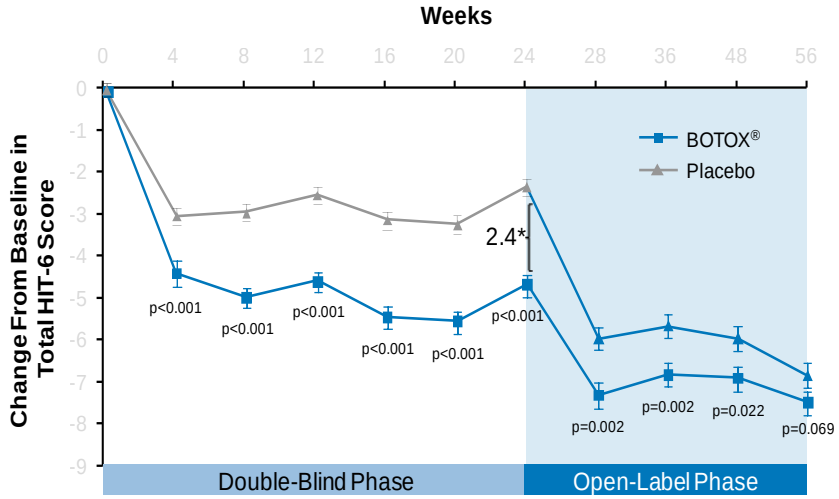
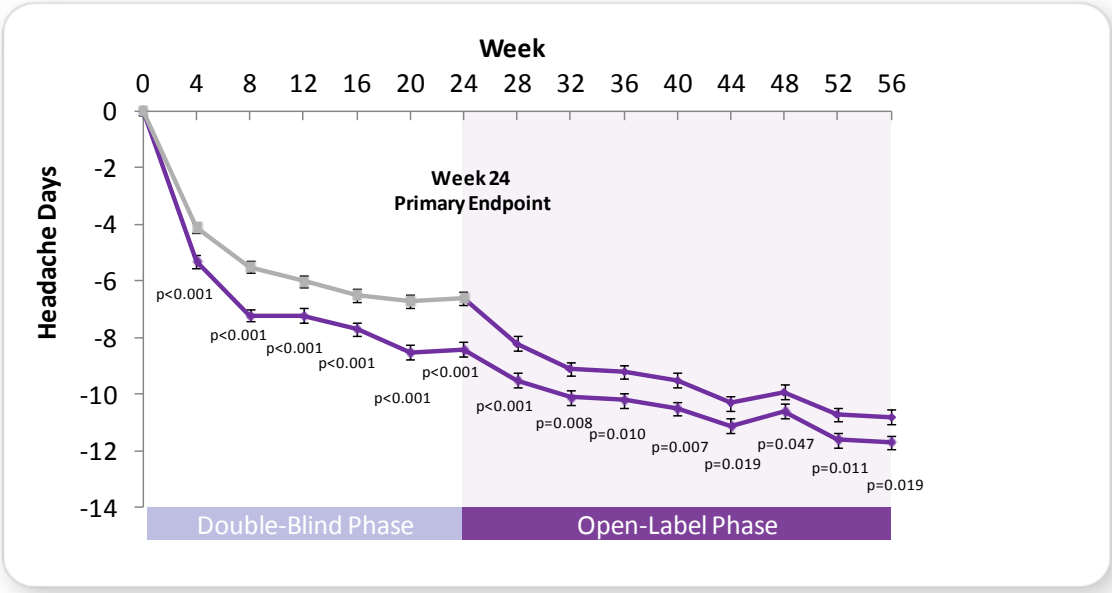


Figure 5.12: Mean change from baseline at week 24 for HIT-6 results in pooled phase 3 studies (ITT population) (Aurora, 2009b)

Manufacturer response to Q A.17b

Data from these studies demonstrated across a number of efficacy measures that with each subsequent treatment cycle, there was continued improvement from baseline. At week 56, statistically significant differences favouring those subjects who received Botox in the DB and OL phases (Botox/Botox) were seen versus those patients who received placebo in the DB phase and Botox in the OL phase (Placebo/Botox) for multiple efficacy endpoints such as the frequency of headache days (-12.1 Botox/Botox, -11.1 Placebo/Botox; p=0.035; **Error! Reference source not found.**), migraine days (-11.6 Botox/Botox, -10.6 Placebo/Botox; p=0.038), and moderate/severe headache days (-11.0 Botox/Botox, -10.1 Placebo/Botox; p=0.042). Also, the percent of patients with a ≥50% reduction from baseline in headache days and migraine days was significantly greater for Botox/Botox at Week 56 (p=0.023 and p=0.006, respectively). For the other measures such as, cumulative hours of headache on headache days, headache episodes, and percentage with severe Headache Impact Test (HIT)-6 score, total HIT-6 and Migraine-Specific Quality of Life questionnaire scores, there continued to be large mean decreases from baseline observed over the 56 weeks of these studies. These between group differences seen for early Botox treatment (Botox/Botox) versus later Botox treatment (Placebo/Botox) suggest that the later exposed Botox patients do not “catch up” to the response observed in the earlier treated Botox group.

Mean Change from Baseline in Frequency of Headache Days (Primary)



During the OL phase, when all patients were treated with Botox, the 95% CIs for all efficacy variables evaluated, including mean total HIT-6 score, indicated that there were statistically significant within-group improvements from baseline at week 56 for both the Botox/Botox and Placebo/Botox treatment groups. In the Botox/Botox group, the incremental improvements in efficacy measures were directional similar in the DB and OL phases, demonstrating continued improvements after each treatment cycle.

A.18 *EQ-5D utility scores are known to exhibit a ceiling effect, where a large proportion of subjects rate themselves in full health with a utility score of 1, and hence the data can be interpreted as being bounded or censored at 1. The ERG believes that ignoring the bounded nature of the EQ-5D will result in biased and inconsistent estimates. Please clarify how the upper censoring limit of 1 of the EQ-5D was taken into account in the mapping?*

Manufacturer response to Q A.18

The limitation of the EQ-5D described by the ERG is a valid one.

In order to account for this limitation, a two-step modelling method presented by Dakin et al. (2010) was explored. Logistic regression was used to predict whether or not an individual had perfect health (EQ-5D score of 1) using the HIT-6 total score or the MSQ domain scores. OLS (preferred model) was then used to predict the utility of those individuals who did not have perfect health. In order to produce overall predictions, all individuals predicted to have ≥50% probability of having perfect health were assumed to have a predicted utility of one, while the predicted utilities for the remaining individuals were based on the utility predicted by OLS. In completing this analysis in episodic and chronic migraine for the HIT-6 and MSQ samples, we observed the percentage of individuals predicted to have perfect health (≥50% probability of having perfect health) was very low (0 or <0.2%). For this reason, straight-forward OLS was considered adequate for mapping, and the use of a two-step model unnecessary.

Importantly, the two-step model presented in Dakin et al. also did not perform any better than OLS.

A.19 *The mapping model used in the submission is an OLS. The squared terms (quadratic terms) are designed to pick up non-linearities in the relationship between dimension scores and the EQ-5D index was also investigated but not retained in the final model. Please clarify why the OLS was used instead of an additive model (for instance censored least absolute deviations (CLAD) or tobit model) which imposes no restrictions on the relationship between dimensions?*

Manufacturer response to Q A.19:

Tobit or CLAD have on the whole in the mapping literature not given distinct advantages over OLS (Brazier, 2009). However, we did explore 2-part models in order to address the ceiling effect of the EQ-5D and potentially improve the prediction accuracy of the mapping algorithms (described above in response to A.18; Dakin, 2010).

A.20 *The ERG explains that interaction terms are important since there is evidence from other measures that dimensions are not additive. Please clarify why the interaction between MSQ and HIT was not investigated in the pooled data?*

Manufacturer response to Q A.20:

The preferred algorithms only contain the MSQ or the HIT-6. Therefore, exploring the interaction between these measures is not necessary/applicable for the preferred algorithms. This said, if both measures were to be used in conjunction with one another in the same mapping algorithm the interaction between the MSQ and HIT-6 should be explored. As demonstrated in response to question A.6 the use of both measures within a mapping algorithm does not alter the results obtained.

A.21 *With reference to the low drop-out rate: were patients told at recruitment that there would be an extension study in which they would all get Botox?*

Manufacturer response to Q A.21

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.

The drop-out rates were low in both treatment groups; 88.2% of Botox treated patients and 90.4% of placebo treated patients completed the 24-week double blind phase. The low drop-out rate during the DBPC phase is most likely attributed to the overall favourable risk-benefit profile of Botox to patients with chronic migraine. The incidence of adverse events leading to discontinuation in the Phase 3 Chronic Migraine population was consistent and low across the DBPC, open-label and any Botox exposure groups. During DBPC exposure, 3.8% (26/687) in the Botox group and 1.2% (8/692) in the placebo group discontinued due to adverse events. Furthermore, the incidence of AEs related to localised pharmacological effects of Botox tended to decrease from one treatment cycle to the next, suggesting that repeated exposure to Botox did not pose an additional cumulative toxicity or additional safety risk to patients.

The proportion of subjects that completed the 56-week study (DBPC + Open label phase) was also high (72.6%) indicating a favourable tolerability profile for Botox. Only 2.5% of all patients in the DB phase and 2.6% in the OL phase discontinued the study because of AEs, confirming no significant alteration in tolerability when transitioning from the DB to the OL phase of the study. It is of note that Botox appeared to be well tolerated in the 56 week DB and OL phases of the study in comparison to the known difficulties with current oral headache prophylaxis treatments.

In summary, although subjects were informed at recruitment that they would receive Botox in the open label phase of the study, it is unlikely that this accounts for the low drop-out rate. In the phase 3 studies substantial clinical benefit was demonstrated

across a range of efficacy measures including patient reported outcomes, with a comparatively low rate of discontinuations due to adverse events.

A.22 *In the SMC guidance, there is mention of Botox being given at 18 week intervals in year 2. Is there any evidence that frequency of injections can be reduced without losing effect?*

Manufacturer response to Q A.22

No data exist to inform assumptions around extended intervals between treatment in chronic migraine, and the subsequent impact on clinical effectiveness, although this is reported anecdotally from practice. In the absence of this information, this was not considered as a scenario analysis in the submission made to NICE.

A.23 *IBMS reports that 11.5% of people with CM have fibromyalgia. Please explain why these people were excluded from the PREEMPT trials?*

Manufacturer response to Q A.23:

Fibromyalgia is a complex pain syndrome and common cause of chronic widespread pain. Although pain is the dominant feature, fibromyalgia is also associated with other symptoms such as fatigue, problems sleeping, stiffness, problems with concentration, depression, anxiety, headaches, migraine, and paraesthesia. The PREEMPT studies were designed with specific exclusion criteria for patients with a concurrent diagnosis of fibromyalgia or other co-morbid chronic pain conditions, in order to avoid confounding the efficacy results. Patients with co-morbid chronic pain conditions, other than the disorder of interest, were not permitted to receive treatments for this condition since there is overlap with such potential treatments and migraine prophylaxis (e.g., antidepressants). This could not only confound study results, but enrolling patients into such a long study (56-weeks) during which they could not receive treatment for the chronic pain condition was felt to be unethical and not in the patient's best interest.

A.24 *Please clarify whether the IBMS data give EQ-5D by the same headache bands as in the modelling?*

Manufacturer response A.24

Data collected in IBMS showed a continuous spectrum from patients in episodic migraine, through to patients with daily, or near daily migraine. This data was then reanalysed by the health states used in the model from the patient level data.

A.25 *The PREEMPT trials used 31 to 39 injections. Do the additional 8 injections relate to the "follow-the-pain" method described in an abstract by Aurora and colleagues (P05.280) at the annual meeting of the American Academy of Neurology? There does not seem to be any reference to "follow-the-pain" in the submission. Please provide further information on the marginal benefits of the extra Botox if available.*

Manufacturer response to Q A.25

Eight additional injection sites across 3 head and neck muscles (temporalis, occipitalis and/or trapezius), were permitted as part of the phase 3 treatment paradigm, at the discretion of the injector, using the follow-the-pain (FTP) method, as described by Aurora et al (P05.280).

The PREEMPT phase 3 studies were not designed to evaluate the FSFD versus the FTP injection paradigm. Patients were not stratified during the randomization to a specific injection paradigm, in order to scientifically confirm the benefits of the additional FTP injections. All patients treated in the phase 3 studies received the FSFD 155 U injection paradigm. Only some of the patients received the additional FTP injection paradigm, which was based on the judgment of the investigator using pre-specified criteria including: patient-reported usual location of predominant pain, severity of the muscle tenderness, while palpating the muscle prior to injection and clinician's best judgment on the potential benefit of additional doses in the specified muscles to treat the patient-specific pattern of pain. The final dose and injection paradigm used could also vary across the five treatment cycles of these

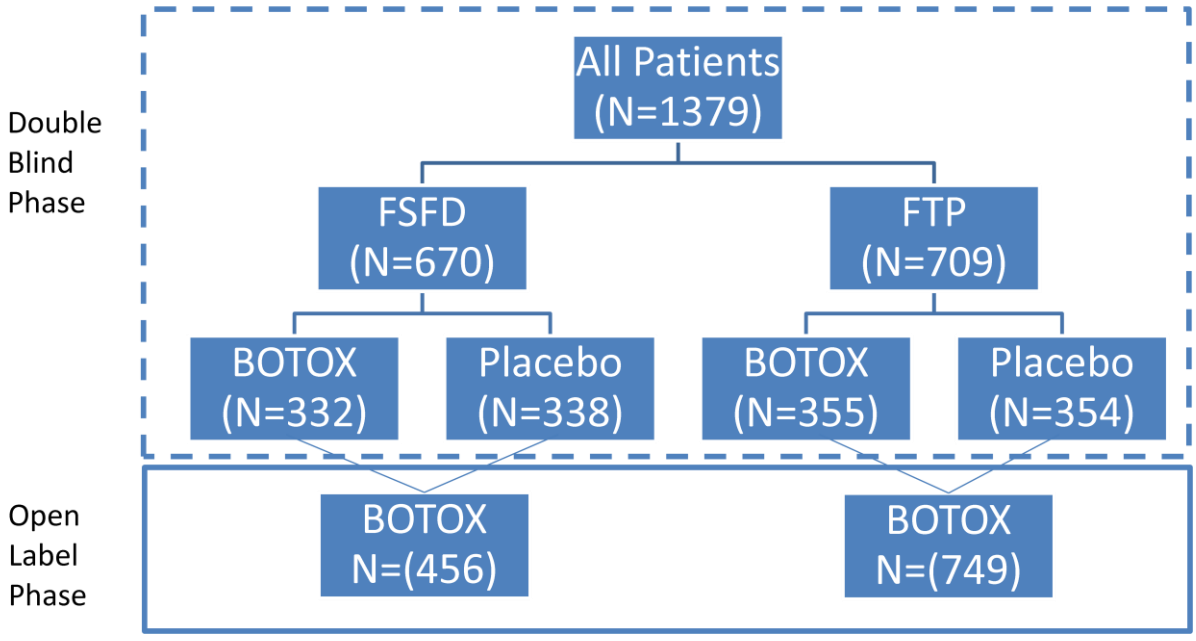
studies since there was no protocol requirement to standardize the use of FTP from one injection cycle to another.

Of 1384 subjects enrolled in the PREEMPT phase 3 studies, 1379 received ≥1 injection cycle in the double-blind phase (N=670 FSFD and N=709 FTP; Figure 2). In the open label phase, 1205 subjects were treated (N=456 FSFD; N=749 FTP). Across the entire program, 4648 injection cycles of BOTOX were given. The majority (53.9%) of all BOTOX cycles were 155 U using FSFD (Table 1). A total of 544 subjects with any BOTOX exposure received only FSFD for all of their treatment cycles (Table 1 Total Cycles of Botox Administered Throughout the 56-Week Program

	TOTAL CYCLES of BOTOX	<155 U N (%)	155 U N (%)	>155 U N (%)
Double Blind Phase (2 treatment cycles)	1312	2 (0.2)	726 (55.3)	584 (44.5)
Open Label Phase (3 treatment cycles)	3336	16 (0.5)	1779 (53.3)	1541 (46.2)
Entire Study (5 treatment cycles)	4648	18 (0.4)	2505 (53.9)	2125 (45.7)

Table 2). The exposure by injection paradigm in the double blind and open label phases is summarized in Figure 2.

Figure 2 Patient flow and treatment exposure (FSFD vs FTP)*



* In this table, patients were assigned to treatment group as treated at Day 0. For the double-blind (DB) phase, the max dose during the DB phase was used. For the open-label phase, the max dose over the entire study was used.

Table 1 **Total Cycles of Botox Administered Throughout the 56-Week Program**

	TOTAL CYCLES of BOTOX	<155 U N (%)	155 U N (%)	>155 U N (%)
Double Blind Phase (2 treatment cycles)	1312	2 (0.2)	726 (55.3)	584 (44.5)
Open Label Phase (3 treatment cycles)	3336	16 (0.5)	1779 (53.3)	1541 (46.2)
Entire Study (5 treatment cycles)	4648	18 (0.4)	2505 (53.9)	2125 (45.7)

Table 2 **Pattern of Botox Exposure in the Phase 3 Studies**

Dose Pattern	Double Blind Phase		Open Label Phase	Any BOTOX Exposure
	BOTOX (N=687) N (%)	Placebo (N=692) N (%)	Total (N=1205) N (%)	Total (N=1300) N (%)
< 155 U	1 (0.1)	0 (0)	1 (0.1)	1 (0.1)
155 U (stable)	330 (48.0)	337 (48.7)	521 (43.2)	544 (41.9)
> 155 U (stable)	152 (22.1)	156 (22.5)	251 (20.8)	214 (16.5)
Increased	102 (14.8)	94 (13.6)	142 (11.8)	137 (10.5)
Decreased	102 (14.8)	105 (15.2)	165 (13.7)	160 (12.3)
Fluctuated	NA	NA	125 (10.4)	244 (18.8)

Baseline demographics such as age and gender were similar between the subgroups; however, at baseline, patients allocated to FTP had significantly longer disease duration (years since chronic migraine onset: 18.5 FSFD/19.9 FTP; p=0.041) and appeared more disabled (% of patients with severe Headache Impact Test [HIT-6] score: 91.3% FSFD versus 94.6% FTP; p=0.016). Both treatment paradigms demonstrated significant improvements with Botox vs placebo for the primary endpoint of mean reduction in headache days (FSFD: -9.0 Botox vs -6.7 placebo, p<0.001; FTP: -7.8 Botox vs -6.4 placebo, p=0.004) (Table 3). Statistically significant differences favouring Botox over placebo were observed for total cumulative hours of headache on headache days and frequency of: migraine days, moderate/severe headache days, total HIT-6 scores and Migraine Specific Quality of Life (MSQ) scores, and % of patients with severe total HIT-6 score in both subgroups. Headache episodes and migraine episodes were statistically significantly reduced with Botox vs placebo in the FSFD subgroup; however, the FTP subgroup did not reach statistical significance for these endpoints. Most patients had adverse events in both subgroups (FSFD: Botox 60.5% vs 50.9% placebo; FTP: 64.2% Botox vs 52.5% placebo) (Table

4). Few patients in either subgroup discontinued early because of an adverse event or lack of efficacy.

Table 3 **Efficacy Results for the FSFD and FTP subgroups during the Double-Blind Phase of the PREEMPT Phase 3 studies***

Efficacy Variable (per 28 days)	FSFD			FTP		
	BOTOX (N = 331)	Placebo (N =339)	P-value	BOTOX (N = 354)	Placebo (N = 355)	P-value
Frequency of headache days	**-9.0**	**-6.7**	**<0.001**	**-7.8**	**-6.4**	**0.004**
Frequency of headache episodes	**-5.9**	**-4.8**	**0.004**	-5.0	-4.7	0.381
Frequency of migraine days	**-8.5**	**-6.2**	**<0.001**	**-7.8**	**-6.2**	**0.001**
Frequency of moderate/severe headache days	**-8.2**	**-5.8**	**<0.001**	**-7.3**	**-5.8**	**0.002**
Total cumulative hours of headache on headache days	**-126.7**	**-82.3**	**<0.001**	**-108.9**	**-82.6**	**0.008**
Frequency of migraine episodes	**-5.4**	**-4.3**	**0.002**	-4.8	-4.4	0.312
Frequency of AHPM intakes	-10.1	-9.3	0.501	-10.3	-9.1	0.325
Frequency of AHPM days	**-6.3**	**-5.3**	**0.023**	-5.7	-5.2	0.300

* Patients grouped according to randomization assignment with FSFD vs. FTP subgroups based on maximum dose during the double-blind phase.

Table 4 **Summary of Adverse Events in Double-Blind Phase**

	FSFD			FTP		
	BOTOX (n=332) n (%)	Placebo (n=338) n (%)	Total (n=670) n (%)	BOTOX (n=355) n (%)	Placebo (n=354) n (%)	Total (n=709) n (%)
All adverse events* (AEs)	201 (60.5)	172 (50.9)	373 (55.7)	228 (64.2)	186 (52.5)	414 (58.4)
Treatment-related AEs†	94 (28.3)	41 (12.1)	135 (20.1)	108 (30.4)	47 (13.3)	155 (21.9)
Serious AEs	12 (3.6)	5 (1.5)	17 (2.5)	21 (5.9)	11 (3.1)	32 (4.5)
Treatment-related, serious AEs†	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Discontinuations related to AEs	13 (3.9)	4 (1.2)	17 (2.5)	13 (3.7)	4 (1.1)	17 (2.4)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*All AEs include all reported events, regardless of relationship to treatment.
†Treatment-related AEs are those that in the investigator's opinion may have been caused by the study medication with reasonable possibility. The one treatment-related serious AE was migraine requiring hospitalization

In conclusion, these analyses support the efficacy and safety of using the FSFD (155U Botox) or FTP (up to 195U Botox) treatment paradigms for headache prophylaxis in adults with chronic migraine. In accordance with the Summary of Product Characteristics for Botox, the product is for single use only and any unused solution should be discarded. Given that the approved dose for Botox in chronic migraine is 155 – 195U, a single 200U vial is appropriate and there are no increased costs associated with the FTP approach.

Clarification on manufacturer's submission - wording

B.1 *Page 7 says "two 56 week placebo controlled clinical trials" but duration of the trials was only 24 weeks.*

Manufacturer response B.1

This is an error in the text. The two clinical trials were 56 week trials, however the double blind placebo controlled phase was for 24 weeks, with the remaining period being open label. This has been clarified in the revised submission provided with this document.

B.2 *Page 15 – "difference between the two patient groups still significant at one year" – but this was not so in the HIT-6 results, where p =0.069.*

Manufacturer response B.2

This is an error in the wording. The ERG are correct that significance was not reached in the HIT-6 at 1 year. However significance was achieved and maintained with the MSQ, on which the utility mapping algorithm was based.

B.3 *On page 74, first sentence of last paragraph should refer to table 5.16 not 5.14.*

Manufacturer response B.3

The ERG are correct that this is an incorrect reference, which has been changed in the revised submission provided along with this submission