NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Specification for manufacturer/sponsor submission of evidence

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Executive summary

Chronic migraine (CM) is a complex neurological disorder associated with substantial disability, for which there are few evidence based treatment options available (Blumefeld et al. 2010; Bigal et al. 2008; Harwood et al. 2004; Munakata et al. 2009; Natoli et al. 2010). A patient is defined as having chronic migraine if he or she experiences headaches on at least 15 days per month for ≥ 3months, where ≥ 8 of those days are with migraine (IHS 2011). Patients with CM have lower health-related quality of life (HRQL), are more likely to suffer from severe disability, and use more direct healthcare resources than those with episodic migraine (defined as migraine and <15 headache days per month) (Harwood et al. 2004; Lipton 2009; Munakata et al. 2009).

The efficacy and safety of the medicines that are used to treat episodic migraine have not been established in patients suffering from CM as these patients have often been excluded from clinical trials (Dodick et al. 2010). Currently CM patients in the UK are either managed with acute “rescue” therapies alone or are offered prophylaxis with oral treatments including anti-epileptics, beta blockers and antidepressants. Patients not responding to, or unable to tolerate oral prophylactics might also progress to receive more experimental treatments such as Greater Occipital Nerve block, and methysergide (Bigal et al. 2008; Harwood et al. 2004: BASH 2010; NHS Scotland 2011; SIGN 2008).

This submission specifically addresses the decision problem of chronic migraine patients who have been unsuccessfully treated with ≥3 prior oral prophylactic treatments and where the overuse of acute medications has been appropriately managed.

Botox is the first and only specifically licensed prophylactic pharmacological treatment for headache in adults with chronic migraine. It is administered by intramuscular injection to between 31 and 39 sites divided across 7 specific head and neck muscle areas. The required dose of Botox is between 155-195 Allergan Units per treatment episode, available in the UK at a list price of £276.40 (200 Allergan Unit Vial).

The key evidence to support the efficacy of Botox in the chronic migraine population is taken from a pooled analysis of two 24 week placebo controlled clinical trials (Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies 1 and 2) (Dodick et al. 2010). In the PREEMPT studies patients were administered Botox, or a series of placebo injections using the same injection paradigm with clinicians blinded to the treatment allocation for the first 24 weeks. Patients could continue to receive acute medications in both arms. An open label phase was then conducted, where all patients could be treated with Botox. These trials represent the largest body of scientific evidence (n=1,384 patients) supporting the safe and

effective prophylactic treatment of headaches in adults with chronic migraine, and provide the main source of efficacy information to inform the decision problem.

During the double-blind phase, significant reductions favouring Botox over placebo were observed in the primary endpoint of frequency of headache days per 28 days: Botox treatment resulting in a mean change from baseline of -8.4 days vs. -6.6 days for placebo. This is a treatment difference of -1.8 days [95%CI -2.52, -1.13] (Table 5.26; Figure 5.10) (Dodick et al. 2010). Significant reductions favouring Botox over placebo were also seen in key secondary efficacy endpoints at 24 weeks including mean change in frequency of migraine days, change in frequency of moderate/severe headache days, change in cumulative total headache hours on headache days and change in HRQL measures studied (Migraine Specific Questionnaire, MSQ and Headache Impact Test, HIT-6 scores) (Dodick et al. 2010).

The safety of Botox has been established with over 20 years of use in clinical practice across a range of indications. No deaths and few serious adverse events were observed in Botox-exposed patients in either of the PREEMPT studies. During the double blind phase, discontinuation was low, with only 81/688 (11.8%) of Botox treated patients and 67/696 (9.6%) of placebo treated patients exiting the trial programme (Dodick et al. 2010). This pattern was maintained in the open label phase where there were a further 94/688 discontinuations in patients originally assigned to Botox (13.7%), and 137/696 in patients originally assigned to placebo (19.7%) (Dodick et al. 2010).

The PREEMPT trial program did not specify the number of previous oral prophylactic treatments a patient should have received, however 479/1384 (34.6%) of patients had received ≥3 prior oral prophylactic treatments. Post hoc analyses have demonstrated that efficacy results were consistent across the patient subgroups selected for further exploration, including the groups identified in the NICE Scope with similar findings amongst patients who had a history of previous oral prophylactic failure (the population for this STA), and amongst patients who were and were not overusing acute headache medications at baseline.

In order to demonstrate the cost-effectiveness of Botox, a de novo Markov model was constructed, based on the number of headache days experienced each month by patients. The comparator used is derived from the placebo arm of the PREEMPT trial, in clinical practice this would reflect acute treatment only i.e. triptans and other rescue therapies (the population identified in the scope). As efficacy results are similar in the ≥1 and ≥3 prior oral prophylactic treatments subgroups, the ≥1 prior oral prophylactic treatment subgroup has been used to increase the pool of patients available for analysis. The ≥3 prior oral prophylactic treatments subgroup is provided as a sensitivity analysis to illustrate the consistency of the findings.

Health states, whilst defined by the frequency of headache days observed over a 28 day period, are valued using HRQL data from the pooled PREEMPT dataset. This allows a multidimensional consideration of the impact of therapy in each treatment arm. An examination of secondary efficacy measures demonstrates consistent differences between Botox and placebo across other important determinants of overall health status, such as cumulative headache hours on headache days (duration) and headache impact (Headache Impact Test – HIT6). The MSQ administered to all patients in PREEMPT captures the impact of these changes on the HRQL experienced by patients.

In order to estimate utility, the MSQ findings were mapped to EQ-5D for each of the identified healthstates. In both treatment arms there is a difference of approximately 0.25 in the utility of the best and worst health states, reflecting the degree of impairment seen when ranging from less frequent headache (0 - 3 headaches per 28 days, to near daily headache (24+ headaches per 28 days).

Estimates of medical resource use associated with each healthstate were drawn from the International Burden of Migraine Study (IBMS) (Blumenfeld et al. 2010). The IBMS study was a cross-sectional survey over 10,000 participants from 9 countries, (including the UK), conducted in 2009 which included HRQL measures and an estimation of medical resource utilistion in relation to both episodic and chronic migraine.

Two pragmatic stopping rules were developed in tandem with clinical experts for application within the economic model, specifically to guide continuaton or cessation of Botox treatment at defined timepoints. The first of these was applied in the event of an insufficient response to Botox treatment, whereby treatment for patients who had not improved by ≥2 health states (a minimum of 4 headache days per 28 day period) at week 24 were discontinued, this was termed the ‘negative stopping rule’. Thereafter, these patients were assumed to follow placebo transition probabilities for the remainder of the model. Conversely where patients had converted to a frequency of headache below the threshold of chronic migraine (<15 days of headache per month) treatment was assumed to be successful and hence withdrawn after 1 year. This ‘positive stopping rule’ is in accordance with the recognised use of prophylactic medications in migraine where treatment withdrawal is attempted following a period of stability.

The model results demonstrate that Botox is cost-effective, with a base case ICER of £5,828 over a 2 year period. Over this period Botox is predicted to incur additional costs of £549 (£2,388 vs £1,839). Incremental drug and administration costs (£1,130 vs £267) are partially offset, through reductions in resource use, with an estimated offset of £314 over 108 weeks (all values discounted).

Results are robust to all scenario analyses and subgroups considered, including the number of prior oral prophylactic treatments patients have received and the presence or absence of acute medication overuse at baseline. The model is most sensitive to the time horizon used, with the ICER increasing to £27,162 over a 24 week time horizon (the duration of the RCT phase of PREEMPT) and the removal of stopping rules. Over a two year time horizon, when the 'negative stopping rule' is removed and patients not experiencing sufficient response are assumed to continue treatment, the ICER increases to £7,946. Similarly if the 'positive stopping rule' is removed and patients are assumed to require maintenance treatment throughout the second year, the ICER increases to £12,486. Removing both stopping rules together increases the ICER to £15,294.

The robustness of the model is reflected in probabilistic sensitivity analysis, where Botox is cost effective in 69% of scenarios at a threshold of £20,000 per QALY.

The scope for this submission includes only patients who have been treated with ≥3 prior oral prophylactic treatments, and therefore have a high level of unmet need. It is estimated that there are approximately 50,000 patients with a confirmed diagnosis of chronic migraine meeting this profile in England and Wales. Not all patients are engaged with specialist services or would be considered individually suitable for treatment. Assuming uptake of Botox treatment of 2.5% in the first year of availability, increasing to 15% in year 5, the cumulative cost to the NHS over a 5 year period is estimated to be in the region of £20.4 million in drug cost, however this falls to £14.0 million when including both administration and reductions in medical resource utilisation. In reality the budget impact is likely to be lower, due to cost offsets from other treatments that might otherwise have been given, and other medical resources that patients might otherwise have required. Potential offsets from other treatments available to limited numbers of patients in tertiary centres (some of which are outside the scope of this submission) are investigated within a separate, exploratory analysis described in Appendix 18.

Given the cost-effective nature of this treatment and the limited numbers of patients requiring and accessing specialist treatment, we believe that Botox should be made available for patients who have failed ≥3 prior oral prophylactic treatments and where issues pertaining to acute medication overuse have been appropriately managed. The use of Botox in this population will significantly improve patient outcomes, whilst also having the potential to deliver an overall cost saving to the NHS relative to more invasive procedures.

Table E1: Summary of cost-effectiveness results

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
≥1 prior oral prophylactic population							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,419	1.34	£2,388	1.31	£549	0.09	£5,828
≥3 prior oral prophylactics population							
Placebo	£1,936	1.23	£1,895	1.20			
Botox	£2,471	1.32	£2,438	1.29	£543	0.09	£6,083

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Botulinum toxin type A (Allergan) (Botox®)

Botox consists of botulinum toxin type A (BoNT-A), which is one of the seven serotypes(A–G) of botulinum neurotoxins derived from the bacteria *Clostridium botulinum*. Botox has been marketed for more than 20 years for a range of clinicalindications, including cervical dystonia, post-stroke spasticity in adults and blepharospasm.

Botox is the first and only specifically licensed prophylactic treatment for headache in adults withchronic migraine (headaches on at least 15 days per month of which at least 8 are with migraine).

1.2 What is the principal mechanism of action of the technology?

Botulinum toxin type A blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by pre-clinical and clinical pharmacodynamic studies

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Botox received UK Marketing Authorisation for the indication detailed in this submission on July 8th 2010

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the

EPAR]).If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The MHRA considered that the risk-benefit balance of Botox in the prophylaxis of headache in adult patients with chronic migraine, was favourable based on a review of safety and efficacy data. Botox is recognised as a unique approach to the prophylaxis of headaches in adults with chronic migraine (MHRA 2010).

Population: Definition of Chronic Migraine

The MHRA acknowledged in their report that the diagnostic criteria for chronic migraine published in 2004 by the International Headache Classification Committee (IHCC) in the second version of the International Classification of Headache Disorders (ICHD-2) were not optimal and in June 2006 revised criteria (ICHD-2R) were proposed (Olesen et al. 2006). The MHRA noted that when Allergan initiated the phase III studies (PREEMPT) in the beginning of 2006, the revised criteria had not yet been finalised or published but their protocol criteria were defined by headache experts who were members of the IHS Headache Classification Committee. Furthermore, the MHRA concluded that the population selected in the phase III studies is considered representative of the target population of patients with chronic migraine as currently defined (ICHD-2R) and requested that a further description for chronic migraine be included for the labelled indication, which reads "*Botox is indicated for the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)*".

Although not exactly the same, the study enrolment criteria and current ICHD criteria are similar and overlap. The ICHD-2R criteria for chronic migraine specifically indicates "no medication overuse as defined under 8.2 medication overuse headache" and "not attributed to another causative disorder"(Silberstein et al. 2008a).

In enrolling patients to the phase 3 PREEMPT programme, investigators were required to confirm that patients had a primary migraine headache disorder, suffered with 15 or more headache days per 28 day period, with 50% or more of all headache days being migraine or probable migraine. In addition, investigators excluded patients whose headache they attributed to another disorder, such as Medication Overuse Headache (MOH), which is a secondary headache disorder.

As noted by the baseline characteristics of the majority of patients enrolled into the phase 3 studies, it appears that many reported inadequate pain relief with acute treatments, resulting in frequent intake. Acute medication overuse during the 28 day baseline period, defined as MO-Yes, was observed in 65.5% of the enrolled population) in an attempt to relieve their severe symptoms.

The Task Force of the IHS Clinical Trials Subcommittee published guidelines for controlled trials of prophylactic treatment of chronic migraine in adults (Silberstein et al. 2008a), where they recommend that subjects with chronic migraine overusing acute medications should be included provided the randomisation is stratified accordingly. Such stratification was performed in the PREEMPT studies. Other selection criteria such as age, coexistent disorders, and concomitant therapies are also in full accordance with these guidelines.

Inclusion of patients with and without acute medication overuse did not confound the results from the phase III studies as the data consistently showed statistically significant improvements from baseline across multiple headache symptom measures in both subgroups.

No criterion was formally mentioned about the duration of CM at study entry (more than 6 months is recommended) but the description of the patients actually enrolled showed that this must have been the case in the great majority of patients (mean duration of about 18 years).

It is noted in the MHRA Assessment Report that unlike most other medicines used for prophylaxis of migraine, Botox showed evidence of benefit in chronic migraine subjects who were overusing acute pain medications.

Clinical Endpoints

The key efficacy measures used in the phase 3 PREEMPT study programme were frequency of headache days and frequency of headache episodes. The primary endpoint was based on the change from the 28-day baseline period to the 28 days ending with week 24 (double-blind, placebo-controlled phase). In the pooled phase 3 dataset, the primary efficacy measure was frequency of headache days. In PREEMPT 1, the primary efficacy endpoint was frequency of headache episodes. In PREEMPT 2, the original primary endpoint of frequency of headache episodes was amended prior to unblinding of the study to frequency of headache days, based on several factors including the results of the first phase 3 study PREEMPT 1 and release of updated guidelines from the International Headache Society. This issue was discussed in the MHRA Public Assessment Report which concluded that it would seem acceptable to consider the totality and the consistency of the results between the various endpoints for both trials, which are generally in line with various recommendations, without putting too much emphasis on their prioritisation (MHRA 2010).

Importantly, the MHRA Public Assessment Report goes on to state that “the decision to switch primary endpoint in trial PREEMPT 2 is understandable and it is of note that both the original and the final primary endpoint were highly significant in this trial” (MHRA 2010)

On the basis of baseline disease characteristics of the chronic migraine patients in the phase 3 studies, it is evident that the number of headache days is a more

suitable endpoint to capture the clinically meaningful impact of the treatment on the disease burden that is best characterized by evaluating the frequency, duration, type and severity of headache days.

Allergan's clinical development program has established that in patients with chronic migraine, an evaluation of a change in frequency of headache days is more informative than an evaluation of a change in frequency of headache episodes (Schoenen et al. 2010). The consistency of the results for the assessment of headache days across the phase 3 studies provides confidence in the evidence of efficacy for Botox as a treatment for headaches in adults with chronic migraine.

Repeat Treatment

The effects of treatment over time are considered within the MHRA Public Assessment Report. In each of the phase 3 PREEMPT studies subjects received 2 double-blind treatments followed by 3 open-label Botox treatments, all treatments being separated by 3-month intervals. The group of patients that received Botox from the beginning of the studies continued to improve during the open-label phase such that the difference between the two patient groups (Botox/Botox and Placebo/Botox) was still significant after one year. This is recognised in the SPC for the UK which states that "the recommended treatment schedule is every 12 weeks" (MHRA 2010).

Patient Reported Outcomes

Patients with CM generally report significantly more severe disability, lower HRQL, higher levels of anxiety and depression and greater health care resource utilization compared to those with EM (Blumenfeld et al. 2011). Patient Reported Outcomes (PRO) examined at baseline suggested that the patient population enrolled in the pivotal studies were severely impacted by their condition. Results showing change from baseline on PRO measures in Botox treated patients were considered consistent across the individual studies and met or exceeded suggested thresholds of minimum important difference for within-person and between treatment group clinical improvements. This was observed consistently across both Headache Impact Test (HIT-6) and the Migraine Specific Quality of Life Questionnaire (MSQ) for patients receiving Botox; relevant change in these metrics were not observed in the placebo groups studied (Aurora et al. 2010;Diener et al. 2010;Dodick et al. 2010).

Prior Prophylaxis Usage

The indication granted in the UK is broader than that under consideration by NICE; specifically with regard to the number of previous prophylactic medications that a patient is required to have received prior to becoming eligible for Botox treatment. Data were submitted to the MHRA to explore the impact of prior prophylactic medication usage on clinical outcomes; the MHRA concluded that "when results

were analysed according to previous use of recognised prophylactic medications, the treatment effect was substantial and statistically significant for most outcomes regardless of previous use" (MHRA 2010).

Clinical safety

Clinical safety was commented upon within the MHRA report which noted that intramuscular administration of Botox to muscles of the face, head and neck is not essentially different from other indications and the recommended dose tested in the phase III clinical studies is also in accordance with that seen in other indications. The MHRA noted that no new adverse reactions emerged in this development programme, with the exception of migraine (MHRA 2010).

Allergan has agreed to conduct a post approval observational study in the UK, to describe the utilization of Botox and estimate the incidence of AEs following administration of Botox in actual clinical practice for the prophylactic treatment of chronic migraine. This prospective, observational study will examine adults with chronic migraine treated with Botox for headache prophylaxis. The study will be conducted in the UK and will include adults diagnosed with chronic migraine by their physician and selected by their physician for treatment with Botox in the course of their routine practice as per the approved SmPC (Allergan Ltd. 2010).

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Botox is indicated for the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

No additional evidence is expected to be available in the next 12 months for this indication

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

N/A

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Other non-EU countries with marketing authorization and the date this was received:
United States -15 October 2010
Australia - March 2011
Hong Kong - February 2011
India - June 2011
Korea - March 2011
New Zealand - July 2011
Argentina - February 2011
Brazil - April 2011
Chile - January 2011
Turkey –May 2011
Other EU countries with marketing authorisation:
Estonia – 25 Aug 2010
Slovak Rep – 12 Oct 2010
Malta – 03 Nov 2010
Poland – 02 Jun 2011
Ireland – 30 Aug 2011
Germany – 20 Sep 2011

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Botox was reviewed by the SMC for this indication; the outcome of this appraisal process was published on 11th April 2011.

[redacted]

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 1.1: Unit costs of technology being appraised

Pharmaceutical formulation	Powder for solution for injection
Acquisition cost (excluding VAT)	£77.50 (50 Allergan Unit Vial) £138.20 (100 Allergan Unit Vial) £276.40 (200 Allergan Unit Vial)
Method of administration	31-39 Intramuscular injections along a defined paradigm
Doses	155-195 Allergan Units per treatment session
Dosing frequency	12 weekly
Average length of a course of treatment	One treatment session of 31-39 injections
Average cost of a course of treatment	£276.40 (based on the cost of 1x 200 Allergan Unit vial)
Anticipated average interval between courses of treatments	12 weeks
Anticipated number of repeat courses of treatments	Patient dependent Up to 5 cycles per year
Dose adjustments	N/A

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

It is anticipated that Botox will be administered as part of a Neurology Outpatient Consultation. Botox is subject to restricted prescription and the injections should be administered by appropriately trained personnel in specialist centers.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

The treatment requires no monitoring beyond that seen in usual clinical practice for this condition.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Other headache / migraine symptomatic treatments (for example anti-nausea medications, acute rescue pain medications) are commonly prescribed for this patient population.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Chronic migraine is a disabling condition associated with a high economic and societal burden, estimated to affect around 1.6% of the adult population (Blumenfeld et al. 2011;Natoli et al. 2010). Migraine is considered to be a progressive disorder; every year, between 2.5% and 4.6% of people with episodic migraine (<15 headache days per month) progress to chronic migraine (≥15 headache days per month, of which 8 are migrainous) (Lipton 2009;Munakata et al. 2009). Data also suggests that a proportion of patients with chronic migraine may remit to episodic migraine or other headache types over time (Manack et al. 2011).

According to the World Health Organisation (WHO), migraine is ranked 19th among all single causes for years lived with disability and is associated with significantly diminished health-related quality of life (HRQL) (Harwood et al. 2004). Chronic migraine is associated with higher healthcare costs than episodic migraine due to increased acute medication use, physician visits, hospitalisations and accident and emergency (A&E) visits (Blumenfeld et al. 2011). From a societal perspective, headaches among adults with chronic migraine result in a ≥50% reduction in productivity at work or school (Munakata et al. 2009).

According to UK guidelines and clinicians, patients with migraine are initially treated with a range of oral prophylactics (BASH 2010;NHS Scotland 2011;SIGN 2008) however, there is no specifically licensed treatment option for chronic migraine, and first-line oral treatments used in migraine prophylaxis are often associated with poor tolerability and side-effect profiles that negatively impact adherence and therefore effectiveness (Bigal et al. 2008;Harwood et al. 2004). There is therefore a high unmet medical need for safe, well-tolerated and effective headache prophylaxis treatments for chronic migraine patients who are severely impacted by their condition, and who have often been excluded from other treatment registration programmes.

Botox is the only specifically licensed product indicated for the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine). Botox represents an innovative and locally injected treatment strategy, to be administered by specialists, predominantly located in secondary care settings.

2.2 How many patients are assumed to be eligible? How is this figure derived?

The final scope for this NICE Single Technology Appraisal identifies a specific subgroup within the licensed indication for this technology, specifically:

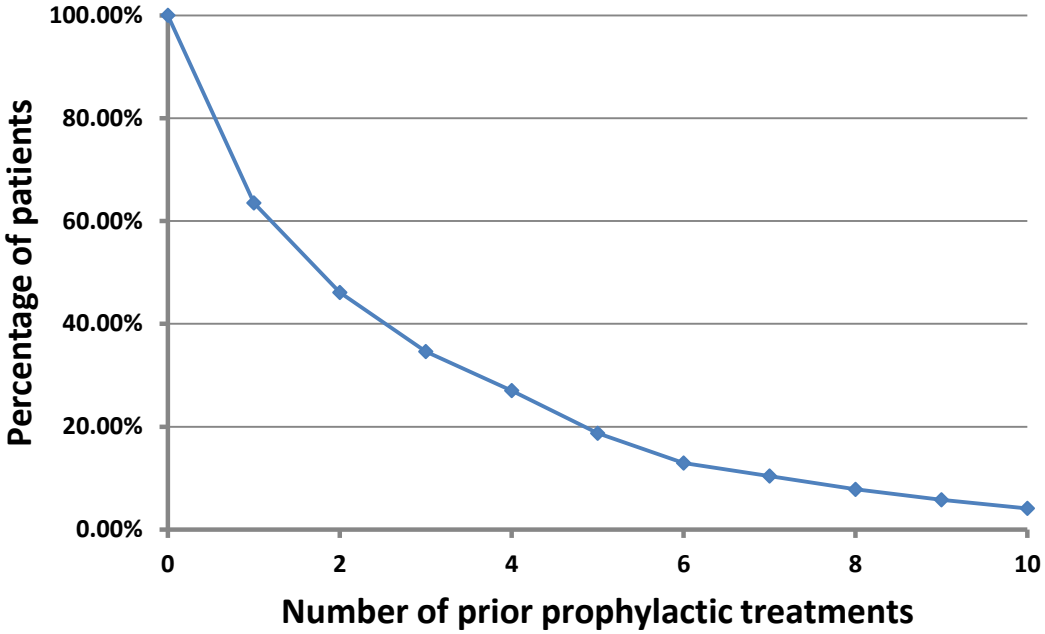
Adults with headaches on at least 15 days per month of which at least 8 days are associated with chronic migraine and i) whose condition has failed to respond to at least three prior pharmacological prophylaxis therapies and ii) medication overuse has been appropriately managed.

Work is ongoing to validate with UK clinicians assumptions regarding the proportion of the population for whom this technology is licensed, who would be considered eligible according to the definition provided in the NICE STA Final Scope in the absence of a published estimate.

In terms of the overall indication, the estimated prevalence of chronic migraine amongst adults is 1.4–2.2% per year (Natoli et al. 2010); with an average estimate of around 1.6% for the UK (Silberstein et al. 2008b). Of this population, it is estimated that approximately 20% have had a confirmed diagnosis of chronic migraine by a Neurologist (Bigal et al. 2008). Market research suggests that less than 17% of chronic migraine patients are seen by a specialist every year (Data on file).

In order to address the specific population described in the NICE STA Final Scope, we can look to the phase 3 PREEMPT study data to understand the proportion of the enrolled population who had previously received oral prophylactic treatments. PREEMPT 1 and PREEMPT 2 are a pair of studies designed to assess efficacy, safety and tolerability of Botox as headache prophylaxis in adults with chronic migraine (Aurora et al. 2010;Diener et al. 2010). In the PREEMPT studies, it was found that, on average, 61.9% of patients had a history of oral prophylactic medication use at baseline and had discontinued due to a lack of efficacy or unmanageable side-effects. Further analysis of the PREEMPT dataset reveals that this trend is repeated for ≥ 2, ≥ 3 and even ≥ 4 prior prophylactic treatments with each data point being approximately 60-70% of the previous figure shown. This is demonstrated graphically in Figure 1 which shows that 34.6% of the total sample would meet the definition requested by NICE in the Final Scope for this STA (Figure 2.1).

Figure 2.1: Baseline distribution of previous treatments in the PREEMPT clinical trial population



Based on the population included in the NICE final scope (≥3 prior oral prophylactic failures), we therefore estimate that of those patients diagnosed with chronic migraine, 34.6% would potentially be eligible for treatment with Botox.

Table 2.1: Estimated patient numbers in England & Wales 2011

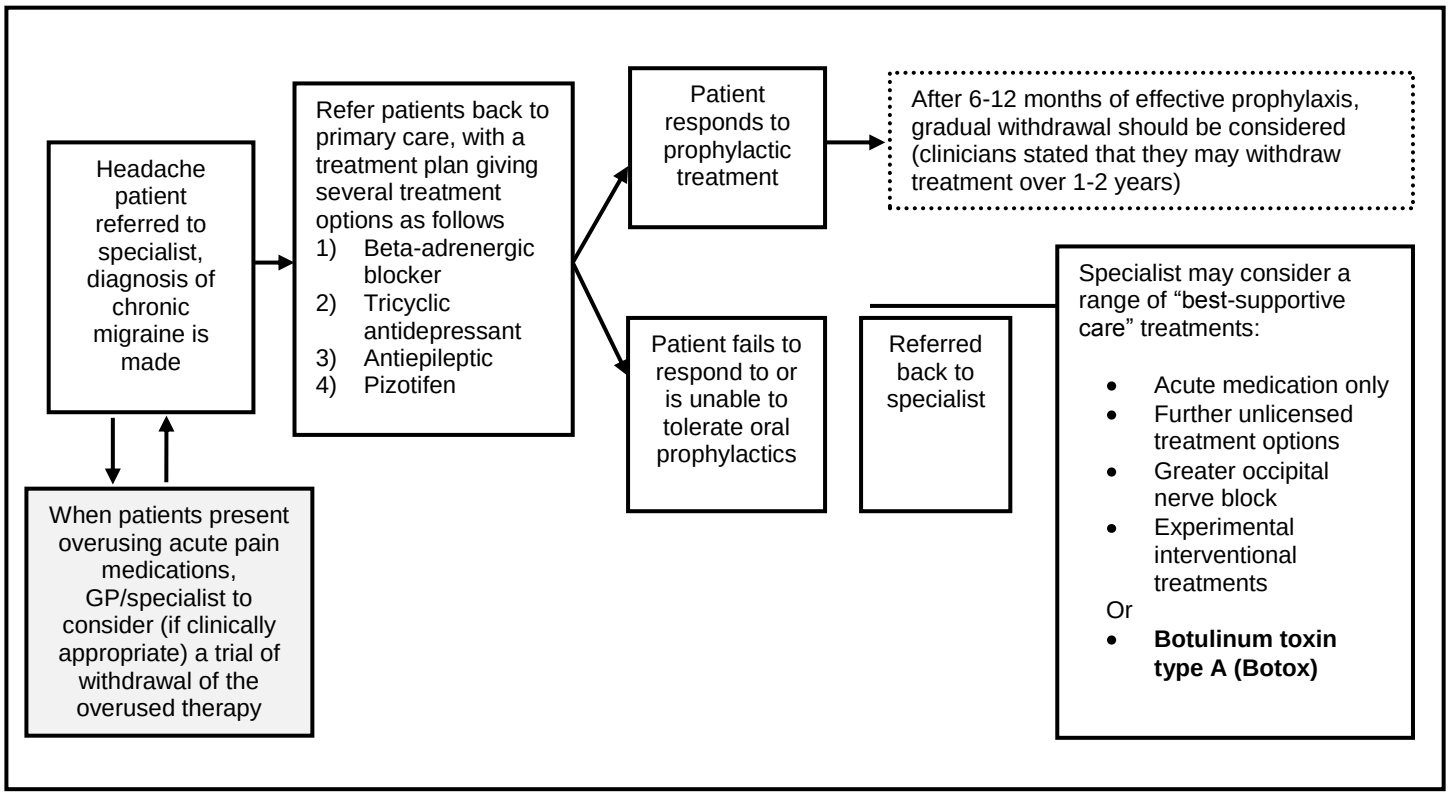
	Year 1
Total population in England & Wales	55,240,500
Adult population	43,570,300
Population with chronic migraine (1.6%)	697,125
Population with diagnosed chronic migraine (20.2%)	140,819
Patients failing ≥3 prior treatments (34.6%)	48,723

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

No other pharmacotherapies are specifically licensed for the indication of prophylaxis of chronic migraine in the UK but a number of oral prophylactic drugs are used to manage this population and recommended in guidelines (typically beta-blockers, antidepressants and antiepileptics). In the context of this submission, Botox is positioned as a prophylactic treatment targeted towards patients with chronic migraine who have previously received 3 or more oral prophylactic headache treatments (or are unable to receive such treatments), and who are under the care of a headache specialist in a secondary care centre.

A flow chart depicting the treatment pathway for patients with chronic migraine in the UK and the proposed therapeutic positioning for Botox can be found below. There has, until now, been no specifically licensed therapeutic option available for chronic migraine patients who have failed on oral prophylaxis in England and Wales. Patients in this population who are seen by a headache specialist are currently managed with “best supportive care” (BSC), which may involve a range of interventional procedures and unlicensed medications or may consist of no prophylactic medication (i.e. acute rescue medications, such as triptans).

Figure 2.2: Patient pathway of care



2.4 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Due to the highly complex nature of this condition, management is limited to specialist centres providing specific services for the diagnosis and appropriate treatment of chronic headache disorders.

2.5 Please identify the main comparator(s) and justify their selection.

No other drugs are specifically licensed for the indication of prophylaxis of headaches in chronic migraine in the UK but a number of oral prophylactic drugs are used to manage this population: typically beta-blockers, antidepressants and antiepileptics (BASH 2010;SIGN 2008). In the context of this submission, Botox is positioned as a prophylactic treatment targeted towards patients with chronic migraine who have received 3 or more previous oral prophylactic headache treatments, and who are under the care of a headache specialist in a secondary care centre. The final scope specifies that the comparator should be standard medical management, excluding interventional procedures.

A systematic review has been conducted which demonstrates that there are no data available for the oral-refractory population described in this scope for any of the prophylactic medications (licensed or unlicensed) used in this area of substantial unmet medical need.

Work is ongoing to further understand the different treatments that might be used, experimentally in this patient population. The base case economic evaluation will be performed using placebo data from the PREEMPT studies of Botox in Chronic Migraine (Dodick et al. 2010). Patients in either treatment arm could continue to use acute rescue medications to manage their headaches, therefore this data can be considered reflective of Standard Medical Management for a refractory population, where standard prophylactic treatments have failed. Data will also be presented from the PREEMPT trials for patients who have previously been treated with topiramate: although not explicitly licensed for chronic migraine (as the drug pre-dates the definition), it is a typically used second or third line treatment option.

2.6 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

N/A

2.7 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Botox in this indication will be administered by trained, experienced injectors in specialist centres as part of an outpatient consultation. No additional tests or resources are envisaged.

We intend to use NHS reference costs, in addition to PSSRU, to calculate the cost of administration of Botox, the total time for this minimally invasive procedure is envisaged to be under 30 minutes.

Training on the injection paradigm is available, and funded by the manufacturer.

2.8 Does the technology require additional infrastructure to be put in place?

No, it is envisaged that Botox will be administered by trained, experienced injectors in specialist centres where clinics for the management of headache disorders are already in place. Therefore Botox could potentially become part of the available care package for a carefully defined population of patients under specialist care, and would not require additional infrastructure.

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

N/A

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

N/A

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

N/A

4 Statement of the decision problem

Table 4.1: Statement of the decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Adults with headaches on at least 15 days per month of which at least 8 days are associated with chronic migraine and i) who condition has failed to respond to at least 3 prior prophylactic therapies and ii) medication overuse has been appropriately addressed	As defined	N/A
Intervention	Botulinum toxin type A (Botox)	As defined	N/A
Comparator(s)	Standard management without botulinum toxin typeexcluding invasive procedures	As defined	N/A
Outcomes	Frequency of headache days Frequency of migraine days Severity of headaches and migraines Number of cumulative hrs of headache or migraine on headache or migraine days Reduction in acute pharmacological medication Adverse effects of treatment Health related quality of life	As defined with the exceptions of severity of migraines (not separately assessed) and migraine days (not separately assessed)	Availability of data from the phase III trial programme limits our ability to respond to these two specific exceptions
Economic analysis	As per NICE methods	As per NICE methods	N/A
Subgroups to be considered	Presence or absence of medication overuse at baseline	Presence or absence of medication overuse	N/A
Special considerations, including issues related to equity or equality	None identified	None identified	N/A

Section B – Clinical and cost effectiveness

5 Clinical evidence

Chapter Summary

Botox has a UK marketing authorisation for the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine). It is administered by intramuscular injection to 31 and up to 39 sites divided across 7 specific head and neck muscle areas.

In the context of this submission Botox is positioned as a prophylactic treatment reserved for adults with headaches on at least 15 days per month of which at least 8 days are with migraine and whose condition has failed to respond to at least three prior oral migraine prophylactic medications and medication overuse has been appropriately managed. It is expected that in many cases prior oral prophylactic medications will include the use of topiramate, a drug which is licensed and recommended for use after beta-blockers and amitriptyline have failed. Given its position as a second or third-line oral prophylactic medication it is not considered an appropriate comparator for Botox in the decision problem for this appraisal.

The key evidence to support the efficacy of Botox in the chronic migraine population is taken from a pooled analysis of two clinical trials (**P**hase 3 **RE**search **E**valuating **M**igraine **P**rophylaxis **T**herapy (PREEMPT) studies 1 and 2) that represent the largest body of scientific evidence (n=1384 patients) supporting the safe and effective prophylactic treatment of headaches in adults with chronic migraine.

Comprehensive literature searches failed to identify any well conducted trials of alternative specialist treatments for use in this specific patient population e.g. Greater Occipital Nerve block, Occipital Nerve Stimulation, methysergide, and IV dihydroergotamine (DHE).

The PREEMPT studies were randomised, multicentre studies consisting of a 28-day baseline phase, a 24-week, double-blind, randomised, placebo-controlled, parallel-group phase followed by a 32-week open-label extension phase (total study duration of 60 weeks per patient).

Key efficacy data presented below are from the pooled analyses, but results are generally consistent within and across the phase 3 clinical studies.

Botox was more effective than placebo in reducing the mean frequency of headache days per 28 days in the double blind phase: Botox showing a mean of -8.4 days vs -6.6 days for placebo. This is a treatment difference of -1.8 days [95%CI -2.52, -1.13] (Table 5.26; Figure 5.10).

Significant reductions favouring Botox over placebo were also seen in key secondary efficacy endpoints at 24 weeks, tabulated below.

Endpoint	Baseline value – Botox	Change from Baseline – Botox	Baseline value – Placebo	Change from Baseline – Placebo	Treatment difference [95% CI]
Frequency of migraine days	19.1	-8.2	18.9	-6.2	-2.0 [-2.67, -1.27]
Change in frequency of moderate/severe headache days	18.1	-7.7	18.0	-5.8	-1.9 [-2.62, -1.26]
Change in cumulative total headache hours on headache days	295.93	-119.7	281.22	-80.5	-39.2 [-48.40, -21.04]
Percent of patients with severe (≥60) HIT-6 score	93.5	-25.9	92.7	-14.5	-10.6 [-15.2, -5.9]
Change in frequency of triptan intake	-	-3.3	-	-2.5	-1.1 [-1.74, -0.61]
Change in MSQ score (treatment difference in Role function-restrictive /10)	6.2	-1.7	6.1	-0.9	-0.8 [-1.08, -0.60]
Change in MSQ score (Role function-preventative/10)	4.4	-1.3	4.4	-0.6	-0.7 [-0.90, -0.43
Change in MSQ score (Emotional function/10)	5.8	-1.8	5.8	-1.0	-0.8 [-1.14, -0.56]

Efficacy results from the following sub group analyses of interest were directionally consistent with the robust efficacy findings from the total study population: patients overusing acute headache medications at baseline (65.5% of the total sample); patients previously treated with at least one oral prophylactic medication (63.5% of the total sample); patients previously treated with at least two oral prophylactic medications (46% of the total sample); patients previously treated with at least three oral prophylactic medications (34.6% of the total sample); and patients previously treated with topiramate (39.4% of the total sample).

During the 32-week open-label phase, further improvements in headache days and all other efficacy endpoints were seen in those patients who continued to receive Botox as well as in those who were crossed over from placebo to Botox.

The safety of Botox in a range of indications has been established with over 20 years of use in clinical practice. In the PREEMPT trials, the incidence of adverse events (AEs) in both the double-blind and open-label periods was generally low but higher in the Botox group compared with the placebo group.

- At 24 weeks, the overall incidence of AEs was 62.4% (429/687) for the Botox group and 51.7% (358/692) for the placebo group.
- Neck pain was the most frequently reported treatment-related AE in the double-blind phase (7.3%) and in the open-label phase (5.8%).
- Most AEs were mild to moderate in severity and transient. The nature of AEs observed was consistent with the known safety and tolerability profile of Botox with multiple intramuscular injections to the head and/or neck.
- No new safety findings were identified that raise concerns over the use of Botox at the labelled doses for the prophylaxis of headaches in adults with chronic migraine.

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 does not pose an additional cumulative toxicity or additional safety risk to patients. For example, in the case of neck pain (the most frequently reported AE) 79 patients (6.1%) reported neck pain during the first treatment cycle, 33 patients (2.8%) reported neck pain with the second treatment cycle, 21 patients (1.9%) with the third cycle, 12 (2.2%) with the fourth cycle and fewer than 1% reported neck pain with the fifth treatment cycle.

Discontinuation due to AEs was low during the double-blind phase: 3.8% (26/687) in the Botox group and 1.2% (8/692) in the placebo group. In the open label phase in total there were 31/1205 (2.6%) patients who discontinued due to AEs.

No deaths and few serious AEs in Botox-exposed patients were reported for either of the studies.

Data from the clinical trial programme demonstrate that Botox is effective and well tolerated for the PREEMPT study population. Population-based epidemiology data provide evidence that the PREEMPT study population is representative of the typical patient with chronic migraine seen in clinical practice. This suggests that results from the PREEMPT studies can be generalised to the wider population of patients with chronic migraine: that is, outside a clinical trial setting. Furthermore, efficacy analysis of a subgroup of patients previously treated with oral prophylactic medications indicate that results from the PREEMPT studies can be applied to the population of chronic migraine patients for whom Botox is indicated within the context of this submission.

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem.

Identifying studies that enrolled the population of interest for the decision problem

Historically, patients with chronic migraine have been excluded from migraine prophylaxis trials because they were considered to be too highly disabled and treatment resistant (Dodick et al. 2010). Few preventative therapies have been investigated, and no pharmacological therapy apart from Botox is currently licensed specifically for the prophylaxis of headaches in patients with chronic migraine. Consequently, there is a lack of effectiveness studies and therefore effectiveness data for patients in the general population of chronic migraine sufferers (Dodick et al. 2010).

Botox is indicated and licensed for the prophylaxis of headaches in adults with chronic migraine; however, the final scope identifies a specific subgroup within the licensed indication for which this technology is to be appraised. Specifically this subgroup comprises adults with headaches on at least 15 days per month of which at least 8 days are associated with chronic migraine and i) whose condition has failed to respond to at least three prior pharmacological prophylaxis therapies and ii) where medication overuse has been appropriately managed. This subgroup, although the primary focus of the decision problem, was unlikely to be identified through standard searches of electronic databases. Thus, the literature searches focused on the wider chronic migraine population.

The classification of chronic migraine has evolved and the following terms have been used interchangeably in the past: ‘chronic daily headache’, ‘transformed migraine’ or ‘chronic migraine’ (Manack et al. 2009).

The current ICHD-IIR classification excludes patients who have medication overuse headache as per ICHD-II 8.2 from receiving a diagnosis of chronic migraine (Figure 5.1) (Olesen et al. 2006). Frequent or regular use of certain medications (e.g., barbiturates, opioids, triptans) as treatment of acute headache episodes can lead to deterioration of a pre-existing primary headache resulting in a secondary medication overuse headache (ICHD-II 8.2) (Silberstein 2005). An important aspect has to be kept in mind; excessive use of acute headache pain medication (often referred to as medication overuse) is not identical to medication overuse headache. For example, a patient might experience 11 migraine days per month and take triptans on 11 days. This fulfils the criteria for excessive use of medication, and technically

also fulfils the ICHD 8.2 criteria for triptan medication overuse headache. However, since differential diagnoses require judgement of the clinician, in this instance the frequency of headache days most probably is not related to the intake of triptans, but the triptan use is as a result of the consequence of frequent migraine headaches. Another migraine patient may have developed daily headache, some of which fulfil the criteria for migraine. If this patient is also taking triptans or opioids on a daily basis and their condition continues to deteriorate there is a high likelihood that this clinical situation is the result of the medication overuse and that the patient is experiencing secondary medication overuse headache, in addition to migraine. An important differentiating factor with regard to the influence of excessive use of medication is that there should be evidence of regular overuse for > 3 months of one or more acute treatment drugs and that the headache has developed or markedly worsened during the period of medication overuse. Clinic-based studies and clinical trials have shown that 50–80% of patients with chronic migraine overuse acute medication (Olesen, 2006). What is not clear from the literature is whether all patients who are excessively using acute medications (overusing) also fulfil clinical criteria for a diagnosis of medication overuse headache. The recent International Headache Society (IHS) guidelines for chronic migraine trials recognises that medication overuse is a confounding factor for this population and therefore it is suggested that due to the high prevalence of excessive use of acute medications by patients with chronic migraine, subjects in trials meeting criteria A to C for chronic migraine, but not D (i.e. patients have medication over-use) may be included in trials for chronic migraine provided that they are stratified accordingly (Silberstein et al. 2008a) as was done in the clinical trials of Botox discussed in section 1.3 (Aurora et al. 2010;Diener et al. 2010).

Figure 5.1: Revised International Headache Society criteria for chronic migraine (International Headache Society (IHS) 2011)

Chronic Migraine

A. Headache (tension-type and/or migraine) on 15 or more days per month for at least 3 months
B. Occurring in a patient who has had at least five attacks fulfilling the ICHD-II criteria for migraine without aura
C. On 8 or more days per month for at least 3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura
    1. Has at least 2 of
        - Unilateral location
        - Pulsating quality
        - Moderate or severe pain intensity
        - Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

       And at least 1 of
        - Nausea and/or vomiting
        - Photophobia and phonophobia
    2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above

D. No medication over-use^ and not attributed to another causative disorder

^ Medication overuse headache as defined under 8.2 *Medication-overuse headache*

Accordingly, the population defined by NICE in the final scope for the technology appraisal of Botox includes those patients whose medication overuse has been appropriately managed. Furthermore, NICE requests that if evidence allows, the presence or absence of medication overuse should be considered as a subgroup.

Intervention and comparators relevant to the decision problem

The intervention of interest in the decision problem is Botox and the comparator is standard management without Botox excluding invasive procedures.

At present in the UK, no drugs, other than Botox, are licensed specifically for prophylaxis of headaches in adults with chronic migraine. However, a number of oral prophylactic drugs are used to manage patients with migraine and are recommended in treatment guidelines (BASH 2010;SIGN 2008). Typically, the types of treatments used include beta-blockers, antidepressants and

antiepileptics. UK guidelines recommend that combinations of oral medications be considered if the patient's condition fails to respond to individual oral medications used alone, although they acknowledge that there is no formal evidence for effectiveness of any drug combination (BASH 2010). In the context of the decision problem, Botox is to be appraised in patients whose condition has failed to respond to at least three prior pharmacological prophylactic therapies. Consequently, given the position of Botox in the treatment pathway: that is, after at least three oral prophylactic therapies have failed, medications recommended in UK guidelines (BASH 2010;SIGN 2008) are not considered relevant comparators for the purposes of this literature search. It is expected that in many cases prior oral prophylactic medications will include the use of topiramate, a drug which is licensed and recommended for use in a general migraine population after beta-blockers and amitriptyline have failed. Given its position as a second or third-line oral prophylactic medication it is not considered an appropriate comparator for Botox in the decision problem specified.

For chronic migraine patients whose condition has failed to respond to oral prophylactic medications there has, until now, been no specifically licensed therapeutic option available in England and Wales. Patients in this population who are seen by a headache specialist may undergo invasive procedures or receive unlicensed medications as part of a tertiary package of care in an attempt to manage their condition. Alternatively, they may be prescribed acute headache pain medications such as triptans rather than prophylactic treatments.

Examples of invasive procedures include minimally invasive procedures such as Greater Occipital Nerve (GON) block (local injections of steroids, local anesthetics or a mixture of both in the area of greater occipital nerve) and more complex procedures including occipital nerve stimulation (the neurostimulator delivers electrical impulses via insulated lead wires tunneled under the skin near the occipital nerves at the base of the head).

Dihydroergotamine (DHE), which is given intravenously, and methysergide (taken orally) are ergot alkaloids. Methysergide is "held in reserve", partly due to its association with retroperitoneal fibrosis and the severe rebound headache experienced by many patients when attempting to withdraw from it after several months use (BASH 2010). DHE is investigational due to insufficient evidence for its effectiveness and is not licensed for use in the UK, therefore it is only available in a small number of tertiary specialist centres (Saper JR and Silberstein S 2006). None of these interventions could be classified as "standard care" due to wide geographical variability of access and practice.

All of these therapies however, are considered potentially relevant comparators, because, like Botox, within the decision problem, they are

considered for use only when patients with chronic migraine have failed on prior oral prophylactic medications. Although these comparator therapies are not licensed for use in chronic migraine, data on their clinical effectiveness would permit an assessment of their relative benefit compared to Botox. Thus, they have been included in the literature searches as comparator treatments, even though some of these approaches, as interventional procedures, are excluded from the scope.

Study outcomes relevant to the decision problem

Study outcomes specified in the decision problem include: frequency of headache days, frequency of migraine days, severity of headaches and migraines, number of cumulative hours of headache or migraine on headache or migraine days, reduction in acute pharmacological medication, adverse effects of treatment and health-related quality of life.

Previously published systematic reviews

The British Association for the study of Headache (BASH) published guidance on diagnosis and management of headache including migraine in 2010 (BASH 2010), although they did not report literature search methods used. A comprehensive literature search was carried out in 2007 by the Scottish Intercollegiate Guidelines Network (SIGN) as part of a systematic review of evidence for a National Clinical Guidance (2008) for Diagnosis and Management of Headache in Adults (SIGN 2008). Section 6.2 of that report presented evidence and recommendations for oral prophylactic therapies for migraine, as well as “Other therapies”, which included evidence for Botox and methysergide among others. Searches covered the year range 2001 to 2007 and full details of the search strategies were published in appendices to the guidance (SIGN 2008).

Current literature search objectives

The approach taken in this literature search was to update the SIGN searches (2007 to present) for Botox and relevant comparators (methysergide and DHE) that were included in the SIGN guidance, and to conduct new searches for therapies that were not included in SIGN such as nerve block and brain stimulation procedures that are relevant to the decision problem.

Literature search methods

For the years 2007 onward the following electronic databases were searched: Medline (via OVID), Embase (via OVID), Cochrane Library: Cochrane database of systematic reviews, Cochrane register of clinical trials, NHS Health Economic Evaluation Database (HEED), Health Technology Assessment (HTA) database (all via Wiley), CINAHL(via NHS Evidence), PsycINFO (via OVID, Econlit (via OVID), Science Citation Index (Web of Knowledge), and Conference Proceedings Index (Web of Knowledge).

The search included terms to describe the intervention of interest (botulinum toxin type A and Botox), other treatments for chronic migraine (oral prophylactic medications, nerve block, occipital nerve stimulation etc.), the population (migraine sufferers), and methodological search filters such as those produced by the SIGN to refine the results to the appropriate types of evidence (RCTs, systematic reviews, economic analyses). The terms within these groups were combined using the Boolean operator OR, then groups were combined using the Boolean operator AND. This approach is the standard 'building block' approach to searching (Booth A 2008). The complete search strategies can be found in Appendices 1 & 2.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process.

Table 5.1: Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	**Population:**adults with chronic migraine^ **Intervention:**Botox and specified comparators (GON block, occipital nerve stimulation, intravenous DHE and methysergide). **Outcomes:** frequency of headache days, frequency of migraine days, severity of headaches and migraines, number of cumulative hours of headache or migraine on headache or migraine days, reduction in acute pharmacological medication, adverse events of treatment and health related quality of life. **Study design:** RCT **Language:** English
Exclusion criteria	**Population:**persons < 18 years of age; diagnosis other than chronic migraine **Intervention:** non-prophylactic therapy **Outcomes:** any outcomes not listed in the inclusion criteria **Study design:** non-RCT **Language:** non-English language

^Headaches on at least 15 days per month of which at least 8 days are with migraine

Population

As highlighted previously, the population of interest with regard to the decision problem is the subgroup of chronic migraine patients whose condition has failed to respond to at least 3 prior oral prophylactic medications. Also, the subgroup to be analysed should include only subjects evaluated in clinical trials with a diagnosis of chronic migraine. Chronic migraine is defined as patients who experience headaches on at least 15 days per month, of which at least 8 days are with migraine. Therefore, only those studies that enrolled patients with chronic migraine or analysed the subset of chronic migraine patients separately were included. Studies that described patients as having "transformed migraine" and/or "chronic daily headache" were included if the definition was clearly described and found to be equivalent to the chronic migraine definition as above.

Study design

Well conducted RCTs are considered to be most appropriate for measures of treatment effect. The review included all RCTs that evaluated Botox (botulinum toxin type A) and relevant comparators in comparison to either an active comparator or to placebo for the treatment of chronic migraine, regardless of design (parallel, cross-over, open-label, single- or double-blinded).

Outcomes

Studies were selected if they included any of the following outcomes, as specified in the decision problem for this submission: frequency of headache days, frequency of migraine days, severity of headaches and migraines, number of cumulative hours of headache or migraine on headache or migraine days, reduction in acute pharmacological medication, adverse effects of treatment and health-related quality of life.

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

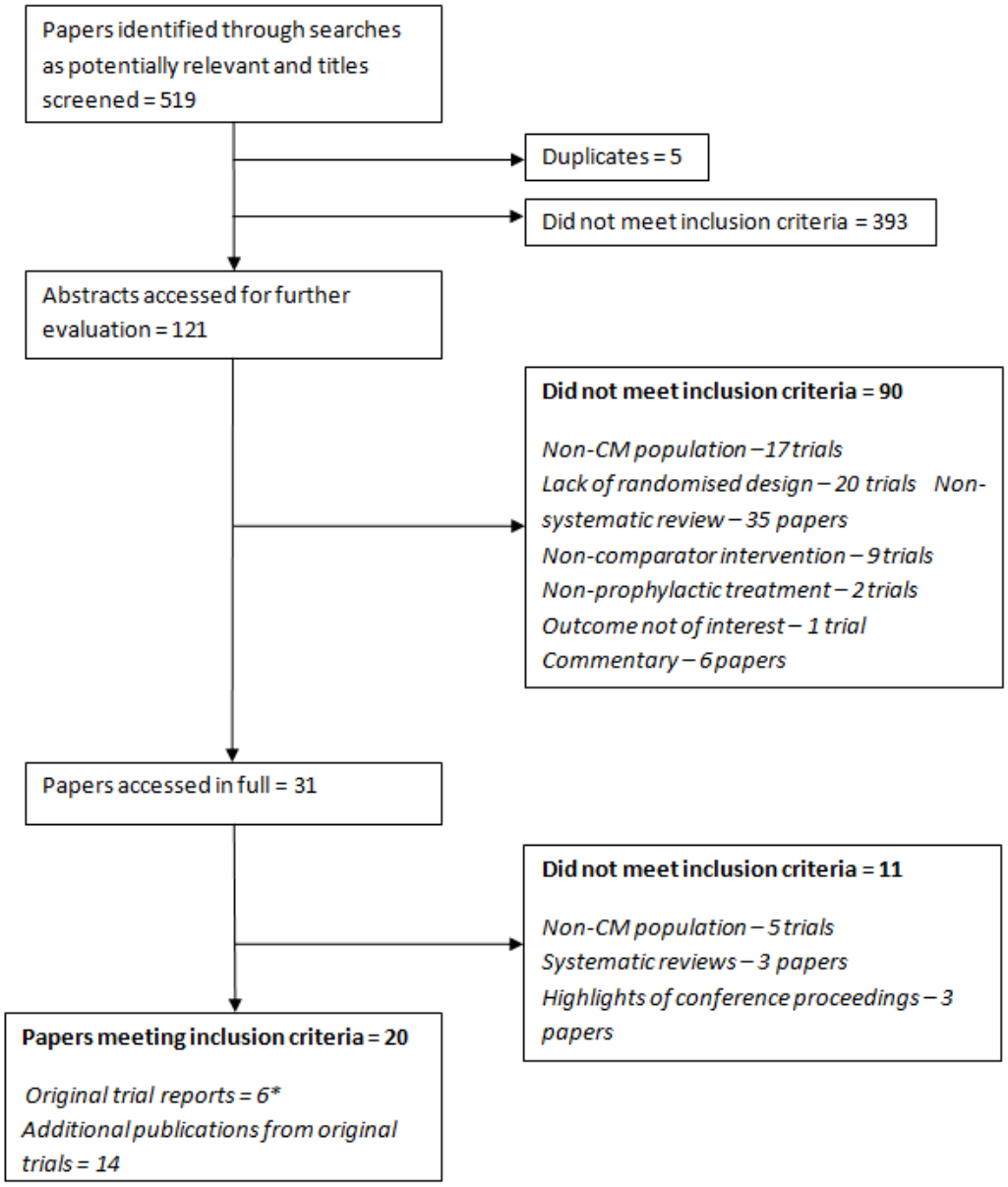
Results of searches for Botox studies

A total of 519 records were identified through database searching (Appendix 2; Figure 5.2). After removal of duplicates and studies which, from their title, clearly did not meet the inclusion criteria, 121 records remained. Abstracts for these studies were obtained and a further 90 were excluded. Full text copies of 31 studies were obtained and from these 20 publications met the inclusion criteria. The 20 publications originated from six primary studies: that is, there were 6 original reports of randomized controlled trials(Aurora et al. 2010;Blumenfeld et al. 2008;Diener et al. 2010;Freitag et al. 2008;Magalhaes et al. 2010;Mathew and Jaffri 2009). An additional study (Cady et al. 2011), published after the Botox literature search was conducted, was identified from the later search for comparator drug studies detailed in Appendix 2. (Table 5.2)

Table 5.2: Seven primary RCTs of Botox identified in literature searches

Study, author, year, study size	**Comparator**
Aurora, 2010, n=679	Placebo
Blumenfeld, 2008, n=14	Divalproex sodium
Cady, 2011, n=59	Topiramate
Diener, 2010, n=705	Placebo
Freitag, 2008, n=60	Placebo
Magalhaes, 2010, n=72	Amitriptyline
Mathew, 2009, n=60	Topiramate

Figure 5.2: Botox literature search flow diagram



*One additional Botox trial was identified in the search for comparator treatments. This was a 2011 publication. The search for Botox publications was completed in Dec 2010 whereas the comparator search was conducted in March 2011.

Results of searches for comparator therapy studies

As discussed previously in this section searches were conducted for a range of invasive procedures and unlicensed medications. Such therapies are considered relevant comparators, because, like Botox, within the decision problem, they are considered for use only when patients with chronic migraine have failed on prior oral prophylactic medications. Although these comparator therapies are not licensed for use in chronic migraine, data on their clinical effectiveness would permit an assessment of their relative benefit compared to Botox.

Only one RCT of occipital nerve stimulation was identified in the searches. In this feasibility study patients were randomized to adjustable stimulation (n=33), preset stimulation (n=17), and medical management (n=17) (Saper et al. 2011). For full details of the literature search strategy and flow diagram for comparator therapies see Appendix 3.

During the preparation of this submission, on 7 September, European approval was received for use of an implanted neurostimulation device for patients with intractable chronic migraine (Business Wire 2011). No further discussion of this device will take place here as the technology is excluded from the scope of this appraisal.

5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Table 5.3 lists additional publications derived from the original primary trials. They include conference proceedings and post hoc analyses of single and pooled studies but did not provide data used within this submission in addition to that reported in the key publications (Aurora et al. 2010;Diener et al. 2010;Dodick et al. 2010).

Table 5.3: Secondary publications from original reports of RCTs of Botox

Study	Author, year	Publication description	Main outcome reported
1	Aurora 2009	Analysis of PREEMPT 1 trial data. Abstract.	Mean change in no. headache episodes. N=679
2	Aurora 2009	Pooled analyses of PREEMPT 1 and 2 trials. Abstract.	Mean change in no. headache days and headache episodes. N=1384
3	Aurora 2010	Pooled analysis of PREEMPT 1 and 2. Abstract.	Safety of FSFD injection vs. FTP injection. N=1384
4	Dodick 2009	Pooled analysis of PREEMPT 1 and 2. Abstract.	Mean change in no. headache days. N=1384
5	Dodick 2009	Analysis of RCT data from PREEMPT 2. Abstract.	Mean change in no. headache days. N=705
6	Dodick 2010	Pooled analysis of PREEMPT 1 and 2. Abstract.	Headache duration. N=1384
7	Dodick 2010	Pooled analysis of PREEMPT 1 and 2. Full text journal article.	Frequency of headache days. N=1384
8	Lipton 2009	Pooled analysis of PREEMPT 1 and 2. Abstract.	Migraine specific quality of life. N=1384
9	Lipton 2010	Pooled analysis of PREEMPT 1 and 2. Abstract.	Headache impact (HIT-6). N=1384
10	Mathew 2008	This is an abstract version of full text Mathew 2009 (Table B1). Abstract.	No. of headache days. N=60
11	Silberstein 2009	Pooled analysis of PREEMPT 1 and 2 chronic migraine subgroup with baseline acute headache medication overuse. Abstract.	Frequency of headache days and headache episodes. N=906.
12	Silberstein 2010	Pooled analysis of PREEMPT 1 and 2. Abstract.	Frequency of headache days and head ache severity. N=1384.
13	Silberstein 2010	Pooled analysis of PREEMPT 1 and 2. Abstract.	Migraine Specific Quality of Life. N=1384.

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

RCTs of Botox compared to active therapies and placebo

The literature searches identified seven studies of Botox (Table 5.4). Only three of these studies included placebo as the comparator (Aurora et al.

2010;Diener et al. 2010;Freitag et al. 2008). The remaining four studies compared Botox to oral prophylactic medications (Blumenfeld et al. 2008;Cady et al. 2011;Magalhaes et al. 2010;Mathew et al. 2009).

Table 5.4: List of RCTs

Study, author, year, study size	**Comparator**	**Primary outcome**
Aurora, 2010, n=679 (PREEMPT 1)	Placebo	Mean change in headache episode frequency per 28 days.
Blumenfeld, 2008, n=14	Divalproex sodium	Multiple outcomes including reduction in headache days per month.
Cady, 2011, n=59	Topiramate	Response to treatment as measured by Physician Global Assessment.
Diener, 2010, n=705 (PREEMPT 2)	Placebo	Mean change in frequency of headache days per 28 days.
Freitag, 2008, n=60	Placebo	Mean change in frequency of migraine episodes.
Magalhaes, 2010, n=72	Amitriptyline	Not specified. Included a mixture of objective and subjective outcomes.
Mathew, 2009, n=60	Topiramate	Response rates as measured by change in Physician Global Assessment.

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

All studies that compared Botox to placebo are relevant to the decision problem. Three such RCTs that were identified are listed in Table 5.5.

Table 5.5: List of RCTs of Botox that include an appropriate comparator

Study, author, year, study size	Clinical Study ID	Comparator	Primary outcome
Aurora, 2010, n=679 (PREEMPT 1)	191622-079	Placebo	Mean change in frequency of headache episodes per 28 days.
Diener, 2010, n=705 (PREEMPT 2)	191622-080	Placebo	Mean change in frequency of headache days per 28 days.
Freitag, 2008, n=60		Placebo	Mean change in migraine episode frequency per 4-week period.

PREEMPT = Phase III REsearch Evaluating Migraine Prophylaxis Therapy.

The primary evidence to support the use of Botox in chronic migraine comes from the pooled analysis (Dodick et al. 2010) of the two phase 3 studies (Table 5.5), PREEMPT 1 and PREEMPT 2 (Aurora et al. 2010;Diener et al. 2010). The PREEMPT study programme is the largest of its kind to investigate outcomes in this patient population. It is therefore important that results from the pooled analysis be presented alongside results for the two separate RCTs.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Five studies of Botox from Table 5.4 were excluded from further discussion in this submission (Table 5.6). Four were excluded because they included comparators that were not relevant to the decision problem (Blumenfeld et al. 2008;Cady et al. 2011;Magalhaes et al. 2010;Mathew et al. 2009).

One pilot study, although it did compare Botox to the appropriate comparator (placebo), was excluded from further discussion because of concerns regarding its quality and relevance to the decision problem. In particular, external validity was compromised due to the small sample size (n=60). Given the absence of a sample size calculation it was unclear how much power the study had to detect differences between treatment groups. Approximately 30% of patients discontinued in the study after being allocated to treatment and therefore only 60% of patients had complete data for the final analysis at week 16. Most patients who discontinued did not receive allocated intervention after randomisation due to medication overuse during the baseline period (patients with medication overuse were explicitly excluded

from the study). In addition, the decision problem could not be addressed from the data in this study because it did not report details of prior oral prophylactic medication use in the study subjects (Freitag et al. 2008).

Similarly, the only study that was identified in the search for comparator therapies (invasive therapies and unlicensed medications) was excluded from further discussion because of concerns about its quality and relevance to the decision problem. It was a small feasibility study and the sample size was chosen to gain experience with the therapy rather than to provide sufficient power for a single primary endpoint. It was an RCT with only 33 patients assigned to adjustable occipital nerve stimulation and 17 assigned to preset stimulation (Saper et al. 2011).

Table 5.6: Studies excluded from further discussion in this submission

Study, author, year, study size	Intervention vs. Comparator	Primary outcome
Botox studies		
Blumenfeld, 2008, n=14	Botox vs. divalproex sodium	Multiple outcomes including reduction in headache days per month.
Cady, 2011, n=59	Botox vs. topiramate	Response to treatment as measured by Physician Global Assessment.
Freitag, 2008, n=60	Botox vs. placebo	Mean change in frequency of migraine episodes.
Magalhaes, 2010, n=72	Botox vs. amitriptyline	Not specified. Included a mixture of objective and subjective outcomes.
Mathew, 2009, n=60	Botox vs. topiramate	Response rates as measured by change in Physician Global Assessment.
Comparator studies		
Saper, 2010, n=110	Adjustable occipital nerve block vs. preset nerve block vs. medical management.	Reduction in number of headache days per month.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs(for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

The two PREEMPT studies evaluated the efficacy and safety of Botox in 1,384 patients and represent the largest, controlled trials in chronic migraine to date. Both studies are considered relevant to the decision problem and thus searches for non-RCT evidence were not deemed necessary.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s)

Study design

Studies PREEMPT 1 and PREEMPT 2 were identical, 56-week-treatment period, randomised, multicentre studies, evaluating the efficacy and safety of Botox as headache prophylaxis in chronic migraine patients.

In the 24-week, double-blind phase, patients received a series of 31-39 intramuscular (IM) injections of Botox or placebo (saline) at day 0 and week 12.

In the 32-week, open-label phase all patients continuing in the studies received Botox treatment at week 24, week 36 and week 48.

Patients meeting the inclusion/exclusion criteria at baseline were randomly allocated to receive either Botox or placebo at a 1:1 ratio in a blinded fashion, stratified by overuse of acute headache pain medications (yes/no) at baseline.

Eligible patients were men or women aged 18 to 65 years with a history of migraine headache disorder. All patients were required to have a baseline count of ≥15 headache days during the first 28 days of the baseline period, with each day consisting of ≥4 hours of continuous headache, of which at least 50% were migraine or probable migraine days, and to have had ≥4 distinct headache episodes each lasting ≥4 hours. Patients were excluded if they used headache prophylactic medications within 4 weeks prior to the start of baseline. Investigators excluded patients whose headache they attributed to other disorders such as medication overuse, however, chronic migraine patients with protocol defined excessive use (overuse) of acute medications were included.

Efficacy measures The primary endpoint in PREEMPT 1 was frequency of headache episodes per 28 days.

The primary endpoint in study PREEMPT 2 was frequency of headache days per 28 days. The primary endpoint for both studies was defined at week 24, which was comprised of data collected from week 20 to week 24.

In line with IHS guidelines and FDA preference, the PREEMPT 2 study protocol and statistical analysis plan were amended, prior to treatment unmasking, to change the primary endpoint from frequency of headache episodes to frequency of headache days.

A number of additional efficacy and HRQL outcomes were captured in order to further investigate the efficacy of Botox in chronic migraine by demonstrating a consistency of improvements across multiple efficacy parameters.

Patient data from both studies were pooled and the efficacy and safety measures reanalysed, using the same primary endpoint as study PREEMPT 2 (frequency of headache days)

Statistical analysis

All efficacy analyses used the intent-to-treat (ITT) population, which included all randomised patients.

For the primary and secondary variables in both studies and the pooled analysis, pre-specified comparisons between treatment groups were done by analysis of covariance (ANCOVA) of the change from baseline

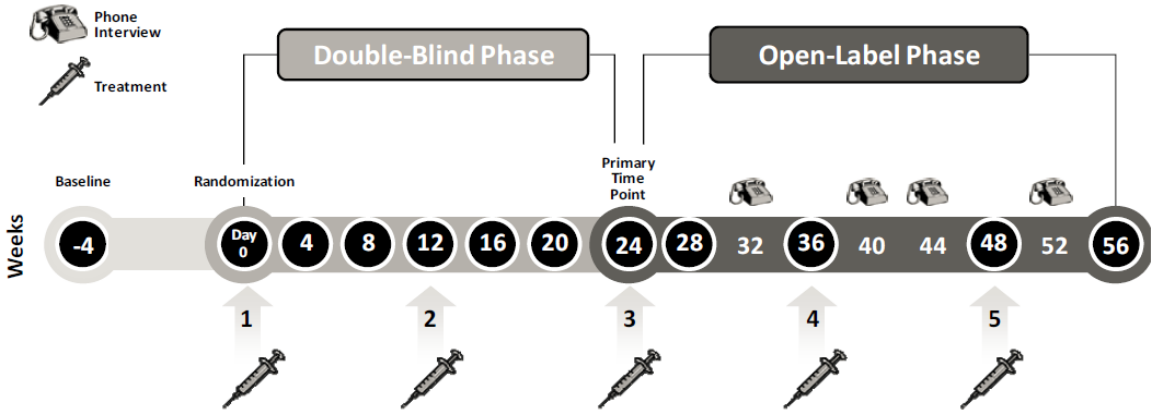
Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments.The following tables provide a suggested format for when there is more than one RCT.

The phase 3 PREEMPT studies 1 and 2 followed an identical study design. Both included a 56-week treatment period and were randomised, multicentre studies, evaluating the efficacy and safety of Botox as headache prophylaxis in adults with chronic migraine. These studies included a 4-week screening/baseline phase (week -4 to day 0), followed by a 24-week, double-blind, randomised, placebo-controlled, parallel-group phase, which was then followed by a 32-week open-label extension phase (Figure 5.3) (Aurora et al. 2010;Diener et al. 2010).

A total of 2 treatment cycles during the double-blind phase and 3 treatment cycles during the open-label phase of the studies were included to ensure sufficient efficacy and safety exposure was obtained at the effective dose and treatment paradigm. Each treatment cycle was 12 weeks in duration.

Figure 5.3: Schematic of phase 3 study design - PREEMPT 1 and PREEMPT 2



* In-office visits were conducted every 4 weeks, except when noted by telephone.

Qualified subjects were randomised (1:1) in a double-blind fashion to Botox or placebo. As per IHS guidelines (Silberstein et al. 2008a), randomisation was stratified based on protocol defined frequency of acute headache pain medication use during baseline (designated as ‘‘medication overuse–yes’’ or ‘‘medication overuse–no’’), with treatments balanced in blocks of four within each medication-overuse stratum for each investigator site (Silberstein, 2008b). Patients in the medication overuse–yes stratum had overused acute headache pain medications during baseline, with intake of simple analgesics

on ≥15 days, or other medication types or combination of types for ≥10 days, with intake ≥2 days/week from the category of overuse. Investigators were trained not to enrol patients who frequently used opioids and barbiturates as their acute headache pain medication.

The randomisation sequence was generated using SAS programming language (SAS Institute, Cary, NC, USA) and was stored in a central server with access granted to the randomisation programmers. The programmers then released the information to personnel who packed the medication kits, and to the vendor who managed the patient electronic diary (Perceptive Informatics, Waltham, MA, USA) for purposes of central implementation of the randomisation and treatment-kit assignment. Throughout the double-blind phase of the study, the patients, the investigators who administered the study treatment and assessed safety and outcomes and the sponsor study management personnel were all masked to the treatment-group assignment. At the end of the baseline screening phase, when the investigator attempted randomisation of a subject, the central implementation computer program determined if the subject met the quantitative inclusion/exclusion criteria as per the patient reported diary data. If qualifications were met, the subject number was linked to the next randomisation number grouped within strata for that site, and the site was notified of the medication kit assigned to that randomisation number.

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial.The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

For enrolment into the PREEMPT studies, each patient had to meet all the following inclusion criteria:

- Male or female, 18 to 65 years old
- History of migraine headache disorder meeting any of the diagnostic criteria listed in ICHDII (2004) Section 1, Migraine, with the exception of “complicated migraine” (International Headache Society 2004)
- Four or more distinct headache episodes during the 4-week baseline phase each with a duration of at least 4 hours

- Fifteen or more headache days during the 4-week baseline phase, with each day consisting of 4 or more hours of continuous headache
- At least 50% of baseline headache days were migraine or probable migraine days
- Written informed consent was obtained
- Written Authorisation for Use and Release of Health Research Study Information (US sites only) was obtained
- Written Personal Information Protection Authorisation (Canadian sites only) was obtained
- Written Data Protection Consent (European sites only) was obtained
- Stable medical condition in the investigator's opinion
- Routine non-headache medications of stable dose and regimen for at least 1 month prior to week -4 and during the baseline phase
- Ability to follow study instructions (including compliance with a daily telephone diary) and likely to complete all required visits
- Negative urine pregnancy test on the day of the first treatment prior to the administration of the study medication (for female patients of childbearing potential)
- For enrolment into the PREEMPT study, each patient had to meet none of the following exclusion criteria
- Uncontrolled clinically significant medical condition other than the condition under evaluation (including alcohol/illicit substance abuse)
- Any medical condition that may have put the patient at increased risk with exposure to Botulinum Toxin Type A Purified Neurotoxin Complex, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other significant disease that may have interfered with neuromuscular function
- Patients who had been diagnosed with the following headache disorders, as listed in ICHD-II (2004) (14) Section 1: complicated migraine (e.g., hemiplegic migraine [1.2.4, 1.2.5], basilar migraine

[1.2.6], ophthalmoplegic migraine [13.17] ,or migrainous infarction [1.5.4])

- Use of any headache prophylactic medication within 28 days prior to week -4

- Headache diagnosis of chronic tension-type headache (ICHD-II 2.3), hypnic headache (ICHD-II 4.5), hemicrania continua (ICHD-II 4.7), or new daily persistent headache (ICHD-II 4.8)

- Headache attributed to another disorder (e.g., cervical dystonia, craniotomy, head/neck trauma)

- Unremitting headache lasting continuously throughout the 4-week baseline period

- Patients with a known or suspected temporomandibular disorder (TMD), including pain in or around the temporomandibular joint (TMJ)

- Patients with a concurrent diagnosis of fibromyalgia

- Beck Depression Inventory score > 24 at week -4

- Psychiatric problems that, in the investigator's opinion, were severe enough to interfere with study participation or results (e.g., bipolar disorder)

- Infection or skin disorder at anticipated injection sites

- Females who were pregnant, nursing, or planning a pregnancy during the study

- Females of childbearing potential, not using a reliable means of contraception

- Previous treatment with botulinum toxin therapy of any serotype for any reason, or immunisation to any botulinum toxin serotype

- Anticipated need for botulinum toxin treatment for any reason during the study (other than study treatment)

- Known allergy or sensitivity to the study medication or its components

- Acupuncture, TENS (transcutaneous electrical nerve stimulation), cranial traction, nociceptive trigeminal inhibition or occipital nerve block treatments, or injection of anaesthetics or steroids into the study target muscles within 4 weeks prior to week -4 or on or after week -4

- Previous participation in any botulinum toxin clinical trial

- Concurrent enrolment in an investigational drug or device study or participation in such a study in the 30 days immediately prior to week -4 or on or after week -4

- Patient had a condition or was in a situation which in the investigator's opinion may have put the patient at significant risk, may have confounded the study results, or may have interfered significantly with the patient's participation in the study

- The patient was not in the baseline phase (week -4 to day 0) for at least 28 days or did not record a minimum of 20 days worth of diary data.

Investigators were to exclude patients whose headache they attributed to medication overuse headache under the exclusion criteria ‘headache distributed to another disorder’. Specifically, investigators had been trained to exclude patients who overused opioids and barbiturates from enrolment in the studies due to their known association with the development of secondary headaches.However, chronic migraine patients excessively using acute medications were included and appropriately stratified (as recommended by the IHS task force) as many chronic migraine sufferers report inadequate pain relief with acute treatments, resulting in frequent intake in an attempt to relieve their severe and frequent symptoms.

Patients could be discontinued prematurely from the study due to adverse events, lack of efficacy, pregnancy, protocol violation, personal reasons, lost to follow-up, or other reasons. In addition, patients could voluntarily withdraw from the study at any time. If the patient exited the study prior to the week 56 visit, all the final measurements were to be performed at the exit visit and recorded on the appropriate case report form (CRF). Notification of early patient discontinuation from the study and the reason for discontinuation was made to the sponsor and was clearly documented on the appropriate CRF.

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a

suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

There were no statistically significant between-group differences with respect to most of the important baseline demographic characteristics for participants of either PREEMPT study (Table 5.7, Table 5.8 and Table 5.9)

However, at baseline, patients in PREEMPT 1 receiving Botox had significantly fewer headache episodes (12.3 Botox vs. 13.4 placebo; p=0.023) and migraine episodes (11.5 Botox vs. 12.7 placebo; p=0.006) than patients receiving placebo, and significantly more cumulative hours of headache occurring on headache days (p=0.022) (Table 5.7).

A headache episode was defined as headache where pain lasted ≥ 4 continuous hours. The combination of both significantly fewer headache episodes (p=.023) and significantly longer cumulative headache duration (p=.022) in the Botox group resulted in these patients having >20 mean cumulative headache hours on headache days more per month than those in the placebo arm.

Most patients overused acute pain medications during the 28-day baseline (65.5% (62.6%-69.8% of the total population of the pooled analyses) and had previously tried at least one prophylactic medication (63.5% (59.5%-66.2) of the total population of the pooled analyses), highlighting the severity of their suffering (Dodick et al. 2010).

Table 5.7: Baseline disease characteristics for primary and secondary efficacy variables in study PREEMPT 1 (Allergan Ltd 2010a;Aurora et al. 2010)

Characteristics	BTX (n=341)	PBO (n=338)	p-value
Mean age (yrs)	41.2	42.1	0.317
Mean time since onset of chronic migraine (yrs)	20.3	20.6	0.839
Women (%)	89.1	85.8	0.187
Caucasian (%)	89.4	91.4	0.381
Mean body mass index (kg/m2)	26.7	27.3	0.147
Mean headache episodes during baseline (SD)	12.3 (5.23)	13.4 (5.71)	0.023
Mean headache days during baseline (SD)	20.0 (3.73)	19.8 (3.71)	0.571
Mean migraine days during baseline (SD)	19.1 (4.04)	19.1 (4.05)	0.978
Mean migraine episodes during baseline (SD)	11.5 (5.06)	12.7 (5.72)	0.006
Mean moderate/severe headache days during baseline (SD)	18.1 (4.22)	18.3 (4.23)	0.674
Cumulative headache hours occurring on headache days during baseline (SD)	295.7 (116.81)	274.9 (110.90)	0.022
Patients who overused acute headache pain medications during baseline (%)	66.3	69.8	0.322
Patients who had previously used ≥1 headache prophylaxis medication (%)	59.5	64.2	0.210
Patients with severe (≥60) HIT-6 score	94.4	94.7	0.888
Mean HIT-6 score	65.4	65.8	0.297

HIT-6 = Headache Impact Test

Table 5.8: Baseline disease characteristics for primary and secondary efficacy variables: PREEMPT 2 (Allergan Ltd 2010b;Diener et al. 2010)

Characteristics	Botox (n=347)	Placebo (n=358)	p-value
Mean age (yrs)	41.0	40.9	0.849
Mean time since onset of chronic migraine (yrs)	18.5	17.6	0.279
Women (%)	86.2	84.6	0.565
Caucasian (%)	89.9	89.7	0.913
Mean body mass index (kg/m2)	26.7	26.1	0.305
Mean headache episodes during baseline (SD)	12.0 (5.27)	12.7 (5.29)	0.067
Mean headache days during baseline (SD)	19.9 (3.63)	19.7 (3.65)	0.682
Mean migraine days during baseline (SD)	19.2 (3.94)	18.7 (4.05)	0.156
Mean migraine episodes during baseline (SD)	11.3 (4.99)	11.7 (5.08)	0.067
Mean moderate/severe headache days during baseline (SD)	18.1 (4.03)	17.7 (4.26)	0.333
Cumulative headache hours occurring on headache days during baseline (SD)	296.2 (121.04)	287.2 (118.09)	0.311
Patients who overused acute headache pain medications during baseline (%)	63.4	62.6	0.819
Patients who had previously used ≥1 headache prophylaxis medication (%)	64.0	66.2	0.536
Patients with severe (≥60) HIT-6 score	92.5	90.8	0.408
Mean HIT-6 score	65.6	65.0	0.106

HIT-6 = Headache Impact Test

The pooled treatment groups again showed no notable differences for most of the important demographic characteristics. However, at baseline the Botox group compared with the placebo group on average had significantly fewer headache episodes (12.2 vs. 13.0; P =0.004) and migraine episodes (11.4 vs. 12.2; P=0.004), and significantly more total cumulative hours of headache occurring on headache days (295.9 vs. 281.2; P =0.021) (Dodick et al. 2010).

Table 5.9: Baseline characteristics for primary and secondary efficacy variables: pooled phase 3 studies (Dodick et al. 2010)

Characteristics	Botox (n=347)	Placebo (n=358)	P value
Mean age (yrs)	41.1	41.5	0.579
Mean time since onset of chronic migraine (yrs)	19.4	19.0	0.488
Women (%)	87.6	85.2	0.185
Caucasian (%)	89.7	90.5	0.602
Mean body mass index (kg/m2)	26.7	27.2	0.080
Mean headache episodes during baseline (SD)	12.2 (5.25)	13.0 (5.5)	0.004
Mean headache days during baseline (SD)	19.9 (3.68)	19.8 (3.68)	0.498
Mean migraine days during baseline (SD)	19.1 (3.99)	18.9 (4.05)	0.328
Mean migraine episodes during baseline (SD)	11.4 (5.02)	12.2 (5.42)	0.004
Mean moderate/severe headache days during baseline (SD)	18.1 (4.12)	18.0 (4.25)	0.705
Cumulative headache hours occurring on headache days during baseline (SD)	295.93 (116.88)	281.22 (114.74)	0.021
Patients who overused acute headache pain medications during baseline (%)	64.8	66.1	0.450
Patients who had previously used ≥1 headache prophylaxis medication (%)	61.8%	65.2%	0.182
Patients with severe (≥60) HIT-6 score	93.5	92.7	0.565
Mean HIT-6 score	65.5	65.4	0.638

HIT-6= Headache Impact Test

Over the 28-day baseline period, patients had, on average, 20 headache days, of which approximately 19 were migraine/probable migraine (M/PM) days. On average, participants had experienced around 20 years of frequent headache and over 60% had previously tried oral prophylactic medications (Dodick et al. 2010).

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes.

The primary endpoint in study PREEMPT 1 was mean change from baseline in frequency of headache episodes for the 28-day period ending with week 24. A headache episode was defined as patient-reported headache with a start and stop time indicating that the pain lasted ≥4 continuous hours (Aurora et al. 2010). A headache episode could cross multiple days if it was classed as continuous.

Subsequent to study initiation, but prior to study completion and treatment unblinding, the protocol and statistical analysis plan for study PREEMPT 2 was amended to change the primary endpoint used in PREEMPT 1, along with a number of secondary endpoints (Table 5.10).

The primary endpoint for study PREEMPT 2 and the pooled analysis was the mean change from baseline in frequency of headache days for the 28-day period ending at week 24 as reflected in the decision problem. A “headache day” was defined as a day where a patient reported at least 4 continuous hours of a headache episode for any period of time in the 24-hour period from midnight (12:00 AM) at the start of the day to 23:59 PM at the end of the day (i.e. a calendar day) (Diener et al. 2010).

This change was made based on several factors, all of which supported using frequency of headache days as the primary outcome measure for chronic migraine, as opposed to the frequency of headache episodes (where a headache episode is defined as headache with a start and stop time indicating that the pain lasted ≥ 4 continuous hours, meaning it could be > 24 hours), including

- The availability of the PREEMPT 1 study data (which showed great variability in the duration of headache episodes among migraine sufferers)
- Guidance provided in the then newly issued IHS clinical trial guidelines for evaluating headache prophylaxis in chronic migraine (Silberstein, 2008a)
- An earlier expressed preference by the FDA to use frequency of headache days as the primary endpoint

This issue was discussed within the MHRA Public Assessment Report which concluded that “the decision to switch primary endpoint in trial PREEMPT 2 is understandable and it is of note that both the original and the final primary endpoint were highly significant in this trial”.

This primary efficacy variable is reported for the total trial population, but then filtered to the population of interest within the decision problem, focusing on patients in whom three alternative prophylactic treatments have failed to produce a response (or were not tolerated) (see section 5.3.7 & 5.5).

Secondary outcomes

Chronic migraine patients suffer greatly according to a number of different dimensions e.g., headache frequency, headache duration, headache severity, secondary disability. Measuring these outcomes helps to describe the overall burden of illness that is not captured by the measurement of frequency of headache days alone. Therefore, additional study endpoints were captured in order to further validate the efficacy in this chronic migraine population by demonstrating a consistency of improvements across multiple efficacy parameters following Botox treatment.

As noted in the decision problem the impact of chronic migraine on the patient's quality of life is considerable (Goadsby PJ 2010). In the phase 3 studies, the impact of Botox on the health related quality of life (HRQL) of patients with chronic migraine was determined using the Headache Impact Test-6 (HIT-6) (Kosinski 2003) and Migraine Specific Quality of Life Questionnaire v2.1 (MSQ) (Cole et al. 2007;Jhingran 1998). Both the HIT-6 and MSQ are disease specific health surveys that assess the impact of headache/migraine on quality of life.

The HIT-6 uses six questions to capture HRQL and the impact of treatment on an individual's functional health. The aim was to develop a tool for assessing the impact of headaches that has broad content coverage but is brief as well as reliable and valid enough to use in screening and monitoring patients in clinical research and practice. The HIT-6 items measure 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 HRQL (Kosinski, 2003). The HIT-6 also measures the severity of headache pain (Yang M et al. 2011). Scores in excess of 60 are considered a "severe" HIT-6 score.

The 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. Scores range from 0 (low function) to 100 (high function). The MSQ is a reliable tool (Cole, 2007) and has been validated in the chronic migraine population (Bagley et al. 2011;Dahlof 2007;Martin 2000).

Key secondary efficacy variables measured for each 28-day period in study PREEMPT 1 and PREEMPT 2 are outlined in Table 5.10 with those outcomes considered relevant to the decision problem highlighted in the table.

Table 5.10: Primary and secondary variables in study PREEMPT 1 and study PREEMPT 2

M/PM = migraine/probable migraine;

Study PREEMPT 1 and original study PREEMPT 2 protocol	**Amended Study PREEMPT 2 protocol**
Primary:	**Primary:**
Frequency of headache episodes	Frequency of headache days
Secondary:	**Secondary:**
Frequency of headache days*	Frequency of M/PM days
Frequency of M/PM days	Frequency of moderate/severe headache days
Frequency of M/PM episodes	Total cumulative hours of headache occurring on headache days
Frequency of acute headache pain medication intakes	Proportion of patients with severe HIT-6 category scores
	Frequency of headache episodes

M/PM = migraine/probable migraine

** In the study protocol and statistical analysis plan for PREEMPT 1 the frequency of headache days was highlighted as the most important secondary efficacy measure and was the only secondary efficacy measure that had pre-specified sensitivity analyses (Aurora* 2010*).*

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses.

The primary null hypothesis was that Botox treatment and placebo were equally effective in decreasing from baseline the mean number of headache days per 28 days. The alternative hypothesis was that Botox had a different effect than placebo.

Planned enrolment for the PREEMPT studies was approximately 650 patients per study. A large sample size was planned because of the long study duration (56 weeks treatment per patient), to allow sufficient sample size for the long-term safety evaluations (>150 patients with five active treatment cycles). The power calculations were developed based on the results of the phase 2 clinical programme.

In study PREEMPT 1, for headache episode frequency, the week 24 minimum retained sample size of n=240 per group, with standard deviation of 5.5,

would have >90% power to detect ≥1.75 between-group difference in mean change from baseline, using two-sided α=0.05.

In study PREEMPT 2, for headache day frequency, a week 24 minimum sample size of n=325 per group, with standard deviation of 6.7, would have >90% power to detect ≥1.75 between-group difference in mean change from baseline, using two-sided α=0.05.

The pooled population sample provided >90% power to detect ≥1.75 between-group difference in mean change from baseline of the primary endpoint (headache days), using two-sided α=0.05.

For the primary and secondary variables in both studies and the pooled analysis, pre-specified comparisons between treatment groups were done by analysis of covariance (ANCOVA) of the change from baseline. The baseline value was a covariate with main effects of treatment group and medication overuse strata. The baseline covariate adjustment was pre-specified as the primary analysis, but sensitivity analyses (e.g., rank-sum test on changes from baseline without a baseline covariate) were also performed .

For binomial variables, the between-group comparisons were done with Pearson's Chi-square or Fisher's exact tests, except that logistic regression with the same variable's baseline as covariate was used for variables with baseline imbalance. A two-sided test with p≤0.05 was considered to be statistically significant. No control of the type-1 error rate for multiple secondary endpoints was pre-specified in study PREEMPT 1. Therefore, a highly conservative Bonferroni adjustment was applied to compare the week 24 p values to a critical level of 0.01, which adjusted the pre-specified type-1 error rate of 0.05 for the five variables that were pre-specified as primary or secondary.

In study PREEMPT 2 and the pooled analysis, to control the type 1 error rate for multiple secondary endpoints in the amended protocol and analysis plan, a fixed-sequence gate-keeping approach was used for the five ranked secondary variables at the week 24 primary visit. If the p value of a secondary endpoint was not ≤0.05, the tests of any lower-ranked secondary endpoints were not considered statistically significant, regardless of individual p value. The secondary efficacy variables were rank ordered as follows: frequency of migraine/probable migraine days, frequency of moderate/severe headache days, total cumulative hours of headache occurring on headache days, proportion of patients with severe HIT-6 category scores, and frequency of headache episodes.

Statistical comparisons in the open-label phase were evaluated as change from baseline for all patients receiving Botox. Additional statistical comparisons in the open-label phase were based on the patients' double-blind phase randomisation to Botox or placebo; treatment groups are thus referred to as the Botox/Botox (BTX/BTX) or placebo/Botox (PBO/BTX) group in the description of the open-label phase results (Aurora et al. 2009).

Validated electronic diaries using a telephone Interactive Voice Response System (IVRS) system were utilised to collect specific study data, including specific headache characteristics and acute headache medication use. This conforms to the recent IHS guideline stating that evaluation of efficacy in controlled clinical studies of prophylactic treatment of chronic migraine should be based on headache diary information (37). Further information about the timings and collection of outcome data can be found in the clinical study reports.

All efficacy analyses used the intent-to-treat (ITT) population, which included all randomised patients. Scores for months with at least 20 days of diary data were prorated to 28-day equivalents. Scores for months with less than 10 days of diary data were estimated using a modified last observation carried forward (mLOCF) methodology. This involved the substitution of the patient's previous 28-day period score multiplied by the ratio of the mean across all patients in the 28-day period of interest divided by the mean across all patients in the previous 28-day period. Scores for months with 10–19 days of diary data were estimated using an average of the prorated and the mLOCF estimates. The mLOCF method of imputation of missing data was pre-specified, but sensitivity analyses were also done (e.g. using observed data, without imputation)

5.3.7 Provide details of any subgroup analyses that were undertaken

Pre-planned subgroup analyses

Primary and secondary efficacy variables were summarized by the following subgroup factors: investigator centre, age (< 40 years/= 40 years), gender (male/female), race (Caucasian/non Caucasian), acute headache pain medication overuse (yes/no), and history of headache prophylactic medication use (yes/no). The primary subgroup analysis was ANCOVA of the mean change from baseline, using mLOCF, with baseline score as covariate.

Specifically the decision problem requests that the presence or absence of medication overuse be considered as a subgroup. Although the current ICHD-IIR classification (2006) excludes patients with medication overuse headache from receiving a diagnosis of chronic migraine (Olesen, 2006), clinic-based studies and clinical trials have shown that 50–80% of patients with chronic migraine overuse acute medication (Olesen, 2006). Recent IHS guidelines for

chronic migraine trials suggest that due to the high prevalence of medication overuse in chronic migraine, subjects meeting criteria A to C for chronic migraine, but not D (i.e. patients have medication over-use, Figure 5.1) may be included in trials for chronic migraine provided that they are stratified accordingly (Silberstein et al. 2008a). Patients in the PREEMPT trials were randomly allocated to receive either Botox or placebo at a 1:1 ratio in a blinded fashion, stratified by overuse of acute headache pain medications (yes/no) at baseline.

Post-hoc subgroup analyses

History of oral prophylactic medication use – number of therapies

Although in the pre-planned subgroup analysis, efficacy variables were summarized by history of headache prophylactic medication use (yes/no), the results from that analysis were insufficient for the decision problem specified in this appraisal. Within the context of this submission Botox is indicated for adults with headaches on at least 15 days per month of which at least 8 days are associated with chronic migraine and whose condition has failed to respond to at least three prior oral prophylactic medications and medication overuse has been appropriately managed. What was needed therefore was a subgroup analysis of patients within the trial whose condition had failed to respond to at least three prior oral prophylactic medications.

Pre-planned subgroup analyses as described above allowed the filtering of the primary efficacy variable results to distinct patient populations of interest. However, the population within the decision problem and thus incorporated within the economic modelling are specifically chronic migraine patients whose condition has failed to respond to at least 3 prior prophylactic therapies. For this reason patients were categorized by the number of prior prophylactic therapies previously received for this condition: ≥ 0 prior treatments (Group A, all trial patients); ≥1 prior treatments (Group B); ≥ 2 prior treatments (Group C) and ≥ 3 prior treatments (Group D). During this exploratory work, primary outcomes were analysed for each of these Groups and the results were then compared to those from the total study population. The aim of these analyses was to discover if there were important differences between the groups with regard to the size of the treatment effect. If efficacy variables were similar for all groups, for example if efficacy was the same for Group A and Group D, then it would be valid to use the larger Group A in any further analysis related to the decision problem. This larger group would permit greater statistical power for the results of that analysis.

History of oral prophylactic medication use – previous topiramate treatment

A subgroup analysis was performed for patients within the trial who had previously received topiramate treatment. Topiramate is the only other treatment that has been evaluated in patients with chronic migraine in a relatively large (n=328) randomised controlled trial (Silberstein et al. 2007). In addition, when patients with migraine have inadequate symptom control using acute therapies, UK guidelines recommend the use of topiramate as an oral prophylactic medication after the patient's condition has failed to respond to first-line oral prophylactic medications beta-blockers and amitriptyline (BASH 2010). In the context of the decision problem it is assumed that eligible patients, where appropriate, would have received a previous trial of topiramate and therefore this subgroup analysis is included for completeness.

Botox Health State Transitions

In a recent study of headache frequency and its consequences, an international survey found that migraine patients experiencing ≥15 headache days per month (chronic migraine) reported significantly more severe disability, lower HRQL, higher levels of anxiety and depression and greater health care resource utilization compared to those with <15 headache days per month (episodic migraine) (Blumenfeld, 2010). Therefore investigating the movement of patients in the PREEMPT studies between different categories of frequency of headache days permits an assessment of the impact of treatment on not only HRQL and disability but also on direct medical resource utilization.

To this end all patients relevant to the decision problem (adults with headaches on at least 15 days per month and who had previously received at least three prophylactic therapies) were included in a post-hoc analysis that measured the numbers of patients in specific health states at different time points in the study. Health states were defined as 0-3, 4-9, 10-14, 15-19, 20-23 and 24+ headache days per 28 days (Table 5.11). Defining health states in this way allowed the benefit of achieving the primary study outcome (reducing headache days per month) to be assessed within the economic modelling (Section 6.2.4).

Table 5.11: Justification for economic model health states

Health State (Headache days per 28 days)	Justification		Reference
0-3	ICHD II (IHS 2004)	Prophylaxis is not indicated for migraineurs with less than 4 Headache days per month	Lipton (2007)
4-9		Patients receive prophylactic treatment at 4 Headache days per month	Lipton (2007)
10-14		Frequent episodic migraineurs at risk of becoming chronic migraineur	Lipton (2009)
15-19	ICHD II-R (IHS, 2011)	Based on distribution of number of Headache days at baseline, mean (SD) = 19.9 (3.68)	PREEMPT phase 3 studies 191622-079 and 080 (Dodick, 2010)
20-23		Distributional assumption	
24+		Distributional assumption	

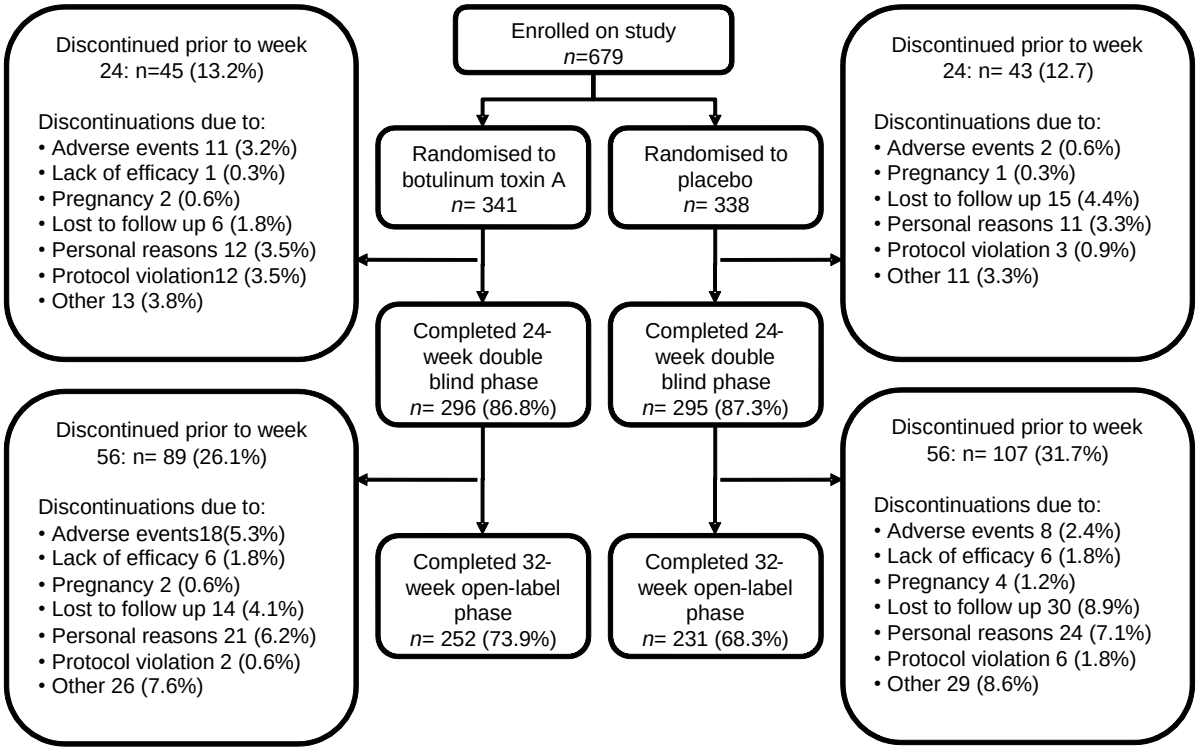
Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

A total of 679 patients were randomised to study PREEMPT 1 (n=341 Botox, n=338 placebo). A total of 87.0% (591/679) completed the double-blind phase and a total of 71.1% (483/679) completed the entire study (double blind plus open label phase) (Figure 5.4) (Aurora et al. 2009;Aurora et al. 2010).

Retreatment rates were high in the Botox group with a total of 73.9% (252/341) in the Botox/Botox group and 68.3% (231/338) in the placebo/Botox group completing the entire 60 week study.

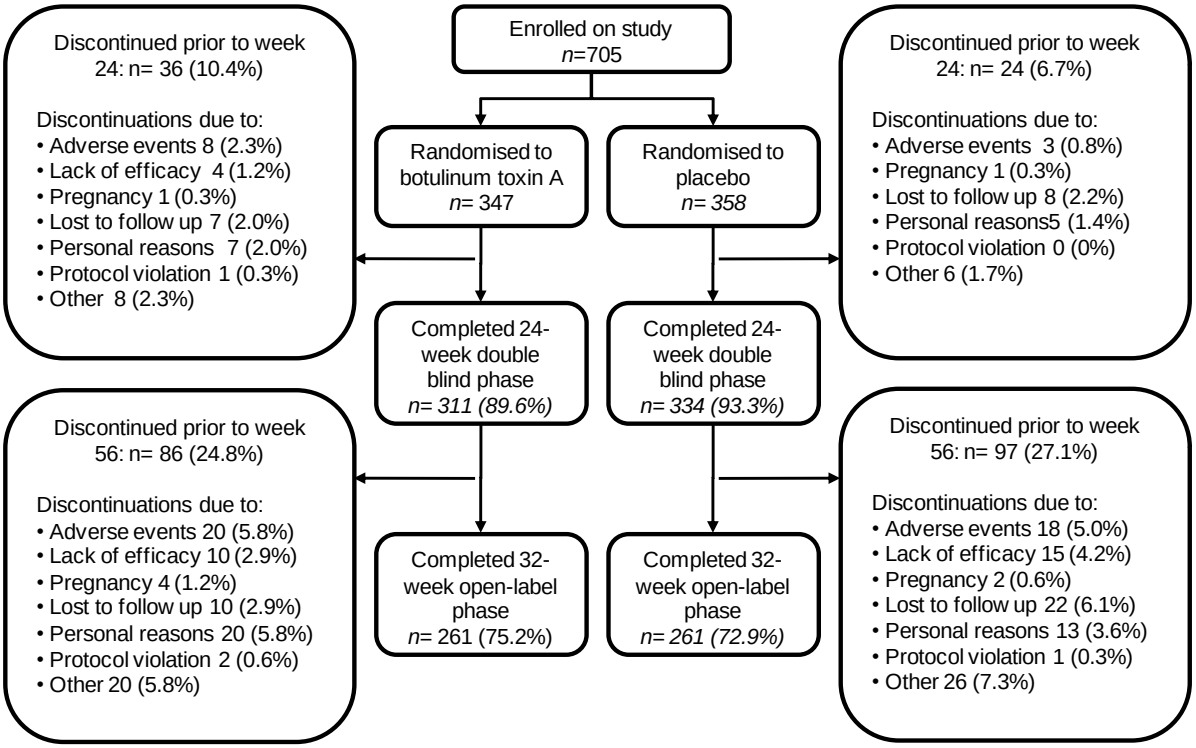
Figure 5.4: Patient disposition for study PREEMPT 1,



A total of 705 patients were randomised to study PREEMPT 2 (n=347 Botox, n=358 placebo) A total of 91.5% (645/705) completed the double-blind phase, and a total of 74.0% (522/705) completed the entire study (double-blind plus open-label phase) (Figure 5.5).

Retreatment rates were also high in this study with 75.2% (261/347) in the Botox/Botox group and 72.9% (261/358) in the placebo/Botox group completing the entire study.

Figure 5.5: Patient disposition for study PREEMPT 2 (double-blind and open-label phases)

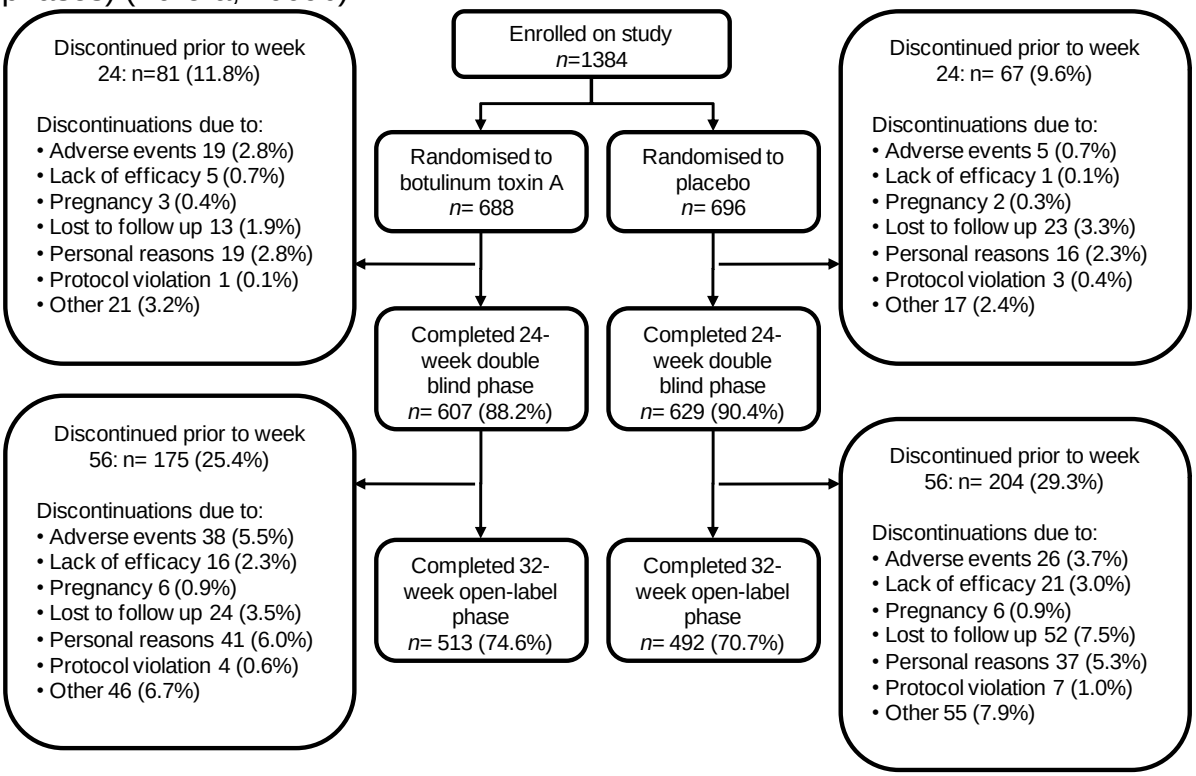


Patient data from both PREEMPT studies were pooled and the efficacy and safety measures reanalysed to give greater statistical power to the overall results.

When the two studies are pooled, a total of 88.2% (607/688) of patients treated with Botox and 90.4% (629/696) of patients treated with placebo completed the double-blind phase. A total of 72.6% (1005/1384) of patients completed the entire study (double-blind plus open-label phase) (Figure 5.6).

Retreatment rates for the pooled population were high in the Botox group

Figure 5.6: Patient disposition in pooled analysis (double-blind and open-label phases) (Aurora, 2009b)



5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

Due to the fact that both PREEMPT 1 & PREEMPT 2 followed exactly the same study protocol for all quality assessment criteria, both RCTs are presented together in Table 5.12.

Table 5.12: Quality assessment results for Botox **RCTs**

Assessment Question	Aurora, 2010; Diener, 2010	Study methods
Was randomisation carried out appropriately?	Yes	Subjects were randomised (1:1) to Botox or placebo and stratified by medication overuse (Yes or No). Randomisation sequence was computer generated and performed centrally.
Was the concealment of treatment allocation adequate?	Yes	In order to maintain treatment masking, patients assigned to placebo had a matching volume with saline injection to simulate the actual procedure. There were concerns about unblinding due to exaggerated local pharmacological effect of Botox. However, the adverse events of interest such as eyelid ptosis, muscular weakness, facial paresis, and dysphagia, occurred at low rates of 3.6%, 3.5%, 2.2%, and 0.7%, respectively, in Botox-treated patients. Notably, eyelid ptosis, muscular weakness, and dysphagia were also reported among placebo-treated patients at rates of 0.3%, 0.3% and 0.1%, respectively (Dodick et al. 2010).
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	At baseline, there were no notable differences between the pooled treatment groups for most of the important demographic characteristics. However, at baseline the Botox group compared with the placebo group on average had significantly fewer headache episodes (12.2 vs. 13.0; P=0.004) and migraine episodes (11.4 vs. 12.2; P=0.004), and significantly more total cumulative hours of headache occurring on headache days (295.9 vs. 281.2; P=0.021) (Dodick et al. 2010).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Throughout the double-blind phase of the studies, the patients, the investigators who administered the study treatment and assessed safety and outcomes and the sponsor study management personnel were all blinded to the treatment-group assignment. To maintain blinding, an individual with no other study responsibilities reconstituted the study medication and filled the syringes for injection.
Were there any unexpected imbalances in drop-outs between groups?	No	There were no unexpected imbalances in drop-outs between groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All measured outcomes were reported and presented in the CSRs and the CTD; only those outcomes relevant to the decision problem are presented within this submission.
Did analysis include an intention-to-treat analysis? If so, was this appropriate and were methods used to account for missing data?	Yes	All efficacy analyses used the intent-to-treat (ITT) population, which included all randomised patients. Scores for months with < 20 days of diary data were prorated to 28-day equivalents. Scores for months with < 10 days of diary data were estimated using a pre-specified modified last observation carried forward (mLOCF) methodology. Scores for months with 10-19 days of diary data were

		estimated using an average of the prorated and mLOCF estimates. However, during the double blind phase, discontinuation was low, with only 81/688 (11.8%) of Botox treated patients and 67/696 (9.6%) of placebo treated patients exiting the trial programme, and thereby minimizing the number of missing data.

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

N/A

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

As stated above, due to the fact that both PREEMPT 1 & PREEMPT 2 followed exactly the same study protocol for all quality assessment criteria, both RCTs are presented together in Table 5.12.

5.5 Results of the relevant RCTs

The key evidence to support the efficacy of Botox in the chronic migraine population is taken from a pooled analysis of two phase 3 clinical trials (Dodick et al. 2010). Both PREEMPT studies were randomised, multicentre studies consisting of a 4-week baseline, a 24-week, double-blind, randomised, placebo-controlled, parallel-group phase followed by a 32-week open-label extension phase (total study duration of 60 weeks). Results of PREEMPT 1 (Aurora et al. 2010) and PREEMPT 2 (Diener et al. 2010) will be presented here followed by results of the pooled analysis.

PREEMPT 1 population

A total of 679 patients were randomised (n=341 Botox, n=338 placebo). A total of 87.0% completed the double-blind phase at 24 weeks and a total of 71.1% completed the entire study (double-blind plus open-label phase) at 56 weeks treatment. The study population was severely impacted by their headaches at baseline with means of >20 years of frequent headache per month, >19.8 headache days per month and over 90% categorised as “severely impacted” (HIT-6 score ≥60). There were no statistically significant differences with respect to important baseline demographic characteristics; however, disease characteristics did differ. Patients receiving Botox had significantly fewer headache episodes and migraine episodes and significantly more hours of headache. This resulted in Botox patients having >20 mean cumulative headache hours on headache days more per month than those in the placebo arm.

PREEMPT 1 results

Despite large within-group decreases observed for all patients treated with Botox compared to baseline, no significant between-group differences were observed for the change from baseline in the frequency of headache episodes at the primary time point (week 24).

Significant between-group differences favouring Botox vs. placebo were observed for key secondary efficacy endpoints, with reductions of -7.8 versus -6.4 headache days (p=0.006) and -7.6 versus -7.1 migraine days (p=0.002) for Botox and placebo respectively.

Botox-treated patients experienced statistically significant and clinically meaningful improvements in functioning and HRQL, as measured by HIT-6 and MSQ instruments, over placebo at week 24.

Efficacy results from subgroup analyses of patients were consistent with the robust efficacy findings from the total study population: patients overusing acute headache medications at baseline (66.3% in Botox arm); and patients previously treated with oral prophylactic medications (60% in Botox).

During the open-label phase, when all patients were treated with Botox, the therapeutic effects were sustained and continued to show improved results with subsequent treatments, with statistically significant within-group improvements from baseline for all efficacy variables evaluated.

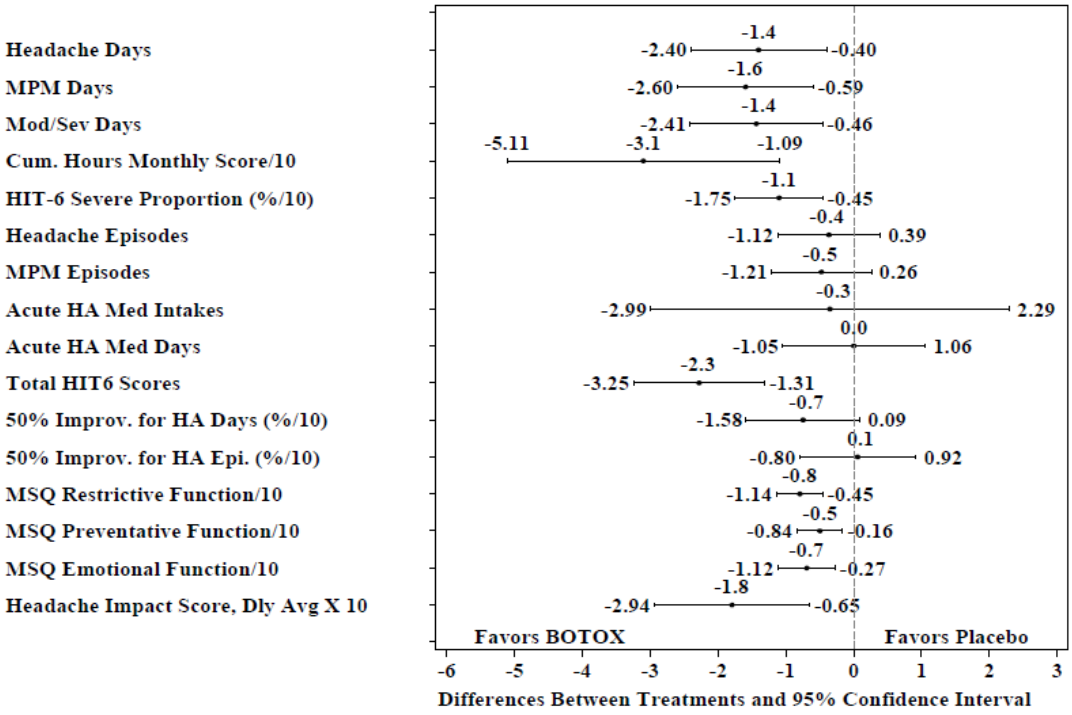
Incidence of AEs was low. Treatment-related AEs were consistent with the known tolerability profile of Botox with the only individual treatment-related AEs occurring during the double-blind, placebo controlled phase at a rate ≥5% and higher than placebo were neck pain (5.9%) and muscle weakness (5.9%).

Although there was no between-group difference for the primary endpoint of headache episodes, significant reductions from baseline were observed for Botox for headache and migraine days, cumulative hours of headache on headache days and frequency of

moderate/severe headache days, which in turn reduced the burden of illness in adults with disabling chronic migraine without associated safety concerns as reflected in the significant improvements in HRQL measurements and AE reports.

Efficacy results for PREEMPT 1 are summarised in Figure 5.7. Efficacy variables with a negative score favour Botox. Further details of primary and secondary study outcomes are reported in following sections.

Figure 5.7: Treatment differences at week 24 for key efficacy variables (ITT population) (Allergan, 2010h)



Differences between treatments are displayed as Botox minus placebo, except that 50% improvement is displayed as placebo minus Botox. Thus, negative scores favour Botox. All variables are summarised using mLOCF, except for acute Headache med days, MSQ scores and 50% improvement, which are summarised using observed data.

Primary efficacy analysis

There was a large mean decrease from baseline at all time points for the frequency of headache episodes in the Botox and placebo groups (Table 5.13). However, there were no statistically significant between-group differences at any post-baseline time point during the double-blind phase of the study based on the statistical model that used the pre-specified baseline covariate adjustments. Controlling for these imbalances using ANCOVA with mLOCF, as well as non-parametric rank test with mLOCF and ANCOVA using observed data did not alter the outcome (Aurora, 2010).

Sensitivity analyses were performed for the primary efficacy variable using the Wilcoxon rank sum test, ANCOVA on the rank of the mean change from baseline with the unranked baseline count as covariate, and ANCOVA using observed data. Results from all 3 analyses were consistent with the results observed for the primary efficacy analysis, including the statistically significant imbalance between treatment groups at baseline.

It is possible that a significant imbalance at baseline for headache episode frequency between the groups may have confounded the results. Indeed, secondary analysis of the primary outcome that used post treatment counts rather than baseline data to calculate changes in headache episode frequency showed significant between-group differences favouring Botox over placebo at week 24 (7.3 Botox vs. 8.1 placebo, p=0.049) (Aurora, 2010).

Table 5.13: Primary analysis of primary outcome in study PREEMPT 1 (ITT population)

Efficacy Variable (per 28 days)	**Botox (N=341)**	**Placebo (N=338)**	**p-value**
Frequency of headache episodes			
Mean (SD) Baseline	12.3 (5.23)	13.4 (5.71)	
Mean Change from Baseline	-5.2	-5.3	0.344

Secondary efficacy analysis

A large mean decrease from baseline with significant between-group difference favouring Botox was observed at all time points in the double-blind phase, including week 24, for the frequency of headache days (treatment difference = -1.4 [-2.40, -0.50]) and frequency of migraine days (treatment difference = -1.6 [-2.60, -0.59]) (Figure 5.7, Table 5.14). A highly conservative Bonferroni adjustment for multiple comparisons at week 24 in which the critical level for p-value comparisons was reduced from 0.05 to 0.01 did not alter the significance of these results (i.e. headache days and migraine days remained significantly improved versus placebo).

Botox may also have an impact on the severity and duration of headache (Table 5.14 and Figure 5.7) as demonstrated by the significant improvement in the frequency of moderate/severe headache days over placebo at week 24 (treatment difference = -1.4, [-2.41, -0.46]) and total cumulative hours of headache on headache days (treatment difference in cumulative hours monthly score/10 = -3.1 [-5.11, -1.09] .

Table 5.14: Secondary efficacy variables week 24 in study PREEMPT 1 (ITT population)

Efficacy Variable	BTX (N=341)	PBO (N=338)	p-value ¥
Frequency of headache days			
Mean (SD) Baseline	20.0 (3.73)	19.8 (3.71)	
Mean Change from Baseline	-7.8	-6.4	0.006
Frequency of migraine days			
Baseline	19.1 (4.04)	19.1 (4.05)	
Mean Change from Baseline	-7.6	-6.1	0.002
Frequency of migraine episodes			
Mean (SD) Baseline	11.5 (5.06)	12.7 (5.72)	
Mean Change from Baseline	-4.8	-4.9	0.206
Frequency of moderate/severe headache days			
Mean (SD) Baseline	18.1 (4.22)	18.3 (4.23)	
Mean Change from Baseline	-7.2	-5.8	0.004
Total cumulative hours of headache on headache days			
Mean (SD) Baseline	295.66 (116.8)	274.88 (110.9)	
Mean Change from Baseline	-106.7	-70.4	0.003

Acute medication

At week 24, large within-group improvements for mean change from baseline in both frequency of acute pain medication intakes and frequency of acute headache pain medication days were shown, but no statistically significant between-group differences were observed (Table 5.15).

In the PREEMPT studies, an intake of acute headache pain medication was defined as the number of times that a patient reported they took medication, regardless of the dose or number of types of medication taken at the same time and there could have been multiple intakes within a given day for each patient. For example, 1 aspirin tablet or 6 aspirin tablets taken at the same time was recorded as 1 intake; similarly, 1 aspirin table and 1 sumitriptan tablet taken at the same time was also recorded as 1 intake. Therefore, the

data presented in Table 5.15 represents acute medication free days increased by a mean of 5.7 & 5.8 for the Botox and placebo groups respectively.

Post-hoc analysis conducted to identify potential patterns of intake by medication class demonstrated that the frequency of triptan intake was significantly reduced from baseline in the Botox group compared to the placebo group (-3.3 Botox vs. -2.5 placebo, p=0.023) at week 24 (Aurora, 2010)

Table 5.15: Acute medication analyses at week 24 in study PREEMPT 1 (ITT population)

Efficacy Variable (per 28 days)	**BTX (N=341)**	**PBO (N=338)**	**p-value**
Frequency of acute headache pain medication days			
Mean (SD) Baseline	15.0 (6.32)	15.4 (6.38)	
Mean Change from Baseline	-5.7	-5.8	0.996
Frequency of acute headache pain medication intakes (all categories)			
Mean (SD) Baseline	29.1 (19.27)	30.4 (22.29)	
Mean Change from Baseline	-10.3	-10.4	0.795

Health related quality of life (HRQL)

Botox treated patients demonstrated a significant and clinically meaningful decrease in disability and improved functioning compared with placebo-treated patients as measured by HIT-6 and MSQ (Table 5.16). At week 24, MSQ scale scores for the Botox group all exceeded the established minimally important within-group differences from baseline of -10.9 (RF-R), -8.3 (RR-P) and -12.2 (RF-EF), whereas none of the placebo group scores met these minimally important (Dodick et al. 2007) differences (Table 5.16).

Table 5.16: Change in HRQL at week 24 in study PREEMPT 1 (ITT population)

Efficacy Variable	BTX (N=341)	PBO (N=338)	p-value ¥
Total HIT-6 score			
Mean (SD) Baseline	65.4 (3.82)	65.8 (4.14)	
Mean Change from Baseline	-4.7	-2.4	<0.001
Proportion of patients with severe HIT-6 category scores			
Baseline	94.4%	94.7%	
Mean Change from Baseline	68.9%	79.9%	0.001
MSQ RF-R scores			
Mean (SD) Baseline	61.3 (0.90)	63.1 (0.93)	
Mean Change from Baseline	-16.8	-8.8	<0.001
MSQ RF-P scores			
Mean (SD) Baseline	43.2 (1.14)	46.0 (1.16)	
Mean Change from Baseline	-12.6	-7.6	0.005
MSQ RF-EF scores			
Mean (SD) Baseline	59.1 (1.28)	60.3 (1.35)	
Mean Change from Baseline	-16.9	-10.0	0.001

RF-P=Role Function-Preventative; RF-R = Role Function-Restrictive; RF-EF = Role Function-Emotional Function; HIT-6 = Headache Impact Test; MSQ = Migraine-Specific Quality of Life Questionnaire. HIT-6 score ranges from 36 to 78 with higher scores indicating greater impact on life: that is, lower HRQL. MSQ is scored from 0 (low function) to 100 (high function).

Subgroup analyses – acute headache pain medication overuse

Considering the number of chronic migraine patients that overuse acute medications in an attempt to control their symptoms, evidence of benefit in such subjects was investigated (where medication overuse was defined per protocol as intake during baseline of simple analgesics on ≥ 15 days or other medication types or combination of types for ≥10 days, with intake ≥2 days/week from the category of overuse).Investigators had been trained to exclude patients who overused opioids and barbiturates from enrolment in the studies due to their known association with the development of secondary headaches.

Large within-group improvements were shown in the frequency of headache episodes in patients enrolled in the study who had acute headache pain medication overuse at baseline (67.9% [461/679]) treated with Botox. This trend was also observed in patients enrolled in the study without baseline acute pain medication overuse (32.1% [218/679]). However, no statistically significant between-group difference was observed in either subgroup (Table 5.17 & 5.18).

Large within-group improvements were also shown with Botox treatment in the frequency of headache days in both patients overusing acute headache pain medications at baseline and those who were not. The between-group differences observed for this efficacy variable favoured the use of Botox in the subgroup of patients enrolled in the study who had acute headache medication overuse at baseline (p0.028) but narrowly missed statistical significance in the subgroup of patients enrolled in the study without baseline acute pain medication overuse (p0.074) (Table 5.17 & Table 5.18).

Outcomes in these sub-populations, though not always statistically significant, are directionally similar to the results of the total population (Table 5.17 & Table 5.18). Although the programme was not powered to evaluate these groups individually, this is of considerable interest and confirms the efficacy of Botox in patients with or without acute medication overuse at baseline.

Table 5.17: Sub-group analyses of patients overusing acute medication at baseline at week 24 in study PREEMPT 1 (ITT population)

Efficacy Variable (per 28 days)	BTX (N=226)	PBO (N=235)	p-value
Frequency of headache episodes			
Mean (SD) Baseline	13 (5.33)	14.3 (5.63)	
Mean Change from Baseline	-5.4 (5.55)	-5.9 (5.65)	0.705
Frequency of headache days			
Mean (SD) Baseline	20.3 (3.77)	19.8 (3.60)	
Mean Change from Baseline	-7.8 (6.42)	-6.7 (6.52)	0.028

Table 5.18: Sub-group analyses of patients not overusing acute medication at baseline at week 24 in study PREEMPT 1 (ITT population)

Efficacy Variable (per 28 days)	BTX (N=115)	PBO (N=103)	p-value
Frequency of headache episodes			
Mean (SD) Baseline	11 (4.76)	11.1 (5.26)	
Mean Change from Baseline	-4.7 (4.64)	-3.9 (6.07)	0.219
Frequency of headache days			
Mean (SD) Baseline	19.3 (3.56)	19.9 (3.96)	
Mean Change from Baseline	-7.9 (6.87)	-6.3 (6.7)	0.074

Open-label phase of study PREEMPT 1

During the open-label phase, when all patients were treated with Botox, the therapeutic effects of Botox were sustained and often continued to show improved results with subsequent treatments. At week 56, the 95% confidence intervals (CIs) indicated that there were statistically significant within-group improvements from baseline for all efficacy variables evaluated (Aurora, 2009a).

Significant within-group improvements in functioning and HRQL, as measured by HIT-6 and MSQ, were also seen at week 56. At baseline, 94.4% of patients had a severe HIT-6 score (≥60); by week 56 only 68.9% of Botox/Botox patients had a severe HIT-6 score.

PREEMPT 2 population
A total of 705 patients were randomised (n=347 Botox, n=358 placebo). A total of 91.5% completed the double-blind phase at 24 weeks and a total of 74.0% completed the entire study (double-blind and open-label phase) at 56 weeks treatment.

The study population was severely impacted by their headaches at baseline, with on average >17 years of frequent headache per month, >19 headache days per month, and over 90% of patients categorised as "severely impacted" by their condition (HIT-6 score ≥60). There were no significant between-group differences in baseline demographics or disease characteristics.

PREEMPT 2 results
Botox was statistically significantly superior to placebo for the primary endpoint: frequency of headache days (-9.0 vs. -6.7; p<0.001) and all secondary efficacy endpoints at week 24, including frequency of headache episodes ()

Botox-treated patients experienced a mean reduction from baseline in the number of headache days per month of -9.0 versus -6.7 for placebo (p<0.001), a mean reduction from baseline in the number of migraine days per month of -8.7 versus -6.3 for placebo (p<0.001, and a mean reduction from baseline in the frequency of headache episodes of -5.3 versus -4.6 for placebo (p=0.003).

Botox treated patients also experienced statistically significant improvements in functioning and HRQL, as measured by the HIT-6 and MSQ instruments, compared to placebo at week 24.

Efficacy results from subgroup analyses of patients were consistent with the robust efficacy findings from the total study population: patients overusing acute headache medications at baseline and patients previously treated with oral prophylactic medications.

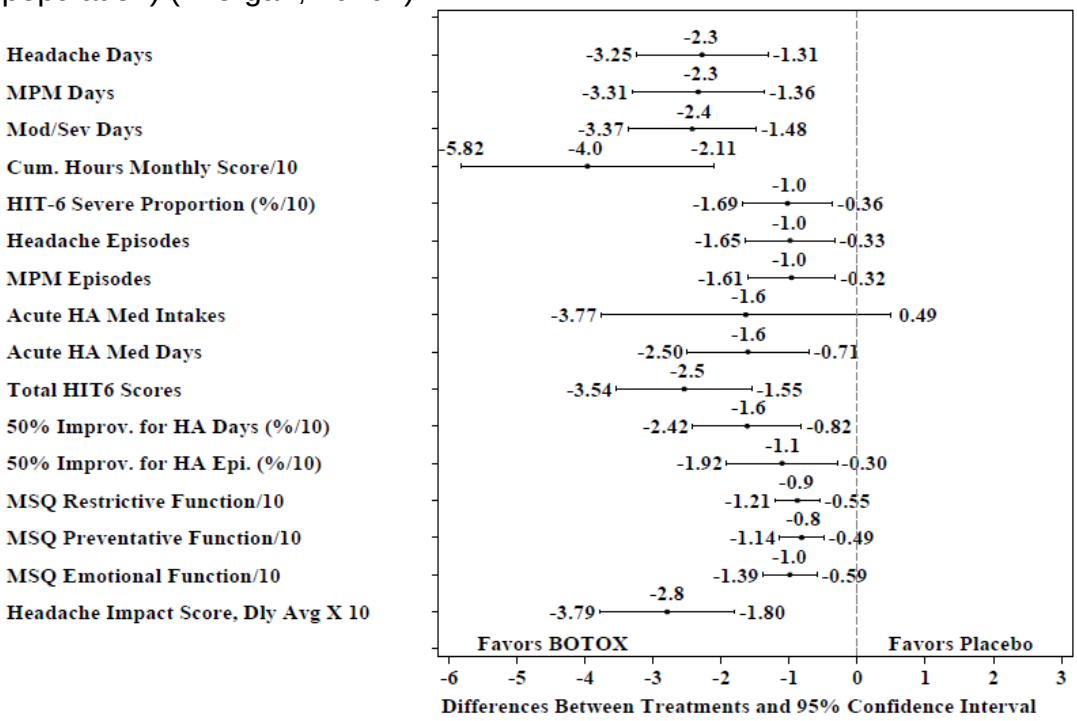
During the open-label phase, when all patients were treated with Botox, the therapeutic effects were sustained and continued to show improved results with subsequent treatments, with statistically significant within-group improvements from baseline for all efficacy variables evaluated.

Incidence of AEs was low. Treatment-related AEs were consistent with the known tolerability profile of Botox with the only individual treatment-related AEs occurring during the double-blind, placebo-controlled phase at a rate of ≥5% and higher than placebo rate were neck pain (7.5%) and muscular weakness (5.2%).

Significant reductions from baseline were observed for Botox across all efficacy measures studied which in turn reduced the burden of illness in adults with disabling chronic migraine without associated safety concerns as reflected in the significant improvements in HRQL measurements and AE reports.

Efficacy results for PREEMPT 2 are summarised in Figure 5.8. Efficacy variables with a negative score favour Botox. Further details of primary and secondary study outcomes are reported in the following sections.

Figure 5.8: Treatment differences at week 24 for key efficacy variables (ITT population) (Allergan, 2010h)



Differences between treatments are displayed as Botox minus placebo, except that 50% improvement is displayed as placebo minus Botox. Thus, negative scores favour Botox. All variables are summarised using mLOCF, except for acute headache med days, MSQ scores and 50% improvement, which are summarised using observed data.

Primary efficacy analysis

Botox was statistically significantly more effective than placebo in reducing the mean frequency of headache days at every visit in the double-blind phase starting at week 4 and including the week 24 primary endpoint (treatment difference = -2.3 [95% CI -3.25, -1.31]) (Table 5.19, Figure 5.8).

Sensitivity analyses were performed for the primary efficacy variable using the Wilcoxon rank sum test, ANCOVA on the rank of the mean change from baseline with the unranked baseline count as covariate, and ANCOVA using observed data. Results from all 3 analyses were consistent with the results observed for the primary analysis, and therefore support the robust findings of this analysis.

Table 5.19: Primary analysis of primary outcome for study PREEMPT 2 (ITT population) at week 24

Frequency of headache days (per 28 days)	**BTX (N=347)**	**PBO (N=358)**	**p-value**
Mean (SD) Baseline	19.9 (3.63)	19.7 (3.65)	
Mean Change from Baseline	-9.0	-6.7	<0.001

Secondary efficacy analysis

As chronic migraine patients suffer greatly according to a number of different dimensions the following secondary results help to represent the severe burden of illness that cannot be captured by the single primary efficacy measurement alone.

Large mean decreases from baseline, with significant between-group differences favouring Botox were observed at 24 weeks, for the frequency of migraine days (treatment difference = -2.3 [95% CI -3.31, -1.36]), frequency of migraine/probable migraine episodes (treatment difference = -1.0 [-1.61, -0.32]) and the frequency of headache episodes (treatment difference = -1.0 [-1.65, -0.33]). Significant between-group differences were observed starting at either the first or second post-treatment study visit and continuing through all subsequent visits (Table 5.20; Figure 5.8).

Botox may also have an impact on the severity and duration of headaches as demonstrated by the significant improvements in the frequency of moderate/severe headache days over placebo at week 24 (treatment difference = -2.4 [-3.37, -1.48] and total cumulative hours of headache on headache days (treatment difference for cumulative hours monthly score/10 = -4.0 [-5.82, -2.11]) (Table 5.21; Figure 5.8).

Table 5. 20: Secondary efficacy variables for study PREEMPT 2 (ITT population) at week 24

Efficacy Variable	BTX (N=341)	PBO (N=338)	p-value
Frequency of migraine days			
Mean (SD) Baseline	19.2 (3.94)	18.7 (4.05)	
Change from Baseline	-8.7	-6.3	<0.001
Frequency of headache episodes			
Baseline	12.0 (5.27)	12.7 (5.29)	
At week 24	-5.3	-4.6	0.003
Frequency of migraine/probably migraine episodes			
Mean (SD) Baseline	11.3 (4.99)	11.7 (5.08)	
Change from Baseline	-4.9	-4.2	0.003
Frequency of moderate/severe headache days			
Mean (SD) Baseline	18.1 (4.03)	17.7 (4.26)	
Change from Baseline	-8.3	-5.8	<0.001
Total cumulative hours of headache on headache days			
Mean (SD) Baseline	296.18 (121.04)	287.2 (118.09)	
Change from Baseline	-132.41	-90.01	<0.001

Acute medication

At week 24, there was a significant difference favouring Botox in the change from baseline for the mean frequency of acute headache pain medication days, but not in the mean frequency of acute medication intakes (Table 5.21).

Post-hoc analysis of acute medication intake by medication class demonstrated that the frequency of triptan intake was significantly reduced from baseline in the Botox compared to the placebo group at week 24 (-3.0 Botox vs. -1.7 placebo, p=<0.001).

Table 5.21: Acute medication analyses at week 24 in study PREEMPT 2 (ITT population)

Efficacy Variable (per 28 days)	BTX (N=347)	PBO (N=358)	p-value
Frequency of acute headache pain medication intakes			
Mean (SD) Baseline	24.7 (18.76)	25.4 (18.87)	
Mean Change from Baseline	-9.9	-8.4	0.132
Frequency of acute headache pain medication days			
Mean (SD) Baseline	14.3 (6.42)	14.4 (6.30)	
Mean Change from Baseline	-6.4	-4.8	<0.001

Health related quality of life (HRQL)

Botox treated patients demonstrated a significant and clinically meaningful decrease in disability and improved functioning during the double-blind phase compared with placebo, as measured by HIT-6 and MSQ. The difference between the treatment groups at week 24 was -2.5 units [-3.54, -1.55] which exceeds the established minimally clinically important between-group difference (Coeytaux et al. 2006) of -2.3 units thus confirming clinical significance. Similarly, at week 24 MSQ scale scores for the Botox group all exceeded the established minimally important within-group differences from baseline of -10.9 (RF-R), -8.3 (RF-P) and -12.2 (RF-EF), whereas none of the placebo group scores met these minimally important (Dodick et al. 2007) differences (Table 5.22, Figure 5.8).

Table 5.22: Mean change for HRQL endpoints in study PREEMPT 2 (ITT population)

Efficacy Variable (per 28 days)	**BTX (N=347)**	**PBO (N=358)**	**p-value** [¥]
Total HIT-6™ scores			
Mean (SD) Baseline	65.6 (4.26)	65.0 (4.46)	
Mean Change from Baseline	-4.9	-2.4	<0.001
MSQ RF-R scores			
Mean (SD) Baseline	61.7 (0.89)	59.7 (0.91)	
Mean Change from Baseline	-17.2	-8.4	<0.001
MSQ RF-P scores			
Mean (SD) Baseline	44.7 (1.16)	42.0 (1.17)	
Mean Change from Baseline	-13.5	-5.4	<0.001
MSQ RF-EF scores			
Mean (SD) Baseline	56.8 (1.32)	55.0 (1.32)	
Mean Change from Baseline	-19.0	-9.1	<0.001

RF-P=Role Function-Preventative; RF-R = Role Function-Restrictive; RF-EF = Role Function-Emotional Function; HIT-6 = Headache Impact Test; MSQ = Migraine-Specific Quality of Life Questionnaire

Subgroup analyses – acute headache pain medication overuse

Patients enrolled in the study who had acute headache pain medication overuse at baseline (63.0% [444/705]) showed statistically significant between-group differences favouring Botox for the primary efficacy variable (mean change from baseline at week 24 in the frequency of headache days) and five of the secondary efficacy variables including the frequency of headache episodes (Table 5.23). In the smaller sub-group of patients without baseline acute pain medication overuse, neither the primary efficacy variable nor the change from baseline in frequency of headache episodes significantly differed between treatment groups, providing confidence in the generalisability of data to the wider population (Table 5.24).

Outcomes in these sub-populations, though not always statistically significant, are again directionally similar to the results of the total population (Table 5.23 & 5.24). Although the PREEMPT 2 programme was not powered to evaluate these groups individually, this direction of change is of considerable interest.

Table 5.23: Sub-group analyses of patients overusing acute medication at baseline at week 24 in study PREEMPT 2 (ITT population)

Efficacy Variable (per 28 days)	**BTX (N=219)**	**PBO (N=224)**	**p-value**
Frequency of headache episodes			
Mean (SD) Baseline	12.6 (5.38)	13.3 (5.29)	
Mean Change from Baseline	-5.3 (5.48)	-4.3 (5.0)	0.004
Frequency of headache days			
Mean (SD) Baseline	19.9 (3.67)	19.8 (3.60)	
Mean Change from Baseline	-8.6 (6.42)	-5.9 (6.48)	<0.001

Table 5.24: Sub-group analyses of patients not overusing acute medication at baseline at week 24 in study PREEMPT 2 (ITT population)

Efficacy Variable (per 28 days)	**BTX (N=128)**	**PBO (N=134)**	**p-value**
Frequency of headache episodes			
Mean (SD) Baseline	10.8 (4.88)	11.6 (5.13)	
Mean Change from Baseline	-5.2 (4.44)	-5.1 (4.54)	0.320
Frequency of headache days			
Mean (SD) Baseline	19.9 (3.57)	19.6 (3.73)	
Mean Change from Baseline	-9.7 (6.7)	-8.1 (6.77)	0.059

Open-label phase PREEMPT 2

During the open-label phase, when all patients were treated with Botox, the therapeutic effects were sustained at often continued to show improved results with subsequent treatments (Table 5.25).

Significant within group improvements in functioning and HRQL, as measured by HIT-6 and MSQ were also seen at week 56. At baseline, 92.5% of patients had a severe HIT-6 score (≥60); by week 56 only 49.9% of Botox/Botox patients had a severe HIT-6 score.

Table 5.25: Mean change from baseline at week 56 in study PREEMPT 2 (ITT population)

Efficacy Variable (per 28 days)	**BTX/BTX (N=347)**	**PBO/ BTX (N=358)**	**p-value**
Headache days	-12.0	-10.7	0.014
Migraine days	-11.5	-10.1	0.015
Moderate/severe headache days	-11.2	-9.7	0.004
Total hours of headache	-173	-150.5	0.051
Headache episodes	-7.5	-7.1	0.005
% with severe HIT-6 (≥60)	49.9%	50%	0.969

Pooled PREEMPT population

The total pooled population comprised of 1,384 patients randomised to Botox(n=688)or placebo (n=696). A total of 89.3% completed the double-blind phase at 24 weeks, and a total of 72.6% completed the entire study (double-blind plus open-label phase) at 56 weeks treatment.

The study population was severely impacted by their headaches at baseline with means of >19.8 headache days per month and over 90% categorised as “severely impacted” (HIT-6 score ≥ 60). There were no statistically significant differences with respect to most important baseline demographic characteristics; however, disease characteristics did differ as a result of the PREEMPT 1 patient population. Patients receiving Botox had significantly fewer headache episodes and migraine episodes and significantly more hours of headache on headache days. This resulted in Botox patients having >20 mean cumulative headache hours on headache days more per month than those in the placebo arm.

Pooled PREEMPT results

The pooled analysis indicates that, overall at week 24, the Botox group experienced significant reductions from baseline per 28-day period across multiple headache symptom measures. Botox was statistically significantly superior to placebo for the primary endpoint of frequency of headache days (treatment difference = -1.8 [95% CI -2.52, -1.13]) and all secondary efficacy endpoints at week 24. For migraine days per month treatment difference = -2.0 [-2.52, -1.13] and for frequency of headache episodes treatment difference = -0.7 [-1.17, -0.17].

Botox treated patients also experienced statistically significant and clinically meaningful improvements in functioning and HRQL, as measured by the HIT-6 and MSQ instruments.

Efficacy results from subgroup analyses of patients were consistent with the robust efficacy findings from the total study population: patients overusing acute headache medications at baseline (64.8% in Botox arm); and patients previously treated with oral prophylactic medications (61.7% in Botox arm).

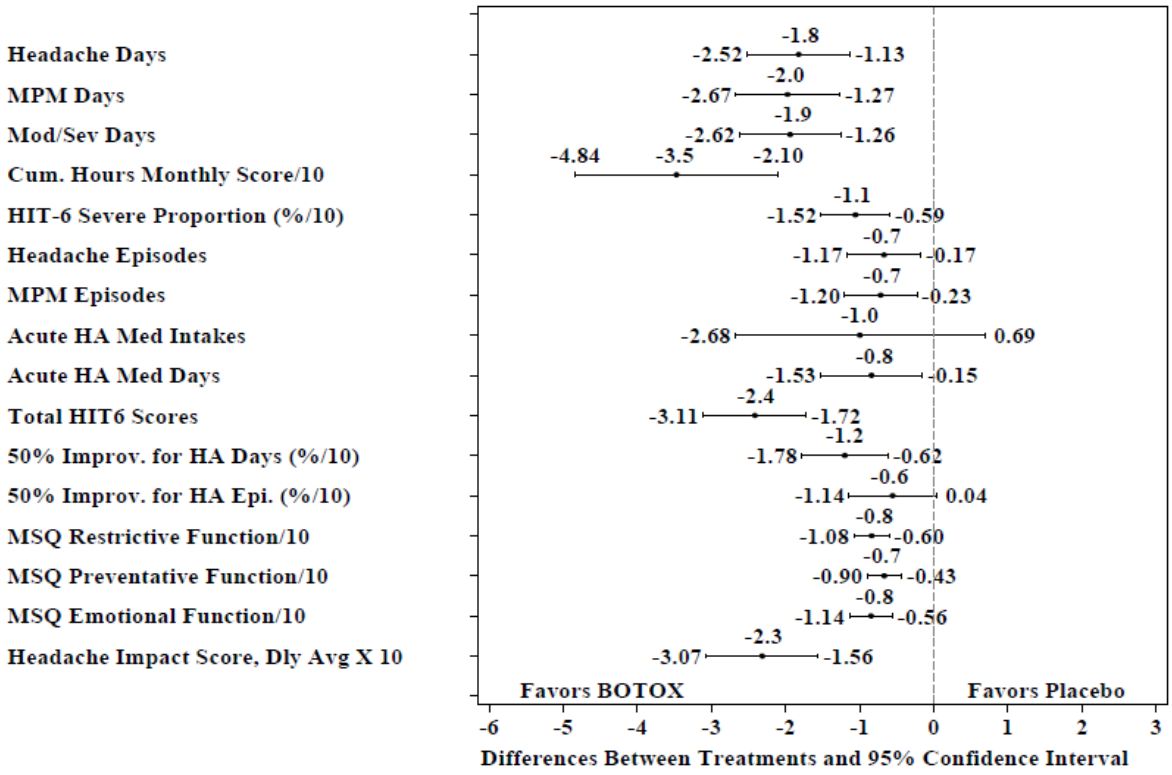
During the open-label phase, when all patients were treated with Botox, the therapeutic effects were sustained and continued to show improved results with subsequent treatments, with statistically significant within-group improvements from baseline for all efficacy variables evaluated.

Incidence of AEs was low. Treatment-related AEs were consistent with the known tolerability profile of Botox with the only individual treatment-related AE occurring at a rate of ≥5% being neck pain (6.7%).

Significant reductions from baseline were observed for Botox in all disease characteristic measurements which in turn reduced the burden of illness in adults with disabling chronic migraine without associated safety concerns as reflected in the significant improvements in HRQL measurements and AE reports.

Efficacy results for the pooled PREEMPT trial programme (Dodick et al. 2010) are summarised in Figure 5.9. Efficacy variables with a negative score favour Botox. Further details of primary and secondary study outcomes are reported in the following sections.

Figure 5.9: Treatment differences at week 24 for key efficacy variables (ITT population) (Allergan, 2010h)



Differences between treatments are displayed as Botox minus placebo, except that 50% improvement is displayed as placebo minus Botox. Thus, negative scores favour Botox. All variables are summarised using mLOCF, except for acute headache med days, MSQ scores and 50% improvement, which are summarised using observed data.

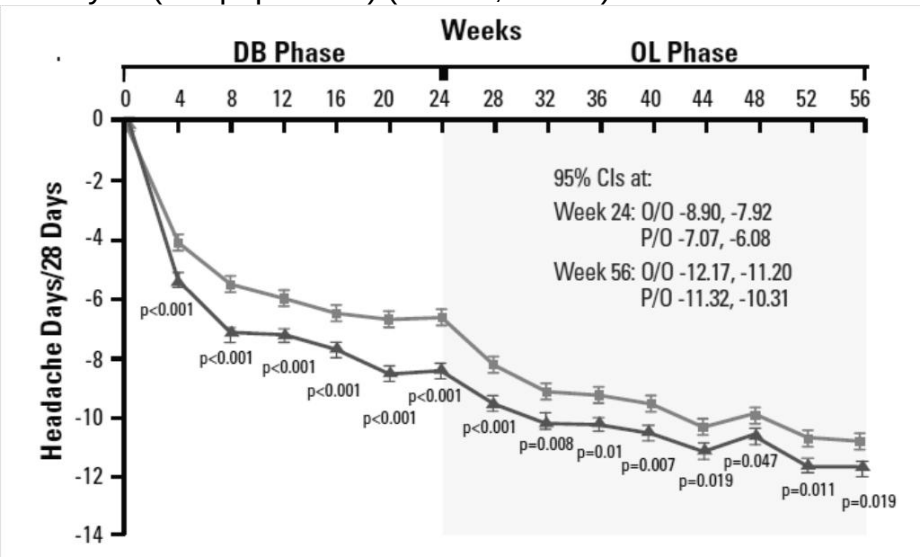
Primary efficacy analysis

Botox was statistically significantly more effective than placebo in reducing the mean frequency of headache days at every visit in the double-blind phase starting at week 4 and including the week 24 primary endpoint (treatment difference = -1.8 [-2.52, -1.13]) (Table 5.26; Figure 5.10) .

Table 5.26: Primary analysis of primary outcome in pooled phase 3 analysis (ITT population) (Allergan, 2010b; Dodick, 2010)

Frequency of headache days (per 28 days)	BTX (N=688)	PBO (N=696)	P-value
Mean (SD) Baseline	19.9 (3.68)	19.8 (3.68)	
Mean Change from Baseline	-8.4	-6.6	<0.001

Figure 5.10: Frequency of headache days per 28-day period in pooled phase 3 analysis (ITT population) (Aurora, 2009b)



Secondary efficacy analysis

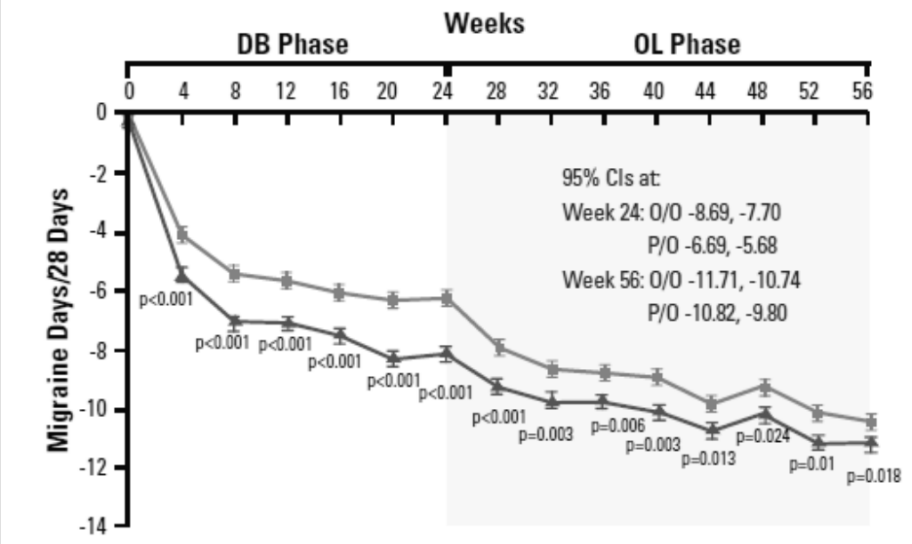
Large mean decreases from baseline, with significant between-group differences favouring Botox were observed at 24 weeks for the mean frequency of migraine days (treatment difference = -2.0 [-2.67, -1.27]) (Figure 5.11, Figure 5.9), mean frequency of migraine/probable migraine episodes (treatment difference =-0.7 [-1.20, -0.23] and the mean frequency of headache episodes (treatment difference = -0.7 [-1.17, -0.17]. Treatment differences were seen starting at the first post-treatment study visit (week 4) and continuing through all subsequent visit (Table 5.27; Figure 5.11).

Botox may also have an impact on the severity and duration of headaches as demonstrated by the significant improvements in the mean frequency of moderate/severe headache days over placebo at week 24 (treatment difference = -1.9 [-2.62, -1.26] and total cumulative hours of headache on headache days (treatment difference in cumulative hours monthly score/10 = -3.5 [-4.84, -2.10] (Table 5.27, Figure 5.9).

Table 5.27: Secondary efficacy variables at week 24 for pooled PREEMPT studies (ITT population) (Allergan, 2010b; Dodick, 2010)

Efficacy Variable	BTX (N=341)	PBO (N=338)	p-value ¥
Frequency of migraine days			
Mean (SD) Baseline	19.1 (3.99)	18.9 (4.05)	
Mean Change from Baseline	-8.2	-6.2	<0.001
Frequency of headache episodes			
Baseline	12.2 (5.25)	13.0 (5.50)	
Mean Change from Baseline	-5.2	-4.9	0.009
Frequency of migraine/probable migraine episodes			
Mean (SD) Baseline	11.4 (5.02)	12.2 (5.42)	
Mean Change from Baseline	-4.9	-4.5	0.004
Frequency of moderate/severe headache days			
Mean (SD) Baseline	18.1 (4.12)	18.0 (4.25)	
Mean Change from Baseline	-7.7	-5.8	<0.001
Total cumulative hours of headache on headache days			
Mean (SD) Baseline	295.93 (118.88)	281.22 (114.74)	
Mean Change from Baseline	-119.73	-80.49	<0.001

Figure 5.11: Frequency of migraine days per 28-day period in pooled phase 3 analysis at week 24 (ITT population) (Aurora, 2009b)



Acute headache pain medication

Mean reductions from baseline in frequency of acute medication days and intakes favouring Botox over placebo were seen at week 24, but the difference was only significant for acute medication days (Table 5.28).

In the PREEMPT studies, an intake of acute headache pain medication was defined as the number of times that a patient reported they took medication, regardless of the dose or number of types of medication taken and there could have been multiple intakes within a given day for each patient. Therefore, post-hoc analyses to identify potential patterns of intakes by medication categories was conducted and demonstrated that there was a statistically significant reduction favouring Botox in the use of triptans at week 24 (P<0.001)

Table 5.28: Change in acute medication intake and days in pooled phase 3 analysis at week 24 (ITT population) (Allergan, 2010b; Dodick, 2010)

Efficacy Variable (per 28 days)	**BTX (N=688)**	**PBO (N=696)**	**P-value** ¥
Frequency of acute headache pain medication intakes			
Mean (SD) Baseline	26.9 (19.13)	27.8 (20.73)	
Mean Change from Baseline	-10.1	-9.4	0.247
Frequency of acute headache pain medication days			
Mean (SD) Baseline	14.6 (6.38)	14.9 (6.35)	
Mean Change from Baseline	-6.1	-5.3	0.016

Health related quality of life (HRQL)

A statistically significant and clinically meaningful difference for Botox versus placebo at all time points starting at the first post-treatment study visit (week 4) and including week 24 was observed in mean change from baseline in total HIT-6 score (Table 5.29; Figure 5.12, Figure 5.9). The difference between the treatment groups at week 24 was -2.4 units [-3.11, -1.72], which exceeds the established minimally clinically important between-group difference (Coeytaux et al. 2006) of -2.3 units thus confirming clinical significance

Furthermore, Botox treatment statistically significantly improved HRQL as measured by changes from baseline in all 3 MSQ domains at week 24. MSQ scale scores for the Botox group all exceeded the established minimally important within-group differences from baseline of -10.9 (Role Function-restrictive), -8.3 (Role Function-preventive) and -12.2 (Role Function-

emotional). Conversely none of the placebo group scores met these minimally important differences (Dodick et al. 2007).

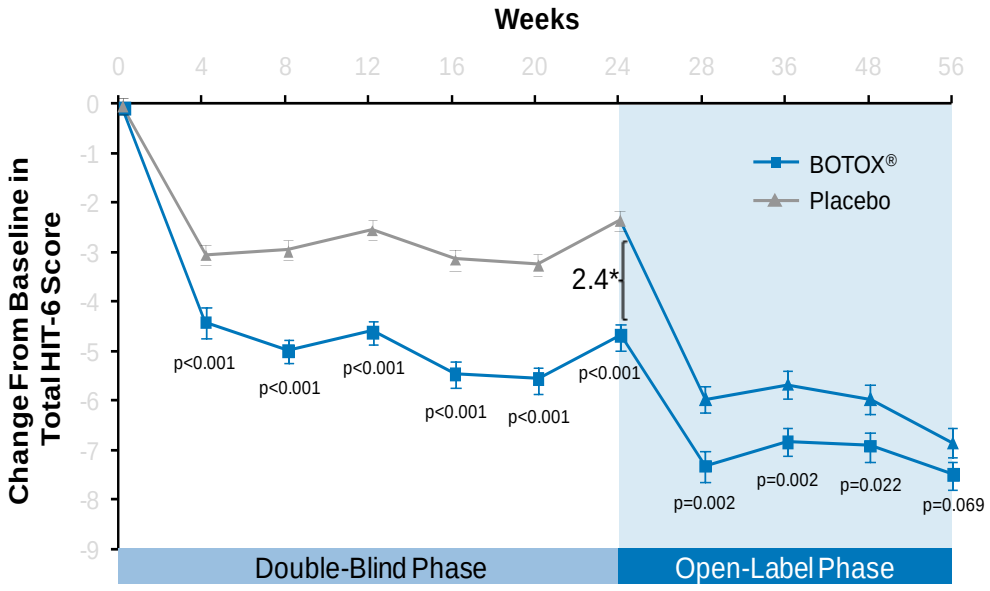
These scales have been used in a separate mapping algorithm to link to the EQ-5D, a standard generic measure of HRQL preferred by NICE. This is described in detail in chapter 6.

Table 5.29: Mean change from baseline at week 24 for HRQL results in pooled phase 3 studies (ITT population) (Allergan, 2010b; Dodick, 2010)

Efficacy Variable (per 28 days)	BTX (N=688)	PBO (N=696)	P-value
Total HIT-6™ scores			
Mean (SD) Baseline	65.5 (4.05)	65.4 (4.32)	
Mean Change from Baseline	-4.8	-2.4	<0.001
MSQ RF-R scores			
Mean (SD) Baseline	61.5 (0.63)	61.3 (0.66)	
Mean Change from Baseline	-17.0	-8.6	<0.001
MSQ RF-P scores			
Mean (SD) Baseline	44.0 (0.81)	43.9 (0.82)	
Mean Change from Baseline	-13.1	-6.4	<0.001
MSQ RF-EF scores			
Mean (SD) Baseline	57.9 (0.92)	57.6 (0.95)	
Mean Change from Baseline	-17.9	-9.5	<0.001

RF-P=Role Function-Preventative; RF-R = Role Function-Restrictive; RF-EF = Role Function-Emotional Function; HIT-6 = Headache Impact Test; MSQ = Migraine-Specific Quality of Life Questionnaire. HIT-6 score ranges from 36 to 78 with higher scores indicating greater impact on life: that is, lower HRQL. MSQ is scored from 0 (low function) to 100 (high function).

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



HIT-6 score ranges from 36 to 78 with higher scores indicating greater impact on life: that is, lower HRQL.

Open-label phase for pooled data

During the open-label phase, when all patients were treated with Botox, the therapeutic effects were sustained and often continued to show improved results with subsequent treatments (Allergan, 2010b; Aurora, 2009b).

Significant within group improvements from baseline in functioning and HRQL, as measured by HIT-6 and MSQ were also seen at week 56. At baseline, 93.5% of patients had a severe HIT-6 score (≥60); by week 56 only 50.6% of Botox/Botox patients had a severe HIT-6 score (Allergan, 2010b; Aurora, 2009b).

Subgroup analyses for pooled data

History of oral prophylactic medication use

The majority (97.5%) of patients in the PREEMPT studies with a history of use of oral prophylactic medications discontinued their use due to lack of efficacy and/or due to side-effects. To more closely reflect the target population for this submission, sub-group analyses of the primary efficacy variable and some key secondary efficacy variables were conducted on patients whose condition failed to respond to ≥3 oral prophylactic medications. Botox was statistically significantly more effective than placebo in reducing the mean frequency of headache days and the mean frequency in migraine days in the double-blind phase for this sub-group (p<0.001) (Table 5.30) (Allergan, 2010b)

Table 5.30: Mean change from baseline for key efficacy outcomes in the pooled analysis of the PREEMPT studies (Patient subgroup = those whose had previously received oral prophylactic medications) (Allergan, 2010b)

Variable per 28 days	**Pooled phase 3 analysis – Prior Failure on Prophylactics**		
	BTX/BTX (n=420)	**PBO / BTX (n=437)**	**P Value**
Frequency of headache days [a]			
Baseline (SD)	[redacted]	[redacted]	[redacted]
Week 24 (SD)	[redacted]	[redacted]	[redacted]
Frequency of headache episodes			
Baseline (SD)	[redacted]	[redacted]	[redacted]
Week 24 (SD)	[redacted]	[redacted]	[redacted]
Frequency of migraine days			
Baseline (SD)	[redacted]	[redacted]	[redacted]
Week 24 (SD)	[redacted]	[redacted]	[redacted]

a: Primary endpoint in pooled analysis History of oral prophylactic medication use – number of treatments

Post-hoc analysis demonstrated that Botox is also effective in the target population in the decision problem, and that the number of previous oral prophylactic medications that a patient had received does not have an impact on the clinical effectiveness of Botox (Table 5.31) (Allergan, 2010c).

History of oral prophylactic medication use – including prior topiramate treatment

As previously reported (section 5.3.7), post-hoc analysis of a subgroup of patients who had previously received topiramate as a prophylactic treatment can be used as a proxy for patients likely to receive Botox in the UK in accorance with the population of the decision problem. Results from this analysis are presented in Table 5.31 and demonstrate that Botox is effective in this subgroup, further supporting its use in the target population.

Table 5.31: Mean change from baseline for key efficacy outcomes in the pooled analysis of the PREEMPT studies for patient subgroups with increasing levels of previous oral prophylactic medications (Allergan, 2010b)

Frequency of headache days (per 28 days)	**BTX**	**PBO**	**p-value**
Patients who had previously received 1 or more headache prophylaxis medications			
	N=425	**N=454**	
Baseline	20.1 (3.6)	20.1 (3.7)	
Change from Baseline	-7.9 (6.5)	-5.6 (6.5)	<0.001
Patients who had previously received 2 or more headache prophylaxis medications			
[redacted]			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
Patients who had previously received 3 or more headache prophylaxis medications			
[redacted]			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
Patients who had previously received topiramate for migraine prophylaxis			
[redacted]			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]

a: Primary endpoint in pooled analysis History of oral prophylactic medication use – number of treatments

Health state transitions used in economic modelling

In Chapter 6 a Markov model approach is used to evaluate the cost-effectiveness of Botox in patients who had previously received ≥3 oral prophylactic medications. In this model, movements between six health states characterised by the number of headache days experienced per 28 days are evaluated over a time horizon of up to 2 years.

The number and proportion of patients in each of these health states is shown in the tables below and demonstrates that there is a significant difference between the distribution of patients in the placebo and Botox arms at weeks 12, 24 and 36 (Table 5.32 & Table 5.33) (Allergan, 2010d).

Table 5.32: Number and proportion (%) of patients in health state in double-blind phase (1 or more prior treatment– pooled sample) (Allergan, 2010d)

Health state (headache days per 28 days)	**Baseline** BTX	PBO	**Week 12*** BTX	PBO	**Week 24*** BTX	PBO
[redacted]						

Table 5.33: Patients classified as responders and non-responders (based on achievement of an improvement of ≥ 2 Healthstates) to Botox after 2 treatment cycles – minimum 4 headache days per month improvement (1 or more prior treatment – pooled sample) (Allergan, 2010f)

Health state at baseline	Health State at Week 24					
	0-3	**4-9**	**10-14**	**15-19**	**20-23**	**24+**
15-19	41(37%)	71 (63%)	0 (0%)	0(0%)	0 (0%)	0 (0%)
20-23	13 (22%)	24 (41%)	22 (37%)	0 (0%)	0 (0%)	0 (0%)
24-28	1 (3%)	12 (32%)	10 (27%)	14 (38%)	0 (0%)	0 (0%)

Responder
Non-Responder

5.6 Meta-analysis

A meta-analysis of relative risks from the two RCTs was not relevant for this submission. Instead a pooled analysis of both PREEMPT clinical trials was performed. Predefined pooling of PREEMPT 1 and 2 studies was performed to confirm the efficacy, safety, and tolerability of Botox for prophylaxis of headaches in adults with chronic migraine and to provide additional statistical power to identify efficacy, safety and tolerability results that could be missed if each study were reported only separately (Dodick et al. 2010).

5.7 Indirect and mixed treatment comparisons

Indirect and mixed treatment comparison methods were not relevant to the decision problem.

A literature search (Section 5.1) identified two clinical trials of Botox in the chronic migraine population. The PREEMPT study programme is the largest of its kind to investigate outcomes in this patient population and the enrolled population is considered to be representative of the chronic migraine population in the UK. The comparator and study outcomes were relevant to the decision problem and thus these trials provide high value data. The key evidence to support the efficacy of Botox in the chronic migraine population is taken from a pooled analysis of the two phase 3 studies (PREEMPT 1 and 2).

The only other potentially relevant RCT of Botox that was identified in the literature searches was a small pilot study. The study compared Botox toplacebo, but was excluded because of serious concerns about its quality and relevance to the decision problem. In particular, external validity was compromised due to the small sample size (n=60) and lack of power to detect differences between treatment groups. Approximately 30% of patients discontinued in the studyafter being allocated to treatment and therefore only 60% of patients had complete data for the final analysis at week 16. Most patients who discontinued did not receive allocated intervention after randomisation due to medication overuse during the baseline period (patients with medication overuse were explicitly excluded from the study). In addition, the decision problem could not be addressed from the data in this study because it did not report details of prior oral prophylactic medication use in the study subjects.(Freitag et al. 2008).

Similarly, the search for comparator therapies, relevant to the decision problem: e.g. GON block, occipital nerve stimulators, methysergide, and IV DHE identified only one small study comparing occipital nerve stimulation with medical management for patients with chronic migraine. Given the still experimental nature of this intervention this publication was a feasibility study and had little external validity (Saper et al. 2011).

There is a clear absence of approved pharmacotherapies or well studied interventions in the management of patients with chronic migraine who have failed to respond to ≥3 prior oral prophylactic medications. The evidence on which to base clinical decisions often relies greatly on the expertise of the treating physician or consultation with tertiary specialists. Thus, in the absence of high quality evidence the comparative effectiveness of these treatments is to be derived from expert opinion as reported in section 5.8

5.8 Non-RCT evidence

No non-RCT evidence was considered.

5.9 Adverse events

Patient exposure

The safety profile of Botox in the Phase 3 Chronic Migraine population was based on a pooled analysis of 1,300 chronic migraine patients who were exposed to at least 1 Botox treatment in the phase 3 studies, providing a total of 12,379 patient-months of exposure (MHRA 2010). A total of 518 patients were exposed to 5 treatment cycles of Botox.

Among the 1,300 chronic migraine patients, the total actual Botox dosages received per cycle ranged from 15 U to 195 U when averaged across cycles 1 to 5 for each patient, with a mean of 164 U. A total of 1,137 patients were exposed to Botox for ≥ 24 weeks and 544 patients were exposed for ≥ 48 weeks at a dose range of 150 U to 200 U. Based on the 4648 actual Botox doses administered across all treatment visits, all but 18 Botox doses were administered at 155 U or higher. The majority were within the target label dose of 155 U to 195 U. Across treatment cycles, the majority of patients continued in subsequent treatment cycles to receive their initial study drug dose; few patients increased, decreased or had their dosage changed from cycle to cycle.

Table 5.34: Duration of exposure (Phase 3 CM population)

Duration	**Treatment Group**	
DBPC Exposure	**Botox (N=687)**	**Placebo (N=692)**
<12 Weeks	41 (6.0%)	34 (4.9%)
12 to <24 Weeks	100 (14.6%)	94 (13.6%)
≥24 Weeks	546 (79.5%)	564 (81.5%)
Open-label Exposure	**Botox/Botox (N=592)**	**Placebo/Botox (N=613)**
<12 Weeks	19 (3.2%)	35 (5.7%)
12 to <24 Weeks	33 (5.6%)	49 (8.0%)
24 to <36 Weeks	475 (80.2%)	467 (76.2%)
≥36 Weeks	65 (11.0%)	62 (10.1%)
Any Botox Exposure	**Any Botox (N=1300)**	
<12 Weeks	76 (5.8%)	
12 to <24 Weeks	87 (6.7%)	
24 to <36 Weeks	495 (38.1%)	
36 to <48 Weeks	98 (7.5%)	
≥48 Weeks	544 (41.8%)	

Botox/Botox patients received Botox during the double-blind phase and the open-label phase. Placebo/Botox patients received placebo during the double-blind phase and Botox during the open-label phase.

Adverse events
Adverse events were converted to MedDRA version 11.0 coding conventions.

Table 5.35: Adverse events reported by ≥ 2% of patients in either treatment group (Phase 3 CM population)

System Organ Class/Preferred Term	Botox (N=687)	Placebo (N=692)
OVERALL	429 (62.4%)	358 (51.7%)
Eye Disorders	38 (5.5%)	10 (1.4%)
Eyelid Ptosis	25 (3.6%)	2 (0.3%)
Gastrointestinal Disorders	49 (7.1%)	54 (7.8%)
Nausea	14 (2.0%)	17 (2.5%)
General Disorders & Administration Site Conditions	60 (8.7%)	57 (8.2%)
Injection site pain	23 (3.3%)	14 (2.0%)
Infections & Infestations	170 (24.7%)	167 (24.1%)
Nasopharyngitis	28 (4.1%)	30 (4.3%)
Sinusitis	28 (4.1%)	27 (3.9%)
Upper respiratory tract infection	27 (3.9%)	37 (5.3%)
Bronchitis	17 (2.5%)	11 (1.6%)
Influenza	11 (1.6%)	16 (2.3%)
Muscoskeletal & Connective Tissue Disorders	169 (24.6%)	85 (12.3%)
Neck pain	60 (8.7%)	19 (2.7%)
Muscoloskeletal stiffness	25 (3.6%)	6 (0.9%)
Muscular weakness	24 (3.5%)	2 (0.3%)
Myalgia	21 (3.1%)	6 (0.9%)
Muscoloskeletal pain	18 (2.6)	10 (1.4%)
Nervous System Disorders	117 (17.0%)	74 (10.7%)
Headache	32 (4.7%)	22 (3.2%)
Migraine	26 (3.8%)	18 (2.6%)
Facial paresis	15 (2.2%)	0 (0.0%)

Phase 3 Chronic Migraine population, double-blind, placebo-controlled exposure

The only individual adverse event occurring at a rate ≥ 5% in the Botox group was neck pain (8.7%). Among the 60 Botox-treated patients who reported neck pain, 8 reported events that were mild and 33 reported events that were moderate in severity. Neck pain is not unexpected based on the known pharmacology and tolerability profile of Botox in indications that involve IM injections to neck muscles.

The most frequently reported adverse events reported at a higher incidence in the Botox than placebo group were: neck pain, headache, migraine, eyelid ptosis, musculoskeletal stiffness, and muscular weakness. Only 3.3% of

Botox- and 2.0% of placebo-treated patients reported injection site pain (Table 5.38).

The adverse events of interest that may be related to an exaggerated local pharmacological effect of Botox, such as eyelid ptosis, muscular weakness, facial paresis, and dysphagia, occurred at low rates of 3.6%, 3.5%, 2.2%, and 0.7%, respectively, in Botox-treated patients. Notably, eyelid ptosis, muscular weakness, and dysphagia were also reported among placebo-treated patients at rates of 0.3%, 0.3%, and 0.1%, respectively.

Adverse reactions

The Marketing Authorisation Holder (MAH) has developed an algorithm to define ADRs, which was applied to the Phase 3 Chronic Migraine population during DBPC exposure; 17 ADRs were identified and are proposed for the prescribing information. All proposed ADRs, except for migraine, have been observed with the use of Botox in other indications.

Migraine, including worsening migraine, was reported in a small number (3.8%) of Botox-treated patients, with the onset occurring in the majority within the first month after treatment. The incidence of migraine observed in placebo-treated patients was 2.6%. Although in a few patients, these reactions recurred at some subsequent treatment cycles, the overall incidences decreased with repeated treatments.

Table 5.36: Adverse drug reactions (Phase 3 CM population, DBPC exposure)

Adverse Drug Reaction	Botox (N=687)	Placebo (N=692)
Common (≥1% to <10%)		
Neck pain	60 (8.7%)	19 (2.7%)
Headache	32 (4.7%)	22 (3.2%)
Eyelid ptosis	25 (3.6%)	2 (0.3%)
Muscoloskeletal stiffness	25 (3.6%)	6 (0.9%)
Migraine	26 (3.8%)	18 (2.6%)
Muscular weakness	24 (3.5%)	2 (0.3%)
Injection site pain	23 (3.3%)	14 (2.0%)
Myalgia	21 (3.1%)	6 (0.9%)
Muscoloskeletal pain	18 (2.6%)	10 (1.4%)
Facial paresis	15 (2.2%)	0 (0.0%)
Muscle spasms	13 (1.9%)	6 (0.9%)
Muscle tightness	9 (1.3%)	3 (0.4%)
Pruritus	7 (1.0%)	2 (0.3%)
Rash	7 (1.0%)	6 (0.9%)
Uncommon (≥0.1% to <1%)		
Dysphagia	5 (0.7%)	1 (0.1%)
Pain of jaw	5 (0.7%)	0 (0.0%)
Pain of skin	5 (0.7%)	2 (0.3%)

Additional data on the adverse events of headache/migraine

Migraine/headache AEs were reported more frequently on Botox (64 subjects; 9.3%) than on placebo (40; 5.8%) ($p = 0.013$) during the double-blind phase of the phase 3 CM trials and in a total of 169 subjects (12.3%) over the whole duration of these trials.

No baseline characteristics allowed these subjects to be distinguished from the whole population of the trials.

Overall, these subjects seemed to respond to Botox similarly to the whole population of the trial although a few subjects reported a greater frequency of headache days at the time of the AE compared to baseline (1.5% vs. 0.7% in the Botox and placebo groups, respectively) or a longer average headache episode duration (4.7% vs. 3.2%, respectively).

Like for other ADRs, the incidence of migraine/headache AEs declined over time. It was higher during the first cycle: 7.0% vs. 3.9% in the Botox and placebo groups, respectively ($p = 0.012$) than during the following cycles (e.g. 3.5% during cycle 3).

The onset of the migraine/headache AEs was observed preferably in the first week after the injection: in cycle1, 1.7% vs. 0.9% (in the Botox and placebo groups, respectively) on the day of the injection, then 2.3% vs. 1.4% between Day 1-7, and subsequent decrease.

There were also more SAEs of migraine/headache, reported as intractable migraine/headache, worsening/exacerbation of migraine, or status migrainous, and prompting hospitalisation in the Botox group (6 cases; 0.9%) than in the placebo group (1 case; 0.1% - but unclear because hospitalisation on the day of the 2nd injection was pre-arranged). There were an additional 5 cases during the open phase of the trials, including a second event in a subject previously affected. Overall, the proportion of subjects with this type of SAE on Botox was 0.7%. Most of them had hospitalisation for migraine prior to the trial. Nevertheless, it is noteworthy that all hospitalisations for migraine/headache occurred in the Botox group (if the pre-arranged hospitalisation is not taken into account). Finally, two patients discontinued Botox due to this serious ADR.

Serious adverse events and death

In the Phase 3 Chronic Migraine population during DBPC exposure, serious adverse events were reported in 4.8% (33/687) of patients in the Botox group and 2.3% (16/692) of patients in the placebo group. The incidence of serious adverse events in the Phase 3 Chronic Migraine population was consistent across the DBPC, open-label, and any Botox exposure groups. The most frequently reported serious adverse events with any Botox exposure were migraine (0.6%), uterine leiomyoma (0.4%), and pneumonia and non-cardiac chest pain (both 0.3%). A majority of the remaining serious adverse events were reported only once (0.1%) and were either evenly distributed between the Botox and placebo groups or higher in the placebo group.

Two of the serious adverse events in patients receiving Botox were considered to be treatment-related by the investigator. Both of these were migraine, both resolved without sequelae, one led to study discontinuation, and the other patient completed the study. Uterine leiomyoma and pneumonia are frequently experienced in the general population with the demographic profile included in these studies. There were no serious adverse events related to the injection procedure. There was no particular pattern or clustering of events to indicate a potential safety signal in relationship to Botox.

Adverse Events Leading to Discontinuation

The incidence of adverse events leading to discontinuation in the Phase 3 Chronic Migraine population was consistent 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. Neck pain was the single most frequent adverse event that led to discontinuation in the Phase 3 Chronic Migraine population. There was no other identified pattern of adverse events that led to discontinuation.

Treatment-related AE rates

Overall, treatment-related AEs were low among the 1,300 chronic migraine patients treated with Botox in either the double-blind or the open-label periods of the phase 3 studies (Table B42). The incidence rates for individual treatment-related AEs were low (all <8%). The most frequently reported treatment-related AEs in those 1,300 patients who had any Botox exposure in phase 3 trials were neck pain (7.3%); muscular weakness (4.3%), eyelid ptosis (3.9%), and injection site pain (3.2%). Neck pain was the most frequently reported treatment-related AE in both the phase 3 double-blind phase and the phase 3 open-label phase. However, this is not an unexpected

event based on the known pharmacology and tolerability profile of Botox when administered as intramuscular injections to the neck muscles.

During open-label exposure, when all patients received Botox, treatment-related AEs were reported in 20.3% of all patients: 26.4% in the placebo/Botox group compared with 14.0% in the Botox/Botox group (Allergan, 2010h). The incidence of adverse events in the Botox group reflecting local pharmacological effects of Botox tended to decrease from one treatment cycle to the next. This pattern suggests that repeated exposure to Botox does not pose an additional safety risk to patients.

Table 5.37: Number (%) of patients with treatment-related AEs reported by ≥ 2% of patients in either treatment group (phase 3 Chronic Migraine Population; open-label exposure) (Allergan, 2010h)

System Organ Class/ Preferred Term	Botox/Botox (N=592)	PBO/Botox (N=613)
Overall	83 (14.0%)	162 (26.4%)
Eye Disorders Eyelid Ptosis	15 (2.5%) 13 (2.2%)	28 (4.6%) 17 (2.8%)
General Disorders & Administration Site Conditions Injection Site Pain	25 (4.2%) 13 (2.2%)	21 (3.4%) 11 (1.8%)
Musculoskeletal & Connective Tissue Disorders Neck pain Muscular weakness Muscular tightness Musculoskeletal stiffness Myalgia	38 (6.4%) 16 (2.7%) 8 (1.4%) 6 (1.0%) 5 (0.8%) 1 (0.2%)	106 (17.3%) 39 (6.4%) 27 (4.4%) 20 (3.3%) 15 (2.4%) 14 (2.3%)
Nervous System Disorders Headache Facial paresis	17 (2.9% 4 (0.7%) 3 (0.5%)	37 (6.0%) 13 (2.1%) 12 (2.0%)

Safety with repeat exposure

The safety of Botox for chronic migraine has been observed over a robust number of patient months. The treatment-related analysis by treatment cycle in the phase 3 program did not reveal any unexpected treatment-related adverse events in patients exposed to multiple treatment cycles (up to 5 cycles). This suggests that there is no cumulative toxicity with long-term Botox exposure.

Such a profile is supported by the fact that the safety of Botox in a range of indications has been established with over 20 years of use in clinical practice.

Long-term safety of Botox

The safety of Botox in a range of indications has been established with over 20 years of use in clinical practice. Compared with all other Botox clinical indications, no new or unexpected treatment-related adverse events were identified and the safety analyses of the phase 3 chronic migraine populations support the known safety and tolerability profile of Botox seen in a large number of other clinical applications, when Botox is administered by intramuscular injection (MHRA 2010).

Further, a systematic review and meta-analysis by Naumann and colleagues (2004) demonstrated that Botox has a favourable safety and tolerability profile across a broad spectrum of therapeutic uses. It was also noted that few, if any, therapeutic agents have been evaluated in as many different therapeutic applications as Botox (Naumann and Jankovic 2004).

Botox safety in chronic migraine

This submission concerns Botox for use in patients experiencing chronic migraine who have previously failed to respond to ≥3 oral prophylactic medications. Detailed analyses that support the safety conclusions have been derived from an integrated safety database of 11 studies that support the application of Botox for the approved indication of the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine) (Allergan Ltd i.)The evidence for safety in the wider indication is expected to be representative of the smaller, more restricted subpopulation discussed herein (patients whose condition failed to respond to oral prophylactic medications).

The safety of Botox is presented in Table 5.38 as discontinuation rates due to treatment related AEs. Similar data for oral prophylactic medications is also provided for context.

Table 5.38: Safety statistics for oral prophylactic medications (discontinuation due to treatment-related AEs)

	Active	**Placebo**
Botox (Dodick 2010)	3.8%	1.2%
Gabapentin (Vukovic 2009)	22.4%	N/A
Gabapentin (Spira 2003)	7.5%*	4.1%*
Topiramate (Silberstein 2007)	10.9%*	6.1%*
Venlafaxine XR (Adelman 2000)	18%	N/A

*Discontinuation due to AEs (treatment-related AE discontinuation rate not reported)

A number of small, independent studies have also been conducted outside the clinical development programme that consider the safety of Botox and are discussed in this section.

The overall safety evaluation plan is presented in Appendix 3.

Raw data is available on the start and stop dates for adverse events and some preliminary analysis on duration of adverse events has been conducted. In general, adverse reactions for Botox occur within the first few days following injection and are short-lived and transient. In very rare cases, adverse reactions may have a longer duration over several months (Botox SPC).

All Chronic Migraine population (Allergan, 2010h)

The safety profile of Botox in the All Chronic Migraine population was based on a pooled analysis of 1,997 patients who were exposed to at least 1 Botox treatment in the phase 2 and phase 3 chronic migraine studies, providing a total of 16,926 patient-months of exposure. Baseline demographic and disease characteristics in the All Chronic Migraine were similar to the pooled Phase 3 Chronic Migraine population.

While the overall nature of the AEs was similar between the All Chronic Migraine population and Phase 3 Chronic Migraine population, the incidences of most AEs were lower in the phase 3 Chronic Migraine population. Neck pain was again the most frequently reported AE during double-blind exposure in the All Chronic Migraine population with an incidence of 13.8% (vs. 8.7% in the phase 3 Chronic Migraine population). The incidence of dysphagia during double-blind exposure was 2.1% in the All Chronic Migraine population vs. 0.7% in the phase 3 chronic migraine population.

The lower incidence of AEs in the phase 3 chronic migraine population may be related to an optimised dosing and injection paradigm. This included:

1) A lower maximum dose used per treatment cycle in the phase 3 studies compare to the phase 2 studies (195 U vs. 260 U)

2) A more defined injection paradigm in the phase 3 studies, which specified a fixed-site, fixed-dose injection regimen in the forehead region, no masseter injections, and injection of the upper cervical paraspinal muscles rather than deeper splenius capitis and semispinalis cervical muscles

3) Uniform use of a 30-gauge (0.5-inch) needle in the phase 3 studies vs. the use of a 30-gauge, 1-inch needle in one of the phase 2 chronic migraine studies and optional use of either a 27-gauge or 30-gauge needle (0.5 to 1.5 inches) in the other phase 2 chronic migraine study

The detailed analyses supporting these conclusions are reported in the Summary of Clinical Safety.

All Migraine population (Allergan, 2010h)

The safety profile in the All Migraine population was based on a pooled analysis of 3,235 patients exposed to Botox for up to 26,685 patient-months of exposure. Baseline demographic and disease characteristics in the All Migraine population were similar to the Phase 3 Chronic Migraine population.

Compared with the other two safety populations, no new safety findings emerged from this larger dataset of the All Migraine population that included 11 studies. Although the overall nature of AEs was similar between the All Migraine population and the phase 3 Chronic Migraine population, the incidences of most AEs were lower in the phase 3 Chronic Migraine population. The lower incidence of most AEs in the phase 3 Chronic Migraine population may be related to the optimised dosing regimen and injection paradigm or the lower maximum dose per treatment cycle used in the phase 3 studies (195 U vs. 260 U) as previously discussed. Furthermore, the inclusion of the episodic migraine patients in this safety population did not result in a different AE profile compared to chronic migraine patients, suggesting that episodic migraine patients are not at additional risk from exposure to Botox.

Additional evidence of safety for Botox in chronic migraine

Planned studies for Botox in chronic migraine

During the assessment of Allergan's submission to the MHRA to gain marketing authorisation for the prophylaxis of chronic migraine, Allergan made a commitment to conduct an observational study in the UK. As part of this process, and to ensure that the study is in line their MHRA expectations, Allergan has agreed the final protocol with the MHRA. The study has been initiated and is ongoing at this time.

The purpose of this post-authorisation, observational study is to monitor the utilisation practices and describe the safety profile of Botox for the prophylactic treatment of headaches in patients with chronic migraine in clinical practice in the United Kingdom (UK).

The primary study objectives are as follows:

- To describe the utilisation of Botox as headache prophylaxis for chronic migraine in actual clinical practice, including description of the demographic and disease characteristics of patients that prescribers select for treatment and details on Botox dose, number of injection sites, and location of injections.

- To estimate the incidence of adverse events experienced by patients who are treated with Botox in actual clinical practice for the prophylactic treatment of chronic migraine. Specific adverse events will include, but are not limited to dysphagia and worsening of migraine (intractable headache).

5.10 Interpretation of clinical evidence

Patients with chronic migraine report significantly lower HRQL, more severe disability, higher levels of anxiety and depression and greater health care resource utilization compared to those with episodic migraine (Blumenfeld et al. 2011). Yet patients with chronic migraine are almost always excluded from migraine prophylaxis trials as they are considered to be too highly disabled and treatment resistant (Lipton and Bigal 2003). However, the high burden of illness suffered by those with chronic migraine calls for the development and evaluation of efficacious, safe and well-tolerated headache prophylaxis therapies.

The results of the pooled analysis of Botox trials demonstrate how this technology impacts on multiple study endpoints including HRQL. Highly significant differences favouring Botox over placebo across multiple headache symptom measures were shown, including in the primary endpoint of headache day frequency and all secondary efficacy endpoints, with the exception of acute pain medication intakes (Dodick et al. 2010).

Subgroup analyses of specific sets of patients identified in the decision problem (those overusing medications and those who were previously treated with oral prophylactic medications) demonstrate that efficacy results achieved were consistent with those of the study population as a whole. This means that results from the pooled studies can be confidently applied to the wider population of chronic migraine patients. In addition this permits further analyses of specific subgroups using the full patient sample from the pooled PREEMPT studies.

The safety of Botox is well established with over 20 years of use in clinical practice. Evidence from PREEMPT trials in chronic migraine patients and from its use in other conditions show that the incidence of AEs is relatively low and that they are mild to moderate in severity.

It is worthy of note that patients in the PREEMPT studies were motivated to undergo a therapy that required a series of 31 to 39 injections around the head and neck in order to possibly find relief from their suffering. Upon enrolling in this study, these patients had experienced on average, frequent headache (mean 20 headache days per month) for two decades and were highly disabled. Their motivation to complete the full study is reflected in the numbers in the Botox who completed the 24- week double blind phase and entered the open-label phase (88%).

Results of the pooled analysis of the PREEMPT trials demonstrate that Botox is a new, safe and effective prophylactic treatment for patients with chronic

migraine who have failed to respond to at least three prior oral prophylactic medications.

5.10.1 Strengths of the clinical evidence base for Botox

Study size

The PREEMPT phase 3 chronic migraine studies are the largest well-designed, controlled studies conducted to date in this severely disabled population and thus represent the largest body of scientific evidence supporting the safe and effective prophylactic treatment of headaches in adults with chronic migraine.

Controlled empirical data on the prophylactic treatment of chronic migraine is limited (Diener et al. 2007;Olesen et al. 2006) and consequently there is little evidence-based medicine available to guide physicians management decisions for these patients.

According to an independent review by Schoenen in Cephalalgia “Both studies undoubtedly do support efficacy in the patients studied and have demonstrated undisputable strengths. They were well-designed, performed by experienced investigators and included large numbers of patients with a long blinded follow-up of 24 weeks and a subsequent open label period of 32 weeks” (Schoenen et al. 2010).

Pooled analysis strength

The virtually identical study design for both PREEMPT studies permits pooling of data for further analysis, which in turn produces more precise and robust efficacy results.

The design of the PREEMPT trials were informed by earlier phase 2 studies (Mathew et al. 2005;Silberstein 2005) and recruited patients in a pragmatic way by reflecting the population of chronic migraine patients generally seen in routine clinical practice.

Due to the severity and frequency of headaches suffered by patients with chronic migraine, there is frequent use of acute headache pain medication, in some instances resulting in medication overuse headache (Lipton et al. 2003). In the PREEMPT studies, around 65% of patients were excessively using acute medications in accordance with IHS definitions; this is reflective of real world practice (Clinical Advisory Board, 2010; Schoenen, 2010).

Current diagnostic criteria for chronic migraine cannot be fulfilled if patients also have medication-overuse headache (a specific secondary headache disorder defined by ICHD-II 8.2). However, the IHS guidance document on clinical trials of prophylactic treatment of chronic migraine allows the inclusion of patients with excessive acute medication use ("medication overuse"), provided assignment to treatment groups is stratified by this criterion (Silberstein et al. 2008a). This approach was taken in the PREEMPT studies and patients were stratified to treatment at baseline based on whether the frequency of their acute headache medication use met protocol defined acute medication overuse or not. Investigators were trained to exclude patients they suspected had medication-overuse headache and those overusing opioids and barbiturates due to their known association with the development of medication-overuse headache.

The PREEMPT trials represent the first significant attempt to study large numbers of patients with chronic migraine, a group who despite substantial unmet need have almost always been excluded from migraine prophylaxis trials.

Compliance & completion

The very high compliance rates of patient diary entry and the low rates of patients discontinuing treatment is an indication of the high quality of the trial management observed.

Choice of efficacy endpoints

The choice of efficacy endpoints reflected the burden of illness associated with chronic migraine. That is, the primary and secondary outcomes included not only frequency, severity and duration of headache days, but HRQL and functioning.

Allergan's clinical development program has established that in patients with chronic migraine an evaluation of a change in frequency of headache days is more informative than an evaluation of a change in frequency of headache episodes (Schoenen, 2010). The consistency of the results for the assessment of headache days across the two Botox phase 3 studies provides confidence in the evidence of efficacy for Botox as a treatment for headaches in adults with chronic migraine.

Significant treatment effect

Botox substantially reduced disease burden as demonstrated by significantly greater reductions in the frequency of headache days than placebo treatment

over the 6-month double-blind phase in two large well-designed, well-controlled clinical trials. Significant improvements after Botox versus placebo treatment were also confirmed across multiple headache symptom measures. Botox had a sustained duration of action and improved functioning, vitality, psychological distress, and overall quality of life. Botox administered at doses of 155 U to 195 U according to a well defined IM injection paradigm repeated every 12 weeks was shown to be safe and well-tolerated. The safety and tolerability profile was consistent with that seen in all other Botox clinical indications with no new safety findings identified that raise concerns over the use of Botox at the proposed recommended doses for the prophylaxis of headaches in adults with chronic migraine.

Consistent efficacy results between full pooled dataset and identified subgroups

Results from subgroup analyses highlighted the generalisability between identified subsets of patients and the total study population. Efficacy results from the following analyses of patients were consistent with the robust efficacy findings from the total study population:

- patients overusing acute headache medications at baseline;
- patients previously treated with at least one oral prophylactic medication;
- patients previously treated with at least two oral prophylactic medications;
- patients previously treated with at least three oral prophylactic medications; and
- patients previously treated with topiramate.

Weaknesses

The PREEMPT trials were not powered to detect differences in primary endpoint in subgroups of patients which form the basis of the decision problem in this appraisal: that is, patients whose condition has failed to respond to at least 3 prior oral prophylactic medications, and whose medication overuse has been appropriately addressed. However, subgroup analyses of specific sets of patients (those overusing medications and those who were previously treated with oral prophylactic medications) demonstrate

that efficacy results were consistent with those of the study population as a whole.

The secondary endpoint ‘frequency of acute pain medication intakes’ may be an inadequate measure of efficacy of treatment, reflected in the apparent discrepancy of a significant reduction in frequency of headache days among Botox-treated patients compared with placebo-treated patients, without an accompanying significant difference in frequency of acute pain medication intakes.

There were complexities with regard to the collection of data from patients related to the interpretation of results from analyses of acute medication intake. Because the daily diary was already quite burdensome to patients in that they were to report all headache associated symptoms in a great level of detail, Allergan elected to simply ask patients yes/no if they had “taken” an acute medication and if they answered yes then we captured the name of the medication only. Therefore, the dataset lacks further detail that would have been helpful to analyze to better understand the changes observed in this study. For example, 1 aspirin tablet or 6 aspirin tablets taken at the same time would have simply been recorded in the diary by the patient as “1 intake of aspirin”; similarly 1 aspirin tablet (unknown strength) and 1 sumitriptan tablet (also of unknown strength) taken at the same time were recorded as “1 intake”. There could have been multiple intakes within a given day for each patient and significant changes within this over the study period.

Because in the Botox phase 3 studies patients were stratified at baseline for medication overuse (yes/no), per protocol, investigators were not allowed to instruct or guide patients on use of their acute medications; it was strictly based on the patients need for acute treatment. It was felt that recommending changes in acute medication type and/or frequency of use could potentially confound any study results. Furthermore, it was felt that this protocol methodology would most similarly reflect patient behaviour “in the real world”. Overall, in this study both treatment groups showed a large mean reduction from baseline in the frequency of acute medication intake (of any type medication), with statistically significantly greater reduction from baseline favouring Botox treatment for triptan intakes and in the population of patients who were using triptans at baseline. There was also a significant reduction favouring Botox in the mean change from baseline in the frequency of acute medication days, both in terms of days taking a triptan and days using multiple analgesic medications.

Irrespective of the limitations in analyzing changes in acute medication intake as described above, what is clear from the data is that a significantly greater proportion of Botox-treated patients compared to placebo-treated patients

achieved a three-month and six-month persistent shift from medication overuse to non-medication overuse during the DBPC phase of these studies, with an increasing proportion of patients with further persistent shift from medication-overuse to non-overuse occurring during the open label phase. Furthermore, there was no evidence that Botox treatment resulted in patients developing medication overuse during the course of the study.

5.10.2 Relevance of the evidence base to the decision problem.

The PREEMPT phase 3 chronic migraine studies are the largest well designed, controlled studies conducted to date in patients suffering with this debilitating condition. The patients studied in the PREEMPT trials reflect patients with chronic migraine who are seen routinely in clinical practice in the UK. This population is also shown to be relevant to the decision problem, which specifies that Botox be reserved for adults with headaches on at least 15 days per month of which at least 8 days are associated with migraine and whose condition has failed to respond to at least three prior oral prophylactic medications and medication overuse has been appropriately managed.

Efficacy results from subgroup analysis of patients overusing acute headache medications at baseline were consistent with the efficacy findings from the wider population, as were efficacy results for patients whose condition had failed to respond to prior oral prophylactic medications.

Furthermore, when this latter subgroup of patients was further broken down by number of prior prophylactic treatments (≥1, ≥2, and ≥3) in post hoc analysis, the efficacy results for these three patient groups were consistent with the findings for the subgroup of previously treated patients as a whole. The same consistent efficacy results were found after a post hoc analysis of the subgroup of patients who had previously been treated with topiramate, a treatment recommended in the UK for patients whose condition has failed to respond to first or second line prophylactic therapies such as beta-blockers and amitriptyline (BASH 2010).

Botox-treated patients experienced statistically significant and clinically meaningful improvements in functioning and HRQL, as measured by HIT-6 and MSQ instruments, over placebo in the PREEMPT trials. The reason this is worthy of note is because of the burden of disease experienced by those living with chronic migraine. It has been well documented that patients with chronic migraine report significantly more severe disability, lower HRQL, higher levels of anxiety and depression and greater health care resource utilization compared to those with episodic migraine(Bigal et al. 2008;Blumenfeld et al. 2011).

Post-hoc subgroup analysis to investigate the movement of patients whose condition had failed to respond to oral prophylactic medications, from the health states of “high frequency of headache days” to the health states associated with “lower frequency of headache days” was conducted on the pooled analysis. Results from that subgroup analysis show a significant difference between patients in the placebo and Botox arms with regard to distribution of study subjects among high and lower headache frequency categories at weeks 12, 24 and 36 of the study. That is, significantly more patients with chronic migraine in the Botox group “moved” into health states with lower frequency headache days compared to patients in the placebo arm of the trial. This is reflected in results from the pooled analysis in which treatment with Botox led to significant improvements from baseline across multiple headache symptom measures including HRQL.

5.10.3 External validity of study results to patients in routine clinical practice

Patient demographics

The majority of patients in the PREEMPT 1 study were from the US, however in PREEMPT 2, there were 4 UK study centres. During an advisory board clinicians agreed that the patient demographics in the PREEMPT study are generally reflective of the chronic migraine population in routine clinical practice in the UK (90% Caucasian, >85% female, mean age of 41). Population-based epidemiology data also provides evidence that the PREEMPT study population is representative of the typical patient with chronic migraine seen in clinical practice (Bigal et al. 2008). Therefore, the results from these studies are expected to be relevant to clinical practice for healthcare professionals who treat patients with chronic migraine.

Disease severity

As noted in the Bulletin of the WHO, severe continuous migraine is considered to be in the most severe class of disability and to have high levels of dependence requiring help from another person at least daily (Harwood et al. 2004). In accordance with this, the PREEMPT trials showed that, at baseline, the PREEMPT study population was highly disabled. Patients had suffered with frequent headache for more than 2 decades and experienced an average of 20 headache days per month. Patients were currently inadequately treated by available medical therapies; approximately two-thirds had previously failed to respond to headache oral prophylactic medications that they found to be ineffective and/or intolerable and between 62% and 70% of patients were overusing acute headache pain medication during the baseline period (Dodick et al. 2010).

Medication overuse

In a recent review, it is described that the high rate of medication overuse in the PREEMPT trials is representative of real-world patients with this condition (Schoenen et al. 2010).

Patients with no prior prophylactic medication use

Schoenen and colleagues (2010) also highlighted that the proportion of patients with previous experience of oral prophylactic medications was low (60%) given that patients had around 20 years of frequent headache at baseline.

In one population based study of CM, a high proportion of persons (87.6%) had sought care to discuss their headaches with a health professional. Yet, only 20.2% of those with CM received a diagnosis of CM, chronic daily headache or transformed migraine (Bigal et al. 2008;Manack et al. 2011;Manack et al. 2009). In this population based study 60% of persons with CM were prophylaxis naïve. In the International Burden of Migraine Study-II (IBMS-II), a web-based population based survey of 8,726 eligible responders from nine countries (Australia, Canada, France, Germany, Italy, Spain, United Kingdom, Taiwan and United States), showed that overall 33.1% of persons with CM were prophylaxis naïve (Blumenfeld et al. 2010). Most (44.8%) persons with CM were not taking migraine prophylaxis at the time of the IBMS-II study (range was 40.7% to 62.0%); only 22% of these persons had previously tried a migraine preventive medication. Patients naïve to prior prophylaxis had a similar response to BOTOX® as compared to patients who were not naïve.

6 Cost effectiveness

- Botox is a highly cost-effective treatment compared to placebo in patients previously treated with ≥3 oral prophylactic treatments with an ICER of £6,083 over a 2 year time horizon
    - Due to larger patient numbers, and similar clinical effectiveness, base case uses the ≥1 oral prophylactic treatments patient population. In this group the ICER is £5,828

- The product remains cost effective in subgroups where
    - Patients have previously received oral prophylactics and are not overusing acute medication (£5,971 per QALY)
    - Patients have previously been treated with topiramate, which is a common 2nd or 3rd line oral prophylactic therapy in UK practice (£8,301 per QALY)

- Probabilistic Sensitivity Analysis estimates Botox is cost-effective in 69.1% of scenarios at a threshold of £20,000 per QALY

- These results are robust to changes in the methods used to calculate utilities, assumptions made around treatment administration and stopping rules

- The ICER is most sensitive to the time horizon used in analysis, with the ICER increasing to £27,162 over the 24 week double blind period, this however is a highly conservative analysis, as at the end of the trial period, treated patients are in better health states.

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor.

Identifying cost-effectiveness studies that enrolled the population of interest for the decision problem

Historically, patients with chronic migraine have been excluded from migraine prophylaxis trials because they were considered to be too highly disabled and treatment resistant (Dodick, 2010). Few preventative therapies have been investigated, and no pharmacological therapy apart from Botox is specifically licensed for chronic migraine prophylaxis. Consequently, there is a lack of effectiveness, and cost-effectiveness data available from studies of patients in the general population of chronic migraine sufferers (Dodick, 2010). This renders identification of data regarding the specific subgroup of patients described in the decision problem under review even more complex.

Botox is indicated and licensed for the prophylaxis of headaches in adults with chronic migraine; however, the final scope identifies a specific subgroup within the licensed indication for which this technology is to be appraised. Specifically this subgroup comprises adults with headaches on at least 15 days per month of which at least 8 days are associated with chronic migraine and i) whose condition has failed to respond to at least three prior pharmacological prophylaxis therapies and ii) where medication overuse has been appropriately managed.

This subgroup, although the primary focus of the decision problem, was unlikely to be identified through standard searches of electronic databases. Thus, the literature searches focused on the wider chronic migraine population.

Intervention and comparators relevant to the decision problem

The intervention of interest in the decision problem is Botox and the comparator is standard management without Botox excluding invasive procedures.

At present, no drugs are licensed for the specific indication of prophylaxis of headache in chronic migraine in the UK. However a number of oral prophylactic medications are used to manage this population and are recommended in guidelines (BASH,2010;SIGN, 2008) . Typically these include beta-blockers, antidepressants and antiepileptics. In the context of the decision problem Botox is to be appraised in patients whose condition has failed to respond to at least three prior pharmacological prophylactic

therapies. As the only other licensed pharmacologic agent for migraine, topiramate is assumed to be included in these treatment choices, as it is routinely used in a 2nd or 3rd line position in UK practice.. Consequently, given the position of Botox in the treatment pathway oral medications recommended in UK guidelines (BASH, 2010; SIGN, 2008) are not considered relevant comparators for the purposes of this literature search

For chronic migraine patients whose condition has failed to respond to oral prophylactic medications, there has, until now, been no specifically licensed or consistently applied therapeutic option available. Patients in this population who are seen by a headache specialist are currently managed with a range of invasive procedures and unlicensed medications or may receive no prophylactic medication (i.e. optimised acute rescue medications, such as triptans and pain relief, only).

Examples of invasive procedures utilised in this population include minimally invasive procedures such as Greater Occipital Nerve (GON) block (local injections of steroids and/or local anaesthetics) in the area of the greater occipital nerve) and more complex procedures such as occipital nerve stimulation (the neurostimulator delivers electrical impulses via insulated lead wires tunnelled under the skin near the occipital nerves at the base of the head). Dihydroergotamine (DHE) which is given intravenously during an inpatient stay and methysergide (taken orally) are ergot alkaloids which are used sparingly in specialist centres. Methysergide is “held in reserve”, partly due to its association with retroperitoneal fibrosis and the severe rebound headache experienced by many patients when attempting to withdraw from it after several months use (BASH, 2010). Intravenous DHE is investigational due to insufficient evidence for its effectiveness and is not licensed for use in the UK (Saper, 2006).

All of these therapies are considered potentially relevant comparators, because they are considered for use only when patients with chronic migraine have failed on prior oral prophylactic medications. Although these comparator therapies are not licensed for use in chronic migraine, data on their clinical effectiveness would permit an assessment of their relative benefit compared to Botox. Thus, they have been included in the literature searches as potential comparator treatments.

Study selection: inclusion criteria

Population

Chronic migraine is defined as the experience of headaches on at least 15 days per month, of which at least 8 days are with migraine as set out in the International Classification of Headache Disorders (IHS, 2004). Therefore, only those studies that enrolled patients with chronic migraine or analysed this subset of patients separately were included. Studies that described patients

as having “transformed migraine” and/or “chronic daily headache” were included if the definition was clearly described and found to be equivalent to chronic migraine.

Study design

Any studies that were described as an economic evaluation were selected. These could include cost-effectiveness studies, cost-minimisation studies or cost-utility studies. The review included all economic studies that evaluated Botox (botulinum toxin type A) and relevant comparators in comparison to either an active comparator or to placebo for the treatment of chronic migraine, regardless of design.

Electronic searches

The following electronic databases were searched: Medline (via OVID), Embase (via OVID), Cochrane Library: Cochrane database of systematic reviews, Cochrane register of clinical trials, NHS Health Economic Evaluation Database (HEED), Health Technology Assessment (HTA) database (all via Wiley), CINAHL(via NHS Evidence), PsycINFO (via OVID, Econlit (via OVID), Science Citation Index (Web of Knowledge), and Conference Proceedings Index (Web of Knowledge). In addition, searches were conducted on the NICE, AWMSG and SMC websites for technology appraisals.

The search included terms to describe the intervention of interest (botulinum toxin type A and Botox, comparators (nerve block, nerve stimulation etc.) which included topiramate for completeness even though this was not considered an appropriate comparator for the decision problem, the population (migraine sufferers) and methodological search filters such as those produced by the Scottish Intercollegiate Guidelines Network (SIGN) to refine the results to the appropriate types of evidence (economic analyses). The full search strategy is provided in Appendix 2.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales..

Botox

No published cost-effectiveness studies of Botox were identified in the literature searches.

The Scottish Medicines Consortium issued advice in 2011 on the use of Botox following a full submission. Allergan submitted a cost-utility analysis comparing botulinum toxin type A injections given every 12 weeks to best supportive care in patients experiencing chronic migraine who had previously failed on oral prophylactic therapy due to side-effects or lack of efficacy and

were in the care of a headache specialist in a secondary care centre (Scottish Medicines Consortium 2011). This study is presented in Table 6.1, with the differences between the approach presented in the SMC submission and NICE submission discussed in Section 6.1.3 (Page 123).

Other treatments

One cost-effectiveness paper (Brown et al. 2006), and one other SMC submission were identified (Scottish Medicines Consortium 2006), both concerning topiramate. These were included even though this treatment was not considered relevant to the decision problem as it could potentially have informed the modelling approach used in this submission. These studies are presented in Table 6.2.

Table 6.1: Summary list of other cost-effectiveness evaluations of Botox

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
Scottish Medicines Consortium Submission	2011	Scotland	Markov model comparing Botox vs placebo treatment for chronic migraine	NS	0.08 QALY gain over 2 years	Incremental cost of £1,394	£17,436
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s); NS, Not Stated							

Table 6.2: Summary list of other cost-effectiveness evaluations of other treatments

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs	ICER (per QALY gained)
Brown et al.	2005	UK / Scotland	1 year decision tree model comparing topiramate and 'no preventative treatment'	NS	0.0384 QALYs gained	£220 additional cost per year	£5,728
Scottish Medicines Consortium Submission	2006	Scotland	1 year decision tree model comparing topiramate and 'acute treatment only'	Between 12 & 65	NS	NS	£5,728
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s); NS, Not Stated							

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified.

Quality assessment – Scottish Medicines Consortium (2011)

The only relevant study identified in Section 6.1.2 for the cost-effectiveness of Botox was from the SMC website, and contains information regarding the Allergan SMC submission for Botox in the prevention of chronic migraine.

The model used in this STA submission is derived from the same basic structure used for the SMC submission, however there are key differences, in terms of the definition of the decision problem, the approach taken in the submission, and modelling approach, these are discussed in Appendix 17.

The changes made allowed precise consideration of some of the questions raised by the SMC.

[redacted]

Quality assessment – Brown (2005) & Scottish Medicines Consortium (2006)

The submission made to the Scottish Medicines Consortium for topiramate for the prophylaxis of migraine headache in adults (note this is not an analysis of *chronic* migraine), is based on the model constructed by Brown et al. (2005). These have therefore been quality assessed together.

Although not relevant to the decision problem as topiramate is not a comparator listed in the scope (as the only other licensed treatment, it would be rational that patients would previously have been treated with topiramate before becoming eligible for Botox treatment as defined in the decision problem), the paper is quality assessed to investigate the modeling methods, and the appropriateness of these in the context of this submission..

The alternatives assessed in the model are topiramate and no preventative treat from the perspective of the UK NHS (with a focus on Scotland), with a societal perspective also included. No attempt was made to compare topiramate to other oral prophylactic therapies routinely prescribed in the UK.

Costs and outcomes were taken from published literature sources, and are clearly stated. Comprehensive results tables were not available, however sensitivity analyses were provided. The key drivers of the model were the number of migraines per month experienced by patients, the risk of triptan usage to treat a migraine, and the disutility associated with a migraine attack..

The conclusion of the paper was that topiramate was a cost-effective treatment from the perspective of the UK NHS, and dominant when a societal perspective was considered. Findings were also robust to sensitivity analyses. The conclusions drawn were supported by the results of the study, which appears to be relatively transparent and well conducted.

The model structure allows patients who respond to treatment to have a reduction in the frequency of Migraines – by ≥75% (Major response), 50% - 75% (Moderate response), and <50% (limited response). This is not appropriate for modeling the cost-effectiveness of chronic migraine however, as the response categories are highly heterogeneous. For example in a chronic migraine population a patient experiencing 26 headache days per 28 days, may have a 'moderate response' and show a corresponding fall in headache days of 50% (to 13), however this would put them in a better health state than a patient beginning with 15 headache days per 28 days, and experiencing only a 'limited response' to 8 headache days per 28 days. Because of this highly variable patient population, this model structure was not used in the economic modeling of Botox in chronic migraine as it is unknown whether utility is a linear function vs change in headache days.

The approach used by Brown et al. should also be considered in the context of the clinical evidence for topiramate, which is a different population from those treated with Botox. (Brown et al. 2006). Brown et al. state:

> "The three pivotal trials of TPM in migraine prevention reported reductions in migraine frequency of approximately 2.1 migraines per month from a baseline of about 5.6"

This is in contrast to clinical trials 191622-079 and 191622-080 where all patients had to experience at least 15 headache days per month, of which 8 were migraines, in order to be eligible for the study and the mean number of migraines at baseline was >19. It may therefore be the case that while the heterogeneity was less of an issue for the Brown et al. model (which looked at a much less severely impacted population) it does render it unsuitable for use in an evaluation of chronic migraine treatments such as Botox.

6.2 De novo analysis

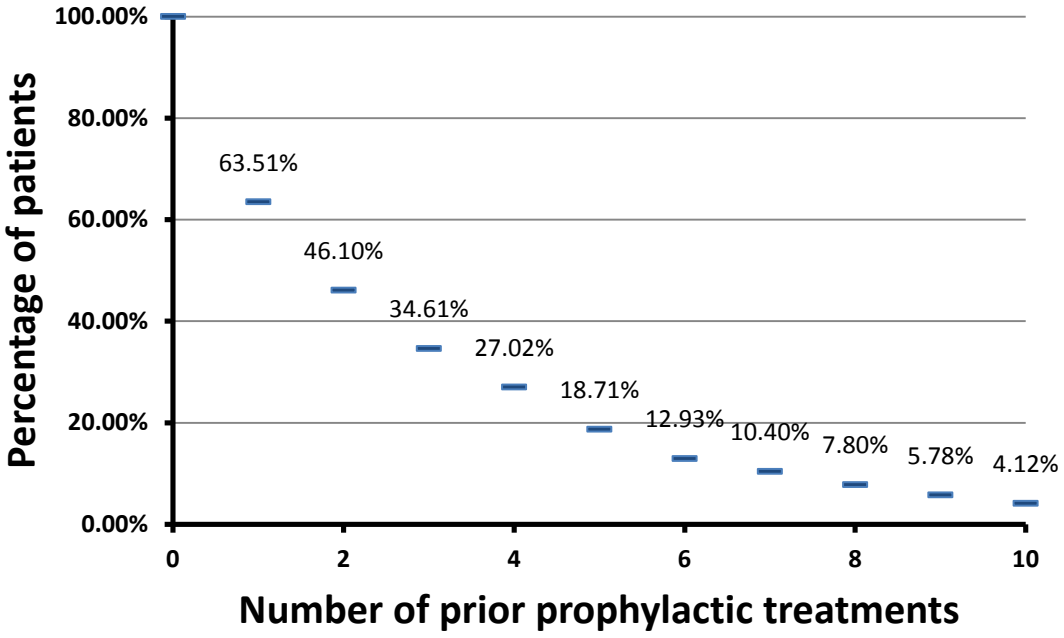
Patients

6.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively?

The population specified in the NICE Final Scope is more restrictive than the population studied in clinical trials, and the UK marketing authorisation. The NICE scope specifies the population of interest to be patients who have failed on three or more prior pharmacological therapies which is viewed as a pragmatic position in therapy in the context of the NHS.

This requirement was not included in the clinical trials program for Botox, consequently the patients enrolled represent a mix of treatment naïve and treatment experienced patients who could have received different levels of prior prophylaxis, during a long history of disease. The proportion of patients who have experienced different levels of oral prophylactic pre-treatment prior to entry in Clinical Studies 191622-079 and 191622-080 is shown in Figure 6.1.

Figure 6.1: Proportion of patients who have been previously treated in clinical studies 191622-079 and 191622-080, and the cumulative number of treatments they have previously received.



Of the patients entering in to the Botox clinical trial program, there are a high number of patients who have received prior prophylactic treatments. For example in the trial program

- 63.5% (879/1384) of patients had received at least 1 prior treatment
- 46.1% (638/1384) of patients had received at least 2 prior treatments
- 34.6% (479/1384) of patients had received at least 3 prior treatments

In Section 5.5 we demonstrate that the effect of Botox relative to placebo remains directionally similar, regardless of the number of previous treatments patients have experienced. Therefore for reasons of power, the dataset of patients who have received at least 1 previous oral prophylactic treatment is used to represent the population specified in the NICE scope. This allows a doubling of the number of patients available for analysis and therefore reduces uncertainty (n=879 vs 479). This assumption is also explored in sensitivity analyses (Section 6.6.1, page162) where the datasets for both the ≥3 prior oral prophylacticsand the whole population dataset (regardless of number of previous treatments and including treatment naïve patients) are used and compared to illustrate validity of this approach.

It is discussed in Section 5.10.4 that the evidence base provided in the Botox clinical trials is representative of the UK chronic migraine population not only in terms of demographic characteristics, but also in terms of acute medication overuse. Therefore while the decision problem is more restrictive than the marketing authorisation and design of the evidence base, the available data allow us to address the decision problem specified.

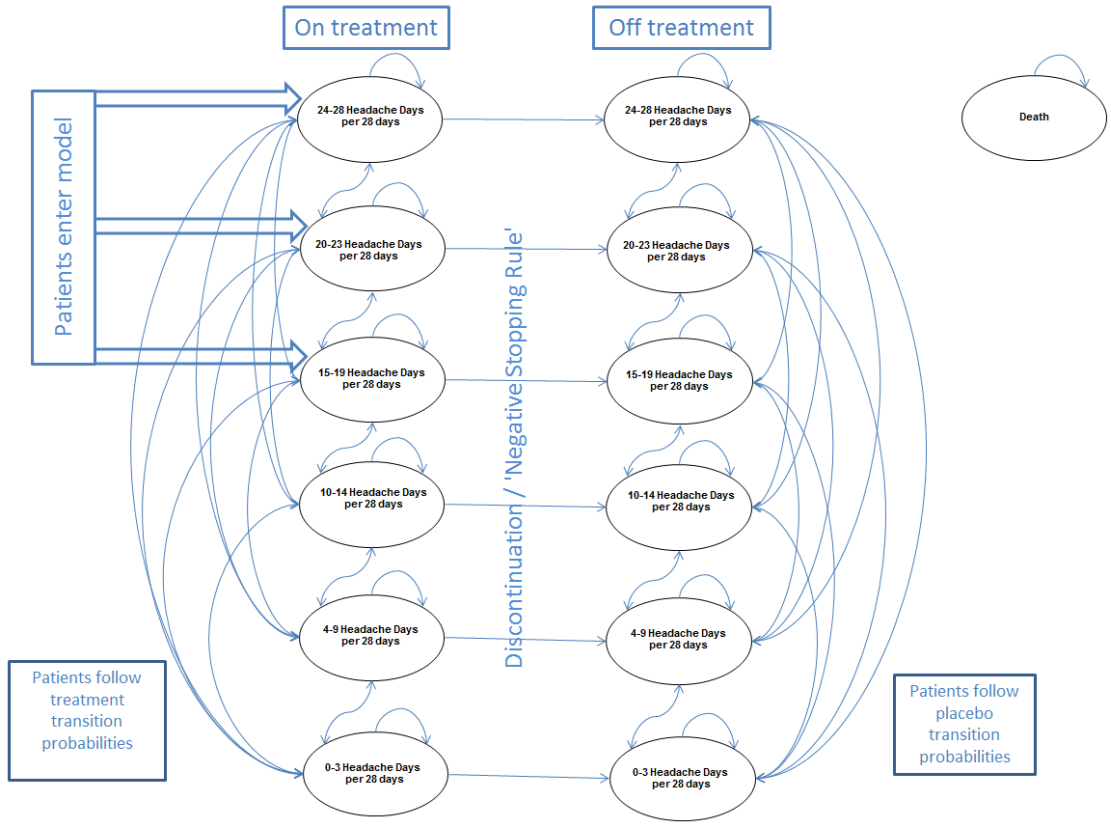
Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

The effect of Botox has been modelled using the results from clinical trials 191622-079 and 191622-080. This model compares the costs and outcomes estimated in treating chronic migraine patients with either Botox or placebo, using transition probabilities observed in the clinical trial programme.

The decision problem however does not fully address the question of value of the role of Botox in the UK as there is a potential for additional cost offsets downstream in the treatment pathway which is not captured in the primary model. Therefore a second exploratory model has been constructed to compare the pathway of care including Botox or excluding Botox. The treatment pathway model looks at the cost of care for patients, using NHS costs and expert opinion of the likely pathway for previously treated patients; this is provided in Appendix 17.

Figure 6.2: Model diagram, Primary economic model (Markov structure)



The primary economic model has a Markov structure in which patients can move between 6 health states defined by the frequency of headache days per 28 days experienced by patients, and the absorbing state of death. The model health states are linked to recognised clinical classifications of migraine with the 3 states with the highest frequency of headache corresponding to ‘chronic’ migraine, and the 3 state with the fewest headaches per 28 days corresponding to ‘episodic’ migraine. The justification for the boundaries of the health states is shown in Table 6.3 (Page 130).

In the model patients start in the ‘chronic migraine’ health states of ‘15-19 Headache Days per 28 days’, ’20-23 Headache Days per 28 days’ and ’24-28 Headache Days per 28 days’. The proportion of patients starting in each state is taken from the combined Botox and placebo arms of 191622-079 and 191622-080 clinical trials for the chosen dataset). In this way the modelled population are representative of the total clinical trial population, which includes 1 patient (treated with placebo) who began with 14 headache days per 28 days and was a protocol deviation.

Transition probabilities are calculated from the clinical trial database, with patients transitioning between health states every 12 weeks (the frequency of

administration of Botox). Patients are assumed to move health states at the beginning of the 12 week period, and remain in that state for the duration of the cycle.

Patients continue to move around the health states defined in the model according to the probabilities linked to the treatment they are on. In each model cycle there is a chance of a patient experiencing treatment discontinuation (either from placebo (sham) treatment or Botox). The probability of discontinuation occurring is taken from either observed values in the clinical trial, or through the application of response-orientated stopping rules described in Section 6.3.2 (Page 135). Once a patient has discontinued they continue to transition between health states using the transition probabilities seen with placebo treatment (regardless of original treatment allocation), but do not incur treatment costs. Patients remain in the discontinuation state for the duration of the model.

There is no evidence to support disease specific mortality relevant to chronic migraine. For this reason the model does not include any altered mortality linked to chronic migraine or the interventions under study. This means that all improvements in QALYs are due to improvements in HRQL. Background mortality is modelled for both arms based on UK life tables.

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The primary economic model is built around the number of headache days experienced by each patient over a 28 day period with an important distinction made between episodic migraine (0-15 headaches per 28 days) and chronic migraine (15+ headache per 28 days). This diagnostic “cut off” is also a major determinant of quality of life, and reflects the primary endpoint for the pooled analysis of studies 191622-079 and 191622-080, as discussed in Section 5.3.6 (Page 58). The definitions used in the model to subdivide healthstates of interest reflect the importance of this endpoint, and are taken from the clinical literature.

In the model, patients who transition to a health state with fewer than 15 headaches per 28 days, may no longer be defined as experiencing ‘chronic migraine’ but instead are exhibiting a frequency of headache days that would be described as “episodic”.

Whilst many important aspects of the condition, and its direct impact, are captured in the absolute number of headaches experienced by patients, it is likely that other aspects such as the severity or duration of individual headaches are not reflected fully. Examination of the secondary endpoints

studied in PREEMPT reveals that Botox treatment also has an important impact on these other important dimensions of overall health status in chronic migraine patients. Section 5.5.3 describes the significant improvement shown in patients treated with Botox on the Patient Reported Outcomes (PROs) of the Migraine Specific Questionnaire (MSQ) and Headache Impact test (HIT-6) which are designed to represent the breadth of clinical effect on HRQL in a more multi-dimensional sense. Furthermore the data from PREEMPT show a decrease in the number of cumulative hours of headache on headache days, also likely to impact quality of life. Section 6.4.8 (Page 151) provides an analysis of cumulative hours of headache on headache days, and an analysis of moderate/severe headache days by healthstate to illustrate how these secondary measures also vary with the primary endpoint considered for modelling.

In order to capture the value in quality of life driven by this improvement in various headache measures, patient responses, as measured by the Migraine Specific Questionnaire (MSQ) in the trial are mapped to the EQ-5D using UK weightings. This algorithm was developed to provide utility scores for each of the health states by treatment in the absence of the inclusion of a suitable generic HRQL instrument in the trial protocol. This approach is described in detail in Section 6.4.4 (Page 146). The MSQ has many scales similar to those seen in generic instruments such as the EQ-5D and SF-36, and was developed specifically to examine the quality of life impact in migraine.

In order to further justify the number of headache days as the basis for the economic modelling, a regression analysis was performed. Using the number of headache days, gender, age as explanatory variables for the EQ-5D score for patients in the International Burden of Migraine Study, detailed in Section 6.4.5 (Page 148),

In the regression analysis, the coefficient attached to headache days is -0.014 (SE: 0.0007, $p<0.001$), gender 0.013 (SE: 0.0084, $p=0.132$) and age -0.002 (SE: 0.0003, $p<0.001$), along with an Intercept of 0.822 (SE: 0.0121, $P<0.001$) (SAS Table ‘2-1029’).

This infers that each additional headache day experienced by a patient over a 28 day period, causes a fall in patient utility of 0.014, all other things being equal.

6.2.4 Please define what the health states in the model are meant to capture.

Details of the health states used in the Markov model are provided in Table 6.3.

Table 6.3: Justification for health states – primary economic model

Health State (Headache days per 28 days)	Justification		Reference
0-3	ICHD II (IHS 2004)	Prophylaxis is not indicated for migraineurs with less than 4 Headache days per month	Lipton (2007)
4-9		Patients receive prophylactic treatment at 4 Headache days per month	Lipton (2007)
10-14		Frequent episodic migraineurs at risk of becoming chronic migraineur	Lipton (2009)
15-19	ICHD II-R (2006) (IHS 2006) Section 6.2.5	Based on distribution of number of Headache days at baseline, mean (SD) = 20 (4)	PREEMPT phase 3 studies 191622-079 and 191622-080
20-23		Distributional assumption to explore movement within the chronic migraine health state	
24+		Distributional assumption to explore movement within the chronic migraine health state	

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2?

The strongest evidence for the use of prophylactic treatment comes from the reduction in headache days experienced by patients. For this reason this endpoint was designated as the primary endpoint in the pooled analysis of clinical trials 191622-079 and 191622-080.

By modelling the number of headache days experienced by patients, we are able to use the endpoint which plays a part in the diagnosis of the condition (in order to be diagnosed as experiencing ‘chronic migraine’, patients must experience 15 or more migraines per 28 days).

Clinical trials 191622-079 and 191622-080 obtained a strong placebo response (discussed in Section 5.10.2).By modelling the number of headaches per 28 days in both the Botox and placebo populations, we are able to understand the incremental value of Botox over the therapeutic effect of placebo treatment in this condition, which is likely to be greater than the results of an observational strategy in real life practice.

6.2.6 Provide a table containing the following information and any additional features of the model not previously reported.

Table 6.4: Key features of the primary (Markov) economic model

Factor	Chosen values	Justification	Reference
Time horizon	2 years	Extrapolation from the clinical trials program informed by Expert Opinion and guidelines regarding the likely length of prophylactic treatment.	Expert opinion regarding likely length of treatment, commensurate with current prophylaxis
Cycle length	12 weeks	Treatment frequency of Botox	Clinical trials 191622-079 and 191622-080
Half-cycle correction	Yes	Necessary given the 12 week time cycle	-
Were health effects measured in QALYs; if not, what was used?	Yes	-	-
Discount of 3.5% for utilities and costs	Yes	-	NICE (2008)
Perspective (NHS/PSS)	NHS	-	NICE (2008)
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5?

The decision problem specified by NICE is narrower than the marketing authorisation for the product (see Section 6.2.1, Page 125). The evidence used is therefore reflective of this restricted positioning, and not of the whole population for whom the product is indicated.

The dosing used in the economic model is that listed in the marketing authorisation for Botox and as used in the clinical trials program of 155 – 195 Units (described Sections 5.9.2. This dosage is unaffected by the restricted population specified in the decision problem.

6.2.8 Has a treatment continuation rule been assumed?

Two stopping rules are applied in the Markov model, termed ‘negative stopping rule’ applied in the absence of a sufficient response and ‘positive stopping rule’ applied at the point that withdrawal of treatment might be attempted following a specified response to treatment.

Negative stopping rule

As part of the development process for the economic model, clinical validation of the structure was received. When asked about the decision process that would be undertaken when deciding whether to continue treatment beyond an initial 1-2 cycles, clinical experts advised that they would not continue to treat patients who have experienced insufficient benefit from therapy. In further discussion this stopping rule was clarified to be that, in general, patients whose headache frequency has not substantially decreased following two successive treatment cycles would discontinue Botox therapy.

Further discussion with clinicians experienced in using Botox for the treatment of chronic migraine has provided additional support for this discontinuation rule. They highlighted that the nature of the therapy (a series of 31-39 injections), causes only ‘motivated’ patients to continue treatment. A sufficient response to treatment was felt to increase the probability of a patient returning for treatment.

In the model, this rule has been implemented in transition probabilities. Patients not experiencing an improvement of at least two health states following two cycles of treatment (a minimum of 4 headache days per 28 days), are assumed to cease treatment and to move to discontinuation. After discontinuation they are assumed to follow placebo transition probabilities with no treatment costs assumed (beyond acute medication and medical resource

use linked to their health state) until the end of the model. The rule can be applied independently to both Botox and placebo.

Scenario analyses are conducted in Section 6.6 (Page 162), which make modifications to this stopping rule. However it is felt in practice that patients not experiencing a sufficient benefit will be unlikely to be retreated, or to be motivated to seek retreatment.

Positive stopping rule

Consultation with clinical experts also informed assumptions beyond the available trial data as to how treatment might be continued, or withdrawn in the event of a sufficient sustained response at the end of the first year of treatment, particularly for patients who might now reside in health states defined as 'episodic migraine'. At this point, Clinical Experts advise that they may attempt to withdraw Botox from the treatment regimen for these patients, re-introducing treatment at a later time point if headaches were to return at a higher frequency (>15 headache days per month).

After 56 weeks of treatment, beyond the available trial data, we therefore assume that patients can either i) continue to receive treatment at 12 weekly intervals or ii) stop treatment to see whether benefit is retained.

- *Continue with Botox treatment.* The patients assigned to this arm continue to be treated with Botox at 12 week intervals, and follow the transition probabilities described in Section 6.3.2 (Page135)
- *Cease Botox treatment.* Patients assigned to this arm are assumed to cease Botox therapy and to remain within their destination healthstate throughout the second year

Clinical experts suggest that the decision as to whether or not to continue treatment may be driven by whether patients remain in a chronic migraine health state (15 or more headache days per 28 days) or alternatively have moved to an episodic migraine health state (fewer than 15 headache days per 28 days).

- Patients who begin the second year of treatment in an episodic health state (0-3, 4-9 or 10-14 headache days per months) are all assumed to discontinue Botox at week 60 (after 5 cycles). It is assumed that patients continue in the same health state with no transitions (aside from death). The assumptions around the outcomes for patients who discontinue Botox in the event of a good response are varied in sensitivity analysis.

  These patients incur the cost of treatment discontinuation, assumed to equate to ongoing medical management of their condition but no additional costs for potential oral prophylaxis are included within the

model, although these treatments might be reattempted for some patients at this point.

- Patients who remain in a chronic migraine state (≥15 headache days per month) after 1 year are all assumed to continue to receive Botox therapy at 12 weekly intervals and to follow the transition probabilities described in Section 6.3.2 (Page 135)

Scenario analyses are conducted in Section 6.6 around this stopping rule and include the impact of removing the stopping rule - allowing all patients to continue on therapy, with the standard transition probabilities.

6.3 Clinical parameters and variables

6.3.1 Please demonstrate how the clinical data were implemented into the model.

Section 5.3.7 (Page 60) discusses the efficacy of Botox in patients who have previously received oral prophylactic treatments. The comparison is made between the whole pooled population of clinical studies 191622-079 and 191622-080, patients previously treated with ≥1 prior oral prophylactic, patients treated with ≥3 prior prophylactics, and patients previously treated with topiramate, a treatment which is used in the treatment of migraine in the UK in a 2nd or 3rd line position, and which has been evaluated for prophylactic use in patients with migraine by the SMC (Scottish Medicines Consortium 2006).

From examining the data presented in Section 5, it can be seen that the response rates seen with both Botox and placebo are similar, with increasing levels of pre-treatment with oral prophylactics, the difference between Botox and placebo remains approximately equal.

The magnitutde of effect seen with Botox relative to placebo is broadly consistent beyond 1 previous treatment. This supports the decision described in Section 6.2.1 (Page 125) to use the ≥1 prior oral prophylactic population to represent the ≥3 prior oral prophylactic population for reasons of statistical power, as it appears to be generalisable to the expected outcomes.

The patient level data from which this data is drawn was then extracted, and used to calculate transition probabilities for each patient subgroup of interest. These were then used in the model to inform individual patient movements between health states.

The specific SAS data used to model each population is presented in Appendix 19. The method for using these SAS data tables to calculate the transition probabilities is described in Section 6.3.2.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

In order to calculate the transition probabilities in the model, patient level data were extracted from the clinical trial database (pooled analysis). The data were examined to calculate at the beginning of each 12 week cycle of treatment (Botox or placebo), which patients had transitioned health states relative to their previous health state, and what transitions they had made.

Patient level data was extracted for every permutation of the following

- Prior treatments (all patients, ≥ 1 prior oral prophylactic, ≥3 prior oral prophylactic, prior treatment with topiramate)

- Negative stopping rule (including negative stopping rule, excluding negative stopping rule)
- Acute medication overuse status (all patients, excluding baseline acute medication overuse patients)

A full set of transition matrices used in the model is provided in Appendix 14, with the source SAS data tables listed in Appendix 19. The method of calculation for probabilities from these patient counts is shown below.

Deterministic

In most cases, the transition probabilities are calculated as:

$$\frac{\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad}{}$$

For example, given the patient movement matrix in Table 6.5, the probability of moving from 10-14 HA days per month to 4-9 HA days per month is 28/88 = 0.318.

Table 6.5: Patient movements, week 12-24, ≥1 prior treatments, not excluding medication overusers, stopping rule of discontinuation if patient has not improved 2 health states in 2 cycles – BOTOX arm

	24 Week Health State							
12 Week Health State	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	Totals
0-3 HA Days per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4-9 HA Days per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10-14 HA Days per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15-19 HA Days per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20-23 HA Days per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24+ HA Days per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

However, there are some exceptions to this as in some cases, there were 0 patients starting in some of the health states. When this occurs, it is not possible to calculate the probability, because we cannot divide by zero.

To counter this, if there were no patients starting in a given state within the transitions observed in the PREEMPT data set, we have assumed that all patients who start in that state within the model, remain within it.

In the 'positive stopping rule', patients can "maintain benefit and remain in their final health state." (This is used in the base case for 100% of episodic patients who cease treatment after year 1.) In this case, the identity matrix is used, so that patients remain in the state they were in when they ceased treatment. This matrix is shown in Table 6.6.

Table 6.6: Identity Matrix

	New Health State							
Existing Health State	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	Totals
0-3 HA Days per month	1	0	0	0	0	0	0	1
4-9 HA Days per month	0	1	0	0	0	0	0	1
10-14 HA Days per month	0	0	1	0	0	0	0	1
15-19 HA Days per month	0	0	0	1	0	0	0	1
20-23 HA Days per month	0	0	0	0	1	0	0	1
24+ HA Days per month	0	0	0	0	0	1	0	1
Discontinued Treatment	0	0	0	0	0	0	1	1

Probabilistic

Where it has been possible to calculate the deterministic transition probabilities using the formula:

The probabilistic transition probabilities have been calculated using random Dirichlet probabilities. This is explained in several stages

1. A prior distribution is assumed. For 0-12 weeks, a table with every value being ‘1’ is assumed. For 12-24 weeks, the prior distribution is the posterior distribution for 0-12 weeks (and for 24+ is 12-24 weeks)
2. Posterior distribution probabilities are calculated, using the posterior distribution and the formula:

---

3. Cumulative Gamma/Normal distributions are calculated. If the patient number for the posterior distribution for movement from state A to state B is less than 0.3 × the total number of patients in the posterior distribution, an inverse gamma distribution is used, otherwise an inverse normal distribution is used.
    a. The inverse gamma distribution is uses a random probability with alpha = patient number for the posterior distribution for movement from state A to state B, and beta = 1.
    b. The inverse normal distribution is uses a random probability with mean = patient number for the posterior distribution for movement from state A to state B, and standard = square root of patient number for the posterior distribution for movement from state A to state B.
4. The Dirichlet probabilities are calculated, using the cumulative gamma/normal distributions and the formula:

Wherever it was not possible to calculate transition probabilities using the formula the transition probabilities are not varied in the PSA. These cases use the identity matrix, which cannot be probabilistically varied – the values are either 0 or 1.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Section 5.5 shows the mean number of headache days experienced by patients in the clinical trials 191622-079 and 191622-080. A large fall in this number is observed for both the Botox and placebo arms of the trials over the first 12 weeks of the trial.

This large reduction in the number of headache days experienced by patients becomes a steady decline for the period from week 12 to 24 (and beyond, in the case of Botox treatment). In order to accurately model this steep fall, then steady decline, the first 24 weeks of the model (RCT period) are modeled using the observed patient movements by applying two separate sets of transition probabilities for movements between weeks 0-12 and weeks 12-24 respectively.

At week 24, the clinical trial was unblinded, becoming an open label study. Patients treated with placebo in the initial 24 week period were switched to Botox therapy. Due to the limited availability of double blind placebo data, the transition probabilities for weeks 12-24 are then used to model weeks 24+ for placebo patients. In the base case for Botox therapy, the open label phase data is also used in the calculation of transition probabilities.

The week 0-12 data were not used in the calculation of transition probabilities for subsequent cycles due to the dramatic fall in the number of headache days seen with treatment (Section 5.5) not being representative of repeat treatment with either Botox or placebo.

The impact of this approach is tested in sensitivity analysis (Section 6.6, Page 162) with a scenario constructed which uses all transition probabilities (including weeks 0-12 and 12-24) to calculate the transition probabilities for the week 24+ period.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example,was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Surrogate outcomes have not been used – the outcome of headache days per month is of importance to patients, and is directly measured in clinical trials 191622-079 and 191622-080.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide details:

Over the course of this project Allergan have undertaken several rounds of expert review to inform both the approach to the cost-effectiveness, and the clinical assumptions used in the model.

Advice from clinicians and an expert involved with the SMC was taken on modeling and approach. Following this further meetings were held with 4 UK clinicians, and Professor Ron Akehurst (ScHARR).

After these meetings we held a combined clinical and economic advisory board to review the draft economic model and data presentation. In addition to the four clinical advisors were Professor Nick Freemantle (UCL), Dr James Chilcott (ScHARR) and Professor Alastair Gray (University of Oxford).To obtain the final clinical assumptions for the economic model, we held two further advisory boards consisting of 7 practicing clinicians from across the UK. One advisory board was held with clinicians practicing in the North of England, and one with clinicians practicing in the South. The aim of the two advisory boards was to understand any local variation in the treatment of chronic migraine and to inform the economic modeling assumptions.

In each of the meetings there was a discussion of the issues, with an attempt then made to reach consensus, or general rules. Where there was disagreement this was reflected in the approach used. Where uncertainty was raised, we have conducted appropriate sensitivity analyses to help inform the decision problem. The resulting assumptions are tabulated in Appendix 15 showing the ranges discussed.

A final advisory panel to review the presentation of data, support for assumptions, and comprehensiveness of sensitivity analyses was then held, attended by Professor Nick Freemantle (UCL), Dr James Chilcott (ScHARR) and Professor Alastair Gray (University of Oxford).

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis

The key settings applied in the economic model are shown in Table 6.7. A full list of variables is presented in Appendix 14, with a justification of the base case of the economic model given in Table 6.8.

Table 6.7: Summary of settings applied in the primary economic model

Variable	**Value**	**Reference to section in submission**
Age	42	Section 5.3.4
Time horizon	2 years (108 weeks)	Section 6.3.7
Number of prior treatments	≥1	Section 6.2.1
Negative Stopping Rule	Applied	Section 6.2.8
Positive Stopping Rule	Applied	Section 6.2.8
Transition probabilities weeks 0 – 12	Placebo: Weeks 0 – 12 Botox: Weeks 0 – 12	Section 6.3.3
Transition probabilities weeks 12 – 24	Placebo: Weeks 12 – 24 Botox: Weeks 24 – 24	Section 6.3.3
Transition probabilities weeks 24 -36 and beyond	Beyond available data, estimations have been as to the appropriate transition probabilities Placebo: Weeks 12 – 24 These probabilities (excluding the effects of any stopping rule) are assumed to be maintained Botox: Weeks 24 – 36, Weeks 36 – 48 and Weeks 48 – 56 (the open label phase), are summed and assumed to represent the likely course of chronic migraine data in Botox treated patients	Section 6.3.3
Utility values	MSQ patient data mapped to EQ-5D	Section 6.2.3, Section 6.4.4

Table 6.8: Base case economic model

Setting	Justification
Patient population ≥1 prior treatments	Outcomes seen in the PREEMPT trials are consistent throughout the number of prior treatments a patient has received. The model therefore uses this population to obtain the maximum sample size, given the number of transition probabilities involved with the 6 treatment related health states (in addition to death, and the event of discontinuation)
Time horizon = 2 years	A time horizon of 2 years was selected in order to allow an adequate exploration of the benefit of reducing the number of migraines patients have down to the level of 'episodic migraine', and maintaining patients at this level. It also reflects clinical advice on the likely total period of treatment that patients would be likely to be offered in the UK. Using a shortened time horizon, particularly the 24 week horizon, is inappropriate as patients at the end of the period are distributed in a very different fashion. The implicit assumption in a shorter time horizon (which does not allow the majority of patients to discontinue treatments), is that patients at the end of the trial period instantly revert to having equal outcomes; this is not supported by the observed patient movements. Patients in the Botox/Botox arm also continue to derive incremental benefit beyond week 24
Negative Stopping Rule	It is unlikely that patients will continue to return for treatment with an invasive procedure which has no benefit. Equally if a treatment is not seen as being beneficial, clinicians are unlikely to continue using that treatment. Application of the stopping rule allows NHS resources to be appropriately directed to patients who experience a sufficient treatment response.
Positive Stopping Rule	If a patient has been successfully treated, clinicians are likely to attempt to withdraw treatment, while seeking to maintain the benefits individual patients have experienced. This reflects the standard use of prophylactic treatment described in UK practice guidelines (BASH 2007).
Utility values	In the base case utilities are mapped by treatment arm from the MSQ (a patient reported outcome). Section 6.4 discusses the values used in the submission, and details the differences seen between the best and worst states Section 6.4.8 details the difference in MSQ and HIT-scores between patients treated in the same health state by treatment arm, and the number of cumulative hours of headache experienced by a patients in the same health state, by treatment arm

Costs applied in the model are described in Section 6.5.5 (Page 158), Utilities in Section 6.4.9 (Page 151) and resource use in Section 6.5.6 (Page 160).

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator?

Clinical trials 191622-079 and 191622-080 consisted of a 24 week double blind treatment period, followed by a 6 month open label extension. Clinical opinion however, was that patients would be treated for up to two years in some cases (Section 6.3.5, Page 140). It was therefore necessary to extrapolate beyond the clinical trial period.

In order to perform the extrapolation to the two year time horizon, the transition probabilities from the last observations captured within the clinical trial for each arm were used to allow patients to continue to 'cycle through' the Markov model states. We have presented the results of this extrapolation in a Markov Trace in Section 6.7.2 (Page 168).

The percentage of patients continuing treatment within the model is also driven by the stopping rules selected (Section 6.2.8, Page 132).

The impact of the time horizon used is explored in sensitivity analyses, with analyses performed across a range from 24 weeks (the double blind period of the clinical trial), to 1 year and 2 years (the base case).

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The key assumptions in the model are listed in Table 6.9 including either a reference to the section in the submission, or a justification of the assumption.

Table 6.9: Table of assumptions & justifications in the primary economic model

Assumption	Justification
The number of headache days experienced by a patient each month influences the level of healthcare utilization and the HRQL experienced by a patient.	This relationship was demonstrated in previous work in the area of chronic migraine (Brown et al. 2006), also in the International Burden of Migraine Study, and 191622-079 and 191622-080 clinical trials. The reduction in headache days was also the primary endpoint of the pooled analysis of the clinical trials program for Botox
Outcomes in the ≥ 3 prior treatment population replicate those in the ≥1 prior	Outcomes are directionally similar across all levels of pre-treatment. Using the ≥ 1 prior treatment group allows the maximum number

treatment population.	of patients to be used in the analysis. Section 6.2.1
Patients are discontinued if they do not improve by 2 health states after 2 treatments (Negative stopping rule).	Clinicians have indicated they would be unwilling to continue treating patients if they do not experience substantial benefit. It is also anticipated that patients would not be motivated to return for (invasive) treatment if their condition had not improved sufficiently. Section 6.2.8
Patients who after 1 year have been successfully treated with Botox, and have reached an “episodic” migraine frequency are discontinued and receive medical management which may or may not include oral prophylactics and acute treatments	Clinicians would discontinue patients from Botox therapy whose condition had improved to the episodic state. These patients would be treated with standard medical management to maintain their condition. Section 6.2.8
Patients who discontinue from either placebo or Botox therapy, transition as placebo patients did in the clinical trial	In the absence of evidence on discontinued patients, the conservative assumption was made that patients would continue to transition as placebo patients did in the clinical trial without incurring prophylaxis costs. Patients continue to experience costs related to the health state in which they are assumed to be in (acute medication and healthcare resource utilisation)
Patients experience a sharp fall in headache days upon commencing treatment (placebo or Botox) that is not considered representative of the treatment effect of repeat treatments	Clinical data shows that patients commencing treatment have a sharp fall in the number of headaches experienced per month, which is not representative of the long term trend. Section 6.3.3
Transition probabilities measured between week 12 and week 24 are representative of	It is assumed that patients will continue to receive benefits from repeat administrations

future anticipated outcomes with placebo treatment.	of placebo. Although double blind data is not available, the assumption appears reasonable from examination of transition probabilities for weeks 24 to 56 in the Botox arm. Section 6.3.3
Utility values differ between treatments within the same health state, due to the impact of Botox treatment on not just frequency, but severity of headaches, duration of headache episodes, pain and other relevant dimensions	Botox showed superiority on both the MSQ and HIT-6 patient reported outcomes, which were secondary endpoints in the clinical trial program (Section 6.2.3 and Section 6.4.4). These values have been converted via a mapping algorithm to produce health state utilities for each treatment. The difference between treatment arms (with a given frequency of migraine) can be seen in Section 6.4.8.
Botox is administered in 30 minutes of consultant time.	Clinician opinion based on private practice is that Botox can be administered in 15 minutes (see section 6.3.5). 30 minutes for each administration within the model allows the physician to also assess and counsel the patient. This is potentially conservative for subsequent treatments where the administration time might be expected to be reduced Section 6.5.5
One 200 Unit vial of Botox is used in each administration (155 – 195 Units), with no potential for vial sharing.	In line with the clinical trial dosing and the Botox SPC, which clinicians state they do not intend to deviate from. Section 6.5.5
Placebo represents outcomes seen in standard management of chronic migraine by a consultant, with one visit assumed every 24 weeks and acute medications administered as needed.	Patients with chronic migraine are assumed to be referred to a specialist consultant to manage their condition and optimize their background therapy/pain relief. Section 6.5.5
No disease specific mortality assumed in the model, nor is any differential mortality assumed between Botox and placebo	No evidence is available to indicate the presence of disease specific mortality, or that treating the disease would lead to improved survival. This has therefore not been included

	in the model.

6.4 Measurement and valuation of health effects

6.4.1 Please describe how a patient's HRQL is likely to change over the course of the condition.

The effective treatment of chronic migraine will result in fewer days on which headaches are experienced, with fewer episodes of headaches. It may also lead to a decreased intensity and/or duration of headaches. This improvement would allow some patients to revert to their usual daily activities, including paid employment.

In clinical trials 191622-079 and 191622-080 Botox demonstrated statistically significant improvements in patient HRQL when measured through both the MSQ and HIT-6 patient reported outcomes (Section 5.5.3). When these results are applied via a mapping function to the EQ-5D, the improvement in HRQL between health states can be seen, and is shown in Section 6.4.9, Page 151 – in both treatment arms there is a difference of approximately 0.25 in the utility of the best and worst health states.

HRQL data derived from clinical trials

6.4.2 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence)

No full generic quality of life instrument was included in either 191622-079 or 191622-080. HRQL results therefore have been mapped using data from the MSQ (Section 6.4.2, Page 146) and International Burden of Migraine Study (Section 6.4.6, Page 148).

Mapping

6.4.3 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.

- Details of the methodology used.
- Details of validation of the mapping technique.

As no generic instrument was used in the clinical trials program (Section 6.4.3, Page 146), a mapping exercise was conducted ([redacted]) .This submitted paper is reproduced in full in Appendix 20.

The International Burden of Migraine Study (IBMS) discussed in Section 6.4.6 was an international survey over 9 countries with 10,650 individuals participating who experienced episodic or chronic migraine. In the survey patients were administered the MSQ, HIT-6 and EQ-5D. Using the responses from these surveys, two mapping exercises were conducted, for both the MSQ and HIT-6 to enable utilities to be estimated from direct PRO measurements in the PREEMPT studies.

In the mapping an OLS regression was used to estimate the EQ-5D scores of patients, given their MSQ or HIT-6 score in the IBMS. Models were selected based on the accuracy of their predictions. The MSQ model was chosen for use in this submission, as it was developed for use in a migraine population (HIT-6 was developed for use in the general headache population). The MSQ is also more sensitive to changes, due to a reduction in ceiling effects, as seen with the HIT-6 algorithm which is not as sensitive at the ends of the spectrum.

[redacted]

[redacted]

This mapping algorithm was then applied to the responses given by patients in clinical trials 191622-079 and 191622-080, separated in to the health states patients were in when they completed the questionnaire (with the ‘chronic migraine’ algorithm used for those experiencing over 15 headache days per month, and the ‘episodic migraine’ algorithm used for those experiencing fewer than 15 headache days per month. The results were presented separately by treatment arm.

By using patient level data, we are able to understand the broader effects of treatment beyond the number of headaches experienced by patients. This includes the side effect profile of Botox, and also the effect of treatment on headache intensity, pain and duration (headache hours), which otherwise would not be captured by the Markov based model, as these health states are based only on the number of headaches experienced, not these other multidimensional considerations of total treatment impact.

In the base case we have used values mapped from the MSQ, listed in Section 6.4.9.

HRQL studies

6.4.4 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology.

Full details of the literature search methods used to identify clinical effectiveness evidence for Botox and relevant comparators can be found in Section 5.2. These searches include studies that measured HRQL.

6.4.5 Provide details of the studies in which HRQL is measured

Studies relevant to the decision problem that reported HRQL outcomes

Studies relevant to the decision problem were selected for inclusion if the study endpoints included HRQL outcomes. Specifically the subgroup of patients relevant to the decision problem are adults with headaches on at least 15 days per month of which at least 8 days are associated with chronic migraine and i) whose condition has failed to respond to at least three prior pharmacological prophylaxis therapies and ii) medication overuse has been appropriately managed. These included studies of Botox vs. placebo, and studies of comparator therapies such as occipital nerve block, nerve stimulation and IV DHE. Those studies relevant to the decision problem are listed in Table 6.10.

Table 6.10: Trials relevant to the decision problem in which HRQL was measured.

Study size and length	Intervention	Comparator	Primary outcome	Health related Quality of life outcomes
(Aurora et al. 2010), n=679 (PREEMPT 1), 24 wks	Botox	Placebo	Mean change in headache episode frequency per 28 days.	HIT-6 score, MSQ v.2 and HIS.
(Diener et al. 2010), n=705 (PREEMPT 2), 24 wks	Botox	Placebo	Mean change in frequency of headache days per 28 days.	HIT-6 score, the MSQ v.2 and HIS.
(Freitag et al. 2008), n=60, 4 mths	Botox	Placebo	Mean change in migraine episode frequency.	MIDAS and headache pain specific QoL measure.
(Saper et al. 2011), n=75, 3 mths.	Occipital nerve stimulation.	Medical management.	Percent reduction in headache days per month.	MIDAS.

HIS=Headache Impact Score, HIT-6 = Headache Impact Test-6, MIDAS=Migraine Disability Assessment Score, MIQ=Migraine Impact Questionnaire, MSQv.2=Migraine Specific Quality of Life Questionnaire version 2

In addition to the studies in Table 6.11, the Brown et al (2006) cost-effectiveness study of topiramate also reported utility figures (Section 6.1.3, Page 123). The results from this study are not generalisable however, as the utilities are taken from the topiramate trials across a broad migraine population (rather than chronic migraine) who on average had far fewer headache or migraine days per month. Also no information was provided on the improvement in headache days per 28 days (the health states used in the de novo model).

Finally work was commissioned by Allergan in order to estimate both HRQL and resource utilisation amongst a migraine population, this was the International Burden of Migraine (IBMS) study.

The IBMS study was a cross-sectional, web-based, observational survey with participants from 9 countries, including the UK, and was conducted from February to April 2009. Potential participants were asked about previous diagnoses of a broad range of health problems.

These responses and validated screening questions were used to assess the diagnostic features of migraine based on the ICHD-II criteria and determine eligibility. Participants were also asked to report the number of days with a headache of any intensity in the last three months. Eligible participants were categorised as either episodic migraine (<15 headache days per month) or chronic migraine (≥15 headache days per month) at the time of survey completion and enrolment continued until a minimum of 50 chronic migraineurs were identified in each country (100 in the US).

A total of 63,001 panellists in nine countries were contacted. Of those, 30.7% (N=19,365) responded to the email invitation and completed the eligibility screening and 55.0% (N=10,650) were eligible to complete the survey based on screening criteria. Surveys were completed by 81.9% (N=8,726) of eligible responders. The proportion of the sample representing the UK was 12.3% for episodic migraine.

Patients in the IBMS were administered the EQ-5D. The EQ-5D responses then had UK weightings applied, and were split by the health states used in the economic model (Blumenfeld et al. 2011).

6.4.6 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Due both to the modeling approach and population under study in the de novo model being different to that of Brown et al (2006), there are no values from the literature to compare with those mapped from the patient population in question. Utility values from Brown et al. may also not be appropriate due to the differences in study population highlighted in Section 6.1.3, however the results do show congruence with those presented by Xu, discussed in Section 6.4.9

Adverse events

6.4.7 Please describe how adverse events have an impact on HRQL.

The frequency of adverse events in clinical trials 191622-079 and 191622-080 was low with only 5.3% of Botox and 2.4% of placebo patients reporting serious adverse events (Section 5.9.2). The difference between treatments in adverse events appears to be mainly linked to musculoskeletal & connective tissue disorders and nervous system disorders**.**

We have captured the adverse event profile of Botox in two ways. Firstly Botox showed a higher rate of discontinuation relative to placebo due to adverse events (4.1% vs 0.9% in the double blind phase). This is incorporated in the model as transition probabilities are taken directly from the patient level data, including these discontinuations.

Secondly the impact of adverse events on HRQL is captured through the use of patient level data in the mapping algorithm. Splitting this by treatment allows us to understand the impact of each treatment on HRQL both in terms of adverse events, and the overall impact on headache severity. Consequently we can investigate whether the positive effects of Botox outweigh the adverse events.

Quality-of-life data used in cost-effectiveness analysis

6.4.8 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8

Base case utility values are presented in Table 6.11, showing the utility values for patients treated with ≥ 1 prior oral prophylactic, split by health state and treatment arm. Extensive sensitivity analyses around the utility values used are presented in Section 6.6.1 (Page 162) including values directly measured in the IBMS.

In the base case differential utilities are used between the two arms, to reflect the difference seen in patient reported outcomes throughout clinical trials 191622-079 and 191622-080. In the clinical trials, patients treated with Botox showed a benefit on both the MSQ and HIT-6. This is shown in Table 6.13

The use of different utilities in the placebo and Botox arms is also supported by data on the mean change from baseline in the number of headaches (Table 6.13). It can be seen that even in the same health state, patients treated with Botox experience fewer hours of headaches in a given health state. For example patients in the 4-9 headaches per 28 days health state at

24 weeks experienced a fall of 182 hours when treated with Botox, but only a fall of 165 hours on placebo, a difference of 17 hours, a difference of 10%.

The utility data used demonstrates that the fewer headache days experienced per month, the higher the utility, while in the same health state based only on headache days, Botox patients experience a utility benefit over placebo.

The utility values generated from the results do contain one inconsistency - the 24+ health state with Botox has a higher utility than the 20-24 health state). This is likely to be a consequence of reduced patient numbers, with few patients (n=43, n=41) in these health states. These results however have not been altered as they are from patient level data, and have been used in the model as they are shown in the table.

Justification for this can be seen in Table 6.13, where the results for the MSQ Total Score are better for Botox in all 6 health states. This pattern is continued where Botox shows better HIT-6 total score data that placebo in 5 out of 6 of the health states. Table 6.12 contains results for the change from baseline in the number of moderate or severe headache days per month. This also consistently shows a benefit for Botox over placebo, even within the same health state - in no cases do patients experience more of these moderate/severe days with Botox when compared to placebo (even at the same number of headache days per month), supporting the hypothesis that Botox affects not only frequency of headaches, but other factors affecting quality of life.

The reduction in length of migraine can be seen in Table 6.12, which shows the change from baseline in the number of cumulative hours of headache experienced by patients, by health state over a 28 day period. When treated with Botox, patients show mean changes from -15.2 to 0.8 hours per 28 days (depending on health state). When treated with placebo, patients show mean changes of -15.2 to 2.2 hours per 28 days (depending on health state).

In one health state (0-3 headaches per 28 days) placebo shows equivalent reductions in cumulative headache hours to Botox, with results worse than Botox in the remaining 5 health states.

Table 6.11: Base case utility values – mapped from the MSQ for patients with ≥1 prior treatment. Utilities split by health state and treatment

Health State	Botox			Placebo		
	N	Mean	SD	n	Mean	S.D
0 - 3	94	0.746	0.013	65	0.724	0.017
4 – 9	160	0.719	0.011	129	0.658	0.011
10 – 14	105	0.652	0.013	126	0.620	0.014
15 – 19	85	0.602	0.018	96	0.568	0.020
20 – 24	41	0.515	0.035	52	0.558	0.028
24 +	43	0.601	0.031	76	0.479	0.025

Table 6.12: Change from baseline in number of moderate/Severe headache days per month by treatment group at week 24.

Health State	Botox			Placebo		
	N	Mean	SD	n	Mean	S.D
0 - 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 – 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 – 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 – 19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 – 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 +	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: SAS Table 2-1157

Table 6.13: HRQL measures from PREEMPT at week 24: change from baseline in cumulative hours of headache per month, MSQ Total Score and HIT-6 total score, by health state

	Change from baseline in cumulative hours of headache per month at week 24						**MSQ at week 24**						**HIT-6 at week 24**					
	Placebo			**Botox**			**Placebo**			**Botox**			**Placebo**			**Botox**		
	N	**Mean**	**SD**	**n**	**Mean**	**S.D**	**N**	**Mean**	**SD**	**n**	**Mean**	**S.D**	**N**	**Mean**	**SD**	**n**	**Mean**	**S.D**
0 - 3	78	-233	104.04	106	-243	99.52	73	26.9	22.95	101	19.7	19.82	78	56.5	9.28	106	53.4	9.28
4 – 9	167	-165	89.25	194	-182	94.73	148	40.6	20.23	179	32.7	21.38	167	61.5	6.39	194	58.9	7.01
10 – 14	166	-102	81.18	159	-114	97.00	142	47.7	20.88	128	44.2	19.78	166	63.8	5.89	159	62.4	5.93
15 – 19	126	-25.3	83.38	117	-62.5	96.59	109	53.0	19.93	102	48.8	20.88	126	64.8	5.06	117	63.6	5.34
20 – 23	69	34.1	99.97	56	17.6	97.85	62	56.9	19.56	49	55.0	23.06	69	64.8	5.67	56	65.1	6.42
24 +	90	81.7	118.14	56	56.9	110.64	86	58.5	22.12	51	53.2	19.08	90	66	5.95	56	65.3	3.83

Sources: Headache days = SAS Table 2-1155, MSQ = SAS Table 2-1026, HIT-6 = SAS Table 2-1027

6.4.9 If clinical experts assessed the applicability of values available or estimated any values, please provide details

No HRQL values were derived by experts, however the mapping algorithm was reviewed for consistency by two experts from the University of Sheffield.

Patients experiencing chronic migraine have reduced HRQL due to the frequency of migraine. An assumption underpinning the model is that reducing the number of headaches experienced by a patient will improve this HRQL. This is highly likely considering the impact of headaches on EQ-5D (Section 6.2.3, Page 128).

The improvement in patient reported outcomes seen with Botox (Section 6.4.4, Page 146 and Section 6.4.8, Page 150) should also be considered, as this indicates Botox has impacts beyond simply the number of migraines experienced by patients, potentially impacting the severity of those migraines.

The utilities generated in this condition should also be considered against other diseases, to explain the severity of the condition.

Addition validation can be seen in the paper by Xu et al (2011), published in Quality of Life Research, titled “EuroQol (EQ-5D) health scores for patients with migraine”.

This paper describes the health related quality of life values of 330 adults who experience between 1 and 6 migraines per month in the United States. Compared to the general population, amigraine day was estimated to result in a utility decrement of approximately

- 0.140 (95% CI 0.0840 – 0.1940) for ‘mild migraine’,
- 0.186 (95% CI 0.1645 – 0.2053) for ‘moderate migraine’, and
- 0.483 (95% CI 0.4100 – 0.5654) for severe migraine.

These values are not directly comparable to those obtained in the analysis presented as they relate to the disutility of individual migraine days, rather than healthstates defined on a number of headache/migraine days per month

The results shown do however provide additional external validity to the healthstate scores observed from the PREEMPT data set.

6.4.10 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No health effects have been excluded from the analysis.

6.4.11 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Patients begin the model experiencing chronic migraine, which is separated in to three health states depending on the number of headache days experienced by the patient over a 28 day period. The starting states of patients for the 191622-079 and 191622-080 clinical trials were added from the Botox and placebo arms in order to construct a theoretical cohort of patients.

Section 6.2.3 (Page 128) discusses the impact of these headache frequencies on HRQL, describing how patients experience an improvement in HRQL through reducing the number of headache days the experience each month. The impact of treatment in reducing the number of headache days has a second order effect in improving HRQL.

6.4.12 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Over time HRQL would be expected to remain constant in each health state, with no increase (or decrease) anticipated. The effect of aging on utility has not been considered due to the short time horizon studied (2 years in the base case).

6.4.13 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

No amendments have been made to the utility values, beyond using the mapping algorithm described in Section 6.4.4 (Page 146) to generate utility values.

6.5 Resource identification, measurement and valuation

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

Chronic migraine patients will initially be seen by GPs, with patients who do not respond to first line therapies or those for whom further investigations are required referred on to specialists, principally neurologists.

The patients specified in the NICE Scope are those who have received ≥3 prior oral prophylactic medications. It is therefore likely that these patients will be managed in specialist centers, and thus consultant led costings are appropriate. Some of the interventions described later in the treatment pathway (Appendix 17) are only available in tertiary referral centres and so attract a different tariff.

Table 6.14: Costs used in the primary economic model

Type of resource	Cost	Code	Source	Note
GP visit	£32.00	N/A	PSSRU 2010	Cost for 11.7 minute consultation
Hospitalisation	£583.67	PA04A/ PA04B/ AA31Z	NHS Reference Costs 2009/10	Weighted (by FCEs) average for all codes relating to non-elective inpatient admissions for headache/ migraine
A&E visit	£90.94	VB09Z	NHS Reference Costs 2009/10	Weighted average for the cost of VB09Z codes
Cost of triptan per attack	£3.35	N/A	Prescription cost analysis (PCA) 2010 England	Weighted average for the mean cost of 1 triptan tablet in NHS England

(Department of Health 2011;PSSRU 2010)

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS Reference costs are appropriate in this condition due to the population treated being variable, and of a reasonable size. Patients in this population are currently managed in secondary care and therefore the figures given in NHS reference costs for outpatient appointments are relevant. It is also our understanding that neurology services are tariff exclusions, and therefore locally commissioned (DoH, 2010)

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies

Details of electronic searches

The following electronic databases were searched: Medline (via OVID), Embase (via OVID), Cochrane Library: Cochrane database of systematic reviews, Cochrane register of clinical trials, NHS Health Economic Evaluation Database (HEED), Health Technology Assessment (HTA) database (all via Wiley), CINAHL(via NHS Evidence), PsycINFO (via OVID, Econlit (via OVID), Science Citation Index (Web of Knowledge), and Conference Proceedings Index (Web of Knowledge).

The search included terms to describe the intervention of interest (botulinum toxin type A and Botox), alternative treatments and comparators (oral prophylactics, nerve block, occipital nerve stimulation etc.), the population (migraine sufferers) and methodological search filters such as those to refine the results to the appropriate types of evidence (economic analyses).

Table 6.15: Published studies identified as potentially relevant to the decision problem

Study	Country	Applicable to UK clinical practice	Cost valuations used in study
(Brown et al. 2006)	UK	No	The Brown study cites a paper by Caro et al, unlikely to be applicable in the UK.
(Fontebasso 2007)	Review of studies in UK and USA.	No	The paper by Fontebasso is a summary of topiramate for the treatment of migraine. While it does state reductions in resource use are possible, few figures are given, and none of use in modeling.
(Yu et al. 2009)	Review of the literature.	No	The paper discussed the methods and limitations of economic models in migraine, however the paper has a US focus, and is therefore unlikely to be applicable to UK clinical practice.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please details

Expert advisory boards were consulted to help outline potential patient pathways, and validate the amount of time needed to administer Botox. The method used for these advisory boards is discussed in Section 6.3.5 (Page 140)

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment

Botox is available in three vial sizes, 50 units (£77.50), 100 units (£138.20) and 200 units (£276.40).

The required dose of Botox in the evaluated indication ranges between 155 and 195 units. In the base case of the model we have therefore assumed the cost of a 200 unit vial of Botox.

Clinicians advised that administration of Botox can be completed within a 30 minute appointment. In the base case it is assumed that Botox will be administrated by a medical consultant - PSSRU 2010 costs an hour of consultant time at £146 (PSSRU, 2010). A 30 minute appointment is therefore assumed to cost £73.00 Sensitivity analyses have been conducted on this value, using a lower cost, assumed to represent Botox being administered by a nurse following 15 minutes with a consultant, and the cost of a neurology outpatient visit from NHS Reference costs (£139.61).

Patients who do not receive Botox do not accrue any technology or administration costs but do incur the costs of acute medications and consultations. Clinicians advised that a patient receiving standard care may have a 30 minute appointment with a medical consultant every 24 weeks as optimization of acute therapy is sought (see section 6.3.5), this cost is used for the administration of placebo within the model. A sensitivity analysis is conducted halving this to one visit every 48 weeks. Patients who discontinue therapy are assumed to incur no technology, administration or medical consultant costs, only costs linked to their health state, estimated from the IBMS (Blumenfeld at al 2010) as described in section 6.17.

The time points at which patients treated with placebo and acute medications only would have their appointments are unknown, therefore these patients are assumed to have a 15 minute appointment each 12 week cycle, costing £36.50 (£146/4). These costs are shown in Table 6.16

Table 6.16: Unit costs associated with the technology in the primary economic model, all costs per 12 week model cycle

Items	Botox (confidence interval)	Ref. in submission	Placebo plus acute medications only (confidence interval)	Ref. in submission
Technology cost	£276.40	Section 6.5.5	£0	Section 6.5.5
Administration cost	£73.00 (£51.10 - £94.90)	Section 6.5.5	£0	Section 6.5.5
Monitoring cost	£0.00	Section 6.5.5	£36.50 (£25.55 - £47.45)	Section 6.5.5
Total	**£349.40**		**£36.50**	

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state.

In the primary economic model, quantities of resources are taken from the International Burden of Migraine Study (Section 6.4.6, Page 148), as this data was collected in the study with results presented in Table 6.17 . Resource costs are taken from NHS reference costs (Section 6.5.2, Page 157) with combined results for these values, with the cost per health state, shown in Table 6.18.

Table 6.17: Resource use associated with each health state in the primary economic model

Health State	GP Visits	ER visits	Hospitalisation	Triptan Usage
0 - 3 migraines per 28 days	0.10	0.12	0.03	1.88
4 - 9 migraines per 28 days	0.30	0.28	0.08	5.07
10 - 14 migraines per 28 days	0.30	0.28	0.08	5.07
15 - 19 migraines per 28 days	0.58	0.63	0.32	7.29
20 - 23 migraines per 28 days	0.58	0.63	0.32	7.29
24+ migraines per 28 days	0.58	0.63	0.32	7.29

Table 6.18: Costs associated with each health state in the primary economic model

Cost per Health State	GP Visits	ER visits	Hospitalisation	Triptan Usage	Cost per 12 week cycle
0 - 3 migraines per 28 days	£3.20	£10.91	£17.51	£6.30	£37.92
4 - 9 migraines per 28 days	£9.60	£25.46	£46.69	£16.98	£98.74
10 - 14 migraines per 28 days	£9.60	£25.46	£46.69	£16.98	£98.74
15 - 19 migraines per 28 days	£18.56	£57.29	£186.78	£24.42	£287.05
20 - 23 migraines per 28 days	£18.56	£57.29	£186.78	£24.42	£287.05
24+ migraines per 28 days	£18.56	£57.29	£186.78	£24.42	£287.05

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9

The rate of adverse events in the trial was low (Section 5.9, Page98), with few events expected to incur treatment costs. The assumption has therefore been made in, that adverse events were handled within the administration of Botox or placebo, with any additional effects being captured in HRQL measures.

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Chronic migraine has a significant impact on productivity. A sensitivity analysis has therefore been conducted including a limited societal perspective in the primary economic model (Section 6.6.1, Page 162 and Section 6.7.9, Page 178). Average earnings data of £14.60 per hour from the Annual Survey on Hours and Earnings (Office for National Statistic 2009) was combined with IBMS data on the number of working hours lost in each health state.

This however will not capture the full societal cost of migraine, as other factors to consider are lost family time, opportunities at work that are not pursued, lost education time, and lost family / personal time.

6.6 Sensitivity analysis

6.6.1 Has the uncertainty around structural assumptions been investigated?

In the primary economic model the structural assumptions that have been made concern the:

- patient dataset,
- stopping rules,
- calculation of transition probabilities,
- model structure
- time horizon,
- source of utility scores, and
- perspective takes (NHS / Societal)

Each of these areas and the sensitivity analyses conducted are discussed in turn. A full list of analyses conducted (split by modeling area), and where the results can be found are listed in Table 6.20.

Patient dataset

In the base case we have used the ≥1 prior oral prophylactic patient group as a proxy for the ≥3 prior oral prophylactic group specified in the NICE scope, after showing consistent and generalisable outcomes across the two groups. However different patient populations can be analysed in the economic model, including the whole trial population (incorporating treatment naïve patients), or an analysis limited to those patients who had failed on prior treatments. Those who failed on prior treatment are categorized into patients who have received:

- ≥1 or more prior oral prophylactic,
- ≥3 or more prior oral prophylactic,and
- Previously treatment with topiramate.

A further set of scenario analysis were performed to examine these populations and consider the inclusion and exclusion of patients who were overusing acute medication at baseline. These analyses are provided in Section 6.9 (Page 182)

Stopping rules

There are two stopping rules that have been implemented within the model framework. The “negative stopping rule” moves Botox patients who have not improved by ≥2 health states after 2 cycles of treatment to the discontinued health states (variations of this rule are also explored in sensitivity analyses).

In this discontinued health state, patients follow placebo transition probabilities.

The “positive stopping rule” allows Botox treated patients to take one of 2 paths after 1 year of treatment, depending on their health state (episodic or chronic migraine):

- Continue treatment as in year 1, or
- Cease treatment with Botox, at which point oral prophylactics may be reattempted

Patients who take the 1st path and continue treatment as in year 1, transition between health states using the transition probabilities generated from clinical trials 191622-079 and 191622-080 (Section 6.3.2). Patients who take the 2nd path and cease treatment are assumed to move to acute management of their condition only, and remain in the health state that they occupied at the cessation of treatment for the remainder of the modeled period. This is explored through sensitivity analyses where patients discontinuing Botox in the event of a good response are assumed to follow the transition probabilities associated with placebo treatment thereafter,

Sensitivity analyses are conducted removing the “negative stopping rule”, removing the “positive stopping rule” and removing both the “negative stopping rule” and the “positive stopping rule” together.

Calculation of transition probabilities

In clinical trials 191622-079 and 191622-080, over the first 12 weeks of treatment, patients show a steep fall in the number of headache days. This effect is only observed in the 1st 12 cycles and is not seen in subsequent treatment cycles. These values are therefore not used in the calculation of transition probabilities beyond weeks 0-12 in the base case (Table 6.20) as they would bias any subsequent extrapolation.

In a sensitivity analysis however, the 0-12 week transition probabilities are included as part of the full 0-24 week dataset in the calculation of transition probabilities for subsequent cycles.

Table 6.19: Source of transition probabilities in the primary economic model base case

Time period	Source of Botox transition probabilities	Source of placebo + acute medications transition probabilities
0 – 12 weeks	Botox weeks 0 – 12	Placebo weeks 0 – 12
12 – 24 weeks	Botox weeks 12 – 24	Placebo weeks 12 – 24
24 weeks +	Botox weeks 24 – 36, 36 – 48, 48 – 56	Placebo weeks 12 – 24

Model structure

A sensitivity analysis is performed which examines the effect altering the model structure. In the sensitivity analysis the model is condensed to a simplified model, where patients are in the health states of 'infrequent migraine' (0-3 headache days per month), 'episodic migraine' (4-14 headache days per month), or chronic migraine (≥ 15 headache days per month). This tests the sensitivity of the model to the boundaries selected for the model health states.

Time horizon

A sensitivity analysis is performed which examines the effect of assuming a time horizon of 24 weeks (the double-blind phase of the trial). This scenario then contains no extrapolation of the observed data for either arm or any benefits of treatment beyond the RCT period. A time horizon of 1 year is then considered in sensitivity analyses, which allows full use of the observed data, with no extrapolation required for Botox treatment.

Source of utility values

There are two sources of utility values presented in the submission:

- MSQ mapped to EQ-5D, and
- EQ-5D directly measured in the International Burden of Migraine Study (IBMS)

Separate MSQ values can be used for Botox and placebo patients (as in the base case), or utilities be taken from the International Burden of Migraine Study (IBMS). Values from the IBMS study are assumed to be the same for both Botox and placebo patients, using the directly measured EQ-5D from IBMS patients, split by the number of headache days experienced by the patient per month (into the same healthstate classifications as used in the economic model).

These will differ from the MSQ derived utilities as they capture the utility associated with the health state according to untreated patients in that health state, however will not capture the benefits (shown to extend beyond purely the number of headache days experienced), or adverse effects, of treatment.

Table 6.20: Scenario analyses conducted in the primary economic model

Scenario	Page
Base case	Page 175
Patient dataset	
Whole trial population (including treatment naïve patients)	Page 178
≥ 3 prior oral prophylactic treatments	Page 178
Prior topiramate treatment	Page 178
Excluding patients who are overusing acute medication at baseline	Page 178
Stopping rules	
Excluding 'negative stopping rule'	Page 178
Excluding 'positive stopping rule'	Page 178
Excluding both 'positive' and 'negative' stopping rules	Page 178
Negative stopping rule adjusted: assumption patients must move improve by ≥ 1 health state(s) to avoid treatment discontinuation	Page 178
Positive stopping rule: assuming 50% of patients continue in current health state, and 50% of patients continue to be treated with Botox in both chronic and episodic migraine	Page 178
Positive stopping rule: assuming patients in an episodic state after Botox at week 60 do not remain in the same health state, but experience placebo transition probabilities and utilities	Page 178
Calculation of transition probabilities	
Inclusion of 0-12 week, and 12-24 week transition probabilities in calculating 24week+ transition probabilities	Page 179
Model structure	
3 health state model	Page 179
Time horizon	
24 week time horizon	Page 179
1 year (60 weeks) time horizon	Page 179
Calculation of utility values	
Utilities taken directly from the IBMS study	Page 179
6.6.1.1 Societal perspective	
Societal perspective taken, including lost working time	Page 179

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The deterministic sensitivity analyses conducted are listed in Table 6.21.

Table 6.21: Deterministic sensitivity analyses conducted in the primary economic model

Scenario	Page
Halving of Botox administration time to 15 minutes of consultant time	Page 175
Botox administration to consist of 15 minutes of consultant time, and 15 minutes of nurse time	Page 175
Botox administration listed as NHS Reference costs Neurology Outpatient visit (£139.61) (Service code 400, NHS Reference costs: Follow up attendance, non admitted, face to face)	Page 175
Patients treated with placebo and acute medication only receiving only one consultant appointment per 48 weeks to optimize acute therapy	Page 175

6.6.3 Was PSA undertaken?

Probabilistic Sensitivity Analysis was conducted, and is presented in Figure 6.7 and Figure 6.8 (Page 177).

Values were sampled from within their distributions for all parameters given in Appendix 14. Transition matrices were varied using a Dirichlet distribution as described in Section 6.3.2.

6.7 Results

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials

Table 6.22 and Table 6.23 present the primary model outcomes compared to the clinical trial outcomes. There are slight differences as a result of ‘merging’ the two starting cohorts to create a theoretical cohort of patients who are equal across both arms.

Table 6.22: Summary of model results compared to clinical trial results for 24 week time horizon.

Outcome	Clinical trial result	Model result
Mean headache days at baseline (Botox)	19.9	20.0
Mean headache days at baseline (Placebo)	19.8	20.1
Mean change from baseline in frequency of headache days (Botox)	-8.4	-9.5
Mean change from baseline in frequency of headache days (Placebo)	-6.7	-6.9
Mean intergroup difference in change in frequency of headache days	-2	-2.6

Table 6.23: Summary of model results (patient numbers) for 24 week time horizon

	Botox		Placebo	
	Clinical Result	Model Result	Clinical Result	Model Result
Number starting in 0-3 HA Days per 28 days Health State	0.00	0.00	0.00	0.52
Number starting in 4-9 HA Days per 28 days Health State	0.00	0.00	0.00	0.00
Number starting in 10-14 HA Days per 28 days Health State	0.00	0.48	1.00	0.52
Number starting in 15-19 HA Days per 28 days Health State	215.00	216.13	232.00	230.87
Number starting in 20-23 HA Days per 28 days Health State	127.00	123.78	129.00	132.22
Number starting in 24+ HA Days per 28 days Health State	83.00	84.61	92.00	90.39
Number ending in 0-3 HA Days per 28 days Health State	55.00	55.00	33.00	33.03
Number ending in 4-9 HA Days per 28 days Health State	107.00	106.98	92.00	91.81
Number ending in 10-14 HA Days per 28 days Health State	32.00	31.94	91.00	91.04
Number ending in 15-19 HA Days per 28 days Health State	14.00	13.96	78.00	78.15
Number ending in 20-23 HA Days per 28 days Health State	0.00	0.00	49.00	49.07
Number ending in 24+ HA Days per 28 days Health State	0.00	0.00	69.00	68.69
Number ending in Treatment Discontinuation	217.00	216.89	42.00	41.97

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time(Markov trace) for each state, supplying one for each comparator.

For the primary economic model a Markov trace is presented in Appendix 15, with the results presented graphically in Figure 6.3 and Figure 6.4.

Figure 6.3: Graphical representation of patient distribution across health states, Botox treated patients

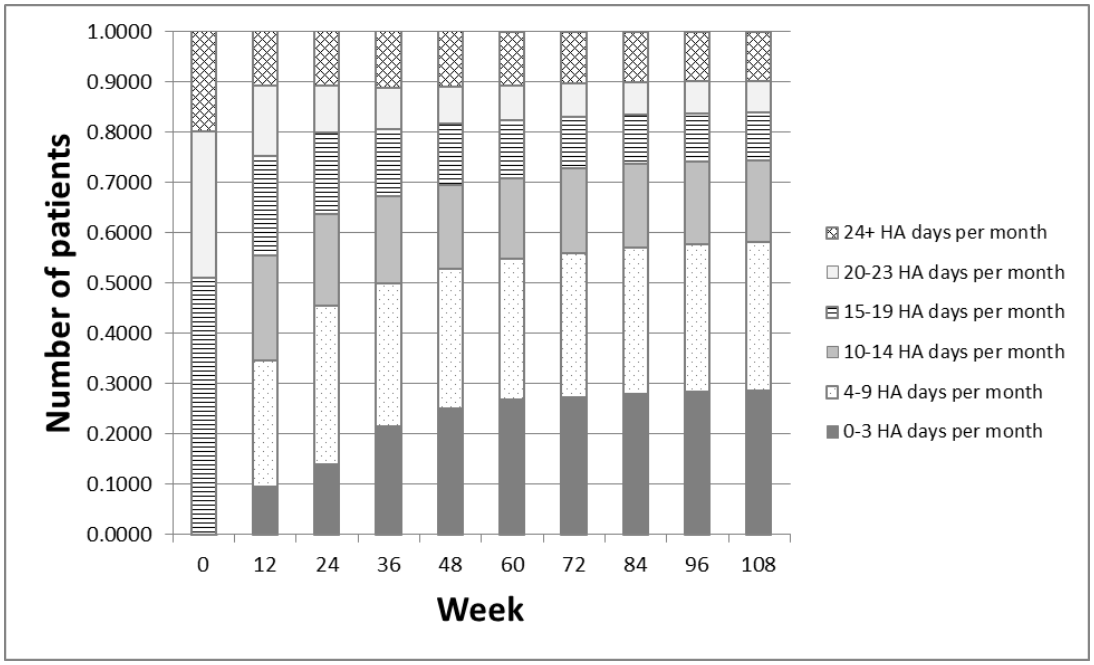
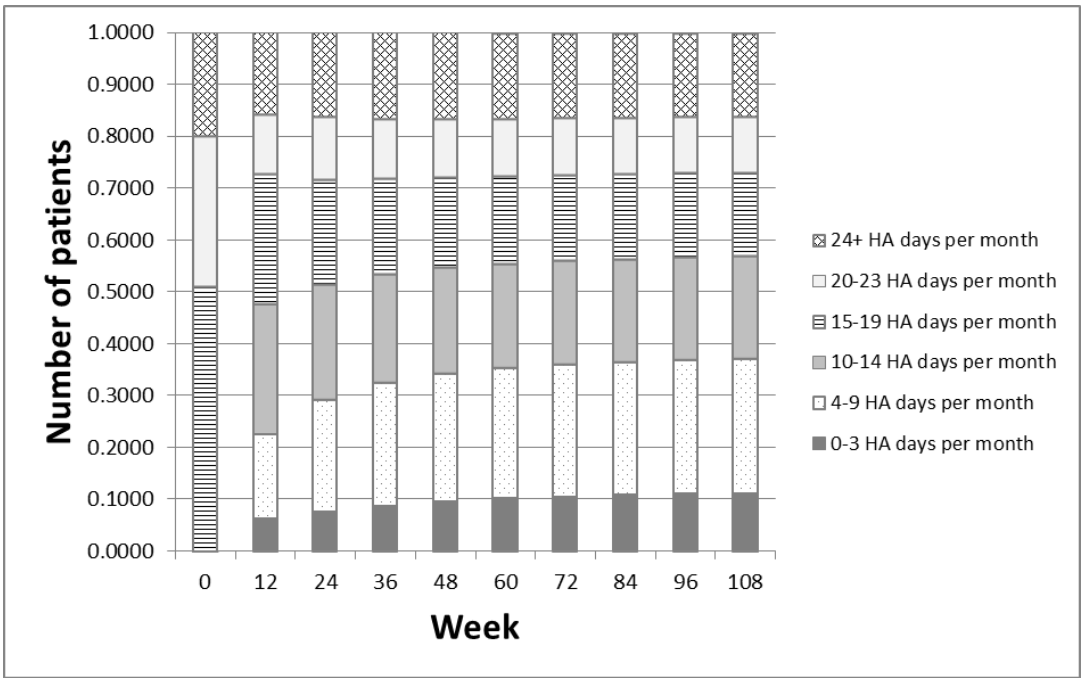


Figure 6.4: Graphical representation of patient distribution across health states, Placebo treated patients



6.7.3 Please provide details of how the model assumes QALYs accrued over time.

Patients accumulate QALYs in the primary economic model for each cycle they spend in each health state. Health states with fewer headaches per 28 days show higher utilities for patients residing in that state.

The gain in QALYs is shown graphically in Figure 6.5 and Figure 6.6, and summarized in. A Markov trace of utility generation is also available in Appendix 16.

Figure 6.5: Graphical representation of QALY accumulation over time by health state, Botox treated patients

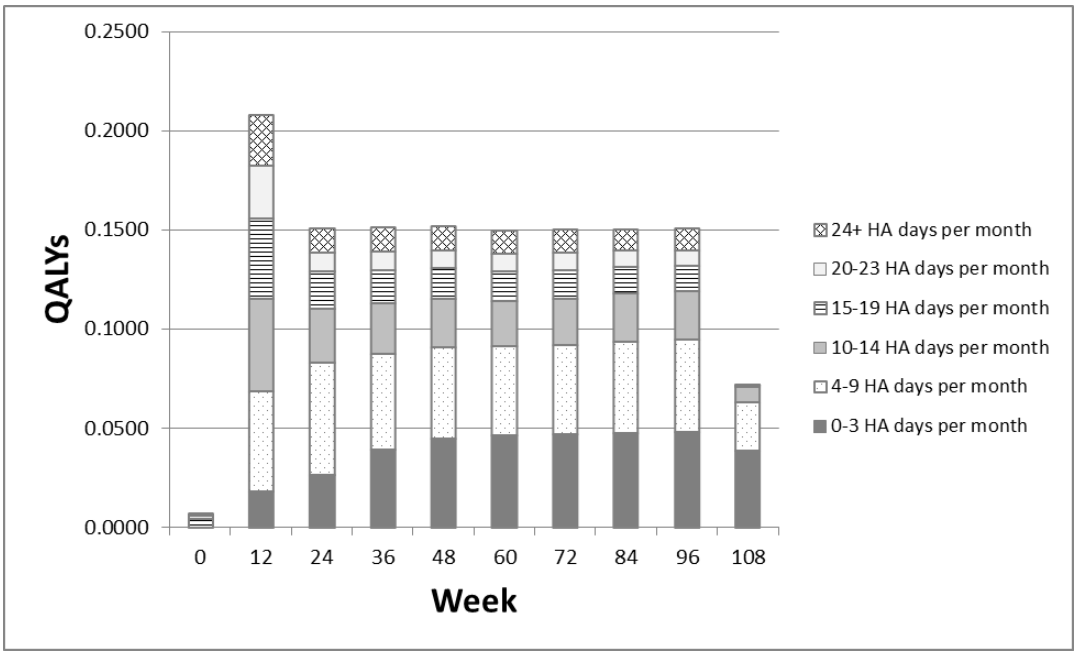
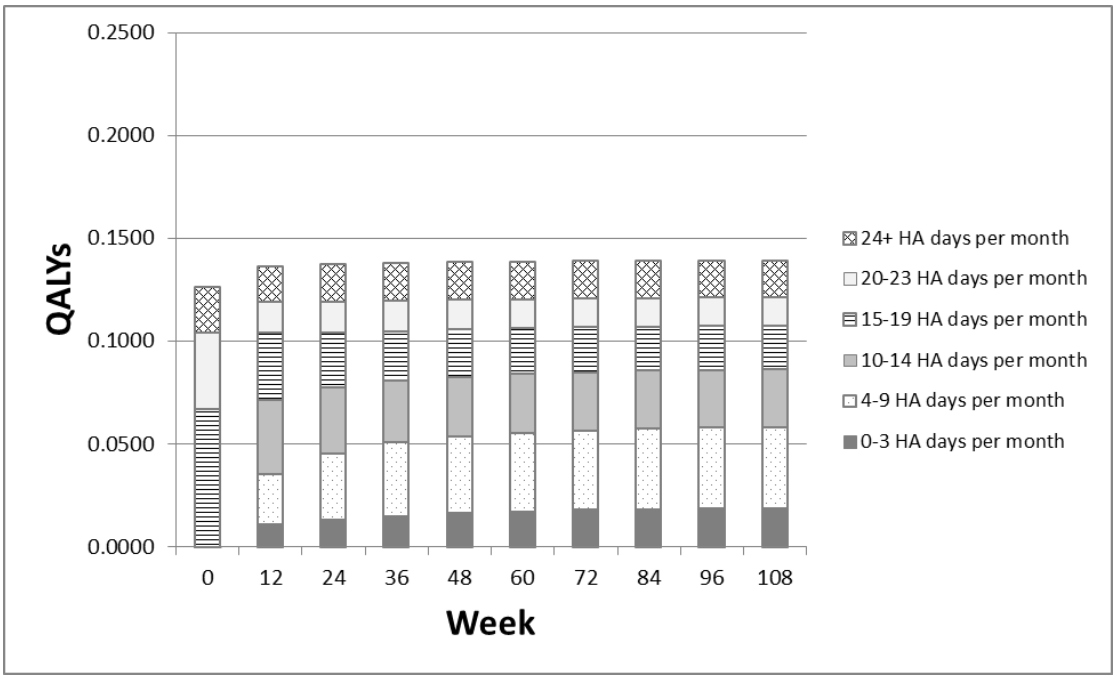


Figure 6.6: Graphical representation of QALY accumulation over time by health state, Placebo treated patients



6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results

Table 6.24 presents the model outputs by clinical outcomes for the primary economic model; the number of Life Years, and QALYs accumulated in each health state by both Botox and placebo patients.

Table 6.24: Life years and QALYs gained and costs incurred by health state in the primary economic model

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	£262	£64	£326	£24	£25	£48
4-9 HA Days per 28 days Health State	0.358	0.378	0.254	0.249	£326	£153	£480	£60	£162	£222
10-14 HA Days per 28 days Health State	0.149	0.341	0.097	0.212	£157	£64	£221	£54	£146	£200
15-19 HA Days per 28 days Health State	0.065	0.284	0.039	0.162	£98	£81	£179	£45	£354	£399
20-23 HA Days per 28 days Health State	0.033	0.184	0.017	0.102	£50	£41	£91	£29	£228	£257
24+ HA Days per 28 days Health State	0.024	0.274	0.015	0.131	£37	£30	£67	£43	£341	£385
Treatment discontinued patients*	1.010	0.416	0.598	0.252	£199	£816	£1,015	£12	£289	£301
Total	2.028	2.028	1.310	1.216	£1,130	£1,248	£2,378	£267	£1,545	£1,812

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

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.

Table 6.25, Table 6.26 and Table 6.27 present disaggregated results of the primary economic model.

Table 6.25: Summary of QALY gain by health state, primary economic model

Health state	QALY intervention (Botox)	QALY comparator (Placebo)	Increment	Absolute increment	% absolute increment
0-3 HA Days per 28 days Health State	0.290	0.109	0.181	0.181	19%
4-9 HA Days per 28 days Health State	0.254	0.249	0.005	0.005	1%
10-14 HA Days per 28 days Health State	0.097	0.212	-0.115	0.115	12%
15-19 HA Days per 28 days Health State	0.039	0.162	-0.123	0.123	13%
20-23 HA Days per 28 days Health State	0.017	0.102	-0.085	0.085	9%
24+ HA Days per 28 days Health State	0.015	0.131	-0.116	0.116	12%
Treatment discontinued patients*	0.598	0.252	0.346	0.346	36%
Total	1.310	1.216	0.093	0.971	100%

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

Table 6.26: Summary of costs by health state, primary economic model

Health state	Cost intervention (Botox)			Cost comparator (Placebo)			Increment	Absolute increment	% absolute increment
	Treatment cost	Other costs	Total	Treatment cost	Other costs	Total			
0-3 HA Days per 28 days Health State	£262	£64	£326	£24	£25	£48	£277	£277	14%
4-9 HA Days per 28 days Health State	£326	£153	£479	£60	£162	£221	£258	£258	13%
10-14 HA Days per 28 days Health State	£157	£64	£221	£54	£146	£200	£21	£21	1%
15-19 HA Days per 28 days Health State	£98	£81	£179	£45	£353	£398	-£219	£219	11%
20-23 HA Days per 28 days Health State	£50	£41	£91	£29	£228	£257	-£166	£166	8%
24+ HA Days per 28 days Health State	£37	£30	£67	£43	£341	£384	-£318	£318	16%
Treatment discontinued patients*	£199	£814	£1,013	£12	£288	£301	£713	£713	36%
Total	£1,129	£1,246	£2,376	£267	£1,542	£1,809	£862	£1,971	100%

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

Table 6.27: Summary of predicted resource use by category of cost, primary economic model

Item	Cost intervention (Botox)	Cost comparator (Placebo)	Increment	Absolute increment	% absolute increment
Drug cost	£894	£0	£894	£894	52%
Admin cost	£236	£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%

Base-case analysis

6.7.6 Please present your results.

The base results of the primary economic model are presented in Table 6.28. Results from the ≥1 prior treatment population are used to represent the ≥3 prior oral prophylactics population for reasons of sample size (Section 6.2.1 Page 125). In order to validate this approach the results for the ≥3 prior oral prophylactics treatment group are also presented in Table 6.28 as a scenario analysis.

The results show Botox to be cost effective with an ICER of £5,828. Although both Botox and placebo have identical life years (no incremental survival advantage is assumed), there is a gain of 0.09 QALYs over the 108 week (2 year) time horizon. Using these results it can be seen the average utility over the treatment period is 0.6135 for placebo, and 0.6611 for Botox.

The sensitivity analysis presented in Table 6.29 demonstrates that the model results in the ≥1 prior oral prophylactic treatment and ≥3 prior oral prophylactic treatments groups are very similar, thus support the use of the larger group to represent previously treated patients.

Table 6.28: Base-case results, primary economic model

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
≥1 prior oral prophylactic population							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,419	1.34	£2,388	1.31	£549	0.09	£5,828
≥3 prior oral prophylactics population							
Placebo	£1,936	1.23	£1,895	1.20			
Botox	£2,471	1.32	£2,438	1.29	£543	0.09	£6,083

Sensitivity analyses

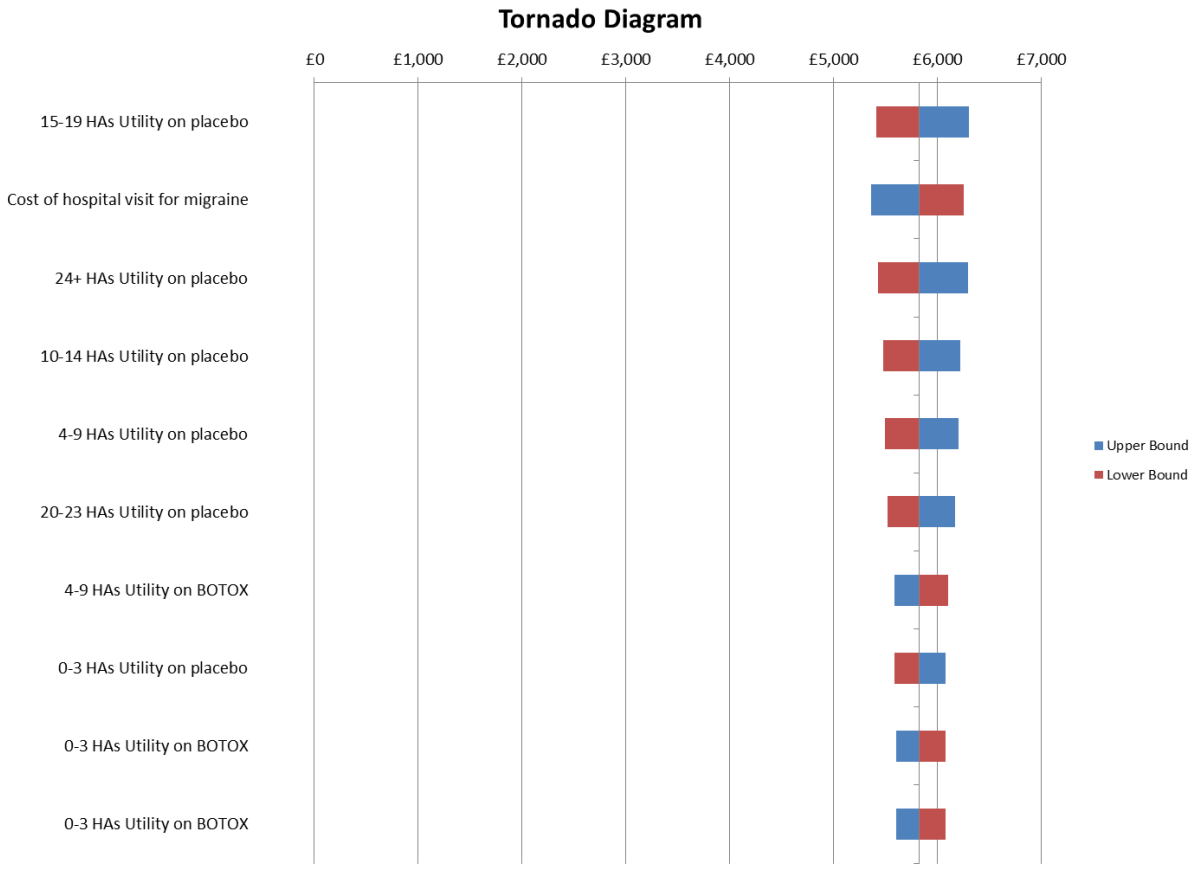
6.7.7 Please present results of deterministic sensitivity analysis.

Table 6.29 presents the results of deterministic sensitivity analyses, along with a tornado diagram (Figure 6.7) showing the sensitivity of the model to changes of parameters their 95% confidence intervals

Table 6.29: Results of deterministic sensitivity analyses conducted in the primary economic model

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Halving of Botox administration time to 15 minutes							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,308	1.34	£2,277	1.31	£438	0.09	£4,654
Administration of Botox consisting of 15 minutes consultant time, 15 minutes nurse time (£46.75)							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,339	1.34	£2,308	1.31	£469	0.09	£4,984
Administration of Botox billed as outpatient appointment (£139.61)							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,621	1.34	£2,590	1.31	£751	0.09	£7,972
Botox patients assumed to have a 10 minute consultant appointment mid-cycle (£73.00 + £24.33)							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,493	1.34	£2,461	1.31	£623	0.09	£6,611
Placebo patients assumed to visit consultant every 48 weeks (50% reduction)							
Placebo	£1,743	1.24	£1,705	1.22			
Botox	£2,382	1.34	£2,352	1.31	£647	0.09	£6,870

Figure 6.7: Tornado diagram, primary economic model



Deterministic sensitivity analyses show the finding of the cost-effectiveness of Botox to be robust to individual changes in the model, with the model being most sensitive to changes in the utility values used for placebo treatment (which is also used in the discontinuation health states), and the cost of hospitalisation.

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

A scatterplot of 1,000 runs performed is presented in Figure 6.8. A cost effectiveness acceptability curve (CEAC) (Figure 6.9) shows that Botox is likely to be cost effective – being under £20,000 per QALY in 69.1% of scenarios and under £30,000 per QALY in 74.30% of scenarios.

The uncertainty in the model is a result of the patient transitions, with small patient numbers in some matrices exaggerating the impact of the prior distribution. Furthermore as the model is only run over 9 cycles (108 weeks)

there is a limited amount of time for values at the tail ends of the distribution to return to the mean.

Figure 6.8: Scatterplot of probabilistic sensitivity analysis, 1,000 simulations

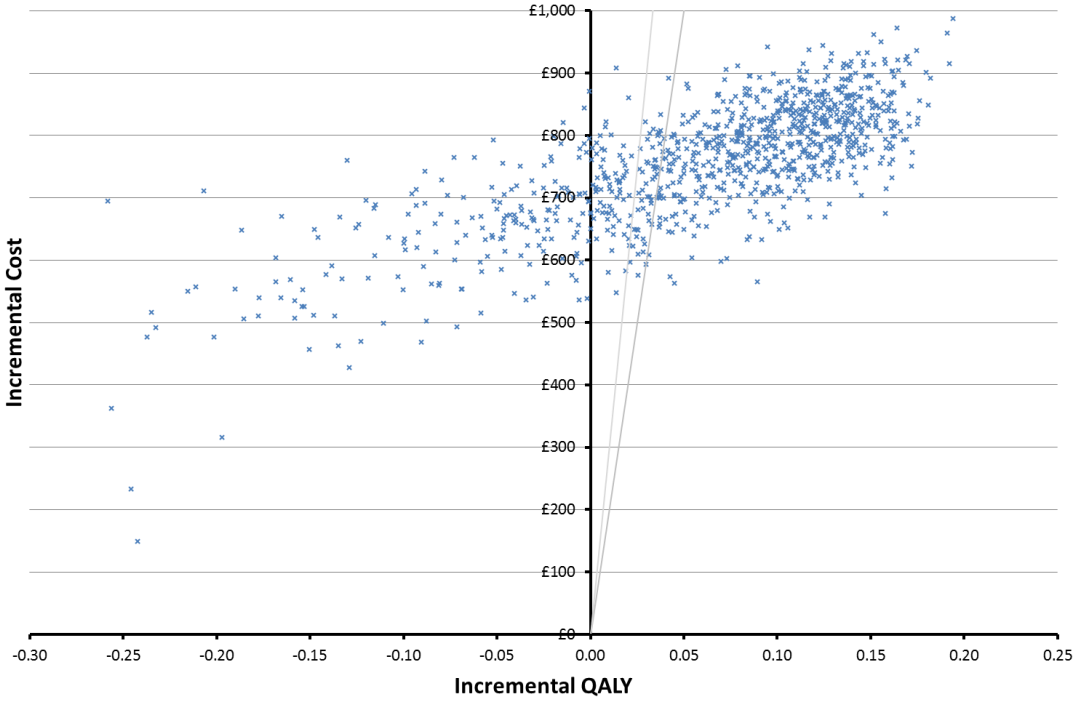
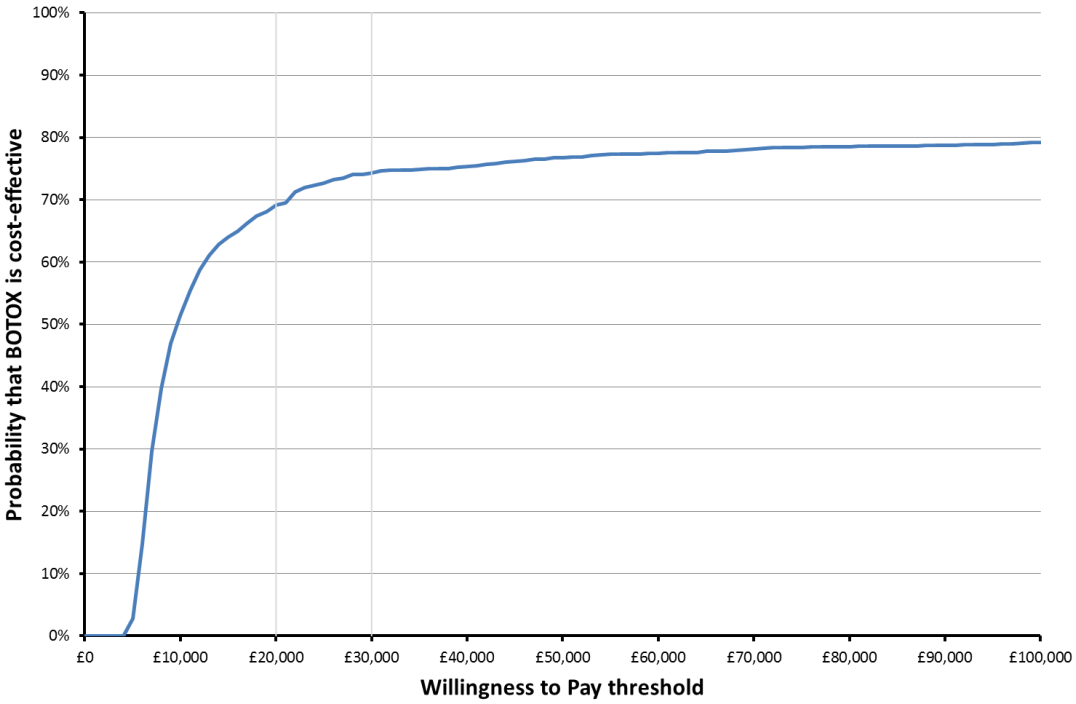


Figure 6.9: Cost-effectiveness acceptability curve of probabilistic sensitivity analysis, 1,000 simulations



6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Scenario analyses are presented in Tables 6.30 to 6.36.

Table 6.30: Scenario analyses – patient dataset

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Whole trial population (including treatment naïve patients)							
Placebo	£1,745	1.26	£1,707	1.23			
Botox	£2,345	1.35	£2,316	1.32	£609	0.09	£6,814
≥3 prior oral prophylactic treatments							
Placebo	£1,936	1.23	£1,895	1.20			
Botox	£2,471	1.32	£2,438	1.29	£543	0.09	£6,083
Prior topiramate treatment							
Placebo	£1,707	1.27	£1,673	1.24			
Botox	£2,329	1.35	£2,301	1.32	£628	0.08	£8,301
Excluding patients who overuse acute medication							
Placebo	£1,803	1.26	£1,765	1.23			
Botox	£2,327	1.35	£2,298	1.32	£533	0.09	£5,971

Table 6.31: Scenario analyses – stopping rules

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Excluding 'negative stopping rule'							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,885	1.37	£2,846	1.34	£1,008	0.13	£7,946
Excluding 'positive stopping rule'							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£3,039	1.34	£2,983	1.31	£1,144	0.09	£12,486
Excluding both 'positive' and 'negative' stopping rules							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£3,798	1.37	£3,722	1.34	£1,883	0.12	£15,294
Negative stopping rule: assumption patients must move improve by≥1 health state to avoid treatment discontinuation after 2 cycles							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,577	1.36	£2,544	1.33	£705	0.12	£6,109
Positive stopping rule: in both Episodic Migraine and Chronic Migraine, 50% of patients continue treatment, 50% of patients stop treatment							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,718	1.34	£2,675	1.31	£836	0.09	£9,080
Positive stopping rule: episodic patients have placebo transitions and utilities after week 60							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,495	1.31	£2,460	1.28	£621	0.07	£9,503

Table 6.32: Scenario analyses – calculation of transition probabilities

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Inclusion of 0-12, and 12-24 week transition probabilities in calculating 24week+ transition probabilities							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,395	1.33	£2,364	1.30	£525	0.09	£5,994

Table 6.33: Scenario analyses – 3 health state economic model

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
3 Health state model							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,419	1.34	£2,388	1.31	£549	0.09	£5,956

Table 6.34: Scenario analyses – time horizon

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
24 week time horizon							
Placebo	£450	0.27	£450	0.27			
Botox	£1,015	0.29	£1,015	0.29	£565	0.02	£27,162
1 year time horizon (60 weeks)							
Placebo	£1,079	0.69	£1,072	0.68			
Botox	£1,804	0.74	£1,798	0.74	£726	0.05	£14,098

Table 6.35: Scenario analyses – calculation of utility values

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Utilities taken directly from the IBMS study							
Placebo	£1,879	1.12	£1,839	1.09			
Botox	£2,419	1.20	£2,388	1.17	£549	0.08	£7,025

Table 6.36: Scenario analyses – societal perspective

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Societal perspective, including lost working time							
Placebo	£5,770	1.24	£5,660	1.22			
Botox	£5,398	1.34	£5,280	1.31	£380	0.09	£4,033

6.7.10 What were the main findings of each of the sensitivity analyses?

The sensitivity analysis investigating the effect of including and excluding different patient populations from the model (Table 6.30) demonstrated that the model is not sensitive to the number of type of treatments that patients have previously received. In no cases does the ICER increase by more than £2,500. This however is driven by the small number of patients included in some analyses.

The stopping rule sensitivity analyses, shown in Table 6.31, demonstrate that the inclusion of both positive and negative stopping rules improve the cost effectiveness of treatment with Botox. Removing the rules increases both the cost and QALYs of treatment with Botox, as more patients receive subsequent treatments, and gain some benefit. However the costs increase is proportionally greater than the benefit. In the 'negative' stopping rule scenario, this is due to patients that do not achieve sufficient (or any) benefit continuing on treatment. In the 'positive' stopping rule scenario, the increase in the ICER is driven by the fact that patients on average receive slightly less benefit as the stopping rule assumes that they remain in the same health state, at a higher cost as they continue to be treated. If no stopping rules are assumed (either positive or negative) then the ICER increases to £15,294. As clinicians are unlikely to continue to treat patients that are not showing any benefit from treatment, it is unlikely that this scenario would ever be observed in practice.

The inclusion of weeks 0-12 and 12-24 in calculating the extrapolation 24+ week transition matrices has a negligible impact on the costs and QALYs gained from treatment (Table 6.32).

The reduction in the number of health states in the model linked to treatment from 6, to 3 (built around clinical definitions), does not affect the cost-effectiveness results (Table 6.33).

The sensitivity analysis investigating the impact of reducing the model time horizon to 24 weeks (the length of the double blind period of the trial) produced an ICER of £27,162 (Table 6.34). This scenario is highly conservative as at the end of the trial, the patients are in very different health states, which is unlikely to disappear the following day (the assumption implicit in the 24 week horizon).

This is also conservative as the cost of Botox is at its highest (per patient), as the cost impact for poorly responding patients is included, while patients having shown a good response have only just transitioned to the lowest cost health states, and not remained there long enough to accrue substantial cost or QALY benefits. That this extreme scenario of the double blind phase only gives an ICER of under £30,000 per QALY gives reassurance as to the robustness of the base case estimates.

The analysis investigating the effect of assuming different sources for the utility values (Table 6.35) demonstrates that the choice of utility has a small effect on the ICER. This is likely as there is no assumed mortality advantage in the model and so all QALY benefits are achieved through health state improvements due to treatment. Nonetheless the ICER remains below £10,000 per QALY, and shows the model is robust to changes in utility

The sensitivity analysis presented in Table 6.36 which includes a societal perspective improves the ICER. Whilst societal costs are outside of the scope of the NICE reference case, this demonstrates the potential benefit of treatment with Botox on the UK economy, and reflects the severity of the impact of chronic migraines to a persons overall life.

6.7.11 What are the key drivers of the cost-effectiveness results?

The main driver of cost effectiveness is the efficacy of treatment with Botox moving patients to a better health state than patients treated with placebo and acute medication alone. The model is also sensitive to the time horizon used, however remains under £20,000 for all reasonable horizons (60 weeks and above).

Given how efficacy is applied via transition matrices, efficacy values have not been varied in isolation as a scenario, however these are varied in probabilistic sensitivity analysis, and demonstrate that there is a high chance that Botox is cost-effective. Furthermore Botox remains cost-effective across all patient subgroups identified within this submission.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model.

In addition to the expert overview of the model described in Section 6.3.5, the model has undergone several quality control steps.

The model was initially created by Veritech, in collaboration with Allergan Inc., after which it was passed to BresMed for review and development. At this stage a quality control process was run in order to identify any errors.

Following the model development, the entire model was then reviewed by a senior health economist at BresMed not involved in the project using the established Drummond checklist. A quality control report was then delivered to the team involved with the modeling, with a list of issues for clarification or correction. These were incorporated before being signed off by the senior health economist.

Given the importance of transition probabilities, these were also double data extracted by two economists independently from the SAS PDF outputs. The Excel sheets were then subtracted from each other, with any discrepancies resolved between the two economists. The SAS outputs were then verified by the Allergan biostatistics group, to ensure the correct results were produced.

6.9 Subgroup analysis

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

The patient group specified in the NICE scope (≥3 previous oral prophylactics) are already a subgroup, however within this population there is a meaningful additional subgroup; patients who are overusing acute headache medication at baseline. This group is discussed in detail in Section 1.4 (Page 12).

6.9.2 Please clearly define the characteristics of patients in the subgroup.

At baseline, the majority of patients enrolled into clinical trials PREEMPT 1 and PREEMPT 2, reported inadequate pain relief with acute treatments, resulting in frequent intake. Acute medication overuse during the 28 day baseline period, was observed in 65.5% of the enrolled population in an attempt to relieve their symptoms. It should be noted that clinicans were encouraged not to enrol patients overusing opiates or barbiturates.

In enrolling patients to clinical studies PREEMPT 1 and PREEMPT 2, investigators were trained to exclude patients whose headache they attributed to another disorder, such as Medication Overuse Headache (MOH), which is a secondary headache disorder (Section 1.4 Page 12).

6.9.3 Please describe how the statistical analysis was undertaken.

Using the same methodology as for the other data cuts, patient level data for patients overusing acute medication at baseline, who had previously been treated with prior medication, was used to calculate transition probability matrices. These were then used in the economic model to produce a cost-effectiveness estimate for this specific patient subgroup.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

The result of this subgroup analysis are shown in Table 6.37. Compared to the base case there is a slight increase in the ICER (£5,971 vs £5,828) however this is minor and well below conventional cost-effectiveness thresholds.

When looking at the ≥3 previous oral prophylactic treatments with medication overuse population, the ICER again rises, however this may be a result of the low patient numbers available for analysis (n=67 for Botox, n=69 for placebo). Again the ICER remains well below conventional cost-effectiveness thresholds at £6,073 per QALY.

Table 6.37: Results of subgroup analysis

Treatment Arm	Totals		Discounted Totals		Incremental Costs	Incremental QALYs	Cost per QALY
	Costs	QALYs	Costs	QALYs			
Base case							
Placebo	£1,879	1.24	£1,839	1.22			
Botox	£2,419	1.34	£2,388	1.31	£549	0.09	£5,828
≥1 previous oral prophylactic, excluding patients with medication overuse at baseline							
Placebo	£1,803	1.26	£1,765	1.23			
Botox	£2,327	1.35	£2,298	1.32	£533	0.09	£5,971
≥3 previous oral prophylactic, excluding patients with medication overuse at baseline							
Placebo	£1,923	1.23	£1,881	1.21			
Botox	£2,468	1.33	£2,435	1.30	£554	0.09	£6,073

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

All groups listed in the NICE scope have been considered.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature?

Although investigating a different product (topiramate), and a different population (not specific to chronic migraine) Brown et al (2006) found the treatment of migraine to be highly cost-effective. Based on these findings the SMC approved topiramate for the treatment of migraine in previously treated patients.

The cost-effectiveness results seen in the model presented echo the previous findings; that the effective prophylaxis of migraine is highly cost effective.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The economic evaluation is relevant to all patients eligible to use the technology, with the Markov model demonstrating the cost effectiveness of Botox compared to placebo with acute treatments only.

In the specified patient population, Botox is highly cost effective, with an ICER well below traditionally accepted cost-effectiveness thresholds. In probabilistic Sensitivity Analysis Botox is cost-effective at listed NICE thresholds in 69-74% of scenarios.

This finding is also robust to sensitivity analyses, with only a highly conservative time horizon showing Botox to have an ICER close to £30,000 per QALY.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The key strength of the economic analysis are that results are robust to all scenarios, with changes in patient population, stopping rules, transition probabilities, model structure and utility values failing to increase the ICER over £30,000 per QALY

When the model is run over the 24 double blind trial period the resultant ICER is close to the £30,000 per QALY threshold. This sensitivity analysis makes no assumptions of extrapolation beyond the trial data or stopping rules, but simply reflects the observed trial outcomes on the number of headache days..

This is a highly conservative analysis as it adds no additional longer term benefits from treatment with Botox and effectively assumes equal outcomes between arms after 24 weeks of treatment, which is not reflected in the trial data. The model is also robust to all other sensitivity and scenario analyses.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Due to the lack of data, a full study of the costs of alternative interventions in chronic migraine patients who have been unsuccessfully treated with oral prophylactics may be useful. Interventions such as methysergide and Occipital Nerve Stimulation are used in the NHS, with high costs to the health service, without any formal appraisal or Tier 1 evidence. As identified in the treatment pathway model (Appendix 19), there is the potential for both cost savings and improved outcomes if patients can be redirected to effective, evidence based therapies.

7 Assessment of factors relevant to the NHS and other parties

7.1 How many patients are eligible for treatment in England and Wales?

It is estimated that 1.6% of the adult population suffers from chronic migraine (Blumenfeld, 2010; Natoli, 2010). The Office of National Statistics (ONS)gives population figures for England and Wales of 56,127,375 in 2012 rising to 57,945,119 in 2016. The ONS also estimates that 81% of these populations are adults (45,525,700 in 2012). This gives an estimated chronic migraine population of 728,411 in 2012 in England and Wales. Bigal et al (2008) estimate that approximately 20% of the chronic migraine population have had their diagnosis confirmed by a neurologist, resulting in an expected diagnosed population of 147,139 in 2012.

The decision problem restricts this population further, to those who have received ≥ 3 prior oral prophylactic treatments. The best data source available for the percentage of patients to whom is applicable are clinical trials 191622-079 and 191622-080, where 34.6% of patients had previously received ≥ 3 prior oral prophylactic treatments.

Using these figures, we estimate that in 2012 (the first year in which NICE guidance would be applicable) 50,910 patients will be eligible for treatment across England and Wales. Table 7.1 shows the calculation of the number of eligible patients in England and Wales over both this, and subsequent years.

Table 7.1: Estimated patient numbers for Botox 2012 – 2016

Year	2012	2013	2014	2015	2016
Total population in England	56,127,375	56,576,394	57,029,006	57,485,238	57,945,119
Adult population (81%)	45,525,700	45,889,906	46,257,025	46,627,081	47,000,098
Population with chronic migraine (1.6%)	728,411	734,238	740,112	746,033	752,002
Population with diagnosed chronic migraine (20.2%)	147,139	148,316	149,503	150,699	151,904
Population who have previously been treated with ≥3 oral prophylactics (34.6%)	50,910	51,317	51,728	52,142	52,559

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

There are therefore no assumptions made for current treatment options in the budget impact analysis as the comparator is acute treatment only (as oral prophylaxis is assumed to have failed).

7.3 What assumption(s) were made about market share (when relevant)?

The Botox market share was estimated to be 2.5% in 2012, increasing by 2.5% per year thereafter.

The cost-effectiveness model calculates the mean number of doses of Botox over the 2 year period. This is then divided by 2, to give the mean number of doses received by a patient in a year in the base case. This calculation takes account of patients discontinuing (due to stopping rules or adverse events.). This also takes account of the assumption that patients who upon reaching an episodic migraine headache frequency cease Botox treatment after 1 year.

Table 7.2: Calculation of estimated patient numbers 2012 – 2016

Year	2012	2013	2014	2015	2016
Population who have previously been treated with ≥3 oral prophylactics (34.6%)	50,910	51,317	51,728	52,142	52,559
Number of untreated patients	50,910	50,045	46,702	42,445	37,557
Estimated market share	2.5%	7.5%	10.0%	12.5%	15.0%
Patients on year 1 of Botox treatment	1,273	3,753	4,670	5,306	5,634
Patients on year 2 of Botox treatment	0	1,273	3,753	4,670	5,306
Total Botox treated population	1,273	5,026	8,424	9,976	10,939

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

In addition to the drug cost, the cost of administration should be considered when assessing the cost of treating patients with Botox. This cost is estimated to be £73 per administration, and described in Section 7.5.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The acquisition cost of Botox is £267.40 for a 200 Allergan unit vial, required for 1 treatment. The cost of treating patients with Botox is assumed to be £73 per administration. This is based on 30 minutes of consultant time, with costs taken from PSSRU 2010.

7.6 Were there any estimates of resource savings? If so, what were they?

The cost effectiveness analysis identified resource saving from triptan medication, GP visits, A&E visits and hospitalisations avoided.

Per patient there is estimated to be a saving in Triptan medications (£75), Physician visits (£55), A&E visits (£163), and hospitalisations (£507). This results in a total per patient cost offset of approximately £314 per year.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact in England & Wales of Botox and administration is estimated to increase from approximately £1,178,493 in 2012, to £5,392,298 in 2016.

Including cost offsets from the reduction in resource use, the net budget impact of Botox is expected to be £2,180,200 in 2012, rising to £3,298,466 in 2016. Over the 5 year period this is a cost of approximately £14 million.

Table 7.3: Estimated budget impact of Botox in England & Wales, 2012 – 2016

Year	2012	2013	2014	2015	2016
Total Botox treated population	2,546	6,203	8,210	9,726	10,668
Drug cost (assuming mean treatment of 3.35 cycles in year 1 and 0.12 cycles in year 2)	£2,356,986	£3,471,418	£4,336,624	£4,941,104	£5,259,136
Administration cost	£622,503	£916,836	£1,145,346	£1,304,995	£1,388,990
Resource savings	-£799,289	-£1,947,867	-£2,578,049	-£3,053,867	-£3,349,661
Budget impact of Botox	**£2,180,200**	**£2,440,387**	**£2,903,921**	**£3,192,232**	**£3,298,466**

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The budget impact analysis accounts for reductions in the use of triptan treatment, GP visits, A&E visits and hospitalisations. This however does not include the cost of any other prophylactic treatments that may be used (for example those in the exploratory treatment pathway model – Appendix 17). The presented analysis is therefore conservative, as the potential cost savings are likely greater than those stated.

In addition the cost of lost working time has not been included in these calculations. When these were included in the primary economic model, Botox treatment became dominant – if this were included, the estimated cost savings would be larger.

8 References

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9 Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

1. exp Migraine Disorders/
2. migraine*.tw.
3. 1 or 2
4. Botulinum Toxin Type A/
5. botulinum.tw.
6. botox.tw.
7. 4 or 5 or 6
8. 3 and 7
9. Randomized controlled trials as Topic/
10. Randomized controlled trial/
11. Random allocation/
12. Double blind method/
13. Single blind method/
14. Clinical trial/
15. exp Clinical Trials as Topic/
16. (clinic$ adj trial$1).tw.
17. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
18. Placebos/
19. Placebo$.tw.
20. Randomly allocated.tw.
21. (allocated adj2 random).tw.22. 20 or 12 or 10 or 18 or 17 or 13 or 21 or 11 or 19 or 9 or 15 or 14 or 16
23. 8 and 22
24. limit 23 to (english language and yr="2007 -Current")

Systematic Reviews Search:

1. exp Migraine Disorders/
2. migraine*.tw.
3. 1 or 2
4. Botulinum Toxin Type A/
5. botulinum.tw.
6. botox.tw.
7. 4 or 5 or 6
8. 3 and 7
9. Meta-Analysis as Topic/
10. meta analy$.tw.
11. metaanaly$.tw.
12. Meta-Analysis/
13. (systematic adj (review$1 or overview$1)).tw.
14. exp Review Literature as Topic/
15. 9 or 10 or 11 or 12 or 13 or 14

16. cochrane.ab.
17. embase.ab.
18. (psychlit or psyclit).ab.
19. (cinahl or cinhal).ab.
20. science citation index.ab.
21. bids.ab.
22. cancerlit.ab.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. reference list$.ab.
25. bibliograph$.ab.
26. hand-search$.ab.
27. relevant journals.ab.
28. manual search$.ab.
29. 24 or 25 or 26 or 27 or 28
30. selection criteria.ab.
31. data extraction.ab.
32. 30 or 31
33. Review/
34. 32 and 33
35. Comment/
36. Letter/
37. Editorial/
38. animal/
39. human/
40. 38 not (38 and 39)
41. 35 or 36 or 37 or 40
42. 15 or 23 or 29 or 34
43. 42 not 41
44. 8 and 43
45. limit 44 to yr="2007 -Current"

1. Introduction and background

At the time when the literature search strategies were designed, the decision problem and consequently the final list of comparator therapies for the technology appraisal of Botox had yet to be confirmed. The search strategies therefore were very broad in scope and were designed to find studies used for the prophylaxis of chronic migraine headache so that when the scope was finalised the searches would have identified all potentially relevant studies. These results were collated in a Reference Manager Database.

The selection of studies however, was conducted after the decision problem was published in the final scope for the technology appraisal. The criteria for selecting studies was therefore based on the final scope and included a limited number of therapies, specifically :Greater Occipital Nerve (GON) block, brain stimulation, methysergide, and intravenous (IV) dihydroergotamine (DHE).

1.1 Published search strategies

In 2007, a comprehensive literature search was carried out by the Scottish Intercollegiate Guidelines Network (SIGN) as part of a systematic review of evidence for a National Clinical Guidance (2008) for Diagnosis and Management of Headache in Adults (SIGN 2008). The search covered the year range 2001 to 2007. The guidance makes recommendations for treating a variety of headache types, and specifically Section 6.2 of the guidance presents recommendations for pharmacological prophylaxis in “patients with recurring migraines that significantly interfere with their daily routine”. These include patients with both episodic and chronic migraine. It is noted in the guideline that the “majority of treatments commonly used do not have a specific licence for this indication in the UK. Therefore, recommendations in the guideline which include the use of licensed drugs outwith the terms of their licence reflect the evidence base reviewed.” This current review aimed to make use of the search strategies developed by the SIGN National Clinical Guidance. In particular, the list of drugs considered for assessment in the guidance was used as a starting point for the literature searches in this review. The British Association for the Study of Headache (BASH) produced guidelines in 2010 but did not publish the strategies they used to compile evidence for the guidance.

2. Methods

2.1 Literature search

A literature review was commissioned from the School of Health and Related Research, University of Sheffield, and conducted by an information specialist in order to identify all relevant clinical effectiveness evidence for Botox and other specified prophylactic treatments. This was based on the question “What is the clinical effectiveness of Botox and other prophylactic therapies when used to treat patients with chronic migraine?” The aim was to identify primary studies: that is, original reports of randomized controlled trials. Two reviewers independently inspected each reference (title and/or abstract/full text) identified by the literature search and applied pre-specified study selection criteria. In cases of disagreement between the 2 reviewers, the full article was inspected by a third person.

2.1.1 Study population

The focus of the review was on patients with chronic migraine or headache. However, older studies have used the terms: "transformed migraine" and "chronic daily headache". Therefore the search terms were deliberately broad in nature and included: "migraine", "chronic migraine", "chronic daily headache", "transformed migraine" and "headache".

2.1.2 Clinical interventions to be identified

The search was designed to find studies used for the prophylaxis of chronic migraine headache and included Botox as well as pharmacological therapies: beta blockers – propranalol, timolol, atenolol, nadolol, metoprolol, bisoprolol; anti-epileptics/anti-convulsants – topiramate, sodium valproate, gabapentin; antidepressants – amitriptyline, venlafaxine, desipramine, nortriptyline, protriptyline; and others – pizotifen, methysergide, flumarizine, candesartan, montelukast, acetazolimide hyperbaric, lanepitant, buspirone, riboflavin, co-enzyme Q10, and cyproheptadine. Finally, the search included terms for non-pharmacological interventions: greater occipital nerve block and implantation of occipital nerve or deep brain stimulators.

In total, three searches were conducted. The first searched for all publications related to the clinical effectiveness of Botox in patients with chronic migraine. This search was done on 6th December 2010. This was followed by a second search for all potential comparator treatments, which was completed on 4th March 2011. The later date for the second search was due to the additional time required to compile a list of relevant comparators for inclusion in the search strategy. As noted earlier, no drugs are licensed for the specific indication of chronic migraine in the UK but a number of oral prophylactic drugs are used to manage this population. The list of comparator treatments was derived from a number of sources. The list of pharmacological therapies considered in the SIGN Guidelines 2008, and BASH Guidelines 2010 (British Association for the Study of Headache) were used as the starting point (BASH 2010). In addition, headache specialists and the draft scope for the NICE Health Technology Assessment were consulted about additional pharmacological therapies. The third search included non pharmacological therapies such as Greater Occipital Nerve Block, Occipital Nerve Stimulation and Deep Brain Stimulation. This was completed on the 15th April 2011.

2.1.3 Limits applied to searches

SIGN guidelines were published in 2008 and the associated searches were conducted in 2007 covering the year range 2001 to 2007 for all interventions that were considered by the guidance. In order to avoid duplication of searches previously conducted, this literature search set out to identify studies published in 2007 and beyond, for any intervention already included in the SIGN guidelines. Exceptions to these date limitations were made for interventions not included in the 2008 guidelines, such as non-pharmacological therapies. No date restrictions were applied to the latter therapies.

2.1.4 Databases searched

Electronic databases searched included Medline (via OVID), Embase (via OVID), Cochrane Library: Cochrane database of systematic reviews, Cochrane register of clinical trials, NHS Health Economic Evaluation Database (HEED), Health Technology Assessment (HTA) database (all via Wiley), CINAHL(via NHS Evidence), PsycINFO (via OVID, Econlit (via OVID), Science Citation Index (Web of Knowledge), Conference Proceedings Index (Web of Knowledge). In addition, reference lists of literature reviews and key papers were scanned for possibly relevant papers.

All the searches included terms to describe the intervention(s) of interest (migraine treatments), the population (migraine sufferers) and methodological search filters such as those produced by the Scottish Intercollegiate Guidelines Network (SIGN) to refine the results to the appropriate types of evidence (RCTs, systematic reviews, economic analyses). The terms within these groups were combined using the Boolean operator OR, then groups were combined using the Boolean operator AND. This approach is the standard 'building block' approach to searching (Booth A 2008). Search strategies can be found in Section 4.

2.2 Study selection

The second stage of the review was the systematic selection of studies for inclusion. Two independent reviewers applied explicit inclusion and/or exclusion criteria to the literature search results. The inclusion/exclusion criteria are set out below.

As set out in the introduction, the focus of the review was the retrieval of primary studies, that is, original reports of RCTs. It is often the case however, that a number of reports are published from one primary study. If the reviewers suspected that two publications originated from the same RCT, they investigated further by examining author names; location and setting; specific intervention details; participant numbers; baseline data; and date and duration of study. If uncertainties remained, the authors were contacted (The Cochrane Collaboration 2009).

2.2.1 Types of studies

Systematic reviews of randomized controlled trials (RCTs) are the best method for revealing the effects of a therapeutic intervention. Therefore, the review included all RCTs which evaluated any of the above interventions in comparison to either an active comparator or to placebo for the treatment of chronic migraine. It also included RCTs regardless of design (parallel, cross-over, open-label, single- or double-blinded).

2.2.2 Types of study participants

The characteristics of patients in the studies were required to be similar to those of a typical patient described in the economic model for studies investigating Botox. Botox is indicated for the prophylaxis of headaches in adults with chronic migraine. This is defined as the experience of headaches on at least 15 days per month, of which at least 8 days are with migraine (Botox Summary of Product Characteristics 2010) as set out in the International Classification of Headache Disorders (Headache Classification Committee of the International Headache Society. 2004). Furthermore, “adults with chronic migraine” is the population of interest in the proposed NICE Health Technology Appraisal. Consequently, only studies that enrolled patients with chronic migraine or analysed this subset of patients separately were thus included. Studies that described patients as having “transformed migraine” and/or “chronic daily headache” were included if the definition was clearly described and found to be equivalent to chronic migraine.

2.2.3 Types of intervention

For chronic migraine patients whose condition has failed to respond to oral prophylactic medications, there has, until now, been no specifically licensed

therapeutic option available in England and Wales. Patients in this population who are seen by a headache specialist may have their condition managed with invasive procedures or unlicensed medications. Alternatively, they may be prescribed acute headache pain medications such as triptans rather than prophylactic medications.

Examples of invasive procedures include minimally invasive procedures such as Greater Occipital Nerve (GON) block (local injections of steroids, local anesthetics or a mixture of both in the area of greater occipital nerve) and more complex procedures including occipital nerve stimulation (the neurostimulator delivers electrical impulses via insulated lead wires tunneled under the skin near the occipital nerves at the base of the head).

Dihydroergotamine (DHE), which is given intravenously, and methysergide (taken orally) are ergot alkaloids. Methysergide is “held in reserve”, partly due to its association with retroperitoneal fibrosis and the severe rebound headache experienced by many patients when attempting to withdraw from it after several months use (BASH 2010). DHE is investigational due to insufficient evidence for its effectiveness and is not licensed for use in the UK, therefore it is only available in a small number of tertiary specialist centres (Saper JR et al. 2006). None of these interventions could be classified as “standard care” due to wide geographical variability of access and practice.

All of these therapies however, are considered potentially relevant comparators, because, like Botox, within the decision problem, they are considered for use only when patients with chronic migraine have failed on prior oral prophylactic medications. Although these comparator therapies are not licensed for use in chronic migraine, data on their clinical effectiveness would permit an assessment of their relative benefit compared to Botox. Thus, they have been included in the literature searches as comparator treatments, even though some of these approaches, as interventional procedures, are excluded from the scope.

2.2.4 Types of clinical outcomes

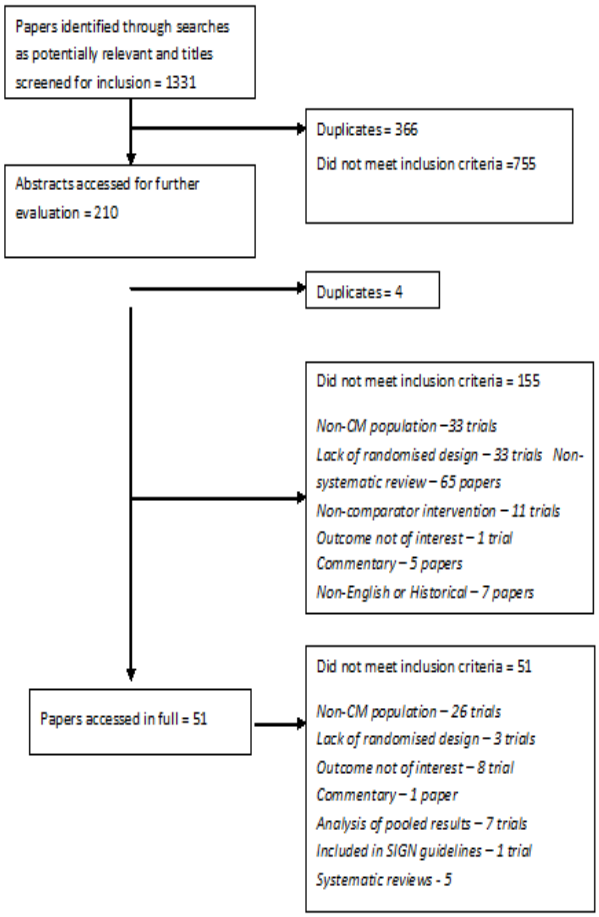
The primary outcome of interest for the systematic review was number of headache days per month at study end (including response rates at 6 months and 12 months). In addition, other outcomes of interest were number of migraine days, number of headache episodes and number of migraine episodes, Headache Impact Test (HIT-6), Migraine Specific quality of life Questionnaire (MSQ v2.1), acute headache pain medication intakes, acute headache pain medication days, and adverse effects/events.

3. Results

3.1 Literature search results from first search

A total of 1331 records were identified through database searching (Figure 1). After removal of
duplicates and studies which, from their title, clearly did not meet the inclusion criteria, 210 records
remained. Abstracts for these studies were obtained and a further 155 were excluded. Full text copies of 51 studies were obtained and none of them met the inclusion criteria.

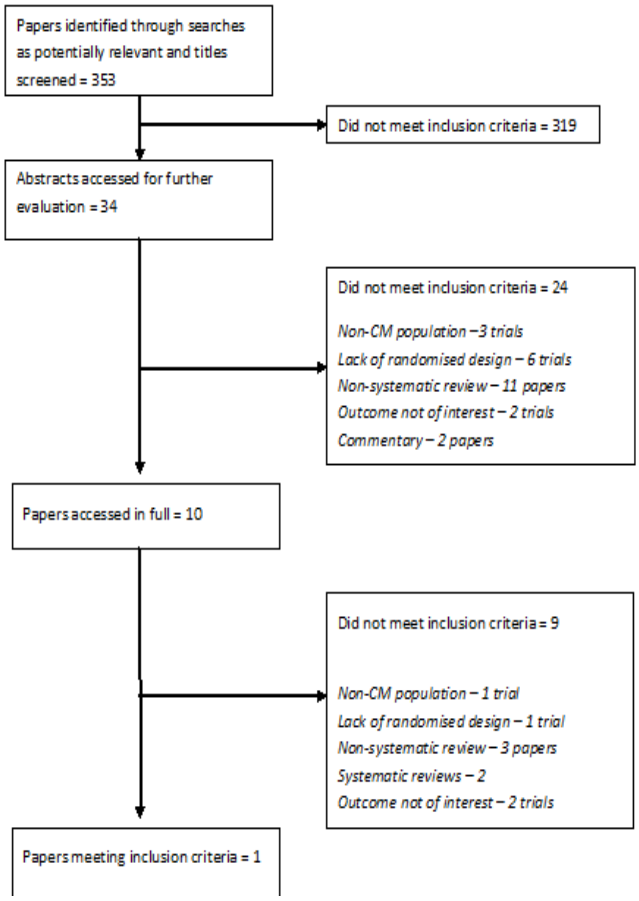
Figure1 : Results from first literature search for comparator studies



3.2 Literature search results from second search

A total of 353 records were identified through database searching (Figure 2). After removal of studies which, from their title, clearly did not meet the inclusion criteria, 34 recordsremained. Abstracts for these studies were obtained and a further 24 were excluded. Full text copies of 10 studies were obtained and from these 1 met the inclusion criteria. This was a study of occipital nerve stimulation in patients with chronic migraine (Saper et al. 2011).

Figure 2: Results from second literature search for comparator studies



4. Search strategies

Search strategy number 1 was as follows:

1. Randomized controlled trials as Topic/
2. Randomized controlled trial/
3.Random allocation/
4.Double blind method/
5.Single blind method/
6.Clinical trial/
7.exp Clinical Trials as Topic/
8. (clinic$ adj trial$1).tw.
9. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.

10. Placebos/
11. Placebo$.tw.
12. Randomly allocated.tw.
13. (allocated adj2 random).tw.
14. 12 or 4 or 2 or 10 or 9 or 5 or 13 or 3 or 11 or 1 or 7 or 6 or 8
15. migraine*.tw.
16. exp Migraine Disorders/
17. Headache/ or Cluster Headache/ or Tension-Type Headache/ or exp Headache Disorders/
18. headache*.tw.
19. 15 or 16 or 17 or 18
20. (propanalol or propanolol).tw.
21. (timolol or Blocadren or Timoptol or Timoptic).tw.
22. (atenolol or tenormin).tw.
23. (Nadolol or Corgard or Anabet or Solgol or Corzide or Alti-Nadolol or Apo-Nadol or Novo-Nadolol).mp.
24. (Betaloc or Lopresor or Lopresor SR or metoprolol).tw.
25. (bisoprolol or cardicor).tw.
26. 20 or 21 or 22 or 23 or 24 or 25
27. (topiramate or topamax).tw.
28. (sodium valproate or valproic acid or epilim).tw.
29. (gabapentin or neurontin).tw.
30. 27 or 28 or 29
31. (Amitriptyline or Elavil or Tryptizol or Laroxyl or Sarotex or Lentizol).tw.
32. (Venlafaxine or Effexor or Efexor).tw.
33. (desipramine or Norpramin or Pertofane).tw.
34. (nortriptyline or Sensoval or Aventyl or Pamelor or Norpress or Allegron or Noritren or Nortrilen).tw.
35. (protriptyline or vivactil).tw.
36. 31 or 32 or 33 or 34 or 35
37. (pizotifen or pizotyline or Sandomigran).tw.
38. (methysergide or Sansert or Deseril).tw.
39. flunarizine.tw.
40. (candesartan or Blopress or Atacand or Amias or Ratacand).tw.
41. (montelukast or singulair).tw.
42. (acetazolimide or diamox).tw.
43. hyperbaric.tw.
44. lanepitant.tw.
45. (buspirone or buspar).tw.

46. (riboflavin or e101 or vitamin b2).tw.
47. (co-enzyme q10 or coenzyme Q10 or ubiquinone or ubidecarenone or coenzyme Q or co-enzyme q or CoQ10 or CoQ or Q10).tw.
48. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. (greater occipital nerve block or gon).tw.
50. 26 or 30 or 36 or 48 or 49
51. 19 and 50
52.limit 51 to yr="2007 -Current"
53. 14 and 52

Search strategy number 2 was as follows:

1. Randomized controlled trials as Topic/
2. Randomized controlled trial/
3. Random allocation/
4. Double blind method/
5. Single blind method/
6. Clinical trial/
7. exp Clinical Trials as Topic/
8. (clinic$ adj trial$1).tw.
9. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
10. Placebos/
11. Placebo$.tw.
12. Randomly allocated.tw.
13. (allocated adj2 random).tw.
14. 12 or 4 or 2 or 10 or 9 or 5 or 13 or 3 or 11 or 1 or 7 or 6 or 8
15. migraine*.tw.
16. exp Migraine Disorders/
17. Headache/ or Cluster Headache/ or Tension-Type Headache/ or exp Headache Disorders/
18. headache*.tw.
19. 15 or 16 or 17 or 18
20. (greater occipital nerve block or gon).tw.
21. Deep Brain Stimulation/
22. deep brain stimulation.tw.
23. occipital nerve block.tw.
24. Cyproheptadine.tw.
25. periactin.tw.
26. 20 or 21 or 22 or 23 or 24 or 25
27. 14 and 19 and 26

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1. migraine*.tw.
2. exp Migraine Disorders/
3. Headache/ or Cluster Headache/ or Tension-Type Headache/ or exp Headache Disorders/
4. headache*.tw.
5. 1 or 2 or 3 or 4

6. (greater occipital nerve block or gon).tw.
7. Deep Brain Stimulation/
8. deep brain stimulation.tw.
9. occipital nerve block.tw.
10. Cyproheptadine.tw.
11. periactin.tw.
12. 6 or 7 or 8 or 9 or 10 or 11
13. Meta-Analysis as Topic/
14. meta analy$.tw.
15. metaanaly$.tw.
16. Meta-Analysis/
17. (systematic adj (review$1 or overview$1)).tw.
18. exp Review Literature as Topic/
19. 13 or 14 or 15 or 16 or 17 or 18
20. cochrane.ab.
21. embase.ab.
22. (psychlit or psyclit).ab.
23. (cinahl or cinhal).ab.
24. science citation index.ab.
25. bids.ab.
26. cancerlit.ab.
27. 20 or 21 or 22 or 23 or 24 or 25 or 26
28. reference list$.ab.
29. bibliograph$.ab.
30. hand-search$.ab.
31. relevantjournals.ab.
32. manual search$.ab.
33. 28 or 29 or 30 or 31 or 32
34. selectioncriteria.ab.
35. dataextraction.ab.
36. 34 or 35
37. Review/
38. 36 and 37
39. Comment/
40. Letter/
41. Editorial/
42. animal/
43. human/
44. 42 not (42 and 43)
45. 39 or 40 or 41 or 44
46. 19 or 27 or 33 or 38
47. 46 not 45
48. 5 and 12 and 47

9.3 Appendix 3: Overall Safety Plan (section 5.9)

Phase 3 Chronic Migraine population: Pooled analyses of studies 191622-080 and 191622-079) (N=1300)Phase 3 studies: Short summaries of the individual phase 3 studies are also presented.

All Chronic Migraine population: Pooled analyses of the Phase 3 Chronic Migraine population, and the phase 2 chronic migraine studies 191622-038 and 191622-039 (N=1997)

All Migraine population: Pooled analyses of the All Chronic Migraine population and 7 exploratory phase 2 episodic migraine studies: 191622-005, 191622-009, 191622-024, 191622-026, 191622-036, 191622-037, and 191622-509 (N=3235).

Sources

Aurora SK, Dodick DW, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomised, placebo-controlled phase of the PREEMPT I trial. Cephalalgia 30(7): 793-803

Diener HC, Dodick DW, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomised, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 30(7): 804-814

Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomised, placebo-controlled phases of the PREEMPT clinical program. Headache 2010; 50(6):921-936

Aurora SK *et al.* OnbotulinumtoxinA for Treatment of Chronic Migraine: Analysis of the 56-Week PREEMPT 1 Trial. Poster presented at 14th International Headache Congress, September 10–13, 2009, Philadelphia, PA

Dodick DW *et al.* OnabotulinumtoxinA for Treatment of Chronic Migraine: Analysis of the 56-Week PREEMPT 2 Trial. Poster presented at 14th International Headache Congress, September 10-13, 2009, Philadelphia, PA

Aurora, S. K. *et al.*OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Analyses of the PREEMPT Clinical Program, Including 32-Week, Open-Label Phase. Poster presented at 14th International Headache Congress, September 10-13, 2009. Philadelphia, PA

Clinical Study Report: Study 191622-079

Clinical Study Report: Study 191622-080

Summary of Clinical Efficacy

Allergan (2010) Summary of Clinical Safety

Dodick, D. W., A. Mauskop, *et al*. (2005). Botulinum toxin type A for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomised double-blind, placebo-controlled study. Headache 45(4): 315-324

Mathew, N. T., B. M. Frishberg, *et al*. (2005). Botulinum toxin type A (Botox) for the prophylactic treatment of chronic daily headache: a randomised, double-blind, placebo-controlled trial. Headache 45(4): 293-307

Adverse event collection and recording (Allergan 2010h)

Adverse events (AEs) were monitored throughout all the phase 2 and phase 3 studies. Immediately following the first injection and at each post-baseline visit, the investigator asked patients a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination were then performed as appropriate. All reported AEs were documented on the appropriate case report form (CRF).

An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that did not necessarily have a causal relationship with this treatment. An adverse event could therefore have been any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The severity of an AE was assessed using the following definitions as guidelines:

- Mild: Awareness of sign or symptom, but easily tolerated.
- Moderate: Discomfort enough to cause interference with usual activity.
- Severe: Incapacitating with inability to work or do usual activity.
- Not applicable: In some cases, an adverse event might have been an "all or nothing" finding that could not be graded.

A determination of the relationship (if any) between an adverse event and the study drug was assessed by the study investigator. A causal relationship was present if a determination was made that there was a reasonable possibility that the adverse event may have been caused by the drug.

A serious AE was defined as any AE occurring at any dose that resulted in any of the following outcomes: death, a life-threatening AE, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not have resulted in death, been life-threatening, or required hospitalisation may have been considered serious adverse events

when, based upon appropriate medical judgment, they may have jeopardised the patient and may have required medical or surgical intervention to prevent one of the outcomes listed in this definition. All cancer AEs were considered as serious AEs.

All AEs that were drug-related and unexpected (i.e., not listed as treatment-related in the Clinical Investigator's Brochure) were reported to the governing institutional review board (IRB). Any serious AE whose onset occurred during the study period and/or within at least 8 weeks after the last dose of study drug was immediately reported to a designated Allergan representative and recorded on the appropriate case report forms. All patients with a serious AE were followed up and the outcomes reported.

Adverse events from all studies were converted to Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 coding conventions and integrated across the 3 safety populations described above.

Analyses of adverse events (Allergan 2010h)

In general, AE data were analysed and presented for:

1) Double-blind, placebo-controlled exposure
2) Open-label exposure (Phase 3 Chronic Migraine population only)
3) Any Botox exposure

The number and percentage of patients with AEs were summarised for each system organ class (SOC) and preferred term. All patients were counted only once for each AE when multiple occurrences of the same AE were reported, with one exception. In analyses by treatment cycle, if a patient experienced an AE in multiple cycles, then that AE was counted for the patient in each cycle for which there was a new onset of the AE. For the "by cycle" analysis, an AE that started during one cycle and was ongoing during a subsequent cycle was counted during the subsequent cycle only if it was of worsened severity.

Population analysed (Allergan 2010h)

The Phase 3 Chronic Migraine population represents the safety profile of the target population at the target label dose range, 155 U to 195 U, for which approval has been granted. This population included 1,379 adult patients with chronic migraine, of which a total of 1,300 patients were exposed to Botox, with 1,137 patients exposed for ≥24 weeks, and 544 patients exposed for ≥48 weeks.

Safety analyses were based on 4,076 patients who received at least 1 injection of Botox. For the safety analyses, patient assignment to treatment group was performed according to the first dose of study treatment actually

received (or dose received at the start of each treatment cycle for analyses by treatment cycle). A summary of the sample sizes of each of the 3 safety populations is presented in the below table.

Summary of sample size (N) and overall duration of exposure (patient months) for each safety population analysed

	Botox exposure (N)	**Botox (total patient-months)**
Phase 3 Chronic Migraine	1,300	12,379
All Chronic Migraine	1,997	16,926
All Migraine	3,235	26,685

Phase 3 Chronic Migraine population (Allergan 2010h)

Demographics

The Phase 3 Chronic Migraine population was comprised predominantly of females (86.4%[1192/1379]) and Caucasians (90.1% [1242/1379]) with a high body mass index (BMI) (mean 26.97 kg/m^2), which is consistent with the known demographics of chronic migraine within the general population (62). Patient ages ranged from 18 to 65 years (mean, 41.3 years), and 57.9% (799/1379) were ≥40 years of age. The mean time since onset of frequent migraine was 19.2 years, and the mean age of onset was 21.5 years.

Extent of exposure

The safety profile of Botox in the Phase 3 Chronic Migraine population was based on a pooled analysis of 1,300 chronic migraine patients who were exposed to at least 1 Botox treatment in the phase 3 studies, providing a total of 12,379 patient-months of exposure. A total of 518 patients were exposed to 5 treatment cycles of Botox.

Among the 1,300 chronic migraine patients, the total actual Botox doses received per cycle ranged from 155 U to 195 U when averaged across cycles 1 to 5 for each patient, with a mean of 164.0 U. A total of 1,137 patients were exposed to Botox for ≥24 weeks and 544 patients were exposed for ≥48 weeks at a dose range of 150 U to 200 U. Based on the 4,648 actual Botox doses administered across all treatment visits, all but 18 Botox doses were administered at 155 U or higher. The majority were within the target label dose of 155 U to 195 U. Across treatment cycles, the majority of patients continued in subsequent treatment cycles to receive their initial study drug dose; few patients increased, decreased or had their dosage changed from cycle to cycle.

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

This search was included in the searches described in Appendix 3.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

Quality assessment of comparator RCTs is included in Section 5

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

This search was included in the searches described in Appendix 3.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

Non RCT evidence was quality assessed in Section 5

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

This search was included in the searches described in Appendix 3.

9.9 Appendix 9: Search strategy for cost-effectiveness studies (section 6.1)

This search was included in the searches described in Appendix 3.

9.10 Appendix 10: Quality assessment of cost-effectiveness studies (section 6.1)

Quality assessment of cost-effectiveness studies is performed in Section 6.1

9.11 Appendix 11: Search strategy for section 6.4 (Measurement and valuation of health effects)

This search was included in the searches described in Appendix 3 and Section 6.1

9.12 Appendix 12: Resource identification, measurement and valuation (section 6.5)

This search was described in Section 6.5, with the results quality assessed in that section

9.13 Appendix 13: Parameters

Variable Name	Variable Description	Deterministic value	Standard Error	Distribution	Alpha	Beta	Probabilistic Value
Demographics & Operating Characteristics							
mAge	Mean Age of Population	42	N/A	N/A			42
cycle	Markov Model Cycle Length (weeks)	12	N/A	N/A			12
Chronic Migraine Health State Proportions (week 12)		deterministic	standard error	distribution	alpha	beta	probabilistic
p1_1BOTOX	Baseline to Week 12: probability of staying in 0-3 HA Days per 28 days on BOTOX	1.000	N/A	N/A			1.0000
p1_2BOTOX	Baseline to Week 12: probability of moving from 0-3 TO 4-9 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p1_3BOTOX	Baseline to Week 12: probability of moving from 0-3 TO 10-14 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p1_4BOTOX	Baseline to Week 12: probability of moving from 0-3 TO 15-19 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p1_5BOTOX	Baseline to Week 12: probability of moving from 0-3 TO 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p1_6BOTOX	Baseline to Week 12: probability of moving from 0-3 TO 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p1_dBOTOX	Baseline to Week 12: probability of discontinuing treatment with 0-3 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p2_1BOTOX	Baseline to Week 12: probability of moving from 4-9 TO 0-3 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p2_2BOTOX	Baseline to Week 12: probability of staying in 4-9 HA Days per 28 days on BOTOX	1.000	N/A	N/A			1.0000
p2_3BOTOX	Baseline to Week 12: probability of moving from 4-9 TO 10-14 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p2_4BOTOX	Baseline to Week 12: probability of moving from 4-9 TO 15-19 HA Days per	0.000	N/A	N/A			0.0000

	28 days on BOTOX						
p2_5BOTOX	Baseline to Week 12: probability of moving from 4-9 TO 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p2_6BOTOX	Baseline to Week 12: probability of moving from 4-9 TO 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p2_dBOTOX	Baseline to Week 12: probability of discontinuing treatment with 4-9 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p3_1BOTOX	Baseline to Week 12: probability of moving from 10-14 TO 0-3 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p3_2BOTOX	Baseline to Week 12: probability of moving from 10-14 TO 4-9 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p3_3BOTOX	Baseline to Week 12: probability of staying in 10-14 HA Days per 28 days on BOTOX	1.000	N/A	N/A			1.0000
p3_4BOTOX	Baseline to Week 12: probability of moving from 10-14 TO 15-19 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p3_5BOTOX	Baseline to Week 12: probability of moving from 10-14 TO 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p3_6BOTOX	Baseline to Week 12: probability of moving from 10-14 TO 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p3_dBOTOX	Baseline to Week 12: probability of discontinuing treatment with 10-14 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p4_1BOTOX	Baseline to Week 12: probability of moving from 15-19 TO 0-3 HA Days per 28 days on BOTOX	0.135	N/A	N/A			0.0998
p4_2BOTOX	Baseline to Week 12: probability of moving from 15-19 TO 4-9 HA Days per 28 days on BOTOX	0.349	N/A	N/A			0.3828
p4_3BOTOX	Baseline to Week 12: probability of moving from 15-19 TO 10-14 HA Days per 28 days on BOTOX	0.274	N/A	N/A			0.2343
p4_4BOTOX	Baseline to Week 12: probability of staying in 15-19 HA Days per 28 days on BOTOX	0.112	N/A	N/A			0.1260
p4_5BOTOX	Baseline to Week 12: probability of	0.065	N/A	N/A			0.1025

	moving from 15-19 to 20-23 HA Days per 28 days on BOTOX						
p4_6BOTOX	Baseline to Week 12: probability of moving from 15-19 to 24+ HA Days per 28 days on BOTOX	0.005	N/A	N/A			0.0020
p4_dBOTOX	Baseline to Week 12: probability of discontinuing treatment with 15-19 HA Days per 28 days on BOTOX	0.060	N/A	N/A			0.0526
p5_1BOTOX	Baseline to Week 12: probability of moving from 20-23 TO 0-3 HA Days per 28 days on BOTOX	0.055	N/A	N/A			0.0457
p5_2BOTOX	Baseline to Week 12: probability of moving from 20-23 TO 4-9 HA Days per 28 days on BOTOX	0.205	N/A	N/A			0.2166
p5_3BOTOX	Baseline to Week 12: probability of moving from 20-23 TO 10-14 HA Days per 28 days on BOTOX	0.157	N/A	N/A			0.1540
p5_4BOTOX	Baseline to Week 12: probability of moving from 20-23 TO 15-19 HA Days per 28 days on BOTOX	0.291	N/A	N/A			0.3070
p5_5BOTOX	Baseline to Week 12: probability of staying in 20-23 HA Days per 28 days on BOTOX	0.150	N/A	N/A			0.1187
p5_6BOTOX	Baseline to Week 12: probability of moving from 20-23 TO 24+ HA Days per 28 days on BOTOX	0.087	N/A	N/A			0.0781
p5_dBOTOX	Baseline to Week 12: probability of discontinuing treatment with 20-30 HA Days per 28 days on BOTOX	0.055	N/A	N/A			0.0799
p6_1BOTOX	Baseline to Week 12: probability of moving from 24+ TO 0-3 HA Days per 28 days on BOTOX	0.048	N/A	N/A			0.0468
p6_2BOTOX	Baseline to Week 12: probability of moving from 24+ TO 4-9 HA Days per 28 days on BOTOX	0.072	N/A	N/A			0.0589
p6_3BOTOX	Baseline to Week 12: probability of moving from 24+ TO 10-14 HA Days per 28 days on BOTOX	0.108	N/A	N/A			0.1462
p6_4BOTOX	Baseline to Week 12: probability of moving from 24+ TO 15-19 HA Days per 28 days on BOTOX	0.133	N/A	N/A			0.2015
p6_5BOTOX	Baseline to Week 12: probability of moving from 24+ TO 20-23 HA Days per 28 days on BOTOX	0.229	N/A	N/A			0.1821

p6_6BOTOX	Baseline to Week 12: probability of staying in 24+ HA Days per 28 days on BOTOX	0.361	N/A	N/A			0.2965
p6_dBOTOX	Baseline to Week 12: probability of discontinuing treatment with 24+ HA Days per 28 days on BOTOX	0.048	N/A	N/A			0.0680
p1_1COMP	Baseline to Week 12: probability of staying in 0-3 HA Days per 28 days on Comparator	1.000	N/A	N/A			1.0000
p1_2COMP	Baseline to Week 12: probability of moving from 0-3 TO 4-9 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p1_3COMP	Baseline to Week 12: probability of moving from 0-3 TO 10-14 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p1_4COMP	Baseline to Week 12: probability of moving from 0-3 TO 15-19 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p1_5COMP	Baseline to Week 12: probability of moving from 0-3 TO 20-23 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p1_6COMP	Baseline to Week 12: probability of moving from 0-3 TO 24+ HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p1_dCOMP	Baseline to Week 12: probability of discontinuing treatment with 0-3 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p2_1COMP	Baseline to Week 12: probability of moving from 4-9 TO 0-3 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p2_2COMP	Baseline to Week 12: probability of staying in 4-9 HA Days per 28 days on Comparator	1.000	N/A	N/A			1.0000
p2_3COMP	Baseline to Week 12: probability of moving from 4-9 TO 10-14 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p2_4COMP	Baseline to Week 12: probability of moving from 4-9 TO 15-19 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p2_5COMP	Baseline to Week 12: probability of moving from 4-9 TO 20-23 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p2_6COMP	Baseline to Week 12: probability of moving from 4-9 TO 24+ HA Days per 28	0.000	N/A	N/A			0.0000

	days on Comparator						
p2_dCOMP	Baseline to Week 12: probability of discontinuing treatment with 4-9 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p3_1COMP	Baseline to Week 12: probability of moving from 10-14 TO 0-3 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p3_2COMP	Baseline to Week 12: probability of moving from 10-14 TO 4-9 HA Days per 28 days on Comparator	1.000	N/A	N/A			1.0000
p3_3COMP	Baseline to Week 12: probability of staying in 10-14 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p3_4COMP	Baseline to Week 12: probability of moving from 10-14 TO 15-19 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p3_5COMP	Baseline to Week 12: probability of moving from 10-14 TO 20-23 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p3_6COMP	Baseline to Week 12: probability of moving from 10-14 TO 24+ HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p3_dCOMP	Baseline to Week 12: probability of discontinuing treatment with 10-14 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0000
p4_1COMP	Baseline to Week 12: probability of moving from 15-19 TO 0-3 HA Days per 28 days on Comparator	0.082	N/A	N/A			0.0260
p4_2COMP	Baseline to Week 12: probability of moving from 15-19 TO 4-9 HA Days per 28 days on Comparator	0.241	N/A	N/A			0.2323
p4_3COMP	Baseline to Week 12: probability of moving from 15-19 TO 10-14 HA Days per 28 days on Comparator	0.345	N/A	N/A			0.3481
p4_4COMP	Baseline to Week 12: probability of staying in 15-19 HA Days per 28 days on Comparator	0.177	N/A	N/A			0.1651
p4_5COMP	Baseline to Week 12: probability of moving from 15-19 to 20-23 HA Days per 28 days on Comparator	0.047	N/A	N/A			0.0566
p4_6COMP	Baseline to Week 12: probability of moving from 15-19 to 24+ HA Days per 28 days on Comparator	0.039	N/A	N/A			0.0150
p4_dCOMP	Baseline to Week 12: probability of	0.069	N/A	N/A			0.0520

	discontinuing treatment with 15-19 HA Days per 28 days on Comparator						
p5_1COMP	Baseline to Week 12: probability of moving from 20-23 TO 0-3 HA Days per 28 days on Comparator	0.070	N/A	N/A			0.0972
p5_2COMP	Baseline to Week 12: probability of moving from 20-23 TO 4-9 HA Days per 28 days on Comparator	0.109	N/A	N/A			0.1246
p5_3COMP	Baseline to Week 12: probability of moving from 20-23 TO 10-14 HA Days per 28 days on Comparator	0.202	N/A	N/A			0.1457
p5_4COMP	Baseline to Week 12: probability of moving from 20-23 TO 15-19 HA Days per 28 days on Comparator	0.279	N/A	N/A			0.3178
p5_5COMP	Baseline to Week 12: probability of staying in 20-23 HA Days per 28 days on Comparator	0.194	N/A	N/A			0.1681
p5_6COMP	Baseline to Week 12: probability of moving from 20-23 TO 24+ HA Days per 28 days on Comparator	0.116	N/A	N/A			0.0943
p5_dCOMP	Baseline to Week 12: probability of discontinuing treatment with 20-23 HA Days per 28 days on Comparator	0.031	N/A	N/A			0.0523
p6_1COMP	Baseline to Week 12: probability of moving from 24+ TO 0-3 HA Days per 28 days on Comparator	0.011	N/A	N/A			0.0207
p6_2COMP	Baseline to Week 12: probability of moving from 24+ TO 4-9 HA Days per 28 days on Comparator	0.033	N/A	N/A			0.0306
p6_3COMP	Baseline to Week 12: probability of moving from 24+ TO 10-14 HA Days per 28 days on Comparator	0.087	N/A	N/A			0.1256
p6_4COMP	Baseline to Week 12: probability of moving from 24+ TO 15-19 HA Days per 28 days on Comparator	0.217	N/A	N/A			0.1971
p6_5COMP	Baseline to Week 12: probability of moving from 24+ TO 20-23 HA Days per 28 days on Comparator	0.130	N/A	N/A			0.1564
p6_6COMP	Baseline to Week 12: probability of staying in 24+ HA Days per 28 days on Comparator	0.500	N/A	N/A			0.4449
p6_dCOMP	Baseline to Week 12: probability of discontinuing treatment with 24+ HA Days per 28 days on Comparator	0.022	N/A	N/A			0.0246

Chronic Migraine Health State Proportions (week 24)		deterministic	standard error	distribution	alpha	beta	probabilistic
p1_1BOTOX	Week 12 to Week 24: probability of staying in 0-3 HA Days per 28 days on BOTOX	0.500	N/A	N/A			0.4760
p1_2BOTOX	Week 12 to Week 24: probability of moving from 0-3 TO 4-9 HA Days per 28 days on BOTOX	0.400	N/A	N/A			0.3179
p1_3BOTOX	Week 12 to Week 24: probability of moving from 0-3 TO 10-14 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0330
p1_4BOTOX	Week 12 to Week 24: probability of moving from 0-3 TO 15-19 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0262
p1_5BOTOX	Week 12 to Week 24: probability of moving from 0-3 TO 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0068
p1_6BOTOX	Week 12 to Week 24: probability of moving from 0-3 TO 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0013
p1_dBOTOX	Week 12 to Week 24: probability of discontinuing treatment with 0-3 HA Days per 28 days on BOTOX	0.100	N/A	N/A			0.1388
p2_1BOTOX	Week 12 to Week 24: probability of moving from 4-9 TO 0-3 HA Days per 28 days on BOTOX	0.215	N/A	N/A			0.3120
p2_2BOTOX	Week 12 to Week 24: probability of staying in 4-9 HA Days per 28 days on BOTOX	0.486	N/A	N/A			0.4270
p2_3BOTOX	Week 12 to Week 24: probability of moving from 4-9 TO 10-14 HA Days per 28 days on BOTOX	0.056	N/A	N/A			0.0393
p2_4BOTOX	Week 12 to Week 24: probability of moving from 4-9 TO 15-19 HA Days per 28 days on BOTOX	0.009	N/A	N/A			0.0075
p2_5BOTOX	Week 12 to Week 24: probability of moving from 4-9 TO 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0006
p2_6BOTOX	Week 12 to Week 24: probability of moving from 4-9 TO 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0066
p2_dBOTOX	Week 12 to Week 24: probability of discontinuing treatment with 4-9 HA Days	0.234	N/A	N/A			0.2069

	per 28 days on BOTOX						
p3_1BOTOX	Week 12 to Week 24: probability of moving from 10-14 TO 0-3 HA Days per 28 days on BOTOX	0.114	N/A	N/A			0.1034
p3_2BOTOX	Week 12 to Week 24: probability of moving from 10-14 TO 4-9 HA Days per 28 days on BOTOX	0.318	N/A	N/A			0.4337
p3_3BOTOX	Week 12 to Week 24: probability of staying in 10-14 HA Days per 28 days on BOTOX	0.102	N/A	N/A			0.0625
p3_4BOTOX	Week 12 to Week 24: probability of moving from 10-14 TO 15-19 HA Days per 28 days on BOTOX	0.011	N/A	N/A			0.0186
p3_5BOTOX	Week 12 to Week 24: probability of moving from 10-14 TO 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0020
p3_6BOTOX	Week 12 to Week 24: probability of moving from 10-14 TO 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0003
p3_dBOTOX	Week 12 to Week 24: probability of discontinuing treatment with 10-14 HA Days per 28 days on BOTOX	0.455	N/A	N/A			0.3795
p4_1BOTOX	Week 12 to Week 24: probability of moving from 15-19 TO 0-3 HA Days per 28 days on BOTOX	0.028	N/A	N/A			0.1188
p4_2BOTOX	Week 12 to Week 24: probability of moving from 15-19 TO 4-9 HA Days per 28 days on BOTOX	0.097	N/A	N/A			0.2945
p4_3BOTOX	Week 12 to Week 24: probability of moving from 15-19 TO 10-14 HA Days per 28 days on BOTOX	0.125	N/A	N/A			0.2347
p4_4BOTOX	Week 12 to Week 24: probability of staying in 15-19 HA Days per 28 days on BOTOX	0.069	N/A	N/A			0.1075
p4_5BOTOX	Week 12 to Week 24: probability of moving from 15-19 to 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0510
p4_6BOTOX	Week 12 to Week 24: probability of moving from 15-19 to 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0011
p4_dBOTOX	Week 12 to Week 24: probability of discontinuing treatment with 15-19 HA Days per 28 days on BOTOX	0.681	N/A	N/A			0.1926
p5_1BOTOX	Week 12 to Week 24: probability of	0.000	N/A	N/A			0.0401

	moving from 20-23 TO 0-3 HA Days per 28 days on BOTOX						
p5_2BOTOX	Week 12 to Week 24: probability of moving from 20-23 TO 4-9 HA Days per 28 days on BOTOX	0.058	N/A	N/A			0.1408
p5_3BOTOX	Week 12 to Week 24: probability of moving from 20-23 TO 10-14 HA Days per 28 days on BOTOX	0.154	N/A	N/A			0.1138
p5_4BOTOX	Week 12 to Week 24: probability of moving from 20-23 TO 15-19 HA Days per 28 days on BOTOX	0.115	N/A	N/A			0.2274
p5_5BOTOX	Week 12 to Week 24: probability of staying in 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.1261
p5_6BOTOX	Week 12 to Week 24: probability of moving from 20-23 TO 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0604
p5_dBOTOX	Week 12 to Week 24: probability of discontinuing treatment with 20-30 HA Days per 28 days on BOTOX	0.673	N/A	N/A			0.2914
p6_1BOTOX	Week 12 to Week 24: probability of moving from 24+ TO 0-3 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0280
p6_2BOTOX	Week 12 to Week 24: probability of moving from 24+ TO 4-9 HA Days per 28 days on BOTOX	0.024	N/A	N/A			0.0395
p6_3BOTOX	Week 12 to Week 24: probability of moving from 24+ TO 10-14 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.1076
p6_4BOTOX	Week 12 to Week 24: probability of moving from 24+ TO 15-19 HA Days per 28 days on BOTOX	0.024	N/A	N/A			0.0662
p6_5BOTOX	Week 12 to Week 24: probability of moving from 24+ TO 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.1539
p6_6BOTOX	Week 12 to Week 24: probability of staying in 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.1871
p6_dBOTOX	Week 12 to Week 24: probability of discontinuing treatment with 24+ HA Days per 28 days on BOTOX	0.952	N/A	N/A			0.4178
p1_1COMP	Week 12 to Week 24: probability of staying in 0-3 HA Days per 28 days on Comparator	0.621	N/A	N/A			0.6329

p1_2COMP	Week 12 to Week 24: probability of moving from 0-3 TO 4-9 HA Days per 28 days on Comparator	0.207	N/A	N/A			0.1262
p1_3COMP	Week 12 to Week 24: probability of moving from 0-3 TO 10-14 HA Days per 28 days on Comparator	0.034	N/A	N/A			0.0958
p1_4COMP	Week 12 to Week 24: probability of moving from 0-3 TO 15-19 HA Days per 28 days on Comparator	0.034	N/A	N/A			0.0284
p1_5COMP	Week 12 to Week 24: probability of moving from 0-3 TO 20-23 HA Days per 28 days on Comparator	0.034	N/A	N/A			0.0269
p1_6COMP	Week 12 to Week 24: probability of moving from 0-3 TO 24+ HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0032
p1_dCOMP	Week 12 to Week 24: probability of discontinuing treatment with 0-3 HA Days per 28 days on Comparator	0.069	N/A	N/A			0.0866
p2_1COMP	Week 12 to Week 24: probability of moving from 4-9 TO 0-3 HA Days per 28 days on Comparator	0.081	N/A	N/A			0.0787
p2_2COMP	Week 12 to Week 24: probability of staying in 4-9 HA Days per 28 days on Comparator	0.554	N/A	N/A			0.5265
p2_3COMP	Week 12 to Week 24: probability of moving from 4-9 TO 10-14 HA Days per 28 days on Comparator	0.216	N/A	N/A			0.2364
p2_4COMP	Week 12 to Week 24: probability of moving from 4-9 TO 15-19 HA Days per 28 days on Comparator	0.041	N/A	N/A			0.0786
p2_5COMP	Week 12 to Week 24: probability of moving from 4-9 TO 20-23 HA Days per 28 days on Comparator	0.041	N/A	N/A			0.0180
p2_6COMP	Week 12 to Week 24: probability of moving from 4-9 TO 24+ HA Days per 28 days on Comparator	0.014	N/A	N/A			0.0132
p2_dCOMP	Week 12 to Week 24: probability of discontinuing treatment with 4-9 HA Days per 28 days on Comparator	0.054	N/A	N/A			0.0486
p3_1COMP	Week 12 to Week 24: probability of moving from 10-14 TO 0-3 HA Days per 28 days on Comparator	0.061	N/A	N/A			0.1287
p3_2COMP	Week 12 to Week 24: probability of moving from 10-14 TO 4-9 HA Days per	0.307	N/A	N/A			0.3388

	28 days on Comparator						
p3_3COMP	Week 12 to Week 24: probability of staying in 10-14 HA Days per 28 days on Comparator	0.333	N/A	N/A			0.2571
p3_4COMP	Week 12 to Week 24: probability of moving from 10-14 TO 15-19 HA Days per 28 days on Comparator	0.202	N/A	N/A			0.1974
p3_5COMP	Week 12 to Week 24: probability of moving from 10-14 TO 20-23 HA Days per 28 days on Comparator	0.053	N/A	N/A			0.0266
p3_6COMP	Week 12 to Week 24: probability of moving from 10-14 TO 24+ HA Days per 28 days on Comparator	0.009	N/A	N/A			0.0074
p3_dCOMP	Week 12 to Week 24: probability of discontinuing treatment with 10-14 HA Days per 28 days on Comparator	0.035	N/A	N/A			0.0439
p4_1COMP	Week 12 to Week 24: probability of moving from 15-19 TO 0-3 HA Days per 28 days on Comparator	0.021	N/A	N/A			0.0587
p4_2COMP	Week 12 to Week 24: probability of moving from 15-19 TO 4-9 HA Days per 28 days on Comparator	0.072	N/A	N/A			0.1549
p4_3COMP	Week 12 to Week 24: probability of moving from 15-19 TO 10-14 HA Days per 28 days on Comparator	0.309	N/A	N/A			0.3256
p4_4COMP	Week 12 to Week 24: probability of staying in 15-19 HA Days per 28 days on Comparator	0.309	N/A	N/A			0.2619
p4_5COMP	Week 12 to Week 24: probability of moving from 15-19 to 20-23 HA Days per 28 days on Comparator	0.155	N/A	N/A			0.0649
p4_6COMP	Week 12 to Week 24: probability of moving from 15-19 to 24+ HA Days per 28 days on Comparator	0.062	N/A	N/A			0.0400
p4_dCOMP	Week 12 to Week 24: probability of discontinuing treatment with 15-19 HA Days per 28 days on Comparator	0.072	N/A	N/A			0.0942
p5_1COMP	Week 12 to Week 24: probability of moving from 20-23 TO 0-3 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0475
p5_2COMP	Week 12 to Week 24: probability of moving from 20-23 TO 4-9 HA Days per 28 days on Comparator	0.063	N/A	N/A			0.1396
p5_3COMP	Week 12 to Week 24: probability of	0.104	N/A	N/A			0.2232

	moving from 20-23 TO 10-14 HA Days per 28 days on Comparator						
p5_4COMP	Week 12 to Week 24: probability of moving from 20-23 TO 15-19 HA Days per 28 days on Comparator	0.313	N/A	N/A			0.2206
p5_5COMP	Week 12 to Week 24: probability of staying in 20-23 HA Days per 28 days on Comparator	0.313	N/A	N/A			0.1970
p5_6COMP	Week 12 to Week 24: probability of moving from 20-23 TO 24+ HA Days per 28 days on Comparator	0.188	N/A	N/A			0.1390
p5_dCOMP	Week 12 to Week 24: probability of discontinuing treatment with 20-23 HA Days per 28 days on Comparator	0.021	N/A	N/A			0.0331
p6_1COMP	Week 12 to Week 24: probability of moving from 24+ TO 0-3 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0241
p6_2COMP	Week 12 to Week 24: probability of moving from 24+ TO 4-9 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0246
p6_3COMP	Week 12 to Week 24: probability of moving from 24+ TO 10-14 HA Days per 28 days on Comparator	0.014	N/A	N/A			0.0639
p6_4COMP	Week 12 to Week 24: probability of moving from 24+ TO 15-19 HA Days per 28 days on Comparator	0.086	N/A	N/A			0.1350
p6_5COMP	Week 12 to Week 24: probability of moving from 24+ TO 20-23 HA Days per 28 days on Comparator	0.129	N/A	N/A			0.1167
p6_6COMP	Week 12 to Week 24: probability of staying in 24+ HA Days per 28 days on Comparator	0.743	N/A	N/A			0.6120
p6_dCOMP	Week 12 to Week 24: probability of discontinuing treatment with 24+ HA Days per 28 days on Comparator	0.029	N/A	N/A			0.0238
Chronic Migraine Markov Transition Probabilities (per 12 week cycle AFTER week 24)		deterministic	standard error	distribution	alpha	beta	probabilistic
p1_1BOTOX	Week 24+ : probability of staying in 0-3 HA Days per 28 days on BOTOX	0.754	N/A	N/A			0.7257
p1_2BOTOX	Week 24+ : probability of moving from 0-3 TO 4-9 HA Days per 28 days on BOTOX	0.219	N/A	N/A			0.2496

p1_3BOTOX	Week 24+ : probability of moving from 0-3 TO 10-14 HA Days per 28 days on BOTOX	0.004	N/A	N/A			0.0013
p1_4BOTOX	Week 24+ : probability of moving from 0-3 TO 15-19 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0006
p1_5BOTOX	Week 24+ : probability of moving from 0-3 TO 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0010
p1_6BOTOX	Week 24+ : probability of moving from 0-3 TO 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p1_dBOTOX	Week 24+ : probability of discontinuing treatment with 0-3 HA Days per 28 days on BOTOX	0.022	N/A	N/A			0.0218
p2_1BOTOX	Week 24+ : probability of moving from 4-9 TO 0-3 HA Days per 28 days on BOTOX	0.331	N/A	N/A			0.3269
p2_2BOTOX	Week 24+ : probability of staying in 4-9 HA Days per 28 days on BOTOX	0.504	N/A	N/A			0.5145
p2_3BOTOX	Week 24+ : probability of moving from 4-9 TO 10-14 HA Days per 28 days on BOTOX	0.091	N/A	N/A			0.0525
p2_4BOTOX	Week 24+ : probability of moving from 4-9 TO 15-19 HA Days per 28 days on BOTOX	0.012	N/A	N/A			0.0050
p2_5BOTOX	Week 24+ : probability of moving from 4-9 TO 20-23 HA Days per 28 days on BOTOX	0.012	N/A	N/A			0.0148
p2_6BOTOX	Week 24+ : probability of moving from 4-9 TO 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0056
p2_dBOTOX	Week 24+ : probability of discontinuing treatment with 4-9 HA Days per 28 days on BOTOX	0.050	N/A	N/A			0.0806
p3_1BOTOX	Week 24+ : probability of moving from 10-14 TO 0-3 HA Days per 28 days on BOTOX	0.119	N/A	N/A			0.1099
p3_2BOTOX	Week 24+ : probability of moving from 10-14 TO 4-9 HA Days per 28 days on BOTOX	0.274	N/A	N/A			0.2952
p3_3BOTOX	Week 24+ : probability of staying in 10-14 HA Days per 28 days on BOTOX	0.357	N/A	N/A			0.2292
p3_4BOTOX	Week 24+ : probability of moving from 10-14 TO 15-19 HA Days per 28 days on BOTOX	0.155	N/A	N/A			0.0941
p3_5BOTOX	Week 24+ : probability of moving from 10-	0.012	N/A	N/A			0.0190

	14 TO 20-23 HA Days per 28 days on BOTOX						
p3_6BOTOX	Week 24+ : probability of moving from 10-14 TO 24+ HA Days per 28 days on BOTOX	0.024	N/A	N/A			0.0026
p3_dBOTOX	Week 24+ : probability of discontinuing treatment with 10-14 HA Days per 28 days on BOTOX	0.060	N/A	N/A			0.2501
p4_1BOTOX	Week 24+ : probability of moving from 15-19 TO 0-3 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.1087
p4_2BOTOX	Week 24+ : probability of moving from 15-19 TO 4-9 HA Days per 28 days on BOTOX	0.189	N/A	N/A			0.2654
p4_3BOTOX	Week 24+ : probability of moving from 15-19 TO 10-14 HA Days per 28 days on BOTOX	0.405	N/A	N/A			0.2649
p4_4BOTOX	Week 24+ : probability of staying in 15-19 HA Days per 28 days on BOTOX	0.270	N/A	N/A			0.1265
p4_5BOTOX	Week 24+ : probability of moving from 15-19 to 20-23 HA Days per 28 days on BOTOX	0.081	N/A	N/A			0.0464
p4_6BOTOX	Week 24+ : probability of moving from 15-19 to 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0054
p4_dBOTOX	Week 24+ : probability of discontinuing treatment with 15-19 HA Days per 28 days on BOTOX	0.054	N/A	N/A			0.1828
p5_1BOTOX	Week 24+ : probability of moving from 20-23 TO 0-3 HA Days per 28 days on BOTOX	0.125	N/A	N/A			0.0454
p5_2BOTOX	Week 24+ : probability of moving from 20-23 TO 4-9 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.1623
p5_3BOTOX	Week 24+ : probability of moving from 20-23 TO 10-14 HA Days per 28 days on BOTOX	0.375	N/A	N/A			0.1495
p5_4BOTOX	Week 24+ : probability of moving from 20-23 TO 15-19 HA Days per 28 days on BOTOX	0.375	N/A	N/A			0.2880
p5_5BOTOX	Week 24+ : probability of staying in 20-23 HA Days per 28 days on BOTOX	0.125	N/A	N/A			0.0595
p5_6BOTOX	Week 24+ : probability of moving from 20-23 TO 24+ HA Days per 28 days on	0.000	N/A	N/A			0.0734

	BOTOX						
p5_dBOTOX	Week 24+ : probability of discontinuing treatment with 20-30 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.2219
p6_1BOTOX	Week 24+ : probability of moving from 24+ TO 0-3 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0387
p6_2BOTOX	Week 24+ : probability of moving from 24+ TO 4-9 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.7257
p6_3BOTOX	Week 24+ : probability of moving from 24+ TO 10-14 HA Days per 28 days on BOTOX	0.500	N/A	N/A			0.2496
p6_4BOTOX	Week 24+ : probability of moving from 24+ TO 15-19 HA Days per 28 days on BOTOX	0.500	N/A	N/A			0.0013
p6_5BOTOX	Week 24+ : probability of moving from 24+ TO 20-23 HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0006
p6_6BOTOX	Week 24+ : probability of staying in 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0010
p6_dBOTOX	Week 24+ : probability of discontinuing treatment with 24+ HA Days per 28 days on BOTOX	0.000	N/A	N/A			0.0000
p1_1COMP	Week 24+ : probability of staying in 0-3 HA Days per 28 days on Comparator	0.621	N/A	N/A			0.5492
p1_2COMP	Week 24+ : probability of moving from 0-3 TO 4-9 HA Days per 28 days on Comparator	0.207	N/A	N/A			0.2219
p1_3COMP	Week 24+ : probability of moving from 0-3 TO 10-14 HA Days per 28 days on Comparator	0.034	N/A	N/A			0.0729
p1_4COMP	Week 24+ : probability of moving from 0-3 TO 15-19 HA Days per 28 days on Comparator	0.034	N/A	N/A			0.0433
p1_5COMP	Week 24+ : probability of moving from 0-3 TO 20-23 HA Days per 28 days on Comparator	0.034	N/A	N/A			0.0409
p1_6COMP	Week 24+ : probability of moving from 0-3 TO 24+ HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0127
p1_dCOMP	Week 24+ : probability of discontinuing treatment with 0-3 HA Days per 28 days on Comparator	0.069	N/A	N/A			0.0591

p2_1COMP	Week 24+ : probability of moving from 4-9 TO 0-3 HA Days per 28 days on Comparator	0.081	N/A	N/A			0.0570
p2_2COMP	Week 24+ : probability of staying in 4-9 HA Days per 28 days on Comparator	0.554	N/A	N/A			0.6029
p2_3COMP	Week 24+ : probability of moving from 4-9 TO 10-14 HA Days per 28 days on Comparator	0.216	N/A	N/A			0.2174
p2_4COMP	Week 24+ : probability of moving from 4-9 TO 15-19 HA Days per 28 days on Comparator	0.041	N/A	N/A			0.0509
p2_5COMP	Week 24+ : probability of moving from 4-9 TO 20-23 HA Days per 28 days on Comparator	0.041	N/A	N/A			0.0286
p2_6COMP	Week 24+ : probability of moving from 4-9 TO 24+ HA Days per 28 days on Comparator	0.014	N/A	N/A			0.0182
p2_dCOMP	Week 24+ : probability of discontinuing treatment with 4-9 HA Days per 28 days on Comparator	0.054	N/A	N/A			0.0250
p3_1COMP	Week 24+ : probability of moving from 10-14 TO 0-3 HA Days per 28 days on Comparator	0.061	N/A	N/A			0.0657
p3_2COMP	Week 24+ : probability of moving from 10-14 TO 4-9 HA Days per 28 days on Comparator	0.307	N/A	N/A			0.3000
p3_3COMP	Week 24+ : probability of staying in 10-14 HA Days per 28 days on Comparator	0.333	N/A	N/A			0.2989
p3_4COMP	Week 24+ : probability of moving from 10-14 TO 15-19 HA Days per 28 days on Comparator	0.202	N/A	N/A			0.1906
p3_5COMP	Week 24+ : probability of moving from 10-14 TO 20-23 HA Days per 28 days on Comparator	0.053	N/A	N/A			0.0627
p3_6COMP	Week 24+ : probability of moving from 10-14 TO 24+ HA Days per 28 days on Comparator	0.009	N/A	N/A			0.0214
p3_dCOMP	Week 24+ : probability of discontinuing treatment with 10-14 HA Days per 28 days on Comparator	0.035	N/A	N/A			0.0608
p4_1COMP	Week 24+ : probability of moving from 15-19 TO 0-3 HA Days per 28 days on Comparator	0.021	N/A	N/A			0.0465
p4_2COMP	Week 24+ : probability of moving from 15-	0.072	N/A	N/A			0.1746

	19 TO 4-9 HA Days per 28 days on Comparator						
p4_3COMP	Week 24+ : probability of moving from 15-19 TO 10-14 HA Days per 28 days on Comparator	0.309	N/A	N/A			0.3671
p4_4COMP	Week 24+ : probability of staying in 15-19 HA Days per 28 days on Comparator	0.309	N/A	N/A			0.2062
p4_5COMP	Week 24+ : probability of moving from 15-19 to 20-23 HA Days per 28 days on Comparator	0.155	N/A	N/A			0.0652
p4_6COMP	Week 24+ : probability of moving from 15-19 to 24+ HA Days per 28 days on Comparator	0.062	N/A	N/A			0.0593
p4_dCOMP	Week 24+ : probability of discontinuing treatment with 15-19 HA Days per 28 days on Comparator	0.072	N/A	N/A			0.0811
p5_1COMP	Week 24+ : probability of moving from 20-23 TO 0-3 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0444
p5_2COMP	Week 24+ : probability of moving from 20-23 TO 4-9 HA Days per 28 days on Comparator	0.063	N/A	N/A			0.0675
p5_3COMP	Week 24+ : probability of moving from 20-23 TO 10-14 HA Days per 28 days on Comparator	0.104	N/A	N/A			0.1333
p5_4COMP	Week 24+ : probability of moving from 20-23 TO 15-19 HA Days per 28 days on Comparator	0.313	N/A	N/A			0.3361
p5_5COMP	Week 24+ : probability of staying in 20-23 HA Days per 28 days on Comparator	0.313	N/A	N/A			0.2498
p5_6COMP	Week 24+ : probability of moving from 20-23 TO 24+ HA Days per 28 days on Comparator	0.188	N/A	N/A			0.1482
p5_dCOMP	Week 24+ : probability of discontinuing treatment with 20-23 HA Days per 28 days on Comparator	0.021	N/A	N/A			0.0207
p6_1COMP	Week 24+ : probability of moving from 24+ TO 0-3 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.0154
p6_2COMP	Week 24+ : probability of moving from 24+ TO 4-9 HA Days per 28 days on Comparator	0.000	N/A	N/A			0.5492
p6_3COMP	Week 24+ : probability of moving from 24+ TO 10-14 HA Days per 28 days on	0.014	N/A	N/A			0.2219

	Comparator						
p6_4COMP	Week 24+ : probability of moving from 24+ TO 15-19 HA Days per 28 days on Comparator	0.086	N/A	N/A			0.0729
p6_5COMP	Week 24+ : probability of moving from 24+ TO 20-23 HA Days per 28 days on Comparator	0.129	N/A	N/A			0.0433
p6_6COMP	Week 24+ : probability of staying in 24+ HA Days per 28 days on Comparator	0.743	N/A	N/A			0.0409
p6_dCOMP	Week 24+ : probability of discontinuing treatment with 24+ HA Days per 28 days on Comparator	0.029	N/A	N/A			0.0127
Migraine Frequency (as measured in Headache Days per 28 Days)		deterministic	standard error	distribution	alpha	beta	probabilistic
m1_12wkBOTOX	12wk Mean HA Days per 28 days - 0-3 HA Days on BOTOX	1.80	0	N/A			1.8000
m2_12wkBOTOX	12wk Mean HA Days per 28 days - 4-9 HA Days on BOTOX	6.80	0	N/A			6.8000
m3_12wkBOTOX	12wk Mean HA Days per 28 days - 10-14 HA Days on BOTOX	11.60	0	N/A			11.6000
m4_12wkBOTOX	12wk Mean HA Days per 28 days - 15-19 HA Days on BOTOX	16.90	0	N/A			16.9000
m5_12wkBOTOX	12wk Mean HA Days per 28 days - 20-23 HA Days on BOTOX	21.50	0	N/A			21.5000
m6_12wkBOTOX	12wk Mean HA Days per 28 days - 24+ HA Days on BOTOX	25.80	0	N/A			25.8000
md_12wkBOTOX	12wk Mean HA Days per 28 days - Discontinued Tx on BOTOX	14.90	0	N/A			14.9000
m1_12wkCOMP	12wk Mean HA Days per 28 days - 0-3 HA Days on comparator	1.40	0.24	N/A			1.4000
m2_12wkCOMP	12wk Mean HA Days per 28 days - 4-9 HA Days on comparator	7.20	0.19	N/A			7.2000
m3_12wkCOMP	12wk Mean HA Days per 28 days - 10-14 HA Days on comparator	12.10	0.13	N/A			12.1000
m4_12wkCOMP	12wk Mean HA Days per 28 days - 15-19 HA Days on comparator	17.10	0.15	N/A			17.1000
m5_12wkCOMP	12wk Mean HA Days per 28 days - 20-23 HA Days on comparator	21.10	0.17	N/A			21.1000
m6_12wkCOMP	12wk Mean HA Days per 28 days - 24+ HA Days on comparator	26.40	0.18	N/A			26.4000
md_12wkCOMP	12wk Mean HA Days per 28 days - Discontinued Tx on comparator	14.90	0.78	N/A			14.9000

m1_24wkBOTOX	24wk Mean HA Days per 28 days - 0-3 HA Days on BOTOX	1.70	0	N/A			1.7000
m2_24wkBOTOX	24wk Mean HA Days per 28 days - 4-9 HA Days on BOTOX	6.40	0	N/A			6.4000
m3_24wkBOTOX	24wk Mean HA Days per 28 days - 10-14 HA Days on BOTOX	11.80	0	N/A			11.8000
m4_24wkBOTOX	24wk Mean HA Days per 28 days - 15-19 HA Days on BOTOX	16.90	0	N/A			16.9000
m5_24wkBOTOX	24wk Mean HA Days per 28 days - 20-23 HA Days on BOTOX	21.60	0	N/A			21.6000
m6_24wkBOTOX	24wk Mean HA Days per 28 days - 24+ HA Days on BOTOX	26.50	0	N/A			26.5000
md_24wkBOTOX	24wk Mean HA Days per 28 days - Discontinued Tx on BOTOX	14.40	0	N/A			14.4000
m1_24wkCOMP	24wk Mean HA Days per 28 days - 0-3 HA Days on comparator	1.70	0.22	N/A			1.7000
m2_24wkCOMP	24wk Mean HA Days per 28 days - 4-9 HA Days on comparator	6.90	0.17	N/A			6.9000
m3_24wkCOMP	24wk Mean HA Days per 28 days - 10-14 HA Days on comparator	12.00	0.15	N/A			12.0000
m4_24wkCOMP	24wk Mean HA Days per 28 days - 15-19 HA Days on comparator	16.70	0.16	N/A			16.7000
m5_24wkCOMP	24wk Mean HA Days per 28 days - 20-23 HA Days on comparator	21.20	0.17	N/A			21.2000
m6_24wkCOMP	24wk Mean HA Days per 28 days - 24+ HA Days on comparator	26.90	0.15	N/A			26.9000
md_24wkCOMP	24wk Mean HA Days per 28 days - Discontinued Tx on comparator	14.40	0.64	N/A			14.4000
m1_BOTOX	24wk+ Mean HA Days per 28 days - 0-3 HA Days on BOTOX	1.70	0	N/A			1.7000
m2_BOTOX	24wk+ Mean HA Days per 28 days - 4-9 HA Days on BOTOX	6.40	0	N/A			6.4000
m3_BOTOX	24wk+ Mean HA Days per 28 days - 10-14 HA Days on BOTOX	11.80	0	N/A			11.8000
m4_BOTOX	24wk+ Mean HA Days per 28 days - 15-19 HA Days on BOTOX	16.90	0	N/A			16.9000
m5_BOTOX	24wk+ Mean HA Days per 28 days - 20-23 HA Days on BOTOX	21.60	0	N/A			21.6000
m6_BOTOX	24wk+ Mean HA Days per 28 days - 24+ HA Days on BOTOX	26.50	0	N/A			26.5000
md_BOTOX	24wk+ Mean HA Days per 28 days - Discontinued Tx on BOTOX	14.40	0	N/A			14.4000
m1_COMP	24wk+ Mean HA Days per 28 days - 0-3	1.70	0.22	N/A			1.7000

	HA Days on comparator						
m2_COMP	24wk+ Mean HA Days per 28 days - 4-9 HA Days on comparator	6.90	0.17	N/A			6.9000
m3_COMP	24wk+ Mean HA Days per 28 days - 10-14 HA Days on comparator	12.00	0.15	N/A			12.0000
m4_COMP	24wk+ Mean HA Days per 28 days - 15-19 HA Days on comparator	16.70	0.16	N/A			16.7000
m5_COMP	24wk+ Mean HA Days per 28 days - 20-23 HA Days on comparator	21.20	0.17	N/A			21.2000
m6_COMP	24wk+ Mean HA Days per 28 days - 24+ HA Days on comparator	26.90	0.15	N/A			26.9000
md_COMP	24wk+ Mean HA Days per 28 days - Discontinued Tx on comparator	14.40	0.64	N/A			14.4000
Costs		deterministic	standard error	distribution	alpha	beta	probabilistic
cBOTOX	Cost of BOTOX per treatment	£349.40	0	N/A			£349.40
cCOMP	Cost of Comparator per treatment	£36.50		N/A			£36.50
Utility		deterministic	standard error	distribution	alpha	beta	probabilistic
u1_BOTOX	0-3 HAs Utility on BOTOX	0.746	0.013265306	Beta	802.55	273.26	0.7583
u2_BOTOX	4-9 HAs Utility on BOTOX	0.71	0.010714286	Beta	1272.76	519.86	0.7199
u3_BOTOX	10-14 HAs Utility on BOTOX	0.652	0.013265306	Beta	840.05	448.37	0.6643
u4_BOTOX	15-19 HAs Utility on BOTOX	0.602	0.017857143	Beta	451.72	298.65	0.6186
u5_BOTOX	20-23 HAs Utility on BOTOX	0.515	0.034693878	Beta	106.35	100.16	0.5472
u6_BOTOX	24+ HAs Utility on BOTOX	0.601	0.030612245	Beta	153.19	101.70	0.6295
ud_BOTOX	Discontinued Utility on BOTOX	0.576458333	0.05	Beta	55.72	40.94	0.6231
u1_COMP	0-3 HAs Utility on comparator	0.724	0.017346939	Beta	480.05	183.00	0.7401
u2_COMP	4-9 HAs Utility on comparator	0.658	0.01122449	Beta	1174.63	610.52	0.6684
u3_COMP	10-14 HAs Utility on comparator	0.62	0.01377551	Beta	769.13	471.40	0.6328
u4_COMP	15-19 HAs Utility on comparator	0.568	0.020408163	Beta	334.07	254.08	0.5869
u5_COMP	20-23 HAs Utility on comparator	0.558	0.02755102	Beta	180.75	143.17	0.5836
u6_COMP	24+ HAs Utility on comparator	0.479	0.025	Beta	190.78	207.51	0.5022
ud_COMP	Discontinued Utility on comparator	0.558090909	0.05	Beta	54.50	43.15	0.6047
Acute Headache Costs and Outcomes							
Costs		deterministic	standard error	distribution	alpha	beta	probabilistic
cPvisitmig	Cost of physician visit for migraine	£32.00	£3.20	Gamma	100.00	0.32	£31.78
chospmig	Cost of hospital visit for migraine	£583.67	£58.37	Gamma	100.00	5.84	£558.50
cERvisitmig	Cost of ER visit for migraine	£90.94	£9.09	Gamma	100.00	0.91	£89.36
cucare	Cost of usual care treatment per attack	£0.00	N/A	N/A			£-
ctriptan	Acquisition cost of triptan per attack	£3.35	£0.34	Gamma	100.00	0.03	£3.77
hourwage	Hourly wage	£14.60	£1.46	Gamma	100.00	0.15	£15.15
Acute Headache Treatment (per 12 weeks)		deterministic	standard error	distribution	alpha	beta	probabilistic

m1_Triptan	Mean Number of Treatments with a triptan: 0-3 HA Days per 28 days	1.9	0.09	Normal			1.9966
m2_Triptan	Mean Number of Treatments with a triptan: 4-9 HA Days per 28 days	5.1	0.32	Normal			4.7677
m3_Triptan	Mean Number of Treatments with a triptan: 10-14 HA Days per 28 days	5.1	0.32	Normal			5.0703
m4_Triptan	Mean Number of Treatments with a triptan: 15-19 HA Days per 28 days	7.3	1.04	Normal			6.3754
m5_Triptan	Mean Number of Treatments with a triptan: 20-23 HA Days per 28 days	7.3	1.04	Normal			7.3596
m6_Triptan	Mean Number of Treatments with a triptan: 24+ HA Days per 28 days	7.3	1.04	Normal			5.8494
m1_NonTriptan	Mean Number of Treatments with a non-triptan: 0-3 HA Days per 28 days	37.9	2.04	Normal			39.1154
m2_NonTriptan	Mean Number of Treatments with a non-triptan: 4-9 HA Days per 28 days	75.6	4.11	Normal			80.0310
m3_NonTriptan	Mean Number of Treatments with a non-triptan: 10-14 HA Days per 28 days	75.6	4.11	Normal			73.9459
m4_NonTriptan	Mean Number of Treatments with a non-triptan: 15-19 HA Days per 28 days	127.6	10.92	Normal			120.4303
m5_NonTriptan	Mean Number of Treatments with a non-triptan: 20-23 HA Days per 28 days	127.6	10.92	Normal			133.8442
m6_NonTriptan	Mean Number of Treatments with a non-triptan: 24+ HA Days per 28 days	127.6	10.92	Normal			136.5032
Healthcare Resource Utilization (per 12 weeks)		deterministic	standard error	distribution	alpha	beta	probabilistic
p1_Pvisit	Mean number of physician visits: 0-3 HA Days per 28 days	0.10	0.0055	Normal			0.1001
p2_Pvisit	Mean number of physician visits: 4-9 HA Days per 28 days	0.30	0.0202	Normal			0.2744
p3_Pvisit	Mean number of physician visits: 10-14 HA Days per 28 days	0.30	0.0202	Normal			0.2817
p4_Pvisit	Mean number of physician visits: 15-19 HA Days per 28 days	0.58	0.0798	Normal			0.6411
p5_Pvisit	Mean number of physician visits: 20-23 HA Days per 28 days	0.58	0.0798	Normal			0.5603
p6_Pvisit	Mean number of physician visits: 24+ HA Days per 28 days	0.58	0.0798	Normal			0.6436
p1_hosp	Mean number of Hospitalizations: 0-3 HA Days per 28 days	0.03	0.0062	Normal			0.0390
p2_hosp	Mean number of Hospitalizations: 4-9 HA Days per 28 days	0.08	0.0187	Normal			0.0817
p3_hosp	Mean number of Hospitalizations: 10-14	0.08	0.0187	Normal			0.1018

	HA Days per 28 days						
p4_hosp	Mean number of Hospitalizations: 15-19 HA Days per 28 days	0.32	0.1361	Normal			0.2617
p5_hosp	Mean number of Hospitalizations: 20-23 HA Days per 28 days	0.32	0.1361	Normal			0.5099
p6_hosp	Mean number of Hospitalizations: 24+ HA Days per 28 days	0.32	0.1361	Normal			0.1784
p1_ERvisit	Mean number of ER visits: 0-3 HA Days per 28 days	0.12	0.0079	Normal			0.1117
p2_ERvisit	Mean number of ER visits: 4-9 HA Days per 28 days	0.28	0.0226	Normal			0.2881
p3_ERvisit	Mean number of ER visits: 10-14 HA Days per 28 days	0.28	0.0226	Normal			0.3007
p4_ERvisit	Mean number of ER visits: 15-19 HA Days per 28 days	0.63	0.1870	Normal			0.7780
p5_ERvisit	Mean number of ER visits: 20-23 HA Days per 28 days	0.63	0.1870	Normal			0.6615
p6_ERvisit	Mean number of ER visits: 24+ HA Days per 28 days	0.63	0.1870	Normal			0.6746
Productivity impact (per 12 weeks)		deterministic	standard error	distribution	alpha	beta	probabilistic
m1_lostHrs	Mean lost work hours: 0-3 HA Days per 28 days	6.31	0.63	Normal			7.0498
m2_lostHrs	Mean lost work hours: 4-9 HA Days per 28 days	16.78	1.68	Normal			15.4169
m3_lostHrs	Mean lost work hours: 10-14 HA Days per 28 days	16.78	1.68	Normal			14.4471
m4_lostHrs	Mean lost work hours: 15-19 HA Days per 28 days	41.35	4.14	Normal			41.1274
m5_lostHrs	Mean lost work hours: 20-23 HA Days per 28 days	41.35	4.14	Normal			39.0968

9.14 Appendix 14: Markov Trace – patient distribution

Table 1: Markov Trace: Botox

Number of patients - Botox						
Week	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
0	0.0000	0.0000	0.0011	0.5085	0.2912	0.1991
12	0.0942	0.2513	0.2081	0.1987	0.1383	0.1091
24	0.1395	0.3139	0.1818	0.1633	0.0938	0.1072
36	0.2143	0.2832	0.1745	0.1336	0.0814	0.1123
48	0.2504	0.2775	0.1654	0.1218	0.0738	0.1100
60	0.2682	0.2790	0.1592	0.1149	0.0706	0.1067
72	0.2730	0.2852	0.1685	0.1022	0.0669	0.1025
84	0.2784	0.2900	0.1666	0.0976	0.0651	0.1003
96	0.2829	0.2927	0.1645	0.0953	0.0642	0.0982
108	0.2862	0.2942	0.1631	0.0939	0.0636	0.0964

Table 2: Markov Trace: Placebo

Number of patients - Placebo						
Week	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
0	0.0000	0.0000	0.0011	0.5085	0.2912	0.1991
12	0.0641	0.1619	0.2513	0.2494	0.1155	0.1574
24	0.0780	0.2143	0.2220	0.2025	0.1196	0.1631
36	0.0890	0.2369	0.2086	0.1836	0.1155	0.1657
48	0.0971	0.2469	0.2028	0.1739	0.1122	0.1659
60	0.1029	0.2520	0.1999	0.1687	0.1101	0.1650
72	0.1070	0.2547	0.1984	0.1658	0.1088	0.1636
84	0.1098	0.2564	0.1976	0.1640	0.1080	0.1622
96	0.1118	0.2576	0.1973	0.1628	0.1075	0.1608
108	0.1131	0.2585	0.1971	0.1621	0.1071	0.1596

9.15 Appendix 15: Markov Trace – QALYs

Table 1: Markov Trace: Botox

Number of patients - Botox						
Week	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
0	0.0000	0.0000	0.0000	0.0040	0.0021	0.0011
12	0.0179	0.0506	0.0466	0.0404	0.0266	0.0257
24	0.0264	0.0566	0.0272	0.0190	0.0096	0.0122
36	0.0391	0.0484	0.0256	0.0164	0.0096	0.0122
48	0.0448	0.0460	0.0242	0.0156	0.0091	0.0119
60	0.0466	0.0445	0.0230	0.0150	0.0089	0.0115
72	0.0471	0.0448	0.0231	0.0148	0.0088	0.0112
84	0.0476	0.0457	0.0246	0.0132	0.0084	0.0108
96	0.0483	0.0464	0.0243	0.0127	0.0083	0.0107
108	0.0384	0.0246	0.0077	0.0004	0.0001	0.0000

Table 2: Markov Trace: Placebo

Number of patients - Placebo						
Week	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
0	0.0000	0.0000	0.0002	0.0667	0.0375	0.0220
12	0.0107	0.0246	0.0360	0.0327	0.0149	0.0174
24	0.0130	0.0325	0.0318	0.0265	0.0154	0.0180
36	0.0149	0.0360	0.0298	0.0241	0.0149	0.0183
48	0.0162	0.0375	0.0290	0.0228	0.0145	0.0183
60	0.0172	0.0383	0.0286	0.0221	0.0142	0.0182
72	0.0179	0.0387	0.0284	0.0217	0.0140	0.0181
84	0.0183	0.0389	0.0283	0.0215	0.0139	0.0179
96	0.0187	0.0391	0.0282	0.0213	0.0138	0.0178
108	0.0189	0.0392	0.0282	0.0212	0.0138	0.0176

9.16 Appendix 16: Differences between SMC and NICE economic approaches

As discussed in Section 6.1, there are several key differences between the economic approach used in the SMC submission and the NICE STA submission.

- **Patient population** the patient population considered by the SMC was the full licensed indication although this was narrowed down in the submission by Allergan to be for patients that had previously received at least 1 oral prophylactic treatment.In the NICE submission the decision problem is given as patients who have received ≥3 prior oral prophylactics

- **Utility valuations** are now taken from direct PRO measures within the 191622-079 and 191622-080 clinical studies, using a mapping algorithm to translate between findings on the Migraine Specific Questionnaire (MSQ) and the EQ-5D (UK weights) (Section 6.4.6). The mapping algorithm developed is the subject of a research publication submitted to Value in Health. This revised utility valuation allows directly observed data to be used to estimate HRQL in the Botox and Placebo arms respectively.

- **Implementation of a revised "negative" stopping rule** in the event of a poor response to treatment: based on the Markov Model structure, patients are now assumed to discontinue therapy if they do not show an improvement of ≥ 2 Health States by week 24. This allows continued treatment to be directed towards patients showing the most meaningful response. This stopping rule is discussed in detail in Section 6.2.8

- **Implementation of a new "positive" stopping rule** in the event of a good response to treatment after 56 weeks of treatment. The model submitted to SMC considered that patients continued to receive treatment at 12 weekly intervals throughout the second year. Clinical advice received since, and an examination of

standard protocols for prophylaxis in chronic migraine, reveal that there are groups of patients for whom following a sustained response, treatment withdrawal might be attempted. ICERs are reported at 1 year and 2 years to allow the effect of this change to be understood. This stopping rule is discussed in detail in Section 6.2.8

- **Subgroup analysis** now allows the model to be run for specific groups of particular interest, including for patients who were not overusing acute medications at baseline, this was not referenced in the SMC submission

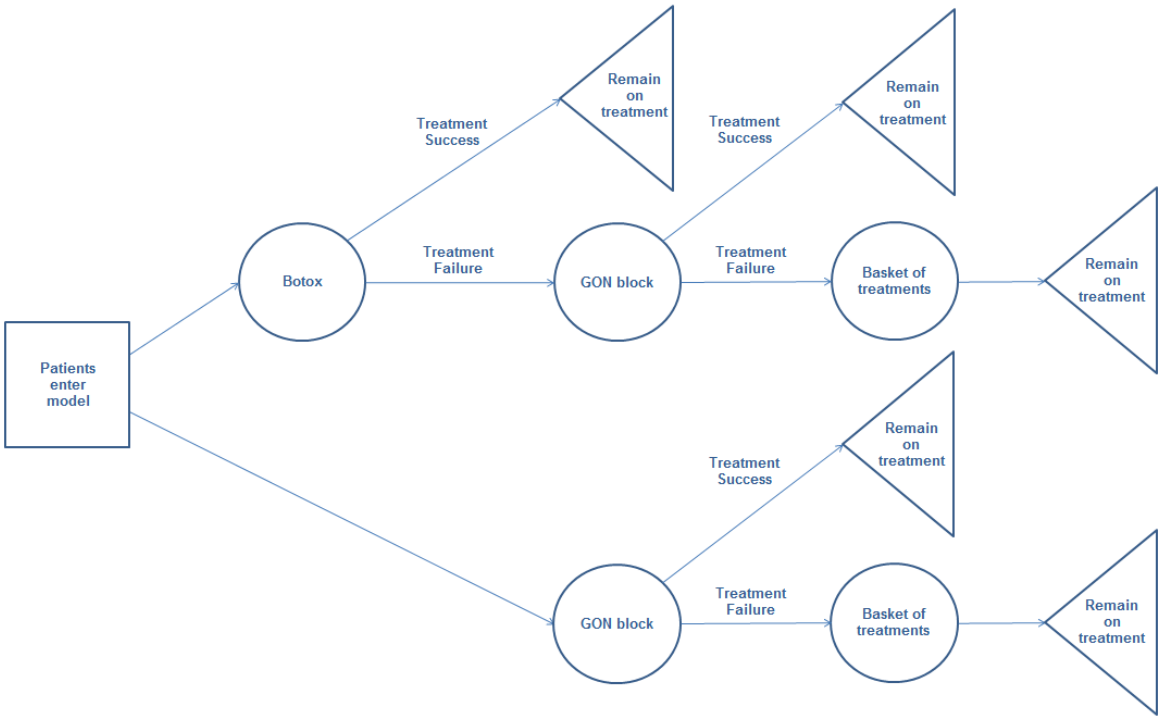
- **Sensitivity analyses** following feedback from both clinicians and the SMC, the range of sensitivity analyses presented has been expanded to explore the robustness of the model to structural changes

- **Updated costs** have been applied to reflect the latest available data from NHS Reference costs and PSSRU

9.17 Appendix 17: Treatment pathway economic model

To investigate the impact of the introduction of Botox into the care pathway on overall NHS costs, a secondary 'treatment pathway' model was constructed. The treatment pathway model estimates the cost impact of introducing Botox as a treatment option for patients who have failed on 3 or more previous oral prophylactic treatments. Due to the weak evidence base available for the identified comparators, this model considers only costs. A diagram of the model is shown in Figure 1.

Figure 1: Model diagram, treatment pathway model



Patients entering the model are assumed to have previously failed on ≥3 prior oral prophylactics. The model then compares two treatment pathways, one in which the first treatment choice for this population is Botox followed by Greater Occipital Nerve (GON) block for treatment failures, and the second pathway, where it is assumed that Botox does not exist as an option, and patients therefore immediately receive GON block.

Patients remain on specified treatments for the model time horizon if they are successfully treated (1 year in the base case).

There are limitations to this proposed analysis, principally around the absence of data. In reality, many patients (see section 6.3.5) might exit a specialist pathway at this point and persist in a chronic migraine state, managed only with acute “rescue” medications. It is assumed that the primary economic analysis examines this latter population through a comparison of Botox to placebo + acute treatments, and therefore this exploratory analysis seeks to address unanswered questions regarding other possibilities, often available only within a tertiary treatment setting.

If treatment with GON block is not successful, then patients are assumed to move onto the remainder of the treatment pathway which is modelled as a basket of potential experimental interventions which are variably available in tertiary centres in the UK.Upon treatment failure with GON block patients will be prescribed other treatments, and incur the costs of these treatments for the remainder of the time horizon. Methysergide, dihydroergotamine IV (DHE) and Occipital Nerve Stimulation are used in the model as secondary treatments. Combinations of treatments have not been considered due to a lack of evidence of the efficacy of this approach (Appendix 2).

Response rates for Botox are taken from the 191622-079 and 191622-080 clinical trials. Response rates for GON block are taken from expert opinion, however these are likely to show variability in practice based on differing treatment protocols and techniques, and there are unanswered questions around longer term repeatability of this type of procedure. For modelling purposes it is assumed that GON blocks could be administered for up to 1 year, however this may be at odds with individual clinical practice.

As no outcomes data are available for subsequent treatments, patients are assumed to remain on the treatment for the remainder of the modelled time horizon which is consequently bound to just one year.

The treatment pathway model looks at the total costs to the NHS of the use of Botox, in comparison to existing experimental therapies that could be used in the chronic migraine patient population who have already been treated with ≥3 oral prophylactics. The key outcome of the model is the cost to the NHS, with the alternative treatments used reflective of the potential clinical pathway of care for these patients in specialist or tertiary centres. The evidence for these treatments is poor (Section 5.7.1), however they represent the treatments that patients may receive if Botox is not available. Evidence of this can be seen in NHS Prescriptions Cost Analysis (DoH, 2011), where in 2010 there were 2,882 prescriptions for methysergide (one of the treatment options in the model) dispensed, with a drug cost of over £71,000. These prescribing figures indicate there are approximately 100 patients treated with the drug at any one time in England & Wales.

There were also limited clinical trial data available to support the efficacy of treatments therefore clinician opinion was used to supplement this evidence base (Section 5.7.1 and Section 6.3.4).

Table 2: Key features of the secondary (treatment pathway) economic model

Factor	Chosen values	Justification	Reference
Time horizon	1 year	Appropriate time horizon over which to measure costs to the healthcare service	-
Cycle length	1 week	Appropriate to use given the different treatment cycles of drugs	-
Half-cycle correction	No	Not necessary given the short cycle length	-
Were health effects measured in QALYs; if not, what was used?	No	The secondary model is meant to purely consider cost outcomes, in the absence of evidence for the comparators.	Section 5.7.1
Discount of 3.5% for utilities and costs	No	Not necessary given the 1 year time horizon	NICE (2008)
Perspective (NHS/PSS)	NHS	-	NICE (2008)
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

As the interventions may be unlicensed and have a poor evidence base clinical expert opinion has been used to derive an understanding of the pathway of care and likely cost consequences.

In the treatment pathway model, patients that do not respond to Botox (if available), then GON block, are assumed to discontinue treatment and move to the last line basket of treatment options (which includes methysergide, IV dihydroergotamine and Occipital Nerve Stimulation). They continue to be treated with these until the end of the 1 year time horizon. If successfully treated with either Botox or GON block, it is assumed patients remain on these treatments until the end of the modeled period. This is a simplifying assumption however, as it is unlikely all patients would remain on treatment for the entire period.

Table 3: Summary of settings applied in the treatment pathway model

Variable	Value	Reference
Treatment success: Botox	70%	Expert Opinion
Treatment regimen: Botox	200mg vial every 12 weeks with 30 minute consultant visit	Clinical study 191822-079 & 191622-080
Treatment success: GON Block	40%	Expert opinion
Treatment regimen: GON Block	GON Block administered every 8 weeks	Expert opinion
Percentage of non-responders receiving methysergide	50%	Expert opinion
Treatment regimen: methysergide	6mg per day, with drug holiday of 4 weeks after 6 months	BNF Volume 62 Section 4.7.4.2 – Prophylaxis of Migraine
Percentage of non-responders receiving IV DHE	20%	Expert opinion
Treatment regimen: IV DHE	Patients administered 10 IV DHE infusions over 4 days, every 3-4 months (3.5 months used in the model)	Personal communication
Percentage of non-responders Occipital Nerve Stimulation	30%	Expert opinion
Treatment regimen: Occipital Nerve Stimulation	Electrodes positioned in one operation, with stimulator implanted in second. No further operations required within 1 year	NHS Hull General Commissioning policy Statement T19/10; Personal communication

Assumptions made in the model are listed in Table 4

Table 4: Table of assumptions & justifications in the treatment pathway model

Assumption	Justification
Patients who receive Botox therapy would otherwise have received GON block	Expert opinion has identified that for a proportion of patients who have received and failed on prior oral prophylactics, GON block

	would be a suitable “minimally invasive” treatment
GON Block is administered in 30 minutes of consultant time	GON block consists mainly of physician time, with the cost of any treatments used being minimal. Therefore it is assumed that the cost of treatment is a 30 minute outpatient appointment, in which the treatment is administered
If unsuccessfully treated with GON block, patients would be treated with either methysergide, IV DHE, or Occipital Nerve Stimulation (ONS)	Expert opinion (and prescribing data) have identified methysergide as a potential specialist treatment option for patients who have received prior prophylactic treatments. IV DHE and ONS have also been identified by physicians as potential treatments for this patient population, whilst in some NHS regions guidance has been produced on the use of Occipital Nerve Stimulation for chronic migraine.
Patients would continue to be treated for the full 1 year time period	It is assumed patients are motivated to continue to the next treatment in line
Patients continue the second treatment from the basket of treatments for the remainder of the 1 year time horizon, regardless of success	There is very little evidence available for the response rates of other treatments, given the short time remaining time horizon, this assumption was made for simplicity

The cost of interventions and the assumed administration costs are shown in Table 5. The treatment pathway model does not include health states, however the total cost of each treatment (including treatment cost, administration costs, and monitoring costs) are shown in Table 6 for each treatment captured within the model.

Table 5: Unit costs associated with the technology in the treatment pathway model

Intervention	Cost of treatment	Frequency of administration	Cost of administration & monitoring	Source REFS
Botox	£276.40	Every 12 weeks	£73.00 (30 minutes consultant time)	Primary economic model
GON Block	£73	Every 8 weeks	Included in procedure cost	Expert opinion
Methysergide	£12.94	60 tablet pack, 3 tablets per day,	£73.00 (30 minutes consultant time) every 3 months. Monitoring costs per year of: - 12x blood tests (£9, PSSRU) - 2x Chest X-ray (£23.41, Wilson et al, 2010) - 2x Echocardiogram (£66.43 NHS Reference costs) 1x Abdominal CT (£112.56, NHS Reference costs)	BNF 61 (page 278), expert opinion
IV DHE	£20 per 1mg vial (Expert opinion, not available in BNF)	10 infusions of 9.25mg given every 3.5 months over 4 days	Cost of infusion taken to be 4x Elective Inpatient Excess Bed Day (HRG Data AA31Z)	Expert opinion, NHS reference costs
Occipital Nerve Stimulation	£17,500 (estimated £10,000 for the stimulator)	One procedure assumed (1 year time horizon). No revision costs accounted for.	Included in procedure cost. 6 monthly neurologist visit (£165.00)	Hull PCT, expert opinion

Disaggregated results of the treatment pathway model are presented in Table 6.

Table 6: Summary of costs by health state for the treatment pathway model

Health state	Cost intervention (Botox pathway)	Cost comparator (GON block pathway)	Increment	% absolute increment
Botox costs	£1,327.72	£0.00	£1,327.72	-
GON Block costs	£56.94	£248.20	-£191.26	-77%
Subsequent Methysergide	£46.78	£214.44	-£167.66	-78%
Subsequent IV DHE	£169.34	£753.06	-£583.73	-78%
Subsequent occipital nerve stimulation	£955.97	£3,200.26	-£2,244.30	-70%

The results of the treatment pathway model are presented in Table 7. In the base case Botox leads to a cost saving of £1,859 per patient.

The addition of Botox to the treatment pathway leads to a drug acquisition and administration cost of £1,328 over the 1 year period. However this cost is more than offset by patients not requiring further treatments.

Table 7: Base-case results, treatment pathway model

Treatment Pathway	Botox treatment costs	GON Block treatment costs	Third line treatment costs	Total Cost
Botox pathway				
Treatment cost	£1,050.32	£56.94	£973.68	£2,080.94
Administration cost	£277.40	£0.00	£198.44	£475.84
Total cost	£1,327.72	£56.94	£1,172.12	£2,556.78
GON Block pathway				
Treatment cost	£0.00	£248.20	£3,278.66	£3,526.86
Administration cost	£0.00	£0.00	£889.24	£889.24
Total cost	£0.00	£248.20	£4,167.89	£4,416.09
Net change	£1,327.72	-£191.26	-£2,995.77	**-£1,859.31**

Sensitivity analyses for the secondary economic model are presented in Table 6.35. These analyses demonstrate that the model is most sensitive to changes in GON block efficacy.

Table 8: Results of deterministic sensitivity analyses conducted in the secondary economic model

Treatment Pathway	Botox treatment costs	GON Block treatment costs	Third line treatment costs	Total Cost
Cost of GON block increased by 50%				
Botox pathway				
Treatment cost	£1,050.32	£85.41	£973.68	£2,109.41
Administration cost	£277.40	£0.00	£198.44	£475.84
Total cost	£1,327.72	£85.41	£1,172.12	£2,585.25
GON Block pathway				
Treatment cost	£0.00	£372.30	£3,278.66	£3,650.96
Administration cost	£0.00	£0.00	£889.24	£889.24
Total cost	£0.00	£372.30	£4,167.89	£4,540.19
Net change	£1,327.72	-£286.89	-£2,995.77	**-£1,954.94**
Cost of Occipital Nerve Stimulation reduced by 25%				
Botox pathway				
Treatment cost	£1,050.32	£56.94	£737.43	£1,844.69
Administration cost	£277.40	£0.00	£198.44	£475.84
Total cost	£1,327.72	£56.94	£935.87	£2,320.53
GON Block pathway				
Treatment cost	£0.00	£248.20	£2,491.16	£2,739.36
Administration cost	£0.00	£0.00	£889.24	£889.24
Total cost	£0.00	£248.20	£3,380.39	£3,628.59
Net change	£1,327.72	-£191.26	-£2,444.52	**-£1,308.06**
Treatment frequency of IV DHE reduced from every 3.5 months to every 2 months				
Botox pathway				
Treatment cost	£1,050.32	£56.94	£980.34	£2,087.60
Administration cost	£277.40	£0.00	£247.15	£524.55
Total cost	£1,327.72	£56.94	£1,227.49	£2,612.15
GON Block pathway				
Treatment cost	£0.00	£248.20	£3,323.06	£3,571.26
Administration cost	£0.00	£0.00	£1,213.96	£1,213.96
Total cost	£0.00	£248.20	£4,537.01	£4,785.21
Net change	£1,327.72	-£191.26	-£3,309.53	**-£2,173.07**

Scenario analyses are shown in Table 9

Table 9: Scenario analyses – Treatment pathway model

Treatment Pathway	Botox treatment costs	GON Block treatment costs	Third line treatment costs	Total Cost
Assume GON block has a 55% treatment success rate				
Botox pathway				
Treatment cost	£1,050.32	£70.08	£730.26	£1,850.66
Administration cost	£277.40	£0.00	£148.83	£426.23
Total cost	£1,327.72	£70.08	£879.09	£2,276.89
GON Block pathway				
Treatment cost	£0.00	£313.90	£2,458.99	£2,772.89
Administration cost	£0.00	£0.00	£666.93	£666.93
Total cost	£0.00	£313.90	£3,125.92	£3,439.82
Net change	£1,327.72	-£243.82	-£2,246.83	**-£1,162.93**
Assume 33% of patients receive Methysergide as a second treatment, 33% IV DHE, and 33% Occipital Nerve Stimulation).				
Botox pathway				
Treatment cost	£1,050.32	£56.94	£1,089.10	£2,196.36
Administration cost	£277.40	£0.00	£286.53	£563.93
Total cost	£1,327.72	£56.94	£1,375.63	£2,760.29
GON Block pathway				
Treatment cost	£0.00	£248.20	£3,674.57	£3,922.77
Administration cost	£0.00	£0.00	£1,279.43	£1,279.43
Total cost	£0.00	£248.20	£4,954.00	£5,202.20
Net change	£1,327.72	-£191.26	-£3,578.37	**-£2,441.91**

All sensitivity analyses investigating structural differences in the treatment pathway model (Table 9) result in continued cost savings when introducing Botox to the treatment pathway.This demonstrates that the treatment pathway model is robust to the structural assumptions.

The main weakness of the treatment pathway analysis is the paucity of available data for the comparators in the treatment pathway mode, which is sparse and of poor quality. This lack of data is also highlighted in the SIGN and BASH guidelines, which give poor quality evidence grades to all comparators. However, treatment with Botox in the analysis remains cost saving across a wide range of efficacy assumptions for the comparators.

9.18 Appendix 18: SAS data tables used to populate economic model transition probabilities

Patient population	Medication overusers?	Stopping rule?	Source	Tables
All patients	Not excluding Medication Overusers	No stopping rule	TP_SR_1HS_NSR	1136.1.1 – 1136.6.1
All patients	Not excluding Medication Overusers	Stopping Rule: 1 HS in 2 cycles	TP_SR_1HS_2cycle	1001.1-1006
All patients	Not excluding Medication Overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS_1cycle	1111.1.1 – 1111.6.1
All patients	Not excluding Medication Overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_2HS_2cycle2	1125.1.1 – 1125. 6.1
All patients	Excluding medication overusers	No stopping rule	TP_SR_1HS_1cycle	1102.1.1 – 1102.6.1
All patients	Excluding medication overusers	Stopping Rule: 1 HS in 2 cycles	TP_SR_1HS_2cycle	1007.1 - 1012
All patients	Excluding medication overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS_1cycle	1110.1.1 – 1110.6.1
All patients	Excluding medication overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_2HS_2cycle2	1124.1.1 – 1124. 6.1
≥1 prior treatments	Not excluding Medication Overusers	No stopping rule	TP_1_NSR_SR1HS2cycles	1154.1.1-1154.6.1
≥1 prior treatments	Not excluding Medication Overusers	Stopping Rule: 1 HS in 2 cycles	TP_1_NSR_SR1HS2cycles	1152.1.1-1152.6.1

≥1 prior treatments	Not excluding Medication Overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS_1cycle	1113.1.1 – 1113.6.1
≥1 prior treatments	Not excluding Medication Overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_2HS_2cycle2	1127.1.1 – 1127. 6.1
≥1 prior treatments	Excluding medication overusers	No stopping rule	TP_SR_1HS_1cycle	1103.1.1 – 1103.6.1
≥1 prior treatments	Excluding medication overusers	Stopping Rule: 1 HS in 2 cycles	TP_1_NSR_SR1HS2cycles	1153.1.1-1153.6.1
≥1 prior treatments	Excluding medication overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS_1cycle	1112.1.1 – 1112.6.1
≥1 prior treatments	Excluding medication overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_2HS_2cycle2	1126.1.1 – 1126. 6.1
≥2 prior treatments	Not excluding Medication Overusers	No stopping rule	TP_SR_1HS_1cycle	1105.1.1 – 1105.6.1
≥2 prior treatments	Medication Overusers	Stopping Rule: 1 HS in 2 cycles	TP_SR_1HS_2cycle2	1030.1 - 1035
≥2 prior treatments	Not excluding Medication Overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS_1cycle	1115.1.1 – 1115.6.1
≥2 prior treatments	Not excluding Medication Overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_2HS_2cycle2	1129.1.1 – 1129. 6.1
≥2 prior treatments	Excluding medication overusers	No stopping rule	TP_SR_1HS_1cycle	1104.1.1 – 1104.6.1
≥2 prior treatments	Excluding medication overusers	Stopping Rule: 1 HS in 2 cycles	TP_SR_1HS_2cycle2	1036.1 - 1041
≥2 prior	Excluding medication	Stopping rule: 1	TP_SR_1HS_1cycle	1114.1.1 – 1114.6.1

treatments	overusers	HS in 1 cycle		
≥2 prior treatments	Excluding medication overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_2HS_2cycle2	1128.1.1 – 1128. 6.1
≥3 prior treatments	Not excluding Medication Overusers	No stopping rule	TP_SR_1HS_1cycle	1107.1.1 – 1107.6.1
≥3 prior treatments	Medication Overusers	Stopping Rule: 1 HS in 2 cycles	TP_SR_1HS_2cycle2	1042.1 – 1047
≥3 prior treatments	Not excluding Medication Overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS_1cycle	1117.1.1 – 1117.6.1
≥3 prior treatments	Not excluding Medication Overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_2HS_2cycle2	1131.1.1 – 1131. 6.1
≥3 prior treatments	Excluding medication overusers	No stopping rule	TP_SR_1HS_1cycle	1116.1.1 – 1116.6.1
≥3 prior treatments	Excluding medication overusers	Stopping Rule: 1 HS in 2 cycles	TP_SR_1HS_2cycle2	1048.1 - 1053
≥3 prior treatments	Excluding medication overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS_1cycle	1106.1.1 – 1106.6.1
≥3 prior treatments	Excluding medication overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_2HS_2cycle2	1130.1.1 – 1130. 6.1
≥4 prior treatments	Not excluding Medication Overusers	No stopping rule	TP_SR_1HS_1cycle	1109.1.1 – 1109.6.1
≥4 prior treatments	Medication Overusers	Stopping Rule: 1 HS in 2 cycles	TP_SR_1HS_2cycle2	1054.1 - 1059
≥4 prior treatments	Not excluding Medication Overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS_1cycle	1119.1.1 – 1119.6.1

≥4 prior treatments	Not excluding Medication Overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_1HS_2cycle2	1133.1.1-1133.6.1
≥4 prior treatments	Excluding medication overusers	No stopping rule	TP_SR_1HS_1cycle	1108.1.1 – 1108.6.1
≥4 prior treatments	Excluding medication overusers	Stopping Rule: 1 HS in 2 cycles	TP_SR_1HS_2cycle2	1060.1 - 1065
≥4 prior treatments	Excluding medication overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS_1cycle	1108.1.1 – 1108.6.1
≥4 prior treatments	Excluding medication overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_1HS_2cycle2	1132.1.1 – 1132.6.1
Topiramate prior	Medication Overusers	No stopping rule	TP_SR_1HS_2cycle2	1066.1 - 1071
Topiramate prior	Medication Overusers	Stopping Rule: 1 HS in 2 cycles	TP_SR_1HS_2cycle2	1078.1 - 1077
Topiramate prior	Not excluding Medication Overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS1cycle_2HS2 cycle_topiramate	1148.1.1 – 1148.6.1
Topiramate prior	Not excluding Medication Overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_1HS1cycle_2HS2 cycle_topiramate	1149.1.1 – 1149.6.1
Topiramate prior	Excluding medication overusers	No stopping rule	TP_SR_1HS_2cycle2	1072.1-1077
Topiramate prior	Excluding medication overusers	Stopping Rule: 1 HS in 2 cycles	TP_SR_1HS_2cycle2	1084.1 - 1089
Topiramate prior	Excluding medication overusers	Stopping rule: 1 HS in 1 cycle	TP_SR_1HS1cycle_2HS2 cycle_topiramate	1150.1.1 – 1150.6.1
Topiramate prior	Excluding medication overusers	Stopping rule: 2 HS in 2 cycles	TP_SR_1HS1cycle_2HS2 cycle_topiramate	1151.1.1 – 1151.6.1

9.19 Appendix 19: Utility manuscript – accepted for publication

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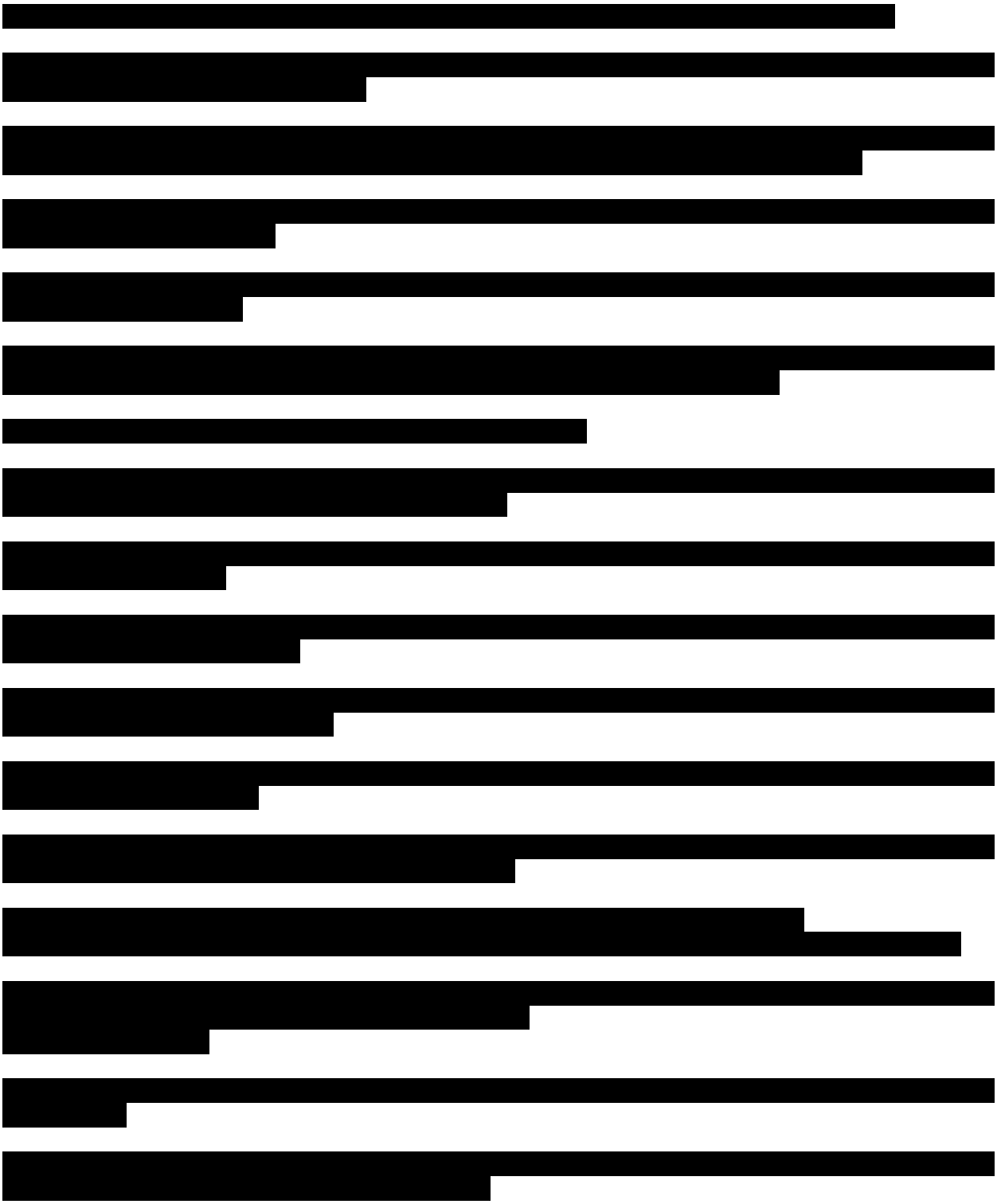

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