Executive Summary

There are a number of areas on which Link Pharmaceuticals would like to provide further comment and information:

1. Overall Survival: PenTAG intimate that carmustine implants have not been proven to confer a significant survival advantage. However an increase in median survival of 2.3 months compared to placebo was shown in the ITT group by a pre-specified, stratified by country, log-rank analysis (p=0.03). Even in the unstratified analysis, the p value for median survival was 0.079, close to the arbitrarily accepted p value of 0.05 for statistical significance. The absolute clinical benefit for carmustine implants, a 29% reduction in the risk of death, is independent of stratification. Additionally long term survival data for carmustine implant compared to placebo demonstrates a statistically significant (p=0.01) 5-fold increase in 3-year survival (9.2% vs. 1.7%) in favour of carmustine implants.

2. Progression Free Survival (PFS): PenTAG use the results for PFS as determined by radiological imaging as an indicator of symptom free survival. For the reasons outlined in our original submission and in this document, the use of radiological imaging for PFS is both inappropriate and inaccurate for patients with glioma who have undergone surgery and/or radiotherapy. We therefore submit that an alternative measure, specifically neuroperformance decline, is a more appropriate measure of symptom free survival in this group of patients and should be used.

3. Price of carmustine implants: this has been incorrectly quoted as £687.50 per implant and should be corrected to the current cost of £650.38 per implant.

4. Therapeutic gap: patients must recover from neurosurgery before starting a course of radiotherapy and this time will vary. There is therefore a therapeutic gap after surgical resection and prior to radiotherapy, when there is nothing to halt tumour regrowth. Local delivery of chemotherapy with carmustine implants at this time bridges this therapeutic gap providing active cytotoxic treatment.

5. Economic analysis: The modelling carried out by PenTAG, while sound in structure, is based on a number of assumptions which are simply incorrect or contentious and which are very damaging to the estimated cost effectiveness of carmustine implant. In particular the estimated mean survival using a Weibull curve approximation underestimates the mean survival observed in the key trial, symptom free survival has been estimated inappropriately

and the costing methodology adopted contradicts the views of NICE's own methodology committee. Correction of these errors and the pricing error halves the estimated cost/QALY shown in the PenTAG report.

We present additional cost effectiveness analyses in Section 5 of this document and ask that the Appraisal Committee consider them carefully in conjunction with their invited experts and not accept the PenTAG cost-effectiveness assumptions without serious consideration.

6. Other Issues:

- **External Validity**
- **Blinding of Westphal study**
- **Imbalance of Grade III vs. Grade IV tumours**
- **Effects of placebo implants**
- **CSF leaks**

All these issues were raised in the PenTAG report and are discussed in this document.

Introduction

High-grade glioma commonly produces profound and progressive disability and leads to death. The overall median survival of high-grade (grade III and grade IV) glioma patients is approximately 12 months reflecting the preponderance of grade IV (glioblastoma multiforme, GBM).

Over the past 20 years there has been little advance in the management of high-grade glioma. A 674 patient, phase III study comparing surgery, radiotherapy and PCV chemotherapy with surgery and radiotherapy demonstrated only a 2 week increase in median survival, a result that was not statistically significant ($p=0.5$).[1] Despite these data PCV continues to be used in the management of high-grade gliomas. Against this background advances in the treatment of glioma are likely to deliver only small increases in survival which will nonetheless be clinically significant and of immense value to patients.

Carmustine implants (Gliadel®) offer improved survival and provide an important advance in the management of newly-diagnosed high-grade glioma. An increase in median survival of 2.3 months (10.0 weeks), and a 5 fold increase in 3 year survival, compared to placebo, coupled with a favourable safety profile, as demonstrated with carmustine implants[2] is considered important and meaningful to patients, carers and clinicians.

Carmustine implant was approved in 2004 across Europe through the mutual recognition procedure as a treatment for newly diagnosed high-grade glioma. A similar approval was granted in the US in 2003 and in over ten further countries worldwide. All issues raised during the regulatory process have been answered to the satisfaction of the respective agencies.

Full reimbursement for carmustine implants is already available in other EU countries, such as France and Spain, and the product was also included in a new, specific Medicare/Medicaid DRG in the USA in Autumn 2004.

1. Overall Survival

The PenTAG assessment report states the following:

"In reporting results from this trial below, we have provided both published (stratified by country) and protocol-specified (unstratified) analyses, where both are available. We are reticent about relying on published findings alone where they are noticeably different from those generated by unstratified tests (for example, where stratified analyses provide p-values which achieve significance but unstratified analyses do not)." [page 37]

"Both RCTs were underpowered." [page 41]

It is important to note that the estimated hazard ratio of 0.71 for survival by the Kaplan Meier method is the same regardless of stratification or non-stratification and represents a 29% mortality risk reduction. The absolute clinical benefit of carmustine implants is therefore not affected by stratification.

Link agrees that to detect a significance value of 0.05 as an unstratified statistic both RCTs are underpowered. However, the clinical trial reported by Stupp et al[3] was similarly underpowered, failing to detect the anticipated 33% difference in overall survival. Indeed the survival benefit seen in both Stupp and Westphal is of the same magnitude i.e. a 20% increase in median survival compared to the control arm.

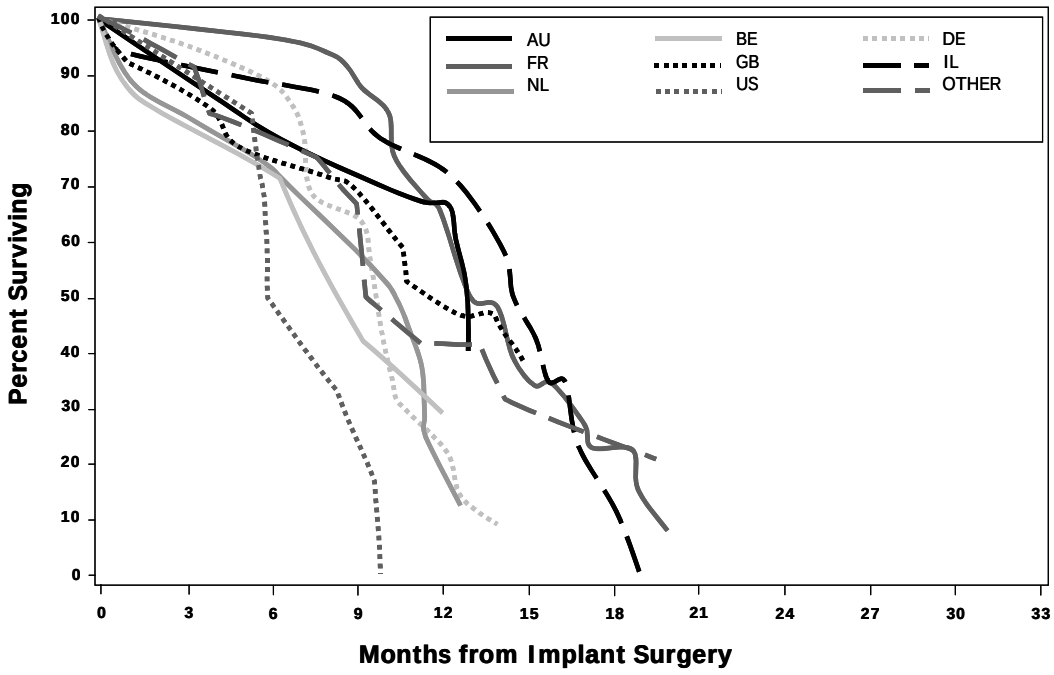
Carmustine implant has been shown to be efficacious in a well designed phase III clinical study. Contrary to the assertion by PenTAG that stratification was not per-protocol, this was a pre-specified endpoint. Statistically significant efficacy in terms of median survival was therefore shown in the ITT group by this pre-specified, stratified by country, log-rank analysis (p=0.03). Even in the unstratified analysis, the p value for median survival was 0.079 which is close to the arbitrarily accepted p value of 0.05 required for statistical significance.

In addition the long term survival analysis conducted at least 36 months after the recruitment of the last patient showed a statistically significant survival benefit for carmustine implant compared to placebo (p=0.02 unstratified log-rank analysis) thus validating the results from the original phase of this study.[4] A statistically significant (p=0.01) 5-fold increase in 3 year survival (9.2% vs. 1.7%) was also shown in favour of carmustine implants.

While PenTAG query the impact of the "tail effect" on the statistical analysis of long term survival it is nevertheless of great clinical importance and offers hope to patients who may be among the small group who will benefit hugely from treatment with carmustine implants.

A similar survival benefit has been demonstrated for carmustine implants in other studies in both newly diagnosed high-grade glioma[5] and recurrent glioblastoma multiforme.[6] This provides further evidence that the outcomes of the Westphal study are consistent across all studies and have not been reached by chance.

In the Westphal study stratification by country was pre-specified in the statistical analysis plan and is a logical analysis given the study design. A review of the survival data for the placebo arm at a country level, presented below, demonstrates a degree of scatter with a median survival range between approximately 6 and 15 months. This variability is potentially greater than the anticipated treatment affect. Country as a variable should therefore be accounted for in the final analysis.



Centres were therefore grouped by country with the very low recruiting countries forming a single group within this analysis. Patients were block randomised at a centre level giving equal numbers across the two study arms. The 9 resulting “countries” are shown in the table below.

Country	Number of patients
Australia	17
Belgium	14
Germany	44
France	48
United Kingdom	32
Israel	32
Netherlands	15
United States	12
Other *	26
Total	240

* Other comprised of Austria, Spain, Greece, Italy, New Zealand and Switzerland who recruited between 1 and 9 patients.

GBM sub-group analysis

Sub-group analysis based on histology was included as a secondary analysis of the Westphal study. The study was not specifically powered for the GBM sub-group analysis. However a median survival difference in favour of carmustine implants of 2.1 months was demonstrated which shows a trend towards statistical significance (p=0.1 stratified by country). A multivariate analysis allowing for the important prognostic factors gives a p value of 0.04. This multivariate analysis is an appropriate statistical analysis based on the impact of prognostic factors such as age and KPS on survival.

2. Progression Free Survival (PFS)

The PenTAG assessment report states the following:

"We also considered post-progression survival (estimated by subtracting median PFS from median overall survival). From the data reported by Westphal and colleagues 2003, we calculated a median life expectancy following recurrence of 8 months for patients treated with BCNU-W compared to 5.7 months for those who received placebo wafers. In the trial reported by Valtonen and colleagues 1997, post-progression survival was doubled in the BCNU-W group at 5.6 v. 2.5 months.

We are unable to undertake significance testing on these second-order measures without access to more extensive data. As neither RCT demonstrated a benefit in terms of PFS, any claimed treatment effect must be due to differences in survival after disease progression." [page 47]

With regard to progression free survival PenTAG state *"there is no good evidence that …. any (other) chemotherapy treatment delivered as first-line therapy for newly diagnosed tumours offers any benefit in slowing the rate of disease progression after recurrence*." *[page 87]*

These two statements on pages 47 and 87 appear to directly contradict each other. We agree with the statement on page 87 and considering the pharmacology and clinical use of carmustine implants **it is intuitive that any clinical benefit can only occur while carmustine is actually present i.e. in the period immediately following implantation and the benefit must therefore be prior to disease progression.**

The infiltrative nature of gliomas means that despite maximal surgical resection there are inevitably residual tumour cells either at the margins of the resection cavity or within 2 or 3cms of the margin. Tumour regrowth over time therefore occurs in virtually all patients. The aim of chemotherapy and radiotherapy is to slow the rate of tumour regrowth and prolong symptom free survival.

Carmustine is an alkylating agent that acts by disturbing the fundamental mechanisms concerned with cell proliferation, in particular DNA synthesis and cell division. Carmustine can act on cells at any stage of the cell cycle however cytotoxicity usually occurs when cells enter the S phase and hence progression through the cycle is blocked.

The effects of applying carmustine locally will therefore result in apoptosis of tumour cells only while carmustine is present to produce its cytotoxic effects i.e. during the period of carmustine release from the implant. Given that 70% of carmustine is released within 3 weeks of implantation and that once released it has a short half-life of 22 minutes, the duration of chemotherapeutic action is likely to be in the region of 5 to 6 weeks. Full pharmacokinetic information was provided in our original submission.

This immediate cytotoxic action at the time of surgery retards tumour regrowth and permits the patient to present for radiotherapy with a lower residual tumour burden than would otherwise be the case. This should enhance the efficacy of subsequent radiotherapy as the tumour burden has been minimised.

Therefore the 2.3 month increase in median survival produced by carmustine implants must be prior to tumour progression as by this point there cannot possibly be any remaining chemotherapeutic activity due to carmustine. Intuitively, and as intimated by PenTAG, carmustine implants cannot affect the course of tumour progression several months after implantation.

From the point of tumour progression the course of the disease would be expected to follow a similar time span for all patients. In a cohort of 240 patients, as in the Westphal study, it is highly unlikely that an imbalance exists between the active and control arms that could account for the median survival benefit seen with carmustine implants in the progressive disease phase. This survival benefit must therefore be due to the action of carmustine prior to progression by retarding tumour regrowth.

Radiological imaging

The evidence available on the difficulties of measurement of PFS by radiological imaging in patients undergoing surgery and radiotherapy, and which is even further confounded by the presence of implants, suggests that the PFS results as measured in this way and reported in the RCTs are flawed. Acceptance of this allows the statement on page 47 to be discounted,(*"As neither RCT demonstrated a benefit in terms of PFS, any claimed treatment effect must be due to differences in survival after disease progression.")*

We presented information in our original submission regarding the difficulties of interpreting radiological imaging in glioma patients following surgery and radiotherapy, even in the absence of implants. However PenTAG appear not to have taken into consideration this very important aspect of our submission. This information is re-presented in Appendix 1. In light of this, alternative measures for symptom free survival should therefore be used in determining the cost effectiveness of carmustine implants.

Based on radiological imaging carmustine implants appear not to have delayed disease progression and therefore this treatment would not be expected to exert a survival effect post-progression. This again confirms that the PFS results, based largely on radiological imaging, are not indicative of actual PFS. The FDA in their analysis acknowledged that PFS is difficult to assess in this patient population previously treated with surgery, radiotherapy or steroids even in the absence of implants.[7,8]

Alternatives to Radiological Imaging for measurement of PFS

The figures for PFS as assessed by radiological imaging from the Westphal study have been shown to correlate poorly with clinical progression and are therefore an inappropriate measure of PFS. An alternative measurement of symptom free survival must therefore be employed.

As indicated in our original submission the measurement of neurological status and functional impairment are considered appropriate methods to assess symptom free survival in this patient group although they are less direct measures of tumour activity. Progression of neurological deficit measured either as performance status or as neurological function is equated with development of symptoms and therefore tumour progression. However, it too can be confounded by other events causing neurological deterioration such as vascular episodes and oedema which are unrelated to tumour progression. Brada and Yung conclude that PFS, as measured by functional and neurological impairment, is an entirely appropriate endpoint in the palliative setting where the aim of new therapy is prolongation of functionally independent survival.[9]

The PenTAG assessment report supports this view, as stated on page 17, "*In the UK recurrence is usually diagnosed clinically (as opposed to radiologically)*."

The Westphal study collated time to neurological performance score deterioration for 11 performance indicators. These data are presented in Table 2.6 of our original submission and are reproduced in Appendix 2 of this document for convenience. The mean of these median times has been calculated as 43.4 weeks for placebo and 51.6 weeks for carmustine implants, a mean advantage to carmustine implants of 8.2 weeks. Correcting for PenTAG's criticism and using a mean of means value gives a symptom free advantage to carmustine implants of 7.4 weeks.

Evidence for carmustine implants shows an increase in median survival of 2.3 months (10.0 weeks) and this neuroperformance data shows an increase in symptom free survival of at least 7.4 weeks.

The FDA questioned the neuroperformance data because of the inclusion of death as an event in the analysis. The methods of censorship used by the FDA and by Westphal are valid. However censoring patients for death results in insufficient data to derive any meaningful differences between treatment arms due to insufficient patient observations.

Given the pharmacokinetic and pharmacological evidence for carmustine implants producing a survival benefit before the return of symptoms, the true figure for symptom free survival is much more likely to approximate the figures for neuroperformance decline stated in Westphal than the stated PFS values. Whilst these may bias in favour of carmustine implants the use of radiological PFS measurement will inevitably be biased against carmustine implants.

For all of these reasons, we therefore submit that the use of the neuroperformance results and not PFS measured radiologically in this group of patients should be used in the determination of cost effectiveness, as they are more likely to be a true measure of the actual clinical situation.

3. Price of carmustine implants

An incorrect price has been used by PenTAG for carmustine implants, a price at variance to our own submission.

As the result of the recent PPRS price reduction the cost of a carmustine implant as from 1st January 2005 is £650.38 per implant and not £687.50 as stated by PenTAG.

4. Therapeutic gap – an additional analysis around time to radiotherapy

PenTAG's report correctly points out that delay to radiotherapy following surgery is commonplace. The use of carmustine implants at the time of surgery delivers active chemotherapy in the time interval between tumour resection and the commencement of radiotherapy.

Local delivery of chemotherapy at the time of surgery adds to the mechanical action of surgery and provides an added opportunity to expand upon this paradigm by bridging the therapeutic gap between surgical resection and the start of radiotherapy, a period which ideally only spans two to four weeks but in reality can be considerably longer.[10] During this period, residual tumour cells, invariably left behind following surgery due to the infiltrative nature of the disease, are left to grow unchecked.

We would like to reiterate the following text that was part of our original submission to NICE. UK guidelines issued by the Royal College of Physicians recommend that the time from surgery to start of radiotherapy should be kept to a minimum; ideally <4 weeks.[11] However, there has been increasing concern by clinical oncologists in the UK about the continuing long waiting times for radiotherapy treatment.[12] In terms of survival the consequences of such delays are serious especially for tumour cells with rapid doubling times[13] such as high-grade glioma. A number of studies have shown that delay in receiving adjuvant radiotherapy can impact survival.[14,15] For example, a recent Australian study showed that in patients with grade III/IV glioma the risk of death increased by 2% for each day of waiting for radiotherapy (waiting time being defined as the clinically relevant "time from presentation to the radiotherapy department to the commencement of radiotherapy"), see Table 1.1.

Table 1.1: Reduction in median survival with increasing waiting time

1 Delay (weeks)	2 Median survival (weeks)[a]	3 Total calculated loss in median survival (weeks)[b]	4 Decrement in survival (weeks)[c]
0	46.0	0.0	0.0
1	41.9	4.1	3.1
2	38.9	7.1	5.1
3	36.7	9.3	6.3
4	35.6	10.4	6.4

[a] Calculated median survival.

[b] Total calculated loss in median survival when compared with 0 week waits = (46 - column 2).

[c] Decrement in survival = (column 3 - column 1).

Furthermore, in a 1998 UK audit of radiotherapy waiting times, only 39% of patients did not receive post-operative adjuvant radiotherapy within the good practice guideline of 4 weeks. This had risen to 62% of patients in a similarly conducted audit carried out in 2003.

Local delivery of chemotherapy during this time period is a logical choice: the toxicities seen with systemic chemotherapy, particularly myelosuppression, which are undesirable in the immediate post-operative period, are avoided and it is possible to deliver a longer duration of higher concentrations of cytotoxic chemotherapy to the tumour site than would be possible with conventionally administered therapy. Treatment with carmustine implants provides such local chemotherapy. See section 2.1.1. Pharmacokinetics of carmustine implants in the original submission for additional information.

As has been discussed above carmustine implants act by preventing cell division. Based on the pharmacokinetics of carmustine release from the implant and on its pharmacology its cytotoxicity will be in the first few weeks following surgery and implantation. If radiotherapy cannot commence within 2 to 4 weeks carmustine implants will continue to exert a cytotoxic activity and it is possible that compared to placebo this could convey a larger survival benefit than seen in the Westphal study. An example of the effect this may have on the cost/QALY is presented as scenario 6 in Section 5 below.

5. Economic analysis

PenTAG in its overall appraisal of our cost-effectiveness modelling states that it is based on a sensible decision model structure but uses incomplete cost estimates and questionable survival assumptions. We would accept that the mean survival advantage, the proportion of that survival which is progression (i.e. symptom) free and the relevant extra costs of

treatment are all important determinants of the estimated cost effectiveness. However, we believe:

a) PenTAG's estimation of the mean addition to life expectancy provided by carmustine implants is wrong, and an underestimate. It is based on a modelled Weibull curve that, despite the claims of the Assessment Team, is a poor fit in crucial part to the real life data. A fuller commentary on this point is presented in Appendix 3 but in summary the PenTAG model underestimates median survival by 27% and also results in an estimated mean survival gain smaller than the median survival gain actually observed in the Westphal study for carmustine implants.

b) The way in which progression free survival has been estimated by PenTAG presents the most disadvantageous case for carmustine implants. We have argued in Section 2 of this document and Appendix 1 that PFS estimated on radiological changes is misleading, and even more so when implants are present to further confound the images. We have also argued that a better PFS estimate would use time to neuroperformance decline. PenTAG note that the statistical significance of the eleven neuroperformance measures depends on the way in which the measures are censored at death. The approach taken in the Westphal study, finds ten of eleven measures to show statistically significant differences. PenTAG note that the recalculation by the FDA, using a different censorship rule, leaves only one measure showing a statistically significant difference. However the FDA's own minutes of the discussion of this issue note that their approach loses much of the data and thus the validity of their analysis must be questioned. The difficulty arises because of the lengthy gap that could arise between the last performance measures being taken and death, requiring some judgement to be made on how long any advantage could be assumed to continue. Censorship at the last observation before death underestimates any advantages achieved in this final period before death while censorship at death probably assumes too generous a benefit during that period.

   As a consequence of their deliberations PenTAG assume in their modelling that there is only 1.3 weeks advantage to carmustine implants over placebo in progression free survival. Given the accepted (albeit underestimated) advantage in overall survival, this is implausible. As we have argued above, the nature of the treatment with carmustine implants is such that its effects must come soon after surgery, i.e. well before progression, and it is likely that most of the survival advantage will therefore be progression free.

c) The PenTAG report criticises our use of the mean of medians in the measurement of

neuroperformance decline. We accept that in principle, means are more appropriate. We include below a calculation based on the mean of means (7.4 weeks) of neuroperformance outcomes rather than mean of medians (8.2 weeks). The results are only moderately sensitive, in this instance, to the choice of means or medians.

d) Importantly, PenTAG criticises the approach taken to costing treatments on grounds of principle. The approach PenTAG recommend was considered by the NICE Methodology Committee at its most recent review of methodology and explicitly rejected (Personal Communication, Prof Mark Sculpher, Chair of Committee). The committee argued that the decision to treat someone, and thus keep them alive, should not be contingent on subsequent, separable decisions. It is quite possible that use of carmustine implants will enable a few patients to live very much longer than they otherwise would and therefore to incur a variety of health care costs, some related to management of glioma and some not. These incurred expenditures are a consequence of success in keeping the patient alive and should not be used to penalise the drug. The extension of the Assessment Team logic could lead to new technologies that keep people alive into old age not being found to be cost-effective because of the high costs of care in old age.

We therefore reject PenTAG's criticism of the costings we have used. In our sensitivity analysis we included the costs of treatment for CSF leaks, and adverse events occurring at a differential rate in the carmustine arm of the Westphal study. We have included the differential costs for CSF leaks for patients receiving carmustine implants compared to placebo in our additional cost effectiveness analyses presented below.

Assessing the importance of the various assumptions for the estimated cost-effectiveness

We do not have available to us an executable copy of the PenTAG model which we can use to explore the effects of varying the key assumptions.

However, we believe that most of the differences in the PenTAG base case and our own base case are from the different assumptions the models embody rather than from differences in their structure. We have, therefore, imported the PenTAG assumptions as closely as the dissimilar structures will allow into our model, to check how close the results are. We then explore the consequences of varying those assumptions as we believe to be appropriate.

Results

We have input the following PenTAG assumptions into our model

- Carmustine implant cost of £687.50 (this is incorrect and addressed above).
- Marginal cost assumptions as per Table 57 of the PenTAG report.
- Mean survival and PFS as in Table 58 of the PenTAG report.
- Utility pre-PFS of 0.888 (mean utility for stable disease state from Table 58 of the PenTAG report).

Based on the above our model gives a cost/QALY of £63,839. This is about 10% higher than that derived in the PenTAG model but of comparable magnitude therefore validating our model against PenTAG's model. Our model can therefore give an informative demonstration of the importance of each of our assumptions and we present alternative scenarios based on these assumptions below.

Scenario 1 Correction of the carmustine implant price error brings the cost/QALY down to £63,447.

Adding in the cost of CSF leaks gives a cost/QALY of £63,900

Scenario 2 Keeping the correct price for carmustine implants and using a mean survival figure of 2.45 months* as derived from individual patient survival data from the Westphal study, rather than from PenTAG's Weibull curve, reduces the cost/QALY by £4,400 to £59,500.

* This mean survival gain is different to the value of 2.6 months used in our original submission as we have now been able to obtain the source data, presented in 4, from the Marketing Authorisation Holder.

Scenario 3 Keeping the correct price for carmustine implants, using the mean survival figure as in scenario 2 above and using a 7.4 week symptom free survival assumption based on the mean of mean times to deterioration in neuro-performance (in line with PenTAG's criticism) lowers the cost/QALY by a further £17,500 to £37,564.

Scenario 4 Taking scenario 3, but using our estimates of the additional costs of treating patients with carmustine implants over surgery alone (including the CSF leaks) rather than PenTAG's costs for added life weeks as discussed in point d) above, reduces the cost/QALY by nearly £10,000 to £27,900.

Scenario 5 We believe the case for making the changes as in 1), 2) and 4) are very strong. We accept that estimating the time to PFS is difficult. Taking an assumption of an increase in PFS due to carmustine implants (4.35 weeks) which is halfway between that estimated by PenTAG (1.3 weeks) and that estimated by ourselves (7.4 weeks) gives a cost/QALY of £33,500.

Scenario 6 If carmustine implants offer protection from tumour regrowth when radiotherapy treatment is delayed the cost/QALY would fall further in practice because delays are commonplace. If a delay of four weeks to RT, resulting in a reduction of 10 weeks survival in the placebo arm but no difference in the carmustine implant arm due to the presence of active chemotherapy in this therapeutic gap, is built into the analysis the cost/QALY would be reduced to £14,000, see Section 4 for more information.

Our view, however, would be that the best estimate is still that reflected in scenario 4) i.e. a cost/QALY of £27,900.

6. Other Issues

- **External Validity:**

PenTAG states:

"The generalisability of the included studies may be compromised by the age profile of the evidence base; both included RCTs excluded patients over 65, while in practice a third of patients with high-grade gliomas fall into this category." [page 38]

The exclusion of patients over 65 years is not uncommon in clinical trial design as these older patients tend to have co-morbidities that may introduce unnecessary variability into the study which in turn may confound analysis.

In addition age has been shown to be a prognostic factor for survival following craniotomy with or without the administration of carmustine implants and exclusion of older patients is therefore justified. The generalisbility of the study results to patients older than 65 is acknowledged to be difficult but the study population is indicative of patients who will actually receive surgery in the management of their high-grade glioma. Patients older than this will often not be considered fit for surgery and have therefore been excluded from consideration.

Dr Henry Brem reported to the FDA that carmustine implants are used routinely in older patients in the US because in these patients systemic chemotherapy is deemed quite risky

and since they are undergoing craniotomies for tumour debulking it is considered the most reasonable way to deliver the adjuvant therapies.

- **Blinding of Westphal study:**

PenTAG states:

"Randomisation methods were identical in the two RCTs and appear relatively sound. Wafers were provided to each centre in blocks of four unmarked boxes (two BCNU-W, two placebo). Following intraoperative confirmation of eligible diagnosis, a blinded box of wafers was chosen for implantation by the investigator. However, the blinding of the wafers was imperfect (see also comments on Detection bias), and it has been noted that, under such circumstances (and especially when block size is consistent), investigators can potentially manipulate a proportion of treatment allocations. However, we believe this to be unlikely, and the multicentre design should minimise any impact." [page 35]

Link believes the blinding of the two RCT studies to be adequate for the following reasons:
The highest recruiting investigator site enrolled only 22 patients over the study period of 19 months. This is an average of only 1.2 patients per month. At this level of usage it is unlikely that individual investigators would develop the experience to differentiate between the two subtly different forms of implant. Thus any concerns that subsequent treatment allocation could be influenced by knowledge of initial treatment are unfounded.

- **Imbalance of grade III and grade IV gliomas:**

PenTAG states:

"FDA assessors were concerned by asymmetry in allocation of "favourable" non-GBM diagnoses, especially anaplastic oligoastrocytomas (eight in BCNU-W arm v. three in placebo arm). As histopathology is a greater predictor of patient outcome than any current therapy, this may be significant despite the small absolute numbers. In addition, the diagnoses of one referee pathologist were considered definitive in the trial and dictated the classification of cases in all subsequent analyses. By way of verification and sensitivity analysis, FDA assessors requested that the data be re-examined on the basis of the alternative trial referee pathologist's diagnoses. This re-analysis showed an increased imbalance in distribution of grade IV tumours (88 BCNU-W v. 99 placebo) which, if accurate, could further bias the trial in favour of the intervention." [page 35]

Given the prognostic significance of histopathology, its confirmation is critical to ensure correct diagnosis and subsequent treatment planning. However it is acknowledged that morphological assessment is confusing, even for trained pathologists.[16] Knowing this, the histopathological diagnosis in the Westphal study was determined by a specific and robust

methodology. This involved review by a local neuropathologist followed by confirmation by a central neuropathologist. Where there was disagreement, a third referee neuropathologist was involved and patients were only included in the GBM subgroup where at least 2 of the 3 pathologists were in agreement.

For the results of just the central pathologist to be taken over that of a review by two, or in the case of dispute 3, pathologists is counterintuitive as he/she is just as likely to be unsure of the exact diagnosis as the other pathologists. Indeed, using the results of just the referee reviewer or the local reviewer would bias the results in favour of the placebo arm.

Thus the results as quoted in the study, based on the judgement of 2 specialists, can therefore be considered to be more robust than those based on just one pathologist's review as requested by the FDA. These data show a balance of grade IV gliomas between the two groups.

In the Westphal study patients were enrolled at the time of surgery based on the presence of a high-grade glioma without knowledge of the exact grade. The mix of glioma in each arm of the study is therefore purely random and could not be accounted for within the study design. It would therefore be impossible to have exactly matched groups.

Indeed in Stupps temozolomide study when randomisation was on average 5 weeks after a biopsy sample was available for analysis it still proved impossible to select purely grade IV gliomas.

- **Effects of placebo implants:**

To allow all the RCTs to be double-blinded carmustine implants have been compared to a placebo implant made of exactly the same polymer. Any other control would have made blinding the trial logistically unfeasible and therefore would have jeopardized the unbiased assessment of outcome. Consequently there is no directly comparable data for surgery and radiation alone.

To address the specific concerns regarding potential detrimental effects of the placebo implant, we reviewed other high-grade malignant glioma trials described in the literature. It should be noted that study designs and patient populations vary considerably among published trials. Thus, comparisons across studies are generally inconclusive, if not inappropriate. Minor differences between patient populations, including tumour histology, patient age, KPS, can greatly alter both median survival and major adverse event frequency. Finally, one must be cautious when comparing adverse event reporting in T-301, a pivotal

phase III study conducted for registration purposes and other studies where adverse event reporting may not be as rigorous.

In summary, as far as comparison with literature is possible, the adverse events reported in the placebo implant-treated group are similar to those reported in patients undergoing craniotomy and/or having brain tumours. Thus, without an increase in adverse events or a decrease in survival time, it is unlikely that the placebo implants impact on the course of the disease or treatment with surgery and radiation. Further information is presented in Appendix 5.

- **CSF (cerebro-spinal fluid) leaks:**

PenTAG highlight the difference in incidence of CSF leaks between the different arms in the Westphal trial. However, in clinical practice, where considerable importance is given to obtaining a water-tight dural closure following resection, CSF leaks have not been found to be a problem and have not led to infection or the need for reoperation in patients with newly-diagnosed high-grade glioma. Therefore in our opinion PenTAG has overestimated the costs associated with CSF leaks.

References:

[1] The MRC Brain Tumour Working Party. Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: A Medical Research Council Trial. J Clin Oncol 2001; 19(2): 509-518

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Appendix 1

Measurement of Progression Free Survival (PFS)

PFS is synonymous with symptom free survival and also tumour recurrence.

Generally tumour activity or progression is assessed by imaging and indeed in the Westphal study, PFS was determined by radiological means in 70% of patients. However there are a number of factors related both to high-grade glioma generally and carmustine implants specifically that make measurement of PFS by radiological means problematic and subject to a high degree of inaccuracy. This much was acknowledged by the FDA who stated that PFS is difficult to assess in this patient population previously treated with surgery, radiotherapy or steroids.[1,2] Knowing this they chose not to undertake an analysis of this endpoint during their deliberations prior to approving carmustine implants for use in newly-diagnosed high-grade glioma.

Factors confounding measurement of PFS by radiological imaging

PFS measured by imaging techniques is assessed as the change in size of a tumour (or the development of a new lesion) on CT or MRI. However accurate measurement may be confounded by several factors making it difficult to reliably assess these scans, even in the absence of implants. The size of an enhancing glioma following surgery and radiotherapy might represent a loss of tumour cells or an alteration in the properties of the blood-tumour barrier or blood brain barrier. Even if there has been some tumour cell kill a number of factors make the interpretation of imaging response in glioma difficult. A high-grade glioma has complex shapes with apparent projections and margins may be indistinct. Different scanning techniques have a major influence on interpretation of images. The timing of the scan following injection of an imaging medium alters the apparent size of an enhancing lesion. In addition, surgery, corticosteroids and excessive doses of radiation all affect the region of enhancement, making an objective assessment of progression difficult.

This is particularly true for carmustine implants where radiologic progression in the presence of the implants may be further confounded by the immediate post-operative oedema and enhancement that the implants themselves may produce.[3] Furthermore, Kleinberg et al have demonstrated that treatment effects such as necrosis can radiographically mimic the findings of recurrent tumour in a proportion of patients.[4] On imaging, the definition of tumour progression is an increase of more than 25% in the size of an enhancing abnormality in relation to previous scans. However different PFS results between studies may reflect the varying interpretations of progression on imaging.

De Wit et al[5] studied a cohort of 32 patients included in the control arm of phase III studies who received only radiotherapy post-operatively. Three of nine patients were evaluated as having progressive lesions at the first MRI assessment after radiotherapy. However subsequent follow up showed that the enhancement previously defined as a progressive lesion was not actually due to tumour regrowth. These 3 patients had a much longer survival than the remaining 6 patients with actual progressive lesions on the first post radiotherapy MRI.

Neurological status and functional impairment

Given the problems associated with radiological imaging there has been some investigation into alternative measures of PFS. Neurologic status and functional impairment are deemed to be equally appropriate, albeit less direct, measurements of tumour activity,[6] especially in the palliative care setting where the aim of new therapy is prolongation of functionally independent survival. However, they too can be confounded by other events causing neurologic deterioration such as vascular episodes and oedema which are unrelated to tumour progression.

References:

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Appendix 2

Time to neuroperformance decline for patients in the Westphal Study: (ITT Population)

Median values

Neuroperformance Measure	Median Time without Deterioration (weeks)		p-value
	Carmustine implant (n=120)	Placebo implant (n=120)	
Vital Signs	54.9	49.1	0.010
Level of Consciousness	52.1	45.4	0.016
Personality	51.7	40.0	0.008
Speech	49.6	36.7	0.003
Visual Status	44.0	42.4	0.087
Fundus	55.1	46.3	0.007
Cranial Nerves II, IV, VI	54.9	49.1	0.016
Cranial Nerves, Other	54.3	46.3	0.003
Motor Status	45.4	31.4	0.013
Sensory Status	51.6	44.1	0.024
Cerebellar Status	54.1	46.7	0.011

The mean in the differences in these median values is 8.2 weeks.

Mean values

Neuroperformance Measure	Mean Time without Deterioration (weeks)	
	Carmustine implant (n=120)	Placebo implant (n=120)
Vital Signs	54.7	48.1
Level of Consciousness	53.0	46.8
Personality	48.5	40.2
Speech	47.0	36.9
Visual Status	54.7	48.1
Fundus	54.0	46.8
Cranial Nerves II, IV, VI	55.3	48.2
Cranial Nerves, Other	54.1	46.4
Motor Status	43.4	36.0
Sensory Status	50.3	42.8
Cerebellar Status	52.3	45.7

The mean in the differences in these mean values is 7.4 weeks.

Appendix 3

Weibull Arguments

PenTAG has approximated the Kaplan-Meier survival curves from the Westphal carmustine implant trial using Weibull curve fitting. These curves are illustrated in Appendix 12 of the PenTAG report along with the table reproduced below.

Comparison of median overall survival reported in RCTs and fitted Weibull median overall survival

Treatment arm	Trial median survival (wks)	Predicted median survival (wks)	% error
BCNU-W placebo	50.26	53.15	5.75
BCNU-W treatment	60.23	60.46	0.14
TMZ control	52.43	52.38	0.09
TMZ treatment	63.26	65.21	3.09

The table indicates that the fitted Weibull curves are reasonably good at predicting the median survival times with the exception of the placebo arm in the Westphal study where there is a greater than 5% error overestimating the median survival time for the placebo arm. As a consequence the 10.0 week observed difference in median survival demonstrated by Westphal et al. is reduced to 7.3 weeks using the PenTAG model. That is, the observed gain in median survival achieved by carmustine implants is underestimated by 27% using the PenTAG model. Using our own model, this disadvantages carmustine by at least £13,000 per QALY.

Incidentally, the Weibull curves make median differences in treatment effect for temozolomide bigger than that observed in the temozolomide trial.

Figure Xiia in appendix 12 illustrates the PenTAG fitted and the observed survival curves. The figure illustrates that the fitted curves are not good at predicting long-term survival for either carmustine implants or temozolomide. The fitted curves underestimate long-term survival for both treatments. This is important for treatments that have been shown to produce significant improvements in long-term survival compared to placebo. The fitted curves for both of the control arms appear to predict long-term survival very well. The consequence of this is that the PenTAG model will underestimate mean overall survival for both carmustine implants and temozolomide treatments.

With respect to carmustine implants treatment, the PenTAG model outputs presented in table 58 of their report, indicate a mean survival gain of only 9.8 weeks. As discussed above, the difference in observed median survival in the Westphal trial was 10.0 weeks. Because of the concave shape of the survival curves for both placebo and carmustine implants, mean survival will always be longer than median survival. Along with the fact that the PenTAG model underestimates median survival gain for carmustine implants by 27%, the fact that the PenTAG model results in a mean survival gain which is smaller than the observed median gain is further indication that the PenTAG model underestimates survival gain from carmustine treatment.

From the plots of the survival curves presented in figure Xiia and the above analysis, the fitted Weibull curves clearly underestimate long term and therefore mean survival gain resulting from treatment with both carmustine implants and temozolomide, but particularly with carmustine implants.

Appendix 4 - Source data for patient duration of survival (DRSURV)

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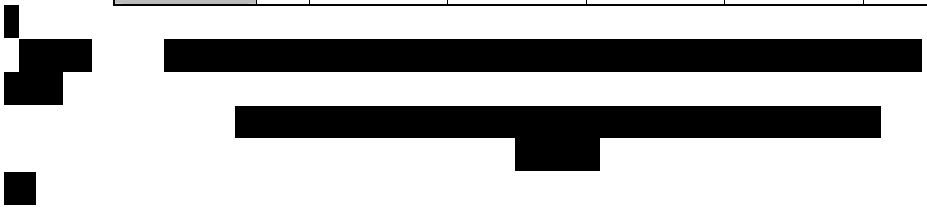

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Appendix 5

Safety review of high-grade malignant glioma trials described in the literature

Median Survival in the Placebo Arm

The range of survival times reported in the literature for patients treated with surgery and radiotherapy alone is 3.3 to 14 months for patients with high-grade glioma according to 13 publications published between 1979 and 2004. Most of these studies enrolled patients after surgery and therefore exclude patients who died in the perioperative period or who potentially had poor functional status (i.e. low Karnofsky scores) after surgical intervention. In contrast in the Westphal study patients were enrolled before surgery and therefore included all patients who may have had poor peri-operative outcomes. Of these 13 publications the majority reported a median survival of less than 10 months.

Adverse Events in the Placebo Arm

Another potential detrimental effect is that the placebo implants resulted in increased rates of complications without affecting overall survival. Adverse events were monitored closely in all the carmustine implant RCT's and the adverse event rates specific to the most common major classes of adverse events for craniotomy patients (i.e. seizures, CSF leaks, oedema, and infections) show no evidence of variation from historical controls who did not receive implants.

Event rates for the most common adverse events associated with craniotomy and/or brain tumours, as demonstrated in the Westphal study and as presented in the literature are summarised in the table below:

Event Rates for Most Common Adverse Events Associated with Craniotomy and/or Brain Tumours

	GLIADEL	Placebo	Literature*
Seizures	33%	37.5%	24-50.8%**
CSF leak	5	1	0.75-5.9%***
Infection	5%	6%	0.5-4%****
Oedema	22.5%	19.2%	not defined*****

* Full list of references is available.
** Overall seizure frequency from surgery through variable length of follow-up
*** Studies of techniques to prevent CSF leaks, including use of fibrin sealant
**** Varying definitions of infections
***** Oedema after craniotomy is a typical occurrence. Use of glucocorticoids (e.g. dexamethasone) has become routine practice in the management of craniotomy patients.

The seizure rate in patients with high-grade glioma is high. Seizures can occur at the initial presentation of patients (20 to 50% - Ropper at al., 2004). Additionally, seizures can occur post-operatively in 24 to 50% of cases where patients are followed for months after their craniotomy (Telfeian, et al 2001, Moots, et al 1995, Tandon et al, 2001). The placebo arm in the Westphal study, in which seizures occurred in 37.5% of patients followed for at least 12 months, falls within the predicted range for patients with the diagnosis of high-grade glioma after surgical resection.

Of the articles that reference post-craniotomy infections in our search, the most relevant articles report a range of infection rates from 0.5 to 4%. Although there are important differences between these studies, the infection rates in the Westphal study are comparable to those reported in the literature.

Wound healing abnormalities are infrequently reported in the literature. One type of wound healing abnormality, CSF leaks, was reported in 4 manuscripts. The reported incidence of leaks was 0.75 to 5.9%, consistent with the 0.8% event rate noted in the placebo implant group. It is important to note that in 3 of the 4 studies reviewed, the investigators were examining new techniques to reduce the incidence of CSF leaks.

Cerebral oedema is a frequent complication that typically occurs in the immediate post-operative period and is effectively treated with corticosteroids. This may be the reason there are few published reports that quantify its occurrence. Several articles were identified that quoted varying rates of post-operative oedema. However, due to the significant differences between these studies (disease states evaluated, treatment differences, definition of oedema events, etc.), no meaningful comparison could be made.

In summary, as far as comparison with literature is possible, the adverse events reported in the placebo implant-treated group are similar to those reported in patients undergoing craniotomy and/or having brain tumours. Thus, without an increase in adverse events or a decrease in survival time, it is unlikely that the placebo implants impact on the course of the disease or treatment with surgery and radiation.