Pegloticase for the treatment of hyperuricaemia in people with symptomatic gout whose disease is refractory to conventional urate-lowering therapy, or in whom conventional urate-lowering therapy is contraindicated or not tolerated

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Dr Kelsey Jordan declared a non-personal pecuniary interest whereby, in her role as Trustee of the UK Gout Society, educational sponsorship monies were received from Menarini, Novartis and Savient. No other competing interests were declared by the clinical advisors to the ERG.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Rachel Archer acted as project lead and systematic reviewer on this assessment, critiqued the manufacturer's definition of the decision problem, led the critique of the clinical effectiveness methods and evidence and contributed to the writing of the report. Sarah Davis acted as health economist on this assessment, critiqued the manufacturer's economic evaluation and contributed to the writing of the report. Lesley Uttley also acted as a systematic reviewer,

critiqued the description of the underlying health problem and current service provision, contributed to the critique of the clinical effectiveness methods and evidence and contributed to the writing of the report. Anna Cantrell critiqued the searches included in the manufacturer's submission and contributed to the writing of the report.

List of abbreviations

AE	Adverse event
BMI	Body mass index
BSR	British Society for Rheumatology
CI	Confidence Interval
CKD	Chronic kidney disease
CV	Cardiovascular
eGFR	Estimated Glomerular Filtration Rate
ERG	Evidence Review Group
EULAR	European League Against Rheumatism
GI	Gastrointestinal
ICER	Incremental cost-effectiveness ratio
IR	Infusion reaction
IRR	Infusion related reaction
ITT	Intention to treat
IV	Intravenous
MS	Manufacturer's Submission
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open label extension
PCS	Physical component summary
PEG	Polyethylene glycol
PSS	Personal Social Services
PUA	Plasma uric acid
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SJC	Swollen joint count
SPC	Summary of product characteristics
STA	Single Technology Appraisal
SUA	Serum uric acid
TJC	Tender joint count
UA	Uric acid
ULT	Urate lowering treatment
XOI	Xanthine oxidase inhibitors

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1. SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The decision problem addressed in the manufacturer's submission (MS) was based on the anticipated licensed indication of pegloticase for the treatment of severe debilitating chronic tophaceous gout in adult patients who have failed to normalise serum uric acid (SUA) with xanthine oxidase inhibitors at the maximum medically appropriate dose, or for whom these medicines are contraindicated. The population outlined in the final scope issued by NICE was adults with hyperuricaemia and symptomatic gout whose disease is refractory to conventional urate-lowering therapy or in whom conventional urate-lowering therapy is contraindicated or not tolerated. The manufacturer noted that, "due to ongoing discussions with the regulatory authorities, this represented a change to the indication discussed with NICE during the Decision Problem meeting." The ERG asked the manufacturer to confirm the current status and definition of the anticipated licensed indication. Following a request by the ERG, the manufacturer confirmed that the anticipated licensed indication would be for the treatment of severe debilitating chronic tophaceous gout in adult patients who may also have erosive joint involvement and who have failed to normalise SUA with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these medicines are contraindicated. Two of the clinical advisors to the ERG considered the populations from the two included phase III trials to accurately reflect the population covered by the anticipated licensed indication. However, a third clinical advisor to the ERG viewed that it was not explicit in the MS whether trial participants had previously received dose-optimised xanthine oxidase inhibitors (and that it was therefore unclear whether trial subjects had truly failed treatment on xanthine oxidase inhibitors) and also whether study participants had failed/been inappropriate for treatment with uricosurics. The ERG agreed that the treatment history of trial participants was not clearly described in the submission.

The scope issued by NICE described the appropriate comparators as being i) best supportive care and ii) febuxostat for adults who are intolerant to allopurinol or for whom allopurinol is contraindicated. However, the manufacturer stated that the only relevant comparator was best supportive care. The manufacturer justified the exclusion of febuxostat as a comparator on the basis that the anticipated licensed indication for pegloticase was for the treatment of patients who had failed to normalise their SUA levels with xanthine oxidase inhibitors (allopurinol and febuxostat) at the maximum medically appropriate dose or for whom xanthine oxidase inhibitors were contraindicated. The manufacturer explained that patients whose symptoms were controlled using xanthine oxidase inhibitors (allopurinol and febuxostat) would not be eligible for pegloticase treatment. It was also stated that, for patients for whom xanthine oxidase inhibitors were contraindicated, best supportive care would be the only treatment option available and thus best supportive care was the only appropriate comparator against which pegloticase should be compared. The British Society for Rheumatology (BSR)[1] and

European League Against Rheumatism (EULAR)[2] guidelines for the management of gout both recommend the use of uricosuric drugs as a second line treatment following treatment with allopurinol. Best supportive care was considered by the clinical advisors to the ERG to represent routine and best practice in the National Health Service (NHS) in patients who are refractory to both xanthine oxidase inhibitors and uricosurics or where treatments from these classes of interventions cannot be used due to contraindications or intolerance. Best supportive care was considered to be an appropriate comparator for the population likely to receive pegloticase in clinical practice.

The outcomes listed in the MS matched the outcomes outlined in the final scope. Whilst the final scope issued by NICE specified that serum uric acid (SUA) response would be assessed, the primary outcome of uric acid response in the two included phase III trials was based on the measurement of plasma uric acid (PUA) as opposed to SUA. However, SUA was used within the economic analysis to determine response to pegloticase.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The clinical effectiveness evidence in the MS was based predominantly on the following 3 studies:

- Two replicate, randomised double-blind placebo-controlled phase III trials (C0405 [GOUT 1] and C0406 [GOUT 2]) (NCT00325195) (primary data source Sundy *et al.*, 2011)[3]
- Open label extension safety study (OLE C0407) (primary data source clinical study report C0407 CSR, identified by the manufacturer from the Savient database)

The two phase III trials (C0405 and C0406) and open label extension (OLE) study (C0407) were considered by the ERG to be relevant to the decision problem as specified in the scope. No additional phase III or open label extension studies were identified by the ERG or clinical advisors to the ERG.

There appeared to be discrepancies in the description of the number of included reports in the MS. Following a clarification request by the ERG, the manufacturer confirmed that a total of 6 abstracts were identified and that, although reference details of the abstracts were provided for completeness, data from the abstracts were not included in the submission (on the justification that the results presented in the submission related to the completed trials). The manufacturer's justification for non-inclusion was considered by the ERG to be unclear, since these abstracts provided further limited (albeit fragmented) evidence on the potential longer-term efficacy and safety of continued pegloticase treatment, which could have been coherently integrated in the original submission.

A completed non-randomised, non-controlled, open label, multicentre re-exposure trial (NCT00675103) (C0409) was identified by the ERG and was not included in the original MS. This small scale trial evaluated efficacy and safety outcomes in subjects who were receiving a 24 week

course of pegloticase and whose last exposure to pegloticase was at least one year before study entry. In response to a request by the ERG, the manufacturer provided a brief synopsis of this trial (Savient trial identifier C0409).

The primary efficacy outcome of the replicate two phase III trials (C0405 and C0406) included in the submission was the proportion of PUA responders (defined as patients having a PUA < 360 μmol/L [6.0 mg/dL] for ≥ 80% of the time during months 3 and 6) in the pegloticase 8 mg every 2 weeks and placebo groups (and matched the selection of the primary efficacy outcome reported by Sundy *et al.*, 2011)[3]. The results for the primary efficacy endpoint from both the individual phase III trials and the simple pooled analysis demonstrated a significantly greater proportion of PUA responders among the pegloticase 8 mg every 2 weeks treatment group than in the placebo arm (pooled results 42% vs. 0%, P<0.001). No placebo group subjects maintained a PUA level below 360 μmol/L [6.0 mg/dL] for ≥ 80% of the time during months 3 and 6.

A significantly greater proportion of patients in the pegloticase 8 mg every 2 weeks treatment group demonstrated tophus resolution compared with the placebo group (40% vs. 7%, P=0.002). Whilst a significantly greater proportion of patients in the pegloticase 8 mg every 2 weeks group experienced gout flares during months 1-3 of the phase III trials than among the placebo group (75% vs. 53%, P=0.02), this finding was reversed for months 4-6, with significantly fewer patients having gout flares in the pegloticase 8 mg every 2 weeks group vs. placebo (41% vs. 67%, P=0.007). Greater reductions from baseline levels in mean numbers of tender joints (-7.4 (SD=11.9) (n=78) vs. -1.2 (SD=12.3) (n=43), statistically significant at P=0.01) and swollen joints (-5.5 (SD=10.5) (n=78) vs. -2.6 (SD=11.6) (n=43), non-significant at P=0.18) were observed in the pegloticase 8 mg every 2 weeks treatment group than in the placebo group. A significantly greater reduction in HAQ pain score was shown in the pegloticase 8 mg every 2 weeks compared with the placebo group (SD) (-11.4 (SD=33.8) (n=78) vs. 1.4 (SD=30.0) (n=43), P=0.03). A significantly greater change in SF-36 Physical Component Summary score was also obtained among pegloticase 8 mg every 2 weeks subjects than placebo group subjects **(**4.4 (SD=9.4) (n=77) vs. -0.3 (SD=9.0) (n=43), P=0.01).

The decision problem outlined in the scope specified that (evidence permitting) consideration would also be given to a subgroup analysis of people with hyperuricaemia and symptomatic gout who were intolerant of allopurinol or for whom allopurinol was contraindicated. The manufacturer stated that this analysis was not performed as pegloticase would be used in patients who are intolerant to both allopurinol and febuxostat or for whom allopurinol or febuxostat is contraindicated or ineffective.

Some limited and fragmentary evidence was available in the manufacturer's clarification responses and from conference abstracts sourced by the ERG that suggested that, for persistent responders, PUA response and some secondary outcomes, including tophus resolution, may be maintained beyond 6 months with continued pegloticase treatment.

Upon request by the ERG, the manufacturer provided a brief synopsis of results from the open label re-exposure trial C0409, which evaluated efficacy and safety outcomes in a small number (n=7) of patients who were re-exposed to a subsequent course of pegloticase treatment following an initial course of treatment.

[redacted]

Safety data were presented for the phase III trials (C0405 and C0406) and the OLE study (C0407). Limited safety data were presented for the re-exposure study C0409. Data from the pooled phase III RCTs indicated that 18% of patients discontinued pegloticase treatment due to an adverse event, compared with 2% of patients in the placebo group. The most commonly reported adverse events were gout flare (76% in pegloticase 8 mg every 2 weeks vs. 81% in the placebo group), infusion related reactions (26% in pegloticase 8 mg every 2 weeks vs. 5% in the placebo group) (despite the provision of prophylaxis against infusion related reactions), headache (9% in pegloticase 8 mg every 2 weeks vs. 9% in the placebo group), and nausea (12% in pegloticase 8 mg every 2 weeks vs. 2% in the placebo group). The manufacturer provided further information on the occurrence of cases of anaphylaxis in patients receiving pegloticase. An analysis of the entire pegloticase clinical study database (including studies C0402, C0403, C0405, C0406, and C0407) resulted in 7 definite and 7 potential cases of anaphylaxis being identified. The manufacturer also provided limited further details from post-marketing data stating that there were [redacted] cases of anaphylactic reaction, anaphylactic shock and anaplylactoid reaction (between 14 September 2010 and 30 June 2012), with [redacted] cases described as serious and a further [redacted] as non-serious.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Data for the primary efficacy outcome of UA response (with a responder being defined as a patient with plasma UA less than 360 µmol/L [6.0 mg/dL] for at least 80% of the time during months 3 and 6) were presented for each individual phase III trial (C0405 and C0406) and also as a simple pooled analysis (in which data were not meta-analysed but simply added together to yield a summary combined result). Data were also presented for secondary outcomes as simple pooled analyses only.

No meta-analyses of primary or secondary outcome data were included in the original MS, with the manufacturer describing meta-analyses in Section 6.6 (page 53) as being "not-applicable." However, the viewpoint of the ERG was that, since the simple pooling of data may yield counterintuitive or spurious results due to a phenomenon known as Simpson's paradox, a more valid approach would have been to undertake a meta-analysis of the included data. The ERG requested that the manufacturer provide data for all primary and secondary efficacy and safety outcomes presented i) for each individual study and ii) combined using meta-analysis. However, the manufacturer maintained that pooling was an appropriate strategy for synthesis of the phase III trial data. The ERG still considers the presentation of data for each individual study and combined data using fixed and random effects meta-analysis to be more transparent and robust. The ERG conducted some exploratory meta-analyses of data for PUA response and complete resolution of tophi, which are presented in Section 4.5. The relative risks for complete tophus resolution calculated manually by the ERG (uncorrected for zero events in a placebo arm) using the simple pooled data appeared to be slightly greater in magnitude than the relative risks calculated using Review Manager (which it should be noted incorporated an automatic correction applied for zero events in a placebo arm). Since the placebo arms of both phase III trials contained zero events for the primary efficacy outcome of PUA response, it was not possible to attempt a comparison of the simple pooled analyses with the meta-analysed data.

No indirect or mixed treatment comparisons were undertaken by the manufacturer. The ERG considered this decision to be appropriate for the decision problem addressed in the submission.

1.4 Summary of cost effectiveness evidence submitted by the manufacturer

The manufacturer's searches identified no published economic evaluations meeting the NICE reference case and so a *de novo* economic evaluation was performed. A Markov model, constructed in Microsoft Excel©, was submitted comparing the cost-effectiveness of pegloticase to best supportive care in the population meeting the draft license indication, over a 20 year time-horizon.

The following clinical continuation rule is applied within the model: "Pegloticase should be discontinued if levels increase to above 360 μmol/L (6 mg/dL), particularly when 2 consecutive levels above 6 mg/dL are observed". The model assumes 6 months of pegloticase treatment for responders, 2 months for non-responders and 1 month for non-completers. The non-completer group is defined as, "patients who are non-persistent to pegloticase treatment." Best supportive care is assumed to consist of standard medical care with non-steroidal anti-inflammatory drugs (NSAIDS), colchicine and corticosteroids but no urate lowering therapy.

Patients who respond to pegloticase are assumed to progress to maintenance therapy with xanthine oxidase inhibitors (allopurinol or febuxostat) and then to best supportive care when they become non-persistent with maintenance therapy. In response to the clarification letter, the manufacturer also incorporated a treatment pathway for those who are intolerant to or contraindicated to xanthine oxidase inhibitors, and these patients are assumed to progress directly to best supportive care after responding to pegloticase treatment.

The Markov model has health states defined by pegloticase persistence/response, current treatment and SUA level. It also tracks the number of flares and the proportion with tophi resolution over time and incorporates a death state to capture mortality. The MS states that short-term clinical outcomes in month 0 to 6 were based on outcomes measured in the clinical trials (C0405 and C0406), with additional data from the literature used to estimate long-term clinical outcomes.

Treatment costs include drug costs for pegloticase and maintenance therapy. Drug costs for best supportive care were only included in the revised basecase analysis and not in the model originally submitted. Drug costs were included for flare prophylaxis, infusion reaction prophylaxis and treatment of adverse events. Pegloticase treatment was also associated with additional SUA monitoring during the 6 month treatment course and additional rheumatology visits that continue beyond the 6 month treatment course.

The price of pegloticase used in the model was £1,770 per 8 mg vial, which is described by the manufacturer as the maximum expected list price pending confirmation of the final NHS list price.
The incremental cost effectiveness ratio (ICER) for the manufacturer's revised basecase analysis was £31,027 when using the deterministic model and £31,031 when using the average incremental costs and quality adjusted life-years (QALYs) from the probabilistic sensitivity analysis.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG identified no significant deviations from the NICE reference case although some of the data sources used to populate the model were poorly described making it difficult for the ERG to fully critique the model.

The manufacturer's revised model, which incorporated appropriate treatment pathways for patients who are contraindicated to or intolerant of allopurinol and febuxostat, was considered by the ERG to address the decision problem as specified in the scope.

The economic model assumes that the benefits of pegloticase treatment achieved by responders during the 6 month treatment period can be maintained in the long-term through treatment with allopurinol or febuxostat. The ERG noted that the scenario analyses, conducted on the manufacturer's original model, showed that 34% of the incremental QALY gains were accrued more than 10 years after starting pegloticase treatment. Furthermore, the ERG had concerns regarding the survival model used to extrapolate persistence with allopurinol, and a scenario analysis in which the rate of discontinuation of allopurinol treatment was increased from 12% to 15% per annum resulted in an increase in the ICER from around £30,000 to around £37,000 per QALY. The ERG considers the extrapolation of benefits over such a long time period to be a significant area of decision uncertainty as no direct evidence has been presented by the manufacturer which shows that the SUA levels achieved following response to pegloticase treatment can be maintained by treatment with allopurinol or febuxostat treatment in the long-term.

Utility in the long-term is derived based on the SUA level, the frequency of flares and the presence of tophi. The data sources used to support these relationships were not well described in the submission and it was unclear whether the relationship between SUA and utility could be confounded by other factors such as the frequency of flares, or the presence of tophi or comorbidities. The ERG also had concerns regarding the strength of the evidence used to support the relationship between SUA levels and flares, the relationship between SUA level and resource use and the size of utility gain associated with the trial outcome of tophi resolution.

The ERG also noted that the model was sensitive to changes in the duration of pegloticase treatment in responders and that the number of doses received in clinical practice could be higher than assumed in the model. Whilst additional treatments beyond 6 months could be associated with additional clinical benefits, the model already assumes that any benefit achieved in the first 6 months is maintained for the duration of maintenance therapy. It is therefore possible that extending the duration of treatment could increase the ICER as the ratio of cost to benefit for additional doses beyond 6 months would be greater than for the initial six months.

The use of an indicative price within the cost-effectiveness analysis is problematic. The manufacturer states that the price assumed in the MS represents the upper price limit, which suggests that the ICERs may in be lower once the final NHS list price is confirmed. However, without confirmation of a final price it is impossible for the ERG to provide an estimate of their most plausible ICER to the committee.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The ERG identified a number of strengths in terms of the robustness of evidence in the submission, including the following points.

- The two phase III trials (C0405 and C0406) and open label extension (OLE) study (C0407) were considered by the ERG to be relevant to the decision problem as specified in the scope.
- The ERG and clinical advisors to the ERG were satisfied that all available phase III RCTs were included in the submission.
- The ERG and clinical advisors to the ERG considered that all appropriate outcomes had been included.
- The clinical continuation rule applied in the economic evaluation is consistent with that specified in the draft SPC.
- The economic model incorporates the utility data directly observed in the two phase III RCTS (C0405 and C0406).
- The economic model incorporates the rate of infusion reactions observed in the trial for pegloticase.
- The manufacturer submitted a revised model addressing many of the concerns raised in the clarification letter including appropriate treatment pathways for patients who are contraindicated to or intolerant of allopurinol and febuxostat.

1.6.2 Weaknesses and areas of uncertainty

With respect to the clinical effectiveness evidence the key areas of uncertainty identified by the ERG are as follows:

- Clinical effectiveness evidence was based predominantly on the findings from simple pooled analyses of primary and secondary efficacy data. The ERG considers that the use of meta-analysis would have been a more robust and transparent method for the combination of these data.

- Primary efficacy data were based on the measurement of PUA levels, as opposed to SUA levels as specified in the scope, although the manufacturer provided a biochemical justification for the selection of PUA measurements.
- The impact of repeated courses of pegloticase 8 mg every 2 weeks on UA levels, secondary outcomes, immunogenicity and adverse events were not clear from the clinical effectiveness evidence in the original submission.
- Importantly, it was unclear from the clinical effectiveness evidence whether benefits of pegloticase would be maintained after the cessation of pegloticase treatment and whether maintenance therapy with other urate-lowering drugs would be successful in maintaining UA levels and other benefits in the long-term.

With respect to the economic evaluation the key areas of uncertainty identified by the ERG are:

- Long-term persistence with maintenance therapy
- Long-term maintenance of SUA levels in pegloticase responders taking maintenance therapy
- Long-term maintenance of reduced tophi burden in responders and non-responders
- Utility benefit attributable to lowering SUA over and above that associated with the reduction in gout flares and any tophi resolution
- Utility benefit attributable to the trial outcome of tophi resolution
- Resource use associated with higher SUA levels over and above that associated with gout flares
- Final price of pegloticase
- Number of pegloticase treatments likely to be used in clinical practice

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted some exploratory meta-analyses of data for PUA response and complete resolution of tophi. It was not possible to incorporate the ERG's meta-analysis results for these outcomes into the economic model as the model uses a different measure of response and estimates tophus outcomes separately for responders, non-responders and non-completers.

The manufacturer's revised basecase assumes that 10% of patients are unable to take xanthine oxidase inhibitors, as maintenance therapy, due to contraindications or intolerance. In this subgroup of the population, who are assumed to switch to best supportive care after discontinuing treatment with pegloticase, the only long-term treatment benefit of pegloticase treatment is from the maintenance of tophi resolution. The ERG were therefore interested in conducting a subgroup analysis according to whether patients are able to take maintenance therapy as this is likely to significantly influence the cost-effectiveness of pegloticase therapy. This resulted in an ICER of £60,800 per QALY for those

unable to take maintenance therapy and an ICER of £28,900 per QALY in the subgroup able to take either allopurinol or febuxostat. (It should be noted that these results are based on the manufacturer's revised basecase which incorporates the costs for best supportive care) This subgroup analysis illustrates the fact that the cost-effectiveness of pegloticase treatment is largely dependent on the assumption that xanthine oxidase inhibitors can be used to maintain the benefits of achieving a successful response to pegloticase treatment in the long-term.

Using the manufacturer's revised basecase, the ERG conducted an exploratory analysis assuming no utility decrement associated with an increase in SUA over and above the utility decrement associated with the increasing frequency of flares. In this analysis the utility gain associated with tophi resolution from the manufacturer's basecase analysis was maintained. This resulted in an ICER of £41,100 per QALY.

The ERG also conducted an exploratory analysis in which an increase in SUA level is not associated with an increase in resource use over and above that associated with managing gout flares. In this analysis we also reduced the number of additional rheumatology visits associated with pegloticase treatment in the years after completing the treatment course and allowed two rheumatology visits, associated with starting and finishing treatment, in pegloticase non-responders and non-completers. This resulted in an ICER of £41,000.

Combining the previous two exploratory analyses, to give an ICER that incorporates the ERG's preferred assumptions regarding both utility gain and resource use, resulted in an ICER of £54,345 which is the ERG's preferred basecase ICER.

The ERG also conducted a sensitivity analysis on the survival curve used to model long-term persistence with maintenance therapy. Using an alternative but still plausible survival curve, with lower rates of persistence, and applying this to the ERG's preferred basecase resulted in a further increase in the ICER. Furthermore, the remaining uncertainties identified in section 1.6.2 all have the potential to increase the ICER with the exception of uncertainty regarding the price as the manufacturer stated that the indicative price applied in the model represents the maximum expected list price.

2. BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem.

The manufacturer's description of the health problem was based on published studies by Annemans *et al.,* 2008[4] and Roddy *et al.,* 2007[5] on the prevalence of gout in the UK and Germany. The manufacturer estimated the prevalence of gout as 1.4%, affecting more men than women, and as 7.3% in men over the age of 65. This was consistent with a further prevalence calculation from the published literature[6] of 1.39% (95% CI 1.37 to 1.41) and an estimated male to female ratio of 3.6:1 in the UK as of 1999. These estimates of the prevalence of diagnosed gout match the figures that are quoted in the British Society for Rheumatology (BSR) guidelines[1] and were confirmed as having face validity by our clinical advisors.

2.2 Critique of manufacturer's overview of current service provision

The MS referred to the British Society for Rheumatology (BSR)[1] guidelines and the European League against Rheumatism (EULAR)[2] guidelines in its recommendation for the use of xanthine oxidase inhibitors (XOI) (allopurinol and febuxostat) as a first line treatment for chronic gout.

The manufacturer stated on page 36 of the MS that "currently, the only treatment for adult patients with severe refractory chronic gout who are symptomatic and have failed to normalise serum uric acid with xanthine oxidase inhibitors (allopurinol and febuxostat) at the maximum medically appropriate dose, or for whom these medicines are contraindicated, is best supportive care." However, the BSR and EULAR guidelines both recommend the use of uricosuric drugs as a second line treatment following treatment with allopurinol (febuxostat was not licensed at the time these guidelines were published). One of the clinical advisors to the ERG considered that one of the uricosuric drugs, benzbromarone, is likely to be effective in some patients but noted that it is currently unlicensed in the UK. However, a second of the ERG's clinical advisors stated that no data were available to suggest that benzbromarone was effective in reducing tophi in patients with severe tophaceous gout and also highlighted that this drug is unlicensed in the UK.

The ERG asked the manufacturer to justify the position of pegloticase in the treatment pathway in relation to uricosuric drugs. The manufacturer responded that "the use of uricosuric drugs such as sulphinpyrazone, benzbromarone and probenecid has not been proven to be effective in the second line setting through RCTs, thus the evidence base is weak in comparison to that for pegloticase. In the absence of any other licensed drug in this specific setting it is accurate therefore to say the only comparator is best supportive care for these patients…[and]…we expect that in clinical practice in England and Wales pegloticase will be used as a last line of treatment when there are no alternatives to best supportive care." A preliminary search by the ERG for RCT evidence for uricosuric drugs had not identified any RCTs in the second line setting at the point of submission of the final ERG report.

The ERG and the clinical advisors agreed with the manufacturer's justification of best supportive care as the appropriate comparator, as pegloticase is likely to be implemented in clinical practice only after the first two lines of treatment recommended in the BSR and EULAR guidelines (xanthine oxidase inhibitors and uricosurics) have been exhausted. For those patients for whom uricosurics are contraindicated and for those whose SUA has failed to normalise and whose signs and symptoms are inadequately controlled with optimally-dosed xanthine oxidase inhibitors, best supportive care is currently the last option of treatment. Best supportive care consists of NSAIDs, colchicine and corticosteroids. The clinical advisors to the ERG agreed that pegloticase would be a last line treatment for a small proportion of patients diagnosed with gout and only after the first two lines of treatment have been exhausted.

3. CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem (Table 1) as outlined in the final scope issued by NICE and addressed in the manufacturer's submission is presented in Table 1.

Table 1. Decision problem as outlined in the final scope issued by NICE and addressed in the manufacturer's submission (based on pages 29-30 of MS but amended by ERG to reflect their opinion of the submission)

	Decision problem outlined in final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with hyperuricaemia and symptomatic gout whose disease is refractory to conventional urate-lowering therapy or in whom conventional urate-lowering therapy is contraindicated or not tolerated	Adult patients with severe debilitating chronic tophaceous gout who have failed to normalise SUA with xanthine oxidase inhibitors at the maximum medically appropriate dose, or for whom these medicines are contraindicated.
Intervention	Pegloticase	Pegloticase
Comparator(s)	i) Best supportive care ii) Febuxostat for adults who are intolerant to allopurinol or for whom allopurinol is contraindicated	Best supportive care only
Outcomes	• Serum urate levels • Gout flares • Reduction in tophus • Pain • Tender and swollen joint count • Physical function • Adverse effects of treatment • Health-related quality of life	• Serum and plasma urate levels • Gout flares • Tophus resolution • Pain • Tender and swollen joint count • Physical function • Adverse effects of treatment • Health-related quality of life (Health Assessment Questionnaire [HAQ], HAQ-Disability Index

	Decision problem outlined in final scope issued by NICE	Decision problem addressed in the submission
		and SF-36)
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be compared from a National Health Service (NHS) and Personal Social Services (PSS).	Cost-effectiveness is presented as an incremental cost per quality-adjusted life year (QALY) Comparator is best supportive care with clinical outcomes based on two phase III clinical trials of pegloticase vs. placebo The time horizon for modelling is 20 years but with shorter (10 years) and longer (40 years) timelines explored Perspective: NHS and PSS
Subgroups to be considered	If evidence allows, consideration will be given to a subgroup analysis for people with hyperuricaemia and symptomatic gout who are intolerant of allopurinol or for whom allopurinol is contraindicated.	Analysis of patients with hyperuricaemia and symptomatic gout who are intolerant of allopurinol or for whom allopurinol is contraindicated will not be performed. Subgroup analysis for PUA responders has been performed for gender, age, body mass (BMI), absence or presence of tophi, disease duration and baseline HAQ-DI score.
Special considerations, including issues related to equity or equality	Not stated	Not applicable

3.1 Population

The population described in the final scope issued by NICE was adults with hyperuricaemia and symptomatic gout whose disease is refractory to conventional urate-lowering therapy or in whom conventional urate-lowering therapy is contraindicated or not tolerated.

Pegloticase is currently being evaluated by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). The manufacturer reported that a positive opinion is expected at the end of October 2012, with marketing authorisation being expected in January 2013. The manufacturer stated in the original submission that the licensed indication of pegloticase is currently being discussed with the CHMP but was anticipated to be for the treatment of severe debilitating chronic tophaceous gout in adult patients who have failed to normalise SUA with xanthine oxidase inhibitors at the maximum medically appropriate dose, or for whom these medicines are contraindicated (page 14 of MS). The manufacturer acknowledged that, "due to ongoing discussions with the regulatory authorities, this is a change to the indication discussed with NICE during the Decision Problem meeting" (page 29 of MS). However, on page 122 of the MS it was further stated that the draft SPC included a potentially more restrictive indication to that addressed in the MS. The SPC indication (page 124) stated that patients "may also have erosive joint involvement", but this clause was not included in the description of the population addressed in the submission. The ERG asked the manufacturer to confirm the current status and definition of the anticipated licensed indication. The manufacturer confirmed that the anticipated licensed indication was for the treatment of severe debilitating chronic tophaceous gout in adult patients who may also have erosive joint involvement and who have failed to normalise SUA with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these medicines are contraindicated.

Adult patients (aged 18 years or older) were eligible for participation in the included phase III trials (C0405, C0406, Sundy *et al.*, 2011)[3] if they had hyperuricaemia with baseline SUA $\geq$ 480 μmol/L (8 mg dL) *and at least one* of the following criteria: 3 or more self-reported gout flares in the preceding 18 months, 1 or more tophi, or gouty arthropathy (Sundy *et al.*, 2011 and Table 6.4, page 39 of MS) (stated by Sundy *et al.*, 2011 as being defined clinically or radiographically as joint damage due to gout) (although the inclusion criteria described in Table 6.1 (page 36 of the MS) refer to gouty arthritis [not defined further in MS]) *and* having contraindication to treatment with allopurinol *or* a history of failure to normalise UA despite 3 or more months of treatment with the maximum medically appropriate allopurinol dose (MS page 39). Inconsistencies were identified by the ERG in how the terms gouty arthritis and gouty arthropathy were used in the manufacturer's submission. These are described further in Section 4.2.2.1.

In the two included phase III trials (C0405 and C0406) [3] participants were described as either being contraindicated to allopurinol or having a history of failure to normalise UA despite 3 or more months of treatment with the maximum medically appropriate dose (determined by the treating physician). In order for patients to be considered to have truly failed allopurinol therapy, the dose of allopurinol should have been escalated optimally to the maximum medically appropriate dose. One clinical advisor considered that, in clinical practice, this rarely happens. The manufacturer clarified that no data were available on the maximum doses administered or duration of any previous urate-lowering treatments, as these data were not collected. It was unclear from the submission whether desensitisation to allopurinol hypersensitivity had been attempted prior to study entry. Therefore, the ERG considered that it was not clear whether patients described as having an allopurinol ineffective history would have been true allopurinol treatment failures. Clinical advice to the ERG indicated that this was an important issue. It is also unclear how representative the trial population (who have failed to respond to or were contraindicated to allopurinol at the maximum medically appropriate dose) would be of patients who had failed to respond to treatment with febuxostat.

Pegloticase treatment is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The manufacturer recommended (MS page 9) that patients at a higher risk of having this enzymatic deficiency should be screened for G6PD deficiency before commencing pegloticase therapy. A review by Reinders and Jansen (2010)[7] stated that pegloticase therapy may also be "complicated" in patients with catalase deficiency. Since the MS did not mention the potential implications of catalase deficiency among patients receiving pegloticase, the ERG requested clarification on this point. The manufacturer clarified that the draft SPC in the contraindications section refers to "glucose-6-phosphate dehydrogenase (G6PD) deficiency and other cellular metabolic disorders known to cause haemolysis and methemoglobinemia. All patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) should be screened for G6PD deficiency before starting KRYSTEXXA." Furthermore, the manufacturer described how, in the Section on Special Warnings and Precautions, there was the following language, which would include patients with catalase deficiency: "It is not known whether patients with deficiency of cytochrome b5 reductase (formerly known as methemoglobin reductase) or other cellular metabolic disorders are at increased risk for haemolysis and/or methemoglobinemia." The ERG requested that the manufacturer clarify whether contraindication due to catalase deficiency would have implications for the numbers of patients eligible for pegloticase treatment. However, the manufacturer stated that they did not have data on the impact of these contraindications on the total number of patients who would be eligible but that they anticipated that impact would be likely to be minimal.

Since the study participants were described as 'outpatients' (page 39), it is not clear to what degree they would be representative of patients managed in UK primary and secondary care. Under-management and poor control of gout symptoms in UK primary care has been described.[5]
The SPC (page 127) stated that "lower response rates were observed in patients with over 100 kg body weight." The ERG requested clarification on i) the proportion of the phase III and OLE trial participants having a weight over 100 kg and ii) the proportion of the UK gout population who are eligible for treatment with pegloticase having a weight over 100 kg. Data provided by the manufacturer and views of the clinical advisors to the ERG on the proportion of the gout clinical population who may have a body weight of over 100 kg are discussed in Section 4. In brief, clinical advisors to the ERG estimated that 10-15% of gout patients in the UK would have a body weight of 100 kg or above.

The manufacturer pointed out that UK centres were not included in the phase III trials (C0405 and C0406) and open-label extension study (C0407) and described this as a limitation of the evidence (page 66 of MS). The two phase III trials were conducted across the USA and Canada (C0405) and USA and Mexico (C0406). The FDA pegloticase submission document[8] stated that 49 sites were included across the USA (190 subjects), 2 sites across Canada (3 subjects), and 4 sites across Mexico (19 subjects). However, the clinical advisors to the ERG did not raise any major concerns with respect to the generalisability of the trial populations to the UK gout clinical population. One clinical advisor stated that they considered it very likely that patients in the trial population would be very generalisable to the UK in terms of disease severity, urate levels and so on. A second clinical advisor noted the potential for differences in ethnic composition between the trial settings of the USA, Canada and Mexico and the gout clinical population in the UK; differences in ethnicity may potentially influence the prevalence of G6PD among these populations, with Black and Mediterranean populations (page 125 of MS) expected to be at higher risk of G6PD.

Two clinical advisors to the ERG stated that they considered the trial populations to accurately reflect the population covered by the anticipated licensed indication and that they represented the patients who would receive pegloticase in clinical practice. However, a third clinical advisor highlighted that it was not explicit whether trial participants had previously received true optimised care with dose-optimised xanthine oxidase inhibitors (and therefore whether they had truly failed treatment on xanthine oxidase inhibitors) and whether they had failed/been inappropriate for treatment with uricosurics.

3.2 Intervention

The intervention described in the MS matches the intervention described in the final scope issued by NICE.

Pegloticase (UK brand name: KRYSTEXXA®) is a PEGylated recombinant mammalian uricase (urate oxidase). The mechanism of action of pegloticase differs from other existing urate-lowering treatments for gout as it catalyses the enzymatic conversion of uric acid into allantoin, which is eliminated from the body by renal excretion. Pegloticase is the first treatment for gout to be delivered via intravenous infusion (MS page 13).

Pegloticase is available as a 2 ml vial containing 1 ml concentrate for one intravenous infusion. The acquisition cost is currently being finalised. However, the manufacturer states that a single vial is anticipated to have an acquisition cost of £1,770.

The recommended dose of pegloticase is 8 mg delivered via intravenous infusion every 2 weeks. Monitoring of patients for infusion reactions is to be undertaken during infusions and approximately one hour following infusion (MS page 16). In order to minimise the potential for gout flares that typically follow the initiation of urate-lowering treatment, it is recommended that pegloticase treatment be accompanied by gout flare prophylaxis with colchicine or a non-steroidal anti-inflammatory (NSAID) drug, commencing one week before initiation of pegloticase treatment and continuing for at least 6 months (except in cases of contraindication or intolerance) (MS page 16). Prophylaxis against infusion reactions is also recommended, consisting of an appropriate antihistamine taken the night before and approximately 30 minutes prior to pegloticase infusion, and also an appropriate dose of paracetamol and a corticosteroid to be administered immediately prior to each infusion (MS page 16).

It is stated in the SPC that "before starting KRYSTEXXA, patients should discontinue oral urate-lowering medication and not institute therapy with oral urate-lowering medication while taking KRYSTEXXA."

There is a requirement for close monitoring of serum uric acid (SUA) levels prior to each infusion. Discontinuation is to be considered should levels increase above 360 µmol/l (6 mg/dL), particularly when two consecutive SUA measurements above this threshold are observed. The manufacturer (page 9 of MS) recommends that patients who fall within this category be considered to be non-responders to treatment with pegloticase.

The MS stated that, whilst the phase III trials were of 6 months duration, the optimal treatment course has not been established and that treatment should be based on maintenance of uric acid response below 360 µmol/l (6 mg/dL) and clinical judgement. The manufacturer estimated that the average length of a course of pegloticase treatment for patients responding to treatment (and who maintain SUA levels below 360 µmol/l (6 mg/dL) was 6 months. The treatment duration for patients not

responding to pegloticase treatment was estimated to be 2 months. The average length of treatment across all patients receiving pegloticase was estimated by the manufacturer to be 4 months. It was not clear in the MS how these estimates were derived. Further details from the two phase III studies (C0405 and C0406) and the open-label extension (C0407) were provided by the manufacturer in response to a request by the ERG. Data on the number of treatments received and the time-to-treatment cessation across these studies suggest an average treatment duration of around [redacted] in pegloticase responders. In non-responders the treatment duration of 2 months appeared to be [redacted]. These data are discussed in more detail in section 5.2.4.2. Importantly, it should be noted that the SPC states that "the data for long-term treatment from controlled clinical studies with KRYSTEXXA are limited. This should be considered when the decision is made for a therapy longer than 6 months" (page 126).

The manufacturer also reported that no information was available on the anticipated number of repeat courses and treatments that may be required by patients receiving pegloticase and that the intervals between treatments would be patient dependent (page 15). It was also acknowledged in the SPC that "very limited data are available about re-treatment after interruption of therapy for more than 4 weeks. Because of the immunogenicity of KRYSTEXXA, patients receiving retreatment may be at increased risk of infusion-related reactions, including anaphylaxis. It is therefore recommended that patients given repeat infusions of KRYSTEXXA after a treatment interruption be monitored carefully (page 127).

3.3 Comparators

The scope issued by NICE described the appropriate comparators to be i) best supportive care and ii) febuxostat for adults who are intolerant to allopurinol or for whom allopurinol is contraindicated.

However, the manufacturer stated that the only relevant comparator was best supportive care (page 25). Therefore, the comparators described in the MS did not match the comparators described in the final scope. The manufacturer justified the exclusion of febuxostat as a comparator on the basis that the anticipated licensed indication for pegloticase was for the treatment of patients who had failed to normalise their SUA levels with xanthine oxidase inhibitors (allopurinol and febuxostat) at the maximum medically appropriate dose or for whom xanthine oxidase inhibitors were contraindicated. The manufacturer explained that patients whose symptoms were controlled using xanthine oxidase inhibitors would not be eligible for pegloticase treatment. It was also stated that for patients for whom xanthine oxidase inhibitors were contraindicated, best supportive care would be the only treatment option available and thus best supportive care was the only appropriate comparator against which pegloticase should be compared.

Best supportive care was considered by the ERG's clinical advisors to represent routine and best practice in the NHS in patients who are refractory to both optimally-dosed xanthine oxidase inhibitors and uricosurics or where treatments from these classes of interventions cannot be used due to contraindications or intolerance. The BSR[1] and EULAR[2] guidelines for the management of gout both recommend the use of uricosuric drugs as a second line treatment following treatment with allopurinol. Two clinical advisors to the ERG indicated that, whilst uricosurics are used rarely, this class of treatments are low cost and can be effective in some patients and would therefore be likely to be tried prior to pegloticase but one acknowledged that in this population, most uricosurics would not be able to be used due to renal impairment among patients. However, one of three of the ERG's clinical advisors did not consider that licensed uricosuric drugs were likely to be effective in the population of patients under consideration. One clinical advisor commented that the uricase rasburicase could be considered to be a relevant comparator, occupying a potentially similar position in the gout patient treatment pathway, but noted that this drug was unlicensed in the UK and available experimental data for rasburicase were sparse.

Best supportive care was therefore considered by the ERG and clinical advisors to the ERG to be the appropriate comparator for the decision problem addressed in the submission.

3.4 Outcomes

The outcomes listed in the MS matched the outcomes outlined in the final scope.

The primary outcome was the proportion of plasma uric acid (PUA) responders in each group. A responder was defined as a patient with PUA < 360 µmol/l (6 mg/dL) for at least 80% of the time during months 3 and 6.

Secondary outcomes were resolution of tophi (with a tophus complete response defined as a 100% decrease in area of at least one pre-specified target tophus without progression or appearance of any new tophus), reduction in the proportion of patients with gout flare and in the number of flares per patient during trial months 1-3 and 4-6, improvement in tender and swollen joint counts, improvement in quality of life (SF-36), and improvement in functional status (Health Assessment Questionnaire Disability Index and HAQ Pain Scale).

The final scope issued by NICE specified that SUA response would be assessed. However, the primary outcome of uric acid response in the two included phase III trials was based on the measurement of plasma uric acid (MS page 29). It was stated in the MS (page 29) that outcomes in the submission would include both serum and plasma uric acid levels. The ERG asked the

manufacturer to justify the use of plasma measurements. The manufacturer clarified that PUA was selected as the primary endpoint as the use of acidified plasma allowed the inactivation of pegloticase immediately after blood was taken from participants, whereas allowing blood samples to clot to obtain a serum sample may have allowed for continued *in vitro* pegloticase activity and spuriously low UA measurements. The methods used to measure both PUA and SUA levels were described by the manufacturer as being validated methods available in clinical laboratories. The manufacturer tested the observed PUA and SUA for agreement using the kappa coefficient and obtained a value of 0.74 ($P<0.001$), which they described as "near excellent" on a scale of 0 to 1 (0 indicating no agreement and 1 indicating complete agreement between methods).

3.5 Other relevant factors

The MS contained a section on equality issues (MS page 27). The manufacturer stated that there were no equality issues applicable to this appraisal.

There is no Patient Access Scheme application currently ongoing (to the best knowledge of the ERG).

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Overall, the searches conducted for the sponsor submission appeared satisfactory. All strategies described in the methods were provided.

The manufacturer confirmed that, at the point at which the systematic reviews within this submission were conducted, the anticipated licensed indication for pegloticase was for the treatment of severe refractory chronic gout and this was reflected in the search terms utilised. Patients were considered to have refractory chronic gout if they met the following conditions: i) SUA > 8mg/dL, ii) failed on maximum medically appropriate dose of allopurinol or febuxostat or contraindicated, iii) one of the severe symptoms *or* two of (not severe) symptoms (whereby severe symptoms were defined as > 4 gout flares in previous 12 months, at least 2 gout tophi, or severe gouty arthritis (defined by at least 3 swollen/tender joint or at least two joint lesions) and not-severe symptoms were classed as > 2 gout flares in previous 12 months, at least 1 gout tophus, or gouty arthritis (defined as at least one swollen or tender joint *or* joint lesion)). The manufacturer highlighted that the likely anticipated indication was a small subset of the RCG population (presumed by the ERG to represent refractory chronic gout) but corresponds to those patients who are likely to receive pegloticase and precisely characterises eligible patients, providing clarity for prescribing clinicians. Relevant evidence should therefore have been identified using the search terms utilised.

The search strategy for each database was provided. The reporting of the searches was confusing in places, making it difficult to replicate the searches. For the Medline and Cochrane Library search strategy, it was unclear whether subject headings or free-text terms were used for certain lines.

For the Medline Health Economic searches, the search strategy started at line #6 (confirmed by the manufacturer as an error). However, search line #11 combines search line #5 with terms for resource use etc. It is therefore not possible to repeat line #11 of the Medline search and determine if the total number of hits reported is correct. For the Cochrane Library search re-running the search retrieved significantly more results than the 4 reported. However, if results from NHSEED and DARE are included there are just 4 results. For the health economics search it would be appropriate to search just NHSEED and DARE and it might be that the reporting on the databases within the Cochrane Library was inaccurate for the health economics searches.

The number of database hits were provided for some but not all of the searches. For Embase, the number of records retrieved was provided for each line of the search strategy. For the clinical effectiveness searches database hits were not reported for databases other than Embase. This means that it is not possible to check if the number of hits from each database matches with the numbers given in the flow diagram.

For the Health Economic searches the number of database hits was reported for each line of the Embase search strategy. For the other database just the total number of hits was provided.

The search strategies appeared appropriate. The statement of the decision problem was illustrated using the PICO framework. PICO was applied correctly. The clinical effectiveness searches combined population, intervention and outcome terms. The inclusion of outcome terms helps to focus a search on relevant outcomes. However, terms related to outcomes might not be mentioned in the abstract meaning that the searches might not have retrieved all relevant references. The manufacturer confirmed that they considered it to be highly unlikely that a report of interest would not have included any of the outcomes of interest in the title or abstract. Combining the condition and intervention terms with an RCT filter would have been more appropriate to retrieve studies for clinical effectiveness. Additional searches could then be completed for references on quality of life, disability and pain. Alternatively, results for the intervention terms were small and would have produced a manageable number for sifting that would have ensured relevant references were not missed and also picked up the references around quality of life, disability and pain.

Subject headings were used on Embase appropriately. However, it was not clear if subject headings were used on Medline or the Cochrane Library. This made the replication of the searches difficult. Free-text terms were used in the searches. Attempts have been made to use synonyms for gout and pegloticase but they were not exhaustive or consistent. The brand name (KRYSTEXXA) was not included in the intervention term part of the clinical effectiveness and health economics searches. However, the manufacturer confirmed that papers which include the brand name would also include another relevant term already in the search strategy. Inclusion of a drug’s brand name in the search helps to ensure that all relevant references are retrieved. Additionally, the term 'recombinant uricase' was used in the Embase health economics search, line #2 for the intervention terms, while it is not used for the health economic searches on the other databases or the clinical effectiveness searches on any of the databases. The manufacturer failed to address this issue in their clarification responses.

The search strategies did not make use of truncation or wildcards. Truncation could have been usefully employed for various terms of the search strategy. For example, in the health economics search, resource use could be truncated to resource us$ to retrieve articles with the term resource usage as well as articles containing the term resource use. The terms Utility or utilities are used when the truncated utilit$ could have been used instead. Spelling errors were not present in the search strategy. Boolean operators appear to have been used to combine different facets of the searches appropriately.

The described methods provide details of the sources searched. Date ranges of the databases would have been helpful for replication of the searches. For the Health Economics searches certain database should be searched as a minimum. The list includes EconLit which was not searched meaning that potentially relevant references might not have been retrieved. The manufacturer confirmed that they considered to highly unlikely that EconLit would yield additional studies of relevance for a UK decision context. Details of searches for conference proceedings and company databases are provided. Hand searching is not reported.

An appropriate limit to humans was applied to the Embase and Medline search. The date range for the searches for conference proceedings was appropriately limited to 2005-2012.

No mention was made of the use of filters to ensure the retrieval of relevant studies. For the clinical effectiveness studies it would have been appropriate to use an RCT and systematic reviews filter. To retrieve studies on adverse events the population and intervention terms should have been combined with a filter designed to retrieve studies on adverse events. Terms to retrieve health economic studies are used but the use of a sensitive filter would have been more appropriate. The terms for health economics were used consistently between the databases.

Additionally, the strategies for searching the conference proceedings were provided. An additional search of the Savient internal database of clinical trials reports was reported although search terms for the search were not provided.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria used in the selection of evidence for the systematic review of clinical effectiveness were presented in the MS (page 33). The table in the MS was labelled as ‘eligibility criteria used in search strategy’ but was presented within the description of the study selection process (Section 6.2.1). It was not clear from the MS how many reviewers were involved in the study selection process for the systematic review of clinical effectiveness. Best practice specifies that two reviewers be involved in the application of inclusion and exclusion criteria in order to limit

bias in study selection. Details of the inclusion and exclusion criteria applied in the MS are presented in Table 2.

Table 2. Inclusion/exclusion criteria used in study selection for trials C0405 and C0406 (as presented by the manufacturer)

Inclusion criteria	Exclusion criteria
Population: adults aged ≥18 years) with severe refractory chronic gout who were symptomatic and had failed to normalise SUA with xanthine oxidase inhibitors (allopurinol and febuxostat) at the maximum medically appropriate dose, or for whom these medicines were contraindicated Interventions: pegloticase, best supportive care or placebo Outcomes: - serum urate levels - plasma urate levels - gout flares - reduction in tophus - pain - tender and swollen joint - physical function and disability - disease specific health-related quality of life - generic health-related quality of life - utility based quality of life measures - treatment-related adverse events - relevant clinical laboratory endpoints - physical examination and vital signs outcomes Study design: - systematic reviews of randomised controlled trials (RCTs) and single RCTs (both parallel, cross-over designs, and studies comparing different doses or schedules of the drugs of interest) that may either be blinded or unblinded and published or unpublished e.g. conference abstracts - open label (extension) studies - registry studies Language restrictions: none	Non-human studies Pre-clinical or biological studies Phase I and II studies Editorial, opinions, reviews (other than systematic reviews) Reports/abstracts where insufficient methodological details to judge study quality were available

No additional justification to the above table for the inclusion and exclusion criteria was provided in the MS. A flow diagram depicting the study selection process was provided as well as descriptions of the citations included in the review.

The inclusion criteria for the review appeared reasonable and relevant to the decision problem.

4.1.3 Critique of data extraction

Data extraction was not referred to in the MS. However, text in Appendix 2, (page 138) Section 10.2.7 of the MS referred to the "data abstraction strategy". The only details provided for the systematic review of clinical effectiveness were that data were abstracted by hand from the original source.

The outcomes selected for extraction were considered by the ERG and clinical advisors to be appropriate. However, it is important to note that although the two phase III clinical trials included two dosing regimens (8mg every two weeks or 8mg every four weeks), only the 8 mg every 2 weeks data were extracted for inclusion in the MS. Data from the 8mg every four weeks dosing regimen were not considered in the assessment of clinical effectiveness in the MS based on trials C0405 and C0406 but data from both the 8mg every 2 weeks and 8mg every four weeks dosing regimens were provided in the original MS for the OLE study C0407.

4.1.4 Quality assessment

The quality assessment results were presented in Section 6.4.3 of the MS (page 46). Quality issues relating to study design were assessed according to criteria based on the Centre for Reviews and Dissemination (2008)[9] guidance. Separate quality assessment forms for the two trials C0405 and C0406 were provided in the Appendices (Section 10.3, page 138-140) of the MS. Quality assessment of the non-RCT evidence (trial C0407 was presented in Appendix 7 (Section 10.7.1, page 141). It was not explicitly stated whether critical appraisal was conducted by a single reviewer or multiple reviewers.

Table 3. Quality assessment results for C0405 and C0406 (as presented by the manufacturer)

Trial no. (acronym)	C0405 (GOUT 1) and C0406 (GOUT 2)
Was randomisation carried out appropriately?	Yes Randomisation used an automated interactive voice response system and was stratified to ensure comparable numbers of patients with tophi in each group
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes The baseline characteristics were similar in all treatment groups and across both studies (see MS Section 6.3.4)
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes All patients who had been randomly assigned to a treatment group and received on [sic] dose of the study medication were included in the modified ITT analysis

Was randomisation carried out appropriately?

Patients were randomised in a 2:2:1 ratio to the 8mg every 2 weeks pegloticase group, pegloticase every 4 weeks group and placebo group respectively. Randomisation was conducted using an automated interactive voice response system with a centralised randomisation scheme. Stratification of patients on the basis of number of tophi was conducted. The manufacturer stated that patients were stratified between treatment and placebo groups to ensure a comparable number of patients with tophi in each group. One of the clinical advisors to the ERG noted that tophi may be subclinical[10] and therefore potentially not visible and so randomisation according to visible tophi only would not take subclinical tophi (and true tophi burden) into account. However, a second clinical advisor to the ERG did not consider this distinction to be clinically relevant. The ERG requested clarification from the manufacturer on the potential issue of subclinical tophi. The manufacturer responded that "subclinical

tophi were not identified and hence were not part of the stratification." The MS also stated that randomisation was balanced across all centres. However, the term "centre" was not defined (e.g., hospital, city, country) in the MS.

Was the concealment of treatment allocation adequate?

The manufacturer appeared to confuse the issue of concealment of treatment allocation with blinding in the description of quality assessment. In relation to the concealment of treatment allocation, it was stated in the MS (page 139 & 140) that all patients received an IV infusion every 2 weeks. However, whilst this is relevant to the issue of blinding in the avoidance of performance bias, it is not relevant to the concealment of allocation of patients to treatment groups, which relates to selection bias and the protection of the randomisation sequence from subversion. Since randomisation in the trials was conducted using an automated interactive voice response system with a centralised randomisation scheme, the ERG consider it likely that concealment of treatment allocation would be adequate.

Were the groups similar at the outset of the study in terms of prognostic factors?

The ERG and clinical advisors to the ERG agreed with the manufacturer that there were no apparent major differences in baseline characteristics of patients in the intervention and control groups in either phase III trial (C0405 and C0406). However, the ERG noted that, in trial C0406, a greater proportion of patients receiving pegloticase 8 mg every 2 weeks had chronic kidney disease (defined as a creatinine clearance of less than 60 ml/min) than in the placebo group (14/42 (33%) and 3/23 (13%) respectively (statistical significance not presented). Furthermore, patients receiving pegloticase 8 mg every 2 weeks in trial C0406 also were more likely at baseline to have diabetes mellitus (11/42, 26% vs. 3/23, 13%) and cardiac arrhythmia (10/42, 24% vs. 1/23, 4%) than subjects in the placebo group (statistical significance not presented).

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?

Trials C0405 and C0406 were described in the MS (page 38) as being "double-blind[ed] (patient and investigator)". The manufacturer stated that blinding was maintained at all levels and that in both studies all patients received gout prophylaxis one week before and prophylaxis against infusion reactions the evening before and immediately prior to each infusion (MS page 36). Trial C0407 was an open label study and the MS states that (page 55) "the investigator and the patient were permitted to select the preferred treatment option while they were still blinded to the randomised treatment schedule. Regimen switches (pegloticase 8 mg every 2 weeks to every 4 weeks and vice versa) were allowed after week 25 of the OLE and once the results of the double-blind studies became available."

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?

It was stated in the MS that there were no unexpected imbalances in drop-outs between groups. However, in trial C0405 5 of 38 (13%) patients in the pegloticase treatment group who were assessed at 3 months had withdrawn from the trial compared with no drop-outs in the 20 who were assessed in the control group. At the end of the study 13 out of the 44 (30%) who were randomised to receive 8mg every 2 weeks pegloticase had withdrawn from the study. The reasons for these withdrawals were n=8 adverse events; n=3 withdrew consent; n=1 protocol violation. In comparison, 1/22 (4.5%) patients randomised to the control group had withdrawn from the trial for which the reason given for withdrawal was 'lost to follow up'. The manufacturer (page 44) states that 8 patients withdrew due to adverse events. However the clarification letter from the manufacturer indicated that [redacted]

In trial C0406 9/33 (27%) patients in the pegloticase treatment group who were assessed at 3 months had withdrawn from the trials compared to no drop-outs in the 23 who were assessed in the control group. At the end of the study 13 out of the 46 (28%) who were randomised to receive 8mg every 2 weeks pegloticase had withdrawn from the study. The reasons for these withdrawals were n=7 adverse events; n=1 death; n=5 withdrew consent. In comparison, 3/24 (12.5%) patients randomised to the control group had withdrawn from the trial. The reasons given were n=1 adverse event; n=1 withdrew consent; n=1 lost to follow up.

The manufacturer reported (page 139) that the number of patients who dropped out of the study was comparable between the study arms and that reasons for drop-outs did not suggest any unexplained biases. The MS does not explain or adjust for the above imbalances in drop-out rates between groups, particularly with regards to the higher number of patients dropping out due to adverse events in both C0405 and C0406 trials. The manufacturer does state that (page 60) the majority of infusion reactions (91%) occurred following a loss of treatment response (plasma urate levels > 360 μmol/L (6 mg/dL), indicating that routine monitoring of urate levels and withdrawal of treatment on loss of response might be expected to mitigate the majority of such reactions[11]. This information may provide a reason for why the drop-out rates were expected but does not sufficiently address the issue that the drop-out rates between groups are substantially imbalanced.

Is there any evidence to suggest that the authors measured more outcomes than they reported?

The ERG do not consider there to be any evidence to suggest that the authors measured more outcomes than they reported in any of the C0405, C0406 or C0407 trials.

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

The analysis used a 'modified intention-to-treat analysis' including all patients who received at least one dose of study medication for trials C0405 and C0406. In trial C0407, the modified intention to treat population was based on subjects who had received at least one dose of study drug and had some follow-up data (and therefore was considered by the ERG to be less appropriate). It was reported (page 43) for trials C0405 and C0406 that if PUA levels were missing at Week 9, Week 13, Week 21 or Week 25 (Visit 20), the patient's baseline PUA value was used for the calculation of the proportion of time that the PUA level was below 360 μmol/L (6 mg/dL) during Month 3 and Month 6. No imputation was to be performed for the other missing PUA levels. Any patients who withdrew before Month 6 were considered to be non-responders for the primary efficacy endpoint. Any subjects with missing data for HAQ-DI were considered to be non-responders for physical function.

The MS does not therefore utilise a true intention-to-treat analysis which would analyse all patients who were randomised, irrespective of whether or not they received their allocated intervention and irrespective of whether data on all outcomes were collected. Inclusion of patients with missing outcome data involves imputation of missing data which was only done if data was missing at the time points stated above. However, the ERG considered the use of the modified intention to treat analysis for the phase III RCTs (whereby patients were included if they had received at least one dose of study drug) to be reasonable.

4.1.5 Evidence synthesis

Primary outcome data (proportion of plasma UA responders in each pegloticase treatment group vs. in the placebo group, with a responder being defined as a patient with plasma UA less than 360 μmol/L [6.0 mg/dL] for at least 80% of the time during months 3 and 6) were presented for each individual phase III trial and also as a simple pooled analysis (in which data were not meta-analysed but simply added together to yield a summary combined result) (Table 6.9, page 47). Data were also presented for secondary outcomes as simple pooled analyses only (pages 48-52).

No meta-analyses of primary or secondary outcome data were included in the original MS, with the manufacturer describing meta-analyses in Section 6.6 (page 53) as being "not-applicable."

However, it has been argued that the simple pooling of data may yield counterintuitive or spurious results due to a phenomenon known as Simpson's paradox and that meta-analysis is a more valid approach to the quantitative combination of data[12- 13]. Simple pooling ignores the characteristics of individual studies and relies on the assumption that there is no difference between individual studies. Furthermore, pooling ignores the validity of comparisons made in the individual studies (Lièvre *et al.*, 2002).[14]

Meta-analysis maintains the effects of randomisation and ensures that each study acts as its own control, minimising the impact of potential confounding variables (Borenstein *et al.*, 2009)[12]. Results obtained from a meta-analysis can show a considerable difference from those obtained by simply pooling the same data (Lièvre *et al.*, 2002)[14] and Bravata and Olkin[13] strongly recommended that simple pooling be avoided where possible.

Chan and Redelmeier (2012)[15] reflected that, although Simpson's paradox is a particular problem in the analysis of observational data, the complex nature of patient lifestyles may influence a range of variables which may cause potentially serious interactions, even in randomised trials. Ameringer *et al.* (2009)[16] make the further point that, for trials with a small sample size, simple randomisation may be not as effective in yielding a proportional distribution of confounding variables between treatment arms. Since the phase III trial populations included in the submission are relatively small (C0405 pegloticase 8mg every 2 weeks n=43, placebo n=20; C0406 pegloticase 8 mg every 2 weeks n=42, placebo n=23) (modified ITT populations), the included evidence may potentially be subject to the influence of unknown confounding variables. Even though the trials were conducted as replicate studies and the baseline characteristics of the two included phase III studies showed only minor differences (as confirmed by the clinical advisors to the ERG) (Table 6.5, page 40), a difference in primary outcome was observed between the two replicate phase III trials and is described as follows. Plasma uric acid response was presented for the two phase III trials in Table 2 of the Appendices (MS page 131). The proportion of responders in the GOUT1 trial (C0405) was higher for the pegloticase 8mg every 2 weeks group (47%) versus the pegloticase 8 mg every 4 weeks group (20%). However, the converse was found in the GOUT2 trial (C0406), where the proportion of responders was lower in the pegloticase 8 mg every 2 weeks group (38%) versus the pegloticase 8 mg every 4 weeks group (49%). The ERG asked the manufacturer to explain this difference in response according to dose between the two trials. This difference suggests that there may potentially be underlying differences between the two trials populations and underlines the standpoint that, rather than simply pooling the data, a more valid approach would have been to undertake a meta-analysis.

(NB: With regards to the difference described above, the manufacturer acknowledged that "overall, no apparent clinical or statistical explanation has been found for the numerical difference observed for

the 8 mg pegloticase 4 week regimen in the two pivotal studies [but that] the 95% CI of the actual PUA responder rates were wide and even overlapped between the 2 studies in most cases [and that] the studies were powered to detect a difference between each pegloticase treatment arm and placebo, not between pegloticase treatment regimens.")

The ERG requested for the manufacturer to provide data for all primary and secondary efficacy and safety outcomes presented i) for each individual study and ii) combined using meta-analysis. However, the manufacturer maintained that pooling was an appropriate strategy for synthesis of the phase III trial data, on the basis that "it was pre-specified that the secondary endpoint data were to be pooled to reach statistical significance in these. In this case, a meta-analysis would not be appropriate." However, since meta-analysis also has the capacity to increase statistical power (Cohn and Becker, 2003; Borenstein *et al.,* 2009)[12,17] the ERG still considers the presentation of data for each individual study and combined data using fixed and random effects meta-analysis to have been more transparent and robust.

The manufacturer provided primary efficacy outcome data for PUA response for each phase III trial and also as a "combined" form. However, it was unclear from the clarification responses whether these "combined" data had been obtained by simple pooling or meta-analysis. The ERG subsequently undertook meta-analyses of data for PUA response and complete tophi resolution. Results are presented in Section 4.5.

The manufacturer stated that subgroup analyses of the individual replicate phase III studies (C0405 and C0406) and of the pooled data for treatment responder and percent non-hyperuricaemic time were performed according to the following subgroups: gender, presence of tophi, BMI (≤ 30 kg/m2, > 30 kg/m2), age group (≤ 55 years, > 55 years), disease duration (< 5 years, ≥5 years), baseline HAQ-DI (≤ 1, > 1), creatinine clearance (< 50 mL/min, ≥ 50 mL/min) and antibody status). Although the ERG requested for results based on meta-analysed trial data from C0405 and C0406 to be provided, the manufacturer did not provide these on the basis that they considered that "pooling data of the two replicate trials is more appropriate that undertaking a meta-analysis with the same two studies." As previously, the ERG considers the use of meta-analysed data to be more robust than simple pooled data.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in and excluded from the clinical effectiveness review

4.2.1.1 Identified studies

The clinical effectiveness evidence in the MS was based predominantly on the following 3 studies:

- Two replicate, randomised double-blind placebo-controlled phase III trials (C0405 [GOUT 1] and C0406 [GOUT 2]) (NCT00325195) (primary data source Sundy *et al.*, 2011)[3]
- Open label extension safety study (OLE C0407) (primary data source clinical study report C0407 CSR, identified by the manufacturer from the Savient database) (full clinical study report not provided in the submission)

The manufacturer stated that "details of analysis of the pooled phase III studies analysing subgroups and responders and non-responders as two separate groups were taken from a Savient internal report (Integrated Summary of Efficacy)"(page 35) (full report not provided in the submission).

The two phase III trials (C0405 and C0406) and OLE study (C0407) were considered by the ERG to be relevant to the decision problem as specified in the scope. No additional phase III or open-label extension studies were identified by the ERG or clinical advisors to the ERG.

Table 4. Identified studies included in the MS

Study	Primary reference	Intervention and comparator
C0405	Sundy *et al.*, 2011[3]	Pegloticase 8 mg IV every 2 weeks n=43[*] Pegloticase 8 mg IV every 4 weeks alternating with placebo every 2 weeks n=41 Placebo n=20
C0406	Sundy *et al.*, 2011[3]	Pegloticase 8 mg IV every 2 weeks n=42 Pegloticase 8 mg IV every 4 weeks alternating with placebo every 2 weeks n=43 Placebo n=23
C0407	Clinical study report C0407 CSR	Pegloticase 8 mg every 2 weeks n= 82/151[†] Pegloticase 8 mg every 4 weeks n=67/151[†] Observation n=2/151[†]

[*]Figures presented for trials C0405 and C0406 represent the modified intention-to-treat population (all randomised patients who received at least one infusion)

[†] These values were taken directly from the Savient briefing document prepared for the FDA[8].

It was stated in the original MS that a total of 7 reports were selected for inclusion (page 34). However, there appeared to be discrepancies in the description of the number of included reports in the MS. For example, it was stated that 6 included reports were in the form of conference abstracts, but only 5 references could be seen for these abstracts. Following a clarification request by the ERG, the manufacturer confirmed that a total of 6 abstracts were identified (and that the conference abstract by Hamburger *et al.* (2011)[18] had been missed in the original MS). Following clarification, the manufacturer also provided details of which study each abstract related to (as presented in the table 5 below).

Table 5 Details of conference abstracts and original data sources

Conference abstract	Original data source
Baraf *et al.*, 2012[11]	Two phase III trials (C0405 and C0406)
Hamburger *et al.*, 2011[18]	Open label extension study (C0407)
Ottery *et al.*, 2012[19]	Two phase III trials (C0405 and C0406)
Somberg *et al.*, 2011[20]	Two phase III trials (C0405 and C0406)
Wolfson *et al.*, 2012[21]	Two phase III trials (C0405 and C0406) and open label extension study (C0407)
Yood *et al.*, 2012[22]	Two phase III trials (C0405 and C0406)

However, following clarification, the manufacturer confirmed that, although reference details of the abstracts were provided for completeness, data from the abstracts were not included in the submission (on the justification that the results presented in the submission related to the completed trials). The ERG sourced the full versions of each abstract in order to verify whether any further relevant data was included in the abstracts. Relevant data identified from the conference abstracts are discussed in Section 4 of this report. The manufacturer's justification for non-inclusion was considered by the ERG to be unclear, since these abstracts provided further limited evidence on the potential long-term efficacy and safety of continued pegloticase treatment and could have been usefully integrated within the original submission.

4.2.1.2 Excluded studies

Evidence from phase I and phase II studies was excluded according to the review eligibility criteria (MS page 33). In response to a request by the ERG, the manufacturer justified the exclusion of the phase I trials, describing these as not relevant to the use of the anticipated licensed dose in the patient population. The exclusion of the phase II trial reported by Sundy *et al.* (2008)[23] was also excluded. Participants in this trial were randomised to 12-14 weeks of treatment with one of 4 doses of IV pegloticase (4 mg every 2 weeks, 8 mg every 2 weeks (ITT n=8), 8 mg every 4 weeks and 12 mg

every 4 weeks) with no placebo group. The exclusion of this study was justified by the manufacturer on the basis that this was a phase II dose finding study.

A completed non-randomised, non-controlled, open label, multicentre re-exposure pegloticase trial (NCT00675103) (C0409) was identified by the ERG (via www.ClinicalTrials.gov). This trial evaluated efficacy and safety outcomes in subjects who were receiving a 24 week course of pegloticase and whose last exposure to pegloticase was at least one year before study entry. In response to a request by the ERG, the manufacturer provided a brief synopsis of this trial (Savient trial identifier C0409).

The manufacturer stated that no new studies were due to be reported within the next 12 months (MS page 14).

The NICE table of responses to consultee and commentator comments on the draft remit and draft scope includes a statement by the manufacturer that, in addition to phase III and OLE study results, a range of other data would be made available to the Appraisal Committee, including i) a series of studies based upon the 2010 and 2011 National Health and Wellness Surveys for the five major EU countries which consider the impact of gout experience on health related quality of life, health status, employment status, absenteeism and presenteeism, ii) the results of a large scale gout chart review for Europe, iii) costing study for the RCG population in the UK based on the IMS Analyser and the GPRD. The ERG asked the manufacturer to clarify whether these data were available and could be provided. The manufacturer stated that, as the indication for pegloticase had altered since the time of scope consultation, these documents were deemed by the manufacturer to be no longer relevant. However, since the ERG did not have sight of these documents, it cannot be confirmed whether any relevant information was presented.

4.2.2 Summary and critique of submitted clinical effectiveness evidence

4.2.2.1 Description of phase III randomised controlled trials (C0405 [GOUT 1] and C0406 [GOUT 2]) (NCT00325195)

The primary data source for the two included phase III trials (C0405 and C0406) was a single publication by Sundy *et al.* (2011) [3]. C0405 and C0406 were two replicate, randomised, double-blind, placebo-controlled multicentre trials that were undertaken across 56 rheumatology practices in the United States, Canada, and Mexico (MS page 70) between June 2006 and October 2007. (The Savient submission to the FDA[8] stated that 49 sites were included across the USA (190 subjects), 2 sites across Canada (3 subjects), and 4 sites across Mexico (19 subjects)). The studies were of 6 months duration.

The ERG noted that, whilst each study had been given a separate trial identifier by the manufacturer (C0405 and C0406), only one trial identifier was assigned on ClinicalTrials.gov (NCT00325195). The rationale behind the design of the included phase III studies as two smaller replicate RCTs as opposed to a single combined RCT was unclear. Following a request for clarification from the ERG, the manufacturer confirmed that the two replicate trials were performed "in order to meet the US FDA requirement for two well controlled clinical trials to establish safety and efficacy."

The objective of the included phase III trials was to evaluate the efficacy and tolerability of pegloticase in the management of refractory chronic gout.

Randomisation was performed according to a 2:2:1 ratio and was implemented using an automated interactive voice response system with a centralised randomisation scheme and was stratified "to ensure [a] comparable number of patients with tophi in each group" (page 38). Patients who were receiving urate-lowering treatments at screening experienced a one week washout period. Participants and investigators were both blinded to treatment allocation (page 38).

Patients were eligible for inclusion if they were aged 18 years or older and met the following criteria for refractory gout: a baseline SUA of at least 8.0 mg/dL and at least one of the following: 3 or more self-reported gout flares in the preceding 18 months, 1 or more tophi, or gouty arthropathy (Sundy *et al.*, 2011 and Table 6.4, page 39 of MS) (stated by Sundy *et al.*, 2011 as being defined clinically or radiographically as joint damage due to gout) (although the inclusion criteria described in Table 6.1 (page 36 of the MS) referred to gouty arthritis (not defined further)). Subjects also had contraindication to treatment with allopurinol or a history of failure to normalise UA despite 3 or more months of treatment with allopurinol at the maximum medically appropriate dose (stated by Sundy *et al.*, 2011 as being determined by the treating physician).

It was unclear how 'gouty arthritis' (MS page 36) and 'gouty arthropathy' (MS page 39) were defined and applied as inclusion criteria for the phase III trials and it was not explicit whether these terms indicated erosive joint involvement. Further clarification was requested by the ERG on the application of these terms and also on the distribution of gout flares, gouty arthritis/arthropathy and tophi among the trial participants in order to assess the severity and persistence of gout among the trial populations.

In their response, the manufacturer stated that gouty arthritis was used as an eligibility criterion, but that "the term gouty arthritis was not defined. It was left to the clinical appreciation of the investigator to decide whether or not the patient was suffering from this condition. The term gouty arthropathy was not in the inclusion criteria. However, patients included in the study were recorded as having or not having gouty arthropathy. Again this term was not defined." Therefore, there appeared to be

contradiction in terms of the manufacturer's description of how the terms gouty arthropathy and gouty arthritis were defined and applied as inclusion criteria in the phase III trials. However, one clinical advisor to the ERG considered that these terms were interchangeable and did not denote the severity of gout. A second clinical advisor agreed there was no agreed definition of the terms but that arthropathy may refer to radiographic erosive involvement and arthritis to flare of symptoms and signs. The manufacturer confirmed that there were no available data on the severity of gouty arthritis/gouty arthropathy among trial participants, but that the number of patients with chronic synovitis/arthropathy in the pooled ITT population was 50 of 85 (58.8%) of patients in the pegloticase every 2 week group and 26 of 43 (60.5%) in the placebo group.

Data on baseline tophi were also provided in the MS (Table 6.5, page 40), which indicated that 67.4% (C0405) and 78.6% (C0406) of the pegloticase 8 mg every 2 weeks groups and 70.0% (C0405) and 65.2% (C0406) of the placebo groups had baseline tophi. The ERG requested additional details on the distribution and severity of flares over the past 18 months among phase III and OLE trial participants. Following a request for clarification by the ERG, the manufacturer provided additional information on gout history and disease status at baseline for participants of trials C0405 and C0406.

Table 6. Gout history and disease status at baseline for participants in trials C0405 and C0406

Disease characteristic	**C0405**		**C0406**	
	8 mg pegloticase every 2 weeks (N=43)	**Placebo (n=20)**	**8 mg peglotic ase every 2 weeks (N=42)**	**Placebo (N=23)**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects describing severity of acute flares as severe (crippling)	31 (72.1%)	12 (63.2%)	22 (53.7%)	11 (50.0%)
Patients with chronic synovitis/arthropathy	27 (62.8%)	13 (65.0%)	23 (54.8%)	13 (56.5%)
Patients having tophi	29 (67.4%)	14 (70.0%)	33 (78.6%)	15 (65.2%)

[redacted]

[redacted]

Table 7. C0405 Subject Eligibility Based on Allopurinol Treatment History (Table presented as provided in manufacturer's clarification responses, details of statistical significance not provided)

	8 mg Pegloticase		Placebo	Total
	Every 2 Weeks (N = 43) n (%)	Every 4 Weeks (N = 41) n (%)	(N = 20) n (%)	(N = 104) n (%)
Allopurinol ineffective	3 (7.0)	7 (17.1)	2 (10.0)	12 (11.5)
History of allergy/hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Renal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
GI intolerance	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

Table 8 C0406 Subject Eligibility Based on Allopurinol Treatment History (Table presented as provided in manufacturer's clarification responses, details of statistical significance not provided)

	8 mg Pegloticase		Placebo	Total
	Every 2 Weeks (N = 42) n (%)	Every 4 Weeks (N = 43) n (%)	(N = 23) n (%)	(N = 108) n (%)
Allopurinol ineffective	13 (31.0)	10 (23.3)	3 (13.0)	26 (24.1)
History of allergy/hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Renal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
GI intolerance	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

The data indicated that more subjects had an allopurinol ineffective history in trial C0406 compared with trial C0405.

The clinical advisors to the ERG noted that, in order for patients to be considered to have truly failed allopurinol therapy, the dose of allopurinol should have been escalated optimally to the maximum medically appropriate dose. One clinical advisor considered that, in clinical practice, this rarely happens. Importantly, the manufacturer clarified that no data were available on the maximum doses administered or duration of any such previous urate-lowering treatments, as these data were not collected. It was unclear from the submission whether desensitisation to allopurinol hypersensitivity had been attempted prior to study entry. Therefore, the ERG considered that it was not clear whether patients described as having an allopurinol ineffective history would have been true allopurinol treatment failures.

Patients were excluded if they had glucose-6-phosphate dehydrogenase deficiency, prior treatment with a uricase-containing agent, were pregnant, had unstable angina, uncontrolled hypertension (>150/95 mm Hg) or cardiac arrhythmia, uncomplicated congestive heart failure, renal dialysis or solid organ transplant. The manufacturer confirmed that subjects with renal impairment were not excluded from the trial unless on dialysis.

One of the clinical advisors to the ERG indicated that patients with renal failure might be considered to be part of the pegloticase target population, although one advisor considered that this would apply to severe renal failure only (CKD stages 4-5). It was also queried by a clinical advisor to the ERG whether pegloticase could be used in patients with advanced chronic kidney disease who were being prepared for dialysis. However, an additional clinical advisor stated that they considered it to be possible for haemodialysis patients to be able to be effectively treated with carefully-titrated doses of allopurinol but noted that end stage renal disease was a contraindication to uricosurics.

As stated previously, two clinical advisors to the ERG stated that they considered the trial populations to accurately reflect the population covered by the licensed indication and that they represented the patients who would receive pegloticase in clinical practice. However, a third clinical advisor highlighted that it was not explicit whether trial participants had received true optimised care, with dose-optimised xanthine oxidase inhibitors (and therefore whether they had truly failed on xanthine oxidase inhibitors) and whether they had failed/been inappropriate for treatment with uricosurics.

In trial C0405 between 70-75% of patients included in the pegloticase 8mg every 2 weeks intervention group and the placebo control group, respectively, were male. The mean age in the intervention group was 58 years and 57 years in the control group. The mean BMI was 34.85 in the intervention group and 33.30 in the control group. Patients in the intervention group had been diagnosed with gout for a mean of 16 years whilst patients in the control group had a mean gout duration of 12 years.

In trial C0406 91% of patients included in both the pegloticase 8mg every 2 weeks intervention group and the placebo control group were male. The mean age in both the intervention group and in the control group was 54 years. The mean BMI was 31 in both the intervention group and in the control group. Patients in both the intervention group and the control group had been diagnosed with gout for a mean of 15 years.

All participants received IV infusions every 2 weeks consisting of pegloticase or placebo. Commencing at week 1, trial participants received 2 hour IV infusions of 250 ml 0.9% sodium chloride containing either pegloticase 8 mg at each infusion (biweekly treatment group [C0405 modified ITT n=43, C0406 modified ITT n=42]), pegloticase 8 mg alternating with placebo (every 4 week or monthly treatment group [C0405 modified ITT n=41, C0406 modified ITT n=43]), or placebo (placebo group [C0405 modified ITT n=20, C0406 modified ITT n=23]). Gout flare prophylaxis (consisting of colchicine 0.6 mg once or twice daily, or a non-steroidal anti-inflammatory drug) was commenced one week before the first infusion and was continued during the study. Infusion-related reaction prophylaxis was administered to all patients prior to each infusion consisting of oral fexofenadine 60 mg the evening before each infusion, oral fexofenadine 60 mg and acetaminophen 1000 mg the morning of the infusion and IV hydrocortisone 200 mg immediately before each infusion (as described in Table 6.3, page 38). However, the ERG noted that there was discrepancy in the description of the prophylaxis regimen in the cost-effectiveness section of the MS (discussed in Section 5).

The Savient KRYSTEXXA briefing document prepared for the FDA[8] (page 31) included data for concomitant medications in ≥ 15% subjects in the pooled RCTs. It was stated that 55/85 (65%) of the pegloticase 8 mg every 2 weeks treatment group and 27/43 (63%) of placebo group subjects were receiving anti-gout preparations. No further information on the type, dose or duration of treatment of these anti-gout preparations was provided. It had been previously stated[3] that patients receiving ULT at screening had undergone a one-week washout period before commencing trial participation. It was therefore unclear whether these data related to the proportions of trial participants receiving colchicine as gout flare prophylaxis.

The primary outcome of the phase III trials was the proportion of plasma UA responders in each pegloticase treatment group versus the placebo group, with a responder being defined as a patient with plasma UA less than 360 µmol/L (6.0 mg/dL) for at least 80% of the time during study months 3 and 6. Plasma UA was measured at baseline, at 2 and 24 hours following the first infusion, before each biweekly infusion and at 5 additional pre-specified time points in both months 3 and 6: 2 hours, 1 day and 7 days following the week 9 and week 21 infusions, and 2 hours and 7 days after the week 11 and

week 23 infusions. The use of plasma UA as opposed to serum UA measurements has already been discussed in Section 3.

Secondary outcomes included tophus resolution (with a tophus complete response classed as a 100% decrease in the area of at least one pre-specified target tophus of baseline diameter of at least 5 mm without progression of any baseline tophus or appearance of any new tophus), reductions in the proportion of patients with gout flare and in the number of flares per patient during months 1-3 and 4-6, reductions in tender joint count (TJC) and swollen joint count (SJC), and patient-reported changes in pain, physical function and quality of life, measured respectively by the Health Assessment Questionnaire (HAQ) pain scale, HAQ-Disability Index (HAQ-DI) and SF-36. Secondary outcomes were measured at baseline, at the week 13 and week 19 visits and the week 25 final visit. Tophus measurement was based on serial standardised digital photographs of hands and feet and up to two other sites with tophi. Gout flare (acute joint pain and swelling requiring treatment as defined by Sundy *et al.*, 2011) occurrence, duration and severity were self-reported by patients at the time of occurrence and confirmed by investigator interview. SJC and TJC were investigator-assessed at 54 specified joints. Participants completed HAQ and SF-36 forms.

Safety assessments were based on biweekly physical examinations and medical history, adverse event updates and monthly complete blood counts, serum chemistry, and urinalysis. An adverse event occurring during infusion or within 2 hours following infusion was classed as an infusion reaction and led to standardised assessment consisting of physical examination, electrocardiogram and measurement of serum tryptase (to assess mast cell degranulation).

Serum samples for the evaluation of pegloticase antibody production and pegloticase neutralisation were taken before infusions at weeks 1, 3, 5, 9, 13, 17, 21 and 25. IgM, IgG and total pegloticase antibody assays were conducted.

The use of uric acid response as the primary outcome and the selection of secondary outcomes were considered by the ERG and clinical advisors to the ERG to be appropriate. The clinical advisors were of the opinion that no important outcomes were missing from the submission (but that it would have been beneficial to have data on the impact of pegloticase on hospital admissions). Two clinical advisors considered that it should be noted that both flares and tophi could be considered to be subjective measures, whilst a third clinical advisor stated that both flares and tophi could be objectively assessed.

Each of the replicate trials were reported to be adequately powered (>80%) to demonstrate a difference in responder rates of 35% vs. 5% between each active treatment group and the respective

placebo treatment group (P=0.05 for each comparison). All efficacy and safety analyses of data from C0405 and C0406 (except deaths) were performed using a modified intention-to-treat population (consisting of randomised patients who had received at least one infusion). The ERG considered the use of such a modified intention-to-treat population to be reasonable. Pegloticase efficacy was determined using responder analyses, in which patients withdrawing before their week 25 final visits were classed as non-responders. This approach assumes that non-completers do not have outcomes worse than those of non-responders. The proportion of responders in each pegloticase treatment group was compared against the corresponding placebo group using the Fisher exact test. Tophus resolution and the number of patients reporting flares were each compared between pegloticase and placebo groups using the Fisher exact test. Flare frequencies, change from baseline in SJC, TJC and pain scores, HAQ-DI scores, and SF-36 domains were compared between pegloticase and placebo groups using the 2-sample *t* test. For patients with absent PUA measurements for the week 9, 13, 21 or 25 time points, the baseline PUA value was used in the calculation of the proportion of time that the PUA level was below 360 μmol/L (6 mg/dL) during months 3 and 6. It was stated that no imputation was performed for the other missing PUA levels. Patients with missing data for HAQ-DI measurements were considered to be non-responders in terms of physical function. Values for SJC, TJC and patient-reported endpoints were imputed using last observation carried forward for patients who did not complete all infusions and the week 25 final study visit. The ERG notes that the use of last observation carried forward data imputation implies an assumption that these benefits would be maintained.

The ERG requested that further details on the statistical analysis of the phase III trial data be provided by the manufacturer. [redacted]

It was reported (page 10 of the MS) that, whilst the two phase III trials included two dosing regimens (pegloticase 8 mg every 2 weeks and pegloticase 8 mg every 4 weeks), only results for the anticipated licensed regimen of pegloticase 8 mg every 2 weeks were presented in the submission. The ERG noted that pooled results for primary and secondary outcomes for pegloticase 8 mg every 4 weeks were available in the trial report published by Sundy *et al.* (2011). It is noted in the prescribing information for KRYSTEXXA[8] that the pegloticase 8 mg every 4 weeks regimen also showed efficacy but was associated with an increased frequency of anaphylaxis and infusion reactions and less efficacy with respect to resolution of tophi.

4.2.2.2 Description of open label extension safety study (OLE C0407)

The primary data source for the open label, multicentre extension (phase IIIb) study (OLE C0407) was the clinical study report C0407 CSR identified by the manufacturer from the Savient database (not provided in full as part of the manufacturer submission).

All participants who completed the phase III trials (C0405 or C0406) were subsequently invited to participate in the open-label extension (OLE) study C0407. Table 6.13 (page 55) of the MS described the OLE study as being of 24 months duration. However, elsewhere in the submission, duration was reported to be up to 30 months (MS pages 37-38). The manufacturer confirmed that, following a protocol amendment, patients could receive pegloticase treatment up to a maximum of 30 months (or until July 1st 2009) followed by a period of 6 months follow-up under observation.

The primary objective of the OLE study (C0407) was to assess the long-term safety of pegloticase (MS page 55). A secondary objective was to evaluate the treatment effects of pegloticase in patients who continued to receive active treatment from the phase III trials and effects in those who were originally randomised to placebo and the duration of benefit (MS page 55). Outcomes included the determination of PUA and SUA response, tophus response, incidence and frequency of gout flares, SJC, TJC, SF-36, HAQ and Clinical Global Assessment of disease activity (MS page 55).

The investigator and patient were allowed to select their preferred treatment option while still blinded to the original randomisation schedule (MS page 55). Participants who elected not to receive pegloticase treatment were permitted to participate in the study under observation. Participants who were enrolled in one of the treatment arms of the study and withdrew consent for treatment or were discontinued from treatment with pegloticase were also eligible to be followed under observation at any point during the study.

It was not clear in the original MS whether the phase III trials (C0405 and C0406) and the OLE study (C0407) ran back-to-back or involved an interruption in pegloticase treatment. However, the data provided by the manufacturer to the ERG (in the clarification responses) relating to [redacted]

A total of 151 participants entered the OLE study (C0407) (page 58). According to the flow chart presented in the MS (MS page 58), 57 patients had received pegloticase 8 mg every 2 weeks in the phase III RCTs, 53 had received pegloticase every 4 weeks in the phase III RCTs and 39 subjects entered from the placebo groups. Two patients (3%) who had previously received pegloticase every 4 weeks in the RCTs selected the option of observation. The Savient briefing document prepared for the

FDA[8] (page 17) stated that "of 74% of subjects (157 of 212) who completed C0405 or C0406, 151 of 157 (96%) enrolled in the OLE, selecting either pegloticase 8 mg every 2 weeks (82 of 151), pegloticase 8 mg every 4 weeks (67 of 151) or observation (2 of 151). Overall, safety exposure was as follows: 12 months or more (121 subjects), 15 months or more (115 subjects), 18 months (95 subjects)."

It was stated in the MS (page 58) that "the convention for group assignments used in the final OLE C0407 CSR was based on the initial treatment regimen received in the double-blind C0405/C0406 studies. This convention was based on an expected carryover effect from the initial pegloticase exposure on several measured outcomes, including tophus elimination and gout flares. Additionally, since multiple regimen switches were allowed during the OLE C0407 study, groups based on OLE regimen were not homogeneous." The ERG requested further details on the regimen switches observed in C0407. The manufacturer confirmed that regimen switches (pegloticase 8 mg every 2 weeks to every 4 weeks and vice versa) were permitted i) following week 25 of the OLE and ii) once the results of the double-blind studies were available. Summarised data were not provided to demonstrate the reasons behind switches at a summary level and how many were due to loss of pegloticase efficacy.

Patients receiving gout flare prophylaxis during the C0405 and C0406 phase III trials continued the same regimen for at least the first 3 months of treatment in the OLE study (C0407). It was stated that gout flare prophylaxis could then be discontinued at the discretion of the investigator (MS page 55).

In the description of the OLE study (Table 6.13, page 55), it was stated that "patients under observation in the study were allowed to receive other urate-lowering therapy at the discretion of the investigator." Further details were requested by the ERG. The manufacturer stated that the only data available were of the proportion of patients under observation taking other medications and provided these data.

[redacted]

Table 9 Concomitant anti-gout medications for all observational subjects during observation period

Anti-gout Medication	Number of observational subjects (N=121)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

It was not explicit from the details provided which patients these values related to. These figures appear to include patients who switched from treatment to 6 months observation at the end of the OLE study. Clinical advisors to the ERG noted that the concomitant use of other urate-lowering treatments would influence the UA levels observed in the subjects under observation when compared with the pegloticase-treated subjects. The ERG requested that efficacy and safety results for the observation group presented according to urate-lowering treatment be provided. However, the manufacturer stated that "no analysis was performed based on urate-lowering treatment."

The manufacturer clarified that a modified intention to treat (ITT) population for the OLE study included all participants who had received at least one dose of study medication in the OLE C0407 study and had some follow-up data. The approach to the statistical analysis of the data originating from the OLE study (C0407) was described on page 58 of the MS. Data from patients treated with pegloticase in the phase III trials (C0405 and C0406) were summarised by the treatment initially received in the phase III trials. Data from patients treated with placebo in the phase III trials were summarised by the first pegloticase treatment received in the OLE study (C0407).

4.2.2.3 Description of trial C0409 (NCT00675103)

This trial was not included in the original MS and was identified by the ERG (via www.ClinicalTrials.gov). Following a request by the ERG, the manufacturer provided a brief synopsis of this trial (Savient trial identifier C0409).

Study C0409 was a non-randomised, multicentre (4 centres across the US), open-label re-exposure study of IV pegloticase 8 mg every 2 weeks in subjects with hyperuricaemia and symptomatic gout who had participated in previous studies (C0402 or C0403) of pegloticase (ie. not the phase III trials C0405 and C0406 included in the submission), and whose last exposure to IV pegloticase was more than one year prior to study entry. The study took place between April 2008 and January 2009. No data were provided to the ERG on the severity of gout or treatment history in the patients who had previously participated in studies C0402 or C0403.

Seven subjects entered the study and all received at least one dose of pegloticase. None had received more than 3 doses of pegloticase during previous studies. All of the subjects had a time lapse of 3.5 to 5 years since their last exposure to pegloticase. [redacted]

4.2.2.4 Key efficacy results from phase III randomised controlled trials (C0405 [GOUT 1] and C0406 [GOUT 2]) (NCT00325195)

For the primary outcome (proportion of PUA responders during months 3 and 6 in the pegloticase treatment vs. placebo groups) results were presented for the individual studies and also as a simple pooled analysis (the methods of which were critiqued by the ERG in Section 4.1.5). Secondary outcomes were presented in the original MS as simple pooled analyses only. Only the results for the anticipated licensed dose (pegloticase 8 mg every 2 weeks) were presented in the submission. Data from C0405 and C0406 were reported using a modified ITT population (including all patients who had received at least one infusion).

Primary efficacy outcome

The proportions of PUA responders (defined as patients having a PUA < 360 µmol/L [6.0 mg/dL] for ≥ 80% of the time during months 3 and 6) in the pegloticase 8 mg every 2 weeks and placebo groups (as reported by Sundy *et al.*, 2011) were tabulated in the MS (Table 6.9, page 47) (as presented below in Table 10).

Table 10 Proportion of PUA responders (table taken directly from MS, page 47)

	Pegloticase 8 mg every 2 weeks	**Placebo**
Study C0405		
No. responders/No. treated (%) [95% CI]	20/43 (47%) [31 to 62]	0/20 (0%) [0 to 17]
p value	<0.001	-
Study C0406		
No. responders/No. treated (%) [95% CI]	16/42 (38%) [24 to 54]	0/23 (0%) [0 to 15]
p value	0.001	-
Pooled results		
No. responders/No. treated (%) [95% CI]	36/85 (42%) [32 to 54]	0/43 (0%) [0 to 8]
P value	<0.001	-

The results for the primary efficacy endpoint from both the individual phase III trials and the simple pooled analysis showed a significantly greater proportion of PUA responders among the pegloticase 8 mg every 2 weeks treatment group than in the placebo arm (pooled results 42% vs. 0%, P<0.001). As can be observed above in Table 10, no placebo group subjects maintained a UA level below 360 µmol/L [6.0 mg/dL] for ≥ 80% of the time during months 3 and 6.

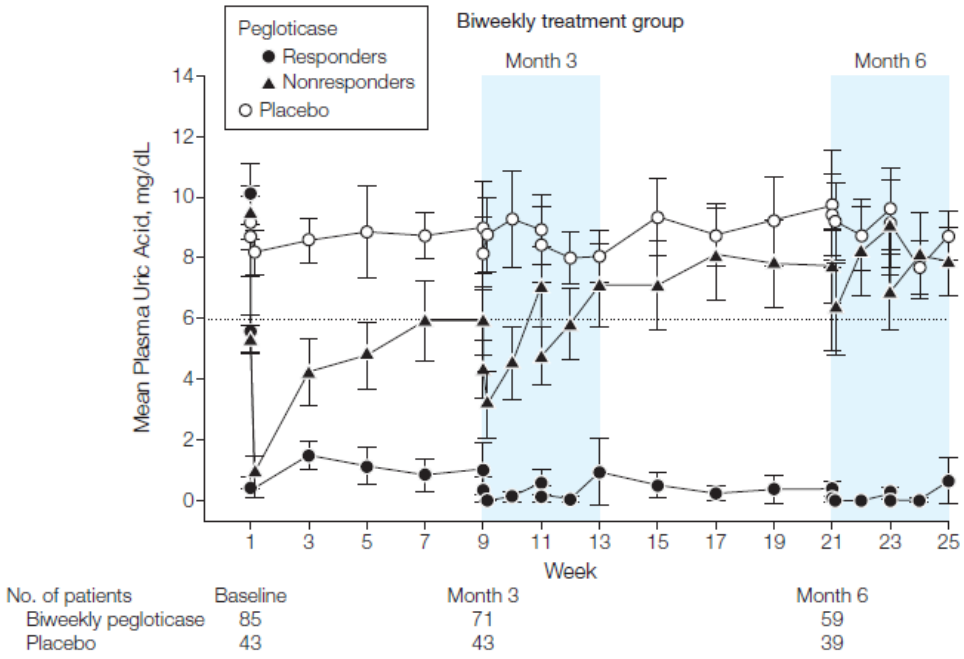
However, these data also indicated that 58% of the pooled patients treated with pegloticase 8 mg every 2 weeks did not maintain their PUA response in months 3 and 6. It was reported in the MS (page 64) that PUA normalised within 24 hours of the initial infusion for all pegloticase-treated patients, but that urate-lowering response was lost in some patients (non-responders). For non-responders, the mean PUA was described as remaining below 360 µmol/L [6.0 mg/dL] until week 10 of the trial, after which point UA levels increased above the target level. The mean PUA for responders was below 360 µmol/L [6.0 mg/dL] for the duration of the 6 month study period.

Clarification was requested from the manufacturer as to why it would be necessary to finish the course of treatment of 6 months in responders who had demonstrated a persistent reduction in SUA and whether such patients could be switched to maintenance therapy before 6 months and still be expected to achieve similar benefits. The manufacturer responded that, whilst they considered it feasible that this may happen in clinical practice, all patients who completed the trials were treated for 6 months and that no data were available to demonstrate what would occur upon earlier cessation of pegloticase therapy or whether gradual resolution of tophi would continue.

[redacted]

Temporal changes in PUA levels were also presented graphically in the MS (Figure 6.2, page 48) as presented in Figure 1 below.

Figure 1. PUA levels over time (Sundy *et al.*, 2011) (figure taken directly from MS page 48)



Marked decreases in PUA levels can be observed at the start of months 3 and 6 (Figure 1). In response to a request by the ERG, the manufacturer confirmed that "PUA levels fall rapidly whenever pegloticase is given" [and that] "the rapid fall in mean PUA levels at the start of months 3 and 6 correspond to periods of sampling immediately post administration when the effect of pegloticase is most pronounced."

It was noted in the SPC (page 127) that "lower response rates were observed in patients with over 100 kg body weight." The manufacturer provided additional data in response to a request by the ERG. Data were presented for body weight at baseline (kg) among subjects treated with 8 mg pegloticase every 2 weeks in the pooled C0405 and C0406 trials (tabulated below). No data were provided for the effect of body weight on PUA response in the OLE study or the re-exposure trial C0409.

Table 11. Effect of baseline body weight on PUA responder status across months 3 and 6 in subjects receiving pegloticase 8 mg every 2 weeks in the C0405 and C0406 phase III trials (N=85) (table generated by the ERG using data provided by the manufacturer in clarification responses)

Body weight (kg)	Number (%) of PUA responders (N=36)	Number (%) of PUA non-responders (N=49)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted] The ERG also noted that in Table 6.16 of the MS, which describes the baseline characteristics of participants in the OLE study (C0407), non-responders had a higher mean body weight (kg) than non-responders (for example, 93.85 kg (SD 22.02) vs. 105.84 kg (SD 24.05) for responders and non-responders respectively from the phase III trials pegloticase 8 mg every 2 weeks group).

The ERG requested data on the proportion of the UK gout population eligible for treatment with pegloticase having a body weight over 100 kg. The manufacturer responded that such data were not readily available but suggested that the proportion would be similar to the estimate made in the sponsor submission for the NICE single technology appraisal of golimumab in rheumatoid arthritis (TA225), in which the proportion of rheumatoid arthritis patients with a weight over 100 kg was estimated as 7%, based on data from the BSR Biologics Register. Clinical advice to the ERG indicated that 10-15% of the UK gout population may have a body weight of 100 kg or above, which is slightly higher than the estimate provided by the manufacturer.

The mean BMI values in the C0405 and C0406 trials were 34.1 and 31 (no decimal place presented in MS page 40) respectively. Published literature from the UK and Germany on the demographics of people with gout estimated that approximately 29% of gout patients have a BMI greater than 30[24,25]. The percentage of patients in trial C0405 with a BMI greater than 30 was 67% and 70% in the pegloticase and placebo arms respectively. The percentage of patients in trial C0406 was 60% and 43% in the pegloticase and placebo arms respectively. It is also interesting to note that responders to pegloticase had a lower BMI than non-responders. Page 59 (Table 6.16) of the MS indicates that non-responders to pegloticase had a higher mean BMI (34.68 [SD 8.80]) than responders to pegloticase (32.42 [SD 7.28]).

It is stated in the SPC (page 125) that "based on similar efficacy and safety profiles of pegloticase in patients with creatinine clearance below and above 50 ml/min, no dose adjustment is required for patients with renal impairment…however, data in patients with severe renal impairment are very limited." A potential difference according to baseline creatinine clearance was noted by the ERG when data from subgroup analyses were considered (presented later in this Section) with [redacted] The manufacturer confirmed that efficacy data were not stratified according to renal, hepatic or cardiovascular function.

An abstract by Yood *et al.* (2012)[22](data not supplied in the MS but sourced by the ERG) concluded that pegloticase treatment response appeared to be independent of baseline CKD stage. Limited data were also available in the abstract by Sundy *et al.* (2012)[26] (data not supplied in MS but identified by ERG) from an open label trial of 30 subjects (sponsor investigator IND 11274) (study not included in the submission) that suggested that PUA levels were controlled in 5 of 7 organ transplant patients (5 renal, 2 renal/pancreas) (although the dose administered (8 mg every 3 weeks IV for 5 doses) was not in accordance with the anticipated licensed indication).

Secondary efficacy outcomes

Simple pooled analyses of secondary outcome data were provided in Table 6.10 of the MS (page 50).

Table 12. Pooled analyses for secondary endpoints (taken directly as presented as Table 6.10, page 50 of MS [Sundy *et al.*, 2011])

Endpoint	Pegloticase 8 mg every 2 weeks	Placebo
Resolution of ≥ tophi,		
No. of patients/no. evaluable patients (%)	21/52 (40)	2/27 (7)
95% CI	27 to 55	1 to 24
p value	0.002	-
Flare incidence. No. patients/No. treated (%)		
Months 1-3	64/85 (75)	23/43 (53)
95% CI	65 to 84	38 to 69
p value	0.02	-
Months 4-6	28/69 (41)	29/43 (67)
95% CI	29 to 53	51 to 81
p value	0.007	-
Flare frequency, No. flares per patient		
Months 1-3, mean [SD]	2.3 (2.1) (n=85)	1.2 (1.6) (n=43)
95% CI	1.8 to 2.7	0.7 to 1.7
p value	0.001	-
Months 4-6, mean [SD]	0.8 (1.2) (n=69)	1.3 (1.5) (n=43)
95% CI	0.5 to 1.1	0.8 to 1.7
p value	0.06	-
Tender joints. No per patient		
Baseline, mean (SD)	11.7 (13.0) (n=84)	14.1 (14.8) (n=43)
95% CI	8.9 to 14.5	9.6 to 18.7
p value	0.36	-
Change at final visit, mean (SD)	-7.4 (11.9) (n=78)	-1.2 (12.3) (n=43)
95% CI	-10.1 to -4.7	-5.0 to -2.6
p value	0.01	
Swollen joints. No per patient		
Baseline, mean [SD]	8.9 (11.1) (n=84)	13.2 (13.7) (n=43)
95% CI	6.5 to 11.3	8.9 to 17.4
p value	0.08	
Change at final visit, mean (SD)	-5.5 (10.5) (n=78)	-2.6 (11.6) (n=43)
95% CI	-7.9 to -3.2	-6.2 to 1.0
p value	0.18	-
HAQ-DI score[a]		
Months 1-3, mean [SD]	1.10 (0.86) (n=83)	1.24 (0.95) (n=43)
95% CI	0.92 to 1.29	0.94 to 1.53

Endpoint	Pegloticase 8 mg every 2 weeks	Placebo
p value	0.43	
Change at final visit, mean (SD) (MCID ≥ 0.22)	-0.22 (0.64) (n=77)	0.02 (0.41) (n=43)
95% CI	0.37 to -0.08	0.11 to 0.15
p value	0.01	-
HAQ pain score[b]		
Months 1-3, mean [SD]	44.2 (27.7) (n=84)	53.9 (28.1) (n=43)
95% CI	38.2 to 50.2	45.3 to 62.5
p value	0.07	-
Change at final visit, mean (SD) (MCID ≥ 0.10)	-11.4 (33.8) (n=78)	1.4 (30.0) (n=43)
95% CI	-19.1 to -3.8	7.9 to 10.6
p value	0.03	-
SF-36 Physical Component Summary score[c]		
Months 1-3, mean [SD]	35.2 (10.9) (n=77)*	31.0 (11.1 (n=43)
95% CI	32.8 to 37.5	27.6 to 34.4
p value	0.05	
Change at final visit, mean (SD) (MCID ≥ 2.5)	4.4 (9.4) (n=77)	-0.3 (9.0) (n=43)
95% CI	2.3 to 6.5	-3.1 to 2.5
p value	0.01	-

* After a request for clarification, the manufacturer confirmed that there were 83 patients at baseline (incorrectly cited in MS as 77) and 77 at final visit

The P values for all the secondary outcomes listed above were statistically significant (at P<0.05), with the exception of swollen joint count (P=0.18).

Under resolution of tophi on Table 6.10 (page 50), the number of evaluable patients was described as being 52 for the pooled pegloticase every 2 weeks group and 27 for the pooled placebo group. The manufacturer confirmed that these numbers represented the number of subjects with evaluable tophi at a final visit, rather than the number in each pooled group at baseline. In response to clarification by the ERG, the manufacturer reported that statistical analyses of tophus responses were conducted on the "tophus evaluable population" (defined as all subjects with a tophus at baseline, as identified by the Investigator, and any subjects who developed new tophi during the study, as identified by either the Investigator or a Central Reader). This would imply that the tophus evaluable population might be expected to be larger than the population made up solely of subjects with tophi at baseline. However

this does not appear to be the case (with, for example, 26 subjects in the tophus evaluable population at final visit in C0405 (clarification responses) and a higher figure of 29 patients who had baseline tophi (as reported in Table 6.5, page 40 of MS), and Sundy *et al*., 2011 [3]). Therefore, the ERG considered that it was unclear how data relating to the total size of the tophus evaluable population at final visit had been derived and why the number of subjects with tophi at baseline had not been used in the analyses of tophi resolution at final visit.

Based on the data presented by the manufacturer in Table 12 above, a significantly greater proportion of patients in the pegloticase 8 mg every 2 weeks treatment group demonstrated tophus resolution compared with the placebo group (40% vs. 7%, P=0.002).

Whilst a significantly greater proportion of patients in the pegloticase 8 mg every 2 weeks group experienced gout flares during months 1-3 of the phase III trials than among the placebo group (75% vs. 53%, P=0.02) (with gout flares often observed upon initiation of ULT), this finding was reversed for months 4-6, with significantly fewer patients having gout flares in the pegloticase 8 mg every 2 weeks group vs. placebo (41% vs. 67%, P=0.007). This pattern was also reflected in terms of flare frequency.

The Savient KRYSTEXXA briefing document prepared for the FDA[8] (page 146) included data on the incidence of gout flares by severity for the pooled phase III trials C0405 and C0406.

Table 13. Incidence of gout flares by severity (pooled phase III trials) (values taken directly from page 146 of FDA briefing document[8] and inserted in ERG-generated table)

	Pegloticase 8 mg every 2 weeks	**Placebo**
Months 1 to 3	**N=85**	**N=43**
Flare incidence	63 (85%*)	22 (51%)
Mild	7 (8%)	9 (21%)
Moderate	37 (44%)	11 (26%)
Severe	19 (22%)	2 (5%)
Months 4 to 6	**N=69**	**N=43**
Flare incidence	28 (41%)	29 (67%)
Mild	11 (16%)	8 (19%)
Moderate	12 (17%)	15 (35%)
Severe	5 (7%)	6 (14%)

* (ERG note: potential error, 63/85 = 74%) (also unclear why number of subjects for months 1 to 3 differ from Table 12 above)

The data suggest that overall flare incidence decreased at months 4 to 6 compared with months 1 to 3 in the pegloticase 8 mg every 2 weeks treatment group. In addition, these data provide limited evidence that the severity of gout flares may have decreased for the pegloticase arm at months 4 to 6 compared with placebo.

Greater reductions from baseline levels in mean numbers of tender joints (SD) (-7.4 (11.9) (n=78) vs. -1.2 (12.3) (n=43), statistically significant at P=0.01) and swollen joints (SD) (-5.5 (10.5) (n=78) vs. -2.6 (11.6) (n=43), non-significant at P=0.18) were also observed in the pegloticase 8 mg every 2 weeks treatment group vs. the placebo group.

A statistically significant reduction was observed for mean (SD) HAQ-DI score was reported for the pegloticase 8 mg every 2 weeks group compared with placebo (-0.22 (0.64) (n=77) vs. 0.02 (0.41) (n=43).

A significantly greater reduction in mean HAQ pain score (SD) was also shown in the pegloticase 8 mg every 2 weeks compared with the placebo group (-11.4 (33.8) (n=78) vs. 1.4 (30.0) (n=43), P=0.03).

A significantly greater change in SF-36 Physical Component Summary score was also obtained among pegloticase 8 mg every 2 weeks subjects than placebo group subjects (4.4 (9.4) (n=77) vs. -0.3 (9.0) (n=43), P=0.01). There were some inconsistencies noted by the ERG between the SF-36 PCS scores from these pooled analyses and the publication reported by Strand *et al.* (2012),[27] which reported higher mean changes from baseline in both groups (approximately 6.5 and -1.0 for pegloticase 8 mg every 2 weeks and placebo arms respectively, not reported as being statistically significant at p=0.05).

Secondary outcome data from both phase III trials were also analysed for PUA responders versus non-responders. Results from the pooled analyses were presented in Table 6.11 of the MS (page 52). The ERG asked for clarification on what each of the denominators in the analyses referred to and reasons for differences from the total quoted number of responders (n=[redacted]) and non-responders (n=[redacted]). A revised table (reproduced as Table 14 below) was submitted by the manufacturer in response to clarification requests (presented below). However, it was still not clear to the ERG what each of the denominators referred to and why there were differences from the total numbers of responders and non-responders. For example, the baseline number of patients with SJC and TJC in the pegloticase 8 mg every 2 weeks group (as referred to by Sundy *et al.*, 2011)[3] were both 84 (as opposed to the [redacted] summed from the above responders and non-responders). The denominators in Sundy *et al.*, 2011)[3] for HAQ pain score, HAQ-DI score and SF-36 physical component summary score were also 84, 83 and 83 respectively, rather than [redacted] as summed above. It was also not explicit where the numbers of responders (n=[redacted]) and non-responders (n=[redacted]) were taken from.

Table 14 Secondary outcomes for PUA responders and non-responders (Savient Data on File: Integrated Summary of Efficacy) (table taken directly from page 44 of clarification responses by manufacturer, P values not provided)

	Pegloticase 8 mg every 2 weeks		Placebo (n = 29)
	Responders (n = 25)	Non-responders (n = 37)	
Resolution of ≥ tophi			
Final visit No. of patients/no. evaluable patients (%)	13/21 (61.9)	8/31 (25.8)	2/27 (7.4)
Flare incidence			
Months 1-3			
n/N (%)	[redacted]	[redacted]	[redacted]
Months 4-6			
n/N (%)	[redacted]	[redacted]	[redacted]
Flare frequency per patient			
Months 1-3			
n/N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Months 4-6			
n/N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Swollen and tender joints			
n/N	[redacted]	[redacted]	[redacted]
Change from baseline to final visit. Mean (SD)	[redacted]	[redacted]	[redacted]
HAQ – Pain			
n/N	[redacted]	[redacted]	[redacted]
Change from baseline to final visit Mean (SD)	[redacted]	[redacted]	[redacted]
HAQ-DI			
n/N	[redacted]	[redacted]	[redacted]
Change from baseline to final visit. Mean (SD)	[redacted]	[redacted]	[redacted]
SF36 – PCS			
n/N	[redacted]	[redacted]	[redacted]

	Pegloticase 8 mg every 2 weeks		Placebo (n = 29)
	Responders (n = 25)	**Non-responders (n = 37)**	
Change from baseline to final visit. Mean (SD)	[redacted]	[redacted]	[redacted]

The manufacturer stated that, when compared with non-responders, the responder group demonstrated a greater proportion of patients with complete tophus response, a reduced incidence of flares during months 1 to 3 (although this was not clear to the ERG), a numerically higher reduction in the number of swollen or tender joints and a greater improvement in mean HAQ pain and SF-36 PCS scores.

On page 51 of the MS it was stated that the responder group had the lowest HAQ-DI score at baseline reflecting the least functional impairment. However, on page 52 it was also stated that no clear pattern or trend was observed in the primary end point when stratified according to HAQ-DI. The ERG requested that mean HAQ-DI scores be provided for the pegloticase responder, the pegloticase non-responder and the placebo groups and for clarification on whether HAQ-DI was a significant treatment effect modifier. Data on HAQ-DI score by treatment group were provided.

Table 15 HAQ-DI scores for pegloticase responders vs. non-responders

	Pegloticase 8 mg every 2 weeks		Placebo N=43
	Responders (N=36)	Non-responders (N=49)	
Baseline visit			
n	35	48	43
Mean (SD)	[redacted]	[redacted]	[redacted]
Final Visit			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to final visit			
n	[redacted]	[redacted]	43
Mean (SD)	[redacted]	[redacted]	0.02 (0.408)

The manufacturer confirmed that they did not consider HAQ-DI score to be a treatment effect modifier.

Subgroup analyses of studies C0405 and C0406

Subgroup analyses (page 30, 52, 53 of the MS) of the individual phase III studies (C0405 and C0406) and of the pooled data for treatment responder and percent non-hyperuricaemic time were undertaken by the manufacturer according to gender, age (≤ 55 years, > 55 years), body mass index (≤ 30 kg/m2, > 30 kg/m2), absence or presence of tophi, disease duration (< 5 years, ≥5 years), and baseline HAQ-DI score (≤ 1, > 1) creatinine clearance (< 50 mL/min, ≥ 50 mL/min) and antibody status. Following a request for clarification by the ERG, the manufacturer confirmed that these analyses were all pre-specified and were selected on the basis that these were "the patient demographic characteristics that *a priori* one might expect to affect response to therapy." Results were presented for the pooled data from the two C0405 and C0406 phase III trials.

The manufacturer stated that "in both studies no clear pattern or trend was observed in the pegloticase 8 mg every 2 weeks treatment group for the primary endpoint when the patients were stratified by gender, presence of tophi, BMI, age, disease duration, or baseline HAQ-DI score" (page 52). The main differences noted by the ERG related to [redacted]

The decision problem outlined in the scope specified that (evidence permitting) consideration would also be given to a subgroup analysis of people with hyperuricaemia and symptomatic gout who were intolerant of allopurinol or for whom allopurinol was contraindicated. The manufacturer stated that this analysis was not performed as pegloticase would be used in patients who are intolerant to both allopurinol and febuxostat or for whom allopurinol or febuxostat is contraindicated or ineffective.

4.2.2.5 Key efficacy results from OLE study C0407

It was reported in the MS that "continuation of…benefits beyond six months is supported by the open-label extension study (OLE C0407)" (page 63). However, these results were not presented in the original MS. The manufacturer provided further details in response to a request by the ERG. A large amount of un-aggregated data from the OLE study on longer-term PUA and SUA levels with continued pegloticase treatment ([redacted] pages) and the immunogenicity of pegloticase ([redacted] pages) was provided by the manufacturer. However, as these data were not presented in summary form, it was not feasible for the ERG to analyse these at the point of submission of the ERG report.

[redacted]

The limited data regarding secondary outcomes in the OLE study (C0407) summarised by the manufacturer in the clarification responses and derived from conference abstracts sourced by the ERG suggested that improvements in secondary outcomes may be maintained with continued pegloticase 8 mg every 2 weeks treatment beyond 6 months.

Baraf *et al.* (2008)[28] presented two case studies of patients from the phase II study (Sundy *et al.*, 2008) [23]. One of these related to a 70 year-old male patient (with a 25 year history of gout, a baseline urate level of 9.2 mg/dL and 20 gout flares in the 12 months before study entry) who received 6 infusions of pegloticase 8 mg every 2 weeks. Hand radiographs taken at 15 months after the termination of pegloticase treatment demonstrated that the soft tissue swelling had resolved, erosion had decreased and surrounding bone cortex had thickened. However, it should be noted that, during the 15 month post-treatment period (when not receiving any urate-lowering therapy), the patient still had hyperuricaemia, with urate levels consistently > 9 mg/dL.

Data from the conference abstract by Hamburger *et al.*[18] were not included in the submission. The ERG found the reference details supplied by the manufacturer to be incorrect but identified the abstract via the EULAR conference 2011 website. Patients who completed the 6 month C0405 and C0406 trials (8 mg every 2 weeks) and entered into the multi-year OLE were evaluated for efficacy and safety, with a focus in the abstract on outcomes among persistent responders. The impact of a treatment gap (12 to 167 days) of pegloticase therapy between the RCT and OLE was also evaluated; however, no data on this outcome was provided in this abstract. Of the 35 persistent responders that entered the OLE, it was reported in the abstract that 19 subjects elected to receive pegloticase therapy 8 mg every 2 weeks. Of these, 84% continued to have a normalised UA level for over 2 years. However, only 2 patients elected to join the observation arm, hence no meaningful control data are available. No further data on UA response was provided in this abstract. Regarding secondary outcomes, it was stated in the abstract that "painful gout flares initially (weeks 2-6) increased RCT [sic] followed by significant declines until most subjects became flare free. By 50 weeks, 90% of subjects had reportedly experienced a complete or partial tophus resolution (78% of all tophi had complete resolution; $p<0.006$ from baseline) and this effect was similar at weeks 78 and 102.

However the ERG noted that there were discrepancies between the figures reported for tophi response in the text of the abstract and the figures presented in the table of the abstract. "Physician- and patient-reported outcomes were improved at 6 months and persisted or improved over 2 years. During the RCT and the OLE, subjects receiving pegloticase and manifesting a persistent normalisation of UA [sic]. Three infusions reactions (IRs) [sic] in 609 RCT infusions and 3 IRs in 810 OLE infusions (24-120 weeks) [sic]. None of these subjects had anaphylaxis." Therefore, this abstract presented limited data suggesting that UA response and tophus resolution may be maintained long-term in persistent responders continuing to receive pegloticase. No data were presented to show whether benefits are maintained after cessation of pegloticase treatment and whether maintenance therapy with other ULT drugs would be effective in maintaining UA response and other clinical benefits. However, one clinical advisor to the ERG indicated that following effective treatment with a uricase it might be possible to maintain a low UA level with oral ULT. This advisor also considered the rapid resolution of tophi to be an advantage of pegloticase.

4.2.2.6 Key efficacy results from trial C0409 (NCT0067510)

Upon request by the ERG, the manufacturer provided a brief synopsis of results from the pegloticase re-exposure trial C0409. This trial evaluated efficacy and safety outcomes in a small number (n=7) of patients who were re-exposed to a subsequent course of pegloticase treatment.

[redacted]

The manufacturer highlighted that these [redacted]

The ERG asked the manufacturer to summarise any additional data from trials or post-marketing studies on the rate of re-treatment with pegloticase in patients who had previously responded to pegloticase treatment.

[redacted]

4.2.2.7 Key safety outcomes from phase III randomised controlled trials (C0405 [GOUT 1] and C0406 [GOUT 2]) (NCT00325195), OLE C0407, and re-exposure study C0409

Safety data were presented for the phase III trials (C0405 and C0406) and the OLE study (C0407). Limited safety data were presented for the re-exposure study C0409.

A large amount of un-aggregated data from the OLE study on long-term adverse events data ([redacted]pages) was provided by the manufacturer. However, as these data were not presented in summary form, it was not feasible for the ERG to analyses these at the point of submission of the ERG report.

The ERG asked the manufacturer to clarify how "serious adverse events" and infusion-related reactions" were defined. It was confirmed that a serious adverse event was defined in the protocol as "any adverse event occurring at any dose that results in any of the following outcomes: i) death ii) is life-threatening iii) inpatient hospitalisation or prolongation of existing hospitalisation iv) permanent, persistent or significant disability v) a congenital anomaly/birth defect vi) is the result of an overdose vii) a medically significant event that may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The manufacturer also clarified that an infusion reaction (IR) was defined as "any infusion-related AE (or cluster of temporally related events) that occurs during or within 2 hours after conclusion of study drug infusion and which cannot be reasonably attributed to another cause, [that] infusion reactions were considered serious if they met the criteria for a serious adverse event and that an IR was considered potentially anaphylactic if symptoms of stridor, wheezing, peri-oral/lingual oedema, or cardiovascular instability were present, especially if associated with rash or urticarial."

A pooled analysis of treatment-emergent adverse events reported during the two phase III trials (C0405 and C0406) was summarised in the MS in Table 6.17 (page 61) (presented below).

Table 16. Treatment-emergent adverse events[*] (Sundy *et al.*, 2011) (table taken directly from page 61 of MS, P values not provided)

Adverse event, N (%)	Pegloticase every 2 weeks N=85	Placebo N=43
Any adverse event	80 (94)	41 (96)
Any serious adverse event	20 (24)	5 (12)
Discontinuation due to an adverse event	15 (18)	1 (2)
Most commonly reported adverse events:		
Gout flare	65 (76)	35 (81)
Infusion reaction	22 (26)	2 (5)
Headache	8 (9)	4 (9)
Nausea	10 (12)	1 (2)
Back pain	3 (4)	2 (5)
Nasopharyngitis	6 (7)	1 (2)
Dyspnoea	4 (5)	2 (5)
Vomiting	4 (5)	1 (2)
Chest pain	5 (6)	1 (2)
Pruritus	3 (4)	0
Contusion	7 (8)	1 (2)
Pyrexia	2 (2)	1 (2)
Constipation	5 (6)	2 (5)
Blood pressure increased	0	0
Adjudicated CV events		
APTC events	2 (2)	0
Non-APTC events	3 (2)	0

[*] Defined by the manufacturer as occurring in ≥ 5% of patients in any treatment group and at least 1% more frequently in patients treated with pegloticase compared with placebo

Commonly reported adverse events included gout flare (76% in pegloticase 8 mg every 2 weeks vs. 81% in the placebo group), infusion related reactions (26% in pegloticase 8 mg every 2 weeks vs. 5% in the placebo group), headache (9% in pegloticase 8 mg every 2 weeks vs. 9% in the placebo group), and nausea (12% in pegloticase 8 mg every 2 weeks vs. 2% in the placebo group). Therefore, it can be seen that infusion reactions occurred frequently in patients receiving pegloticase, despite the provision of prophylaxis against infusion reactions.

[redacted]

[redacted]

However, it should be noted that the numbers associated with these adverse events were very small due to the sample sizes of the trials, emphasising the importance of the reinforcement of safety evidence using long-term follow-up and post-marketing data.

It is interesting to note that, in the phase II trial reported by Sundy *et al.*, (2008)[23] patients receiving pegloticase 8 mg every 2 weeks (n=8) experienced nephrolithiasis (13%), anaemia (38%), muscle spasms (13%) and diarrhoea (13%), but these adverse events were not reported in the phase III trials.

The Savient KRYSTEXXA briefing document prepared for the FDA[8] (page 96) presented data on serious adverse events by class. Serious adverse events were typically based on very low numbers. The ERG noted that the following serious adverse events were reported to occur most frequently: infusion-related reactions (4/85 [4.7%] vs. 0 for pegloticase 8 mg every 2 weeks vs. placebo), gout (presumably gout flares) (4/85 [4.7%] vs. 2/43 [4.7%] for pegloticase 8 mg every 2 weeks than placebo), cardiac arrythmia (2/85 [2.4%] vs. 0 for pegloticase 8 mg every 2 weeks vs. placebo) and gastrooesophageal reflux disease (2/85 [2.4%] vs. 0 for pegloticase 8 mg every 2 weeks vs. placebo).

Data from the pooled phase III trials (Table 16) indicated that 15 patients (18%) discontinued pegloticase treatment due to an adverse event, compared with one patient (2%) in the placebo group. However, the clarification responses provided by the manufacturer describe a total of [redacted] withdrawals from trials C0405 and C0406, with one of those in C0405 being [redacted].

The Savient KRYSTEXXA briefing document prepared for the FDA[8] (page 98) also provided data on the numbers of serious adverse events (excluding deaths) in the pegloticase 8 mg every 2 weeks group (no data provided for the placebo group) that led to discontinuation in trial C0405 (4 discontinuations, 3 due to infusion related reactions and one due to erosive gastritis) and trial C0406 (2 discontinuations, 1 due to infusion reactions, 1 due to gout).

Following a clarification request by the ERG, the manufacturer confirmed that thirteen [serious] adverse events were considered to be possibly/probably related to pegloticase; 11 infusion reactions ([redacted] subjects in the pegloticase 8 mg every 2 weeks (placebo) group and [redacted] subjects in the pegloticase 8 mg every 4 weeks (placebo) group) (the position of the word placebo reflects the use in the clarification

response) 1 event of nephrolothiasis (pegloticase 8 mg every 4 weeks responder group) and 1 event of skin necrosis (pegloticase 8 mg every 4 weeks non-responder group).

The manufacturer provided a brief synopsis of results from re-exposure trial C0409 in response to a request from the ERG, since this trial was not described in the original submission. All 7 participants had received infusion-related reaction prophylaxis with fexofenadine, paracetamol and hydrocortisone as previously described for the phase III studies. The manufacturer stated that a total of 7 infusion reactions were reported in 4 of 7 (57.1%) patients [redacted]

In the phase III trials (C0405 and C0406), [redacted] The manufacturer stated that no infusion reaction was classified during the study as anaphylaxis and that this was investigated in a *post hoc* analysis, which showed that a few serious infusion reactions were later determined to be anaphylaxis, but that not all cases of anaphylaxis met the serious criteria (figures not provided).

The manufacturer provided further details on observed cases of anaphylaxis in response to a request by the ERG. It was described how, during the review period for the U.S. application, a "more conservative" analysis of potential cases of anaphylaxis was undertaken whereby, as part of the application review, the FDA engaged an expert in allergy to make a clinical determination of cases of anaphylaxis. The manufacturer described this analysis as using diagnostic criteria to characterise adverse events as anaphylaxis based on their presenting signs and symptoms regardless of the presence or absence of IgE antibody to the suspected allergen. The FDA consultant was reported to have used the diagnostic criteria proposed by the NIAID/FAAN Joint Symposium on Anaphylaxis (Sampson *et al.*, 2006)[29] in classifying pegloticase-associated infusion reactions as shown below.

Table 17 Clinical Criteria for Diagnosing Anaphylaxis (table taken directly from manufacturer's clarification responses)

Anaphylaxis is highly likely when Criterion 1 and at least any one of the following criteria are fulfilled:
1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue- uvula) AND AT LEAST ONE OF THE FOLLOWING
2) a) Respiratory compromise (e.g., dsypnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia b) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
3) Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours): a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula) b) Respiratory compromise (e.g., dsypnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c) Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
4) Reduced blood pressure after exposure *to known allergen for that patient* (minutes to several hours): a) Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure* b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than 70 mm Hg + [2 x age] from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years

The manufacturer outlined how these criteria represented a "more conservative" definition of anaphylaxis than previously used and that when the definition is applied to the entire pegloticase clinical study database (including studies C0402, C0403, C0405, C0406, and C0407) [redacted] cases of anaphylaxis were identified. The manufacturer also stated that "overall, to be most conservative, [redacted] patients are considered to have had an event of anaphylaxis for an overall incidence of [redacted] [and that] these reactions occurred during or within 2 hours of infusions." Two cases were observed during the first infusion, one case being in a patient who did not receive full infusion reaction prophylaxis, whereas the remaining infusion reactions occurring between the third and sixth infusions.

[redacted]

It was also noted in the SPC (page 129) that "in the post-marketing setting, severe anaphylactic reactions have been reported, including loss of consciousness, circulatory collapse, and cardiac arrest, which required transfer to hospital emergency department."

[redacted]

The MS (page 61) stated that three deaths occurred in patients treated with the anticipated licensed pegloticase dosing regimen. One was non-CV related and occurred outside the treatment period. Two were adjudicated cardiovascular-related events and occurred in patients with cardiovascular disease at baseline. There was an imbalance in cardiovascular serious adverse events (SAEs) for the pegloticase treatment groups compared to placebo.

The following events occurred in the pegloticase 8 mg every 2 weeks treatment group (N=85):

Adjudicated CV events	
APTC events	2
Non-APTC events	3

No CV events occurred in the placebo group.

The Savient KRYSTEXXA briefing document prepared for the FDA[8] (page 101) stated that across the pooled RCTs there were 4/85 (4.7%) cardiac serious adverse events occurring in the pegloticase 8 mg every 2 weeks group (2 cases of arrhythmia, 1 case of cardiac arrest and 1 case of congestive cardiac failure) and none in the placebo group (N=43). Two cases were fatal (arrhythmia and cardiac arrest). The data in the briefing document supports that statement in the submission that there were 2 APTC and 3 non-APTC events in the pegloticase 8 mg every 2 weeks group and none in the placebo group. The briefing document also states that in the pegloticase 8 mg every 2 weeks treatment group in the OLE study (C0407) (N=59) there were 1 APTC and 7 non-APTC events (no data provided for the placebo group).

An abstract reported by Ottery *et al.* (2012)[19] (not included by the manufacturer in the submission but sourced by the ERG) provided limited information on the effects of up to 6 months of pegloticase treatment on renal function in the 49% of patients from the C0405 and C0406 trials who had stage 3-4 chronic kidney disease (CKD). Renal function in patients receiving pegloticase 8 mg every 2 weeks (n=42) and placebo (n=20) was assessed by estimated glomerular filtration rate (eGFR) using the 4-variable MDRD formula (not defined) at screening (Week 0) and weeks 7, 13, 19 and 25 post-randomisation. Results of the model suggested that "change in eGFR was not differentially affected by treatment (treatment X time interaction: p=0.28), independent of age, sex or race. No discontinuation pattern was observed." The authors of the abstract concluded that patients with refractory chronic gout and stage 3-4 CKD did not appear to have adverse renal effects with up to 6 months of pegloticase treatment.

Information provided by the manufacturers, after a request by the ERG for clarification, described

[redacted]

There were a total of 4 deaths in the OLE study (C0407). All 4 subjects had received pegloticase in the phase III studies. The manufacturer stated that all deaths were considered by the Investigator unlikely to be related to the study drug.

The abstract by Wolfson *et al.* (2012)[21] (data not presented in MS but sourced by the ERG) provided limited longer term safety data from patients who had participated in the phase III trials and OLE study. The data suggested that the rates of adverse events (all adverse events, gout flares, infusion-related reactions and serious CV adverse events) were not increased in long-term (apparently 2.5 years) compared with short-term (6 months) consistent treatment with pegloticase 8 mg every 2 weeks. Gout flares became less common with increased duration of pegloticase 8 mg every 2 weeks treatment (6.1 vs. 2.7 gout flares per patient year at 6 months vs. 2.5 years treatment respectively).

An abstract by Baraf *et al.* (2012)[11] (not included by the manufacturer in the submission but sourced by the ERG) assessed the pooled data from the two phase III trials and the OLE study. It was stated that, for all 3 studies, patients with a SUA< 6 mg/dl on the day of infusion had less than 1 infusion reaction per 100 infusions. Furthermore, 91% of infusion reactions in the phase III trials and 88% of infusion reactions in the OLE occurred when SUA exceeded 6 mg/dl on the day of infusion. These findings emphasise the apparent importance of monitoring SUA levels prior to pegloticase infusions in order to reduce the risk of an infusion reaction. It was also reported that, among patients with a first exposure to pegloticase during the RCTs or OLE study (n=208), 12 patients developed infusion reactions with signs and symptoms consistent with anaphylaxis, but that no deaths were considered to be associated with infusion reactions in the RCTs or OLE study.

The statement was made on page 62 of the MS that "the incidence of infusion-related reactions may be lower in clinical practice (where treatment is discontinued) than that observed in the RCTs (where non-responders continue to receive treatment)." The ERG requested that the manufacturer provide evidence to the support this statement, in particular a full description and findings of the risk reduction analysis described on page 65 of the MS. The manufacturer stated that, as UA response was not monitored during the trial to determine loss of pegloticase efficacy, non-responders continued to

receive pegloticase treatment despite loss of response. The manufacturer noted subsequent to the trials that loss of response (defined as an increase of SUA>6.0 mg/dL) occurred in most cases prior to the occurrence of an infusion reaction.

The manufacturer also provided details from a forthcoming conference (Malamet, *et al.*, submitted to American College of Rheumatology conference November 2012)[30] reporting a 61% reduction (95% CI 36.3 to 75.9) in the risk of infusion reactions during the post-approval period vs. the phase III trials (but the abstract noted "substantial limitations" in the methodology used to derive these estimates).

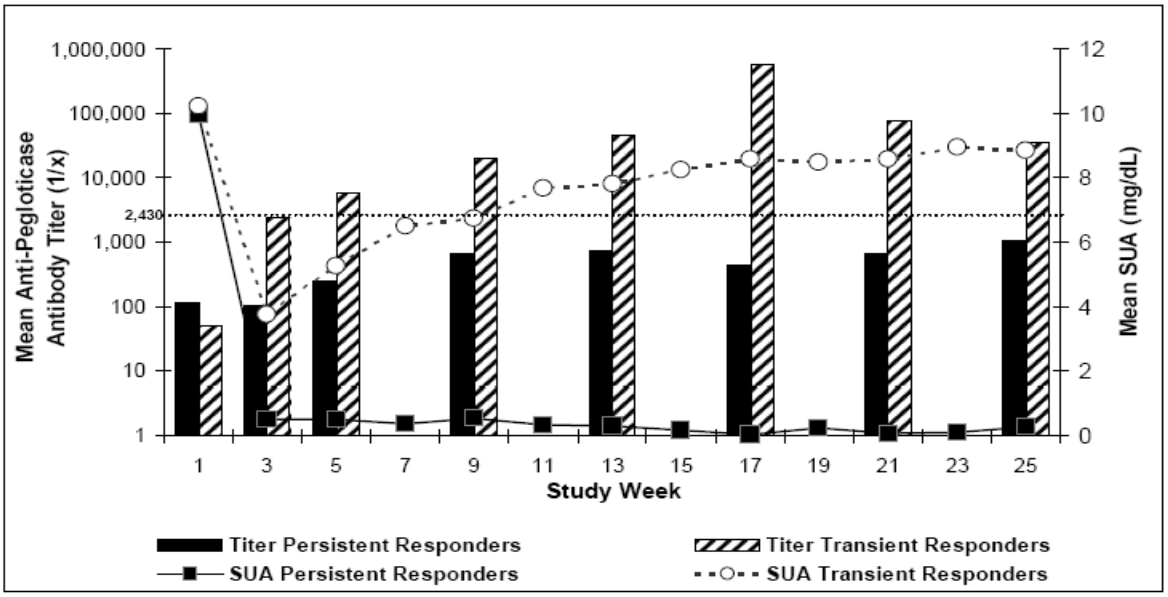
A *post hoc* analysis of the relationships between antibodies to pegloticase, PUA response and infusion reactions was also described briefly on page 60 of the submission. The manufacturer provided additional details in response to a request by the ERG and described this analysis as being a re-evaluation of antibody data from the pooled analyses of phase III trials C0405 and C0406. Anti-pegloticase antibodies were reported to have been detected in 89% of subjects in the pegloticase 8 mg every 2 weeks and pegloticase 8 mg every 4 weeks treatment groups in phase III trials C0405 and C0406. 39% of subjects developed an anti pegloticase antibody titre of >1:2, 430, highlighted by the manufacturer as subjects in whom anti-pegloticase antibody could have potential clinical consequences (eg. transient responsiveness and/or increased risk for infusion reactions). The manufacturer stated that at all time points after dosing, lower mean anti-pegloticase antibody titres were observed in the persistent responders in the pegloticase 8 mg every 2 weeks group to the transient responders.

The manufacturer also considered PUA response and described how the eventual presence of anti-pegloticase antibodies at titres > 1:2,430 was directly correlated to transient versus persistent responsiveness (as measured by PUA/SUA). It was also reported that approximately 90% of transient responders lost SUA response within the first 2 months of treatment.

The pharmacokinetics of pegloticase were described as being significantly influenced by the presence of anti-pegloticase antibodies and the increased clearance of pegloticase with the resultant loss of SUA/PUA response as mediated by anti-pegloticase antibodies.

The manufacturer also confirmed that "associated with low circulating peak and trough levels of pegloticase in the transient responders were higher mean anti-pegloticase antibody titres at all time points compared with persistent responders." The distribution of antibody titres at the time of loss of SUA response is shown below for the pegloticase 8 mg every 2 weeks group.

Figure 2 Relationship between Anti-pegloticase Antibody Titre and SUA Comparing Persistent and Transient Responders; Pegloticase 8 mg/2 weeks Group (Pooled Data C0405/C0406) (figure taken directly from manufacturer's clarification responses)



The manufacturer reported that the broad range of anti-pegloticase antibody titre at the time of loss of SUA/PUA response indicated that the measurement of anti-pegloticase antibody titres could not be considered predictive of the loss of response, but that monitoring SUA is a good surrogate for measuring the development of anti-pegloticase antibodies that subsequently cause increased clearance of pegloticase.

Post hoc analysis by the manufacturer showed that nearly all infusion reactions occurred in subjects who subsequently lost pegloticase response determined by measuring SUA/PUA levels. It was also reported that no relationship was shown between antibody titres and severity of infusion reactions and that most infusion reactions were moderate in severity irrespective of anti-pegloticase antibody titre.

It was noted in the SPC that "the long-term risk of prophylactic medications to prevent infusion reactions, such as glucocorticoids, should also be taken into consideration (page 125)".

The prescribing information for KRYSTEXXA[31] notes that pegloticase should be given in settings and by professionals prepared to manage anaphylaxis and infusion reactions and that the risk of anaphylaxis and infusion reactions is higher following loss of response. A potential increased risk of anaphylaxis and infusion reactions upon re-treatment is described.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect or mixed treatment comparisons were undertaken in the MS, with the manufacturer describing such analyses as being "not-applicable" (Section 6.7, page 53).

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No indirect or mixed treatment comparisons were undertaken by the manufacturer. The ERG agreed that, based on the evidence, network meta-analysis was not appropriate.

4.5 Additional work on clinical effectiveness undertaken by the ERG

4.5.1 Justification and description of methods for ERG meta-analyses

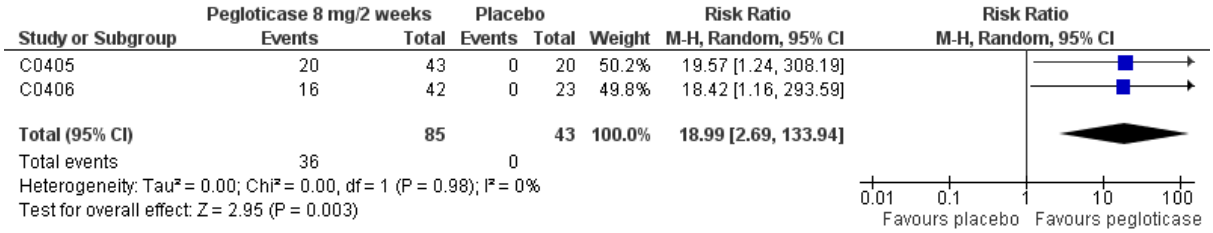
The ERG considered the use of meta-analysis to be a more robust method for the combination of data from trials, as opposed to the method of simple pooling adopted by the manufacturer in their submission. Therefore, the ERG conducted meta-analysis of data from the phase III trials (C0405 and C0406) for the following outcomes i) PUA responder status and ii) tophi resolution. These outcomes were selected by the ERG as PUA responder status was the primary efficacy outcome and tophi resolution was a key driver in the cost-effectiveness model and was considered to be an important outcome in terms of clinical effectiveness.

In response to a request for clarification by the ERG, [redacted] Therefore, the ERG considered that it was unclear how data relating to the total size of the tophus evaluable population at final visit had been derived and why the number of subjects with tophi at baseline had not been used in the analyses of tophi resolution at final visit. Therefore, the ERG conducted two separate meta-analyses for complete tophus resolution, based on the "tophus evaluable population" (Figure 4) and the number of subjects with baseline tophi (Figure 5).

Meta-analysis was performed using the Mantel-Haenszel method, since this is recommended in instances when data are sparse (Higgins *et al.*, 2008).[32] Review Manager (version 5.1) automatically adds a correction of 0.5 to each cell of the 2 x 2 table for studies with zero events in the placebo arm[32]. However, it should be noted that a limitation of the ERG's method is that the use of a constant correction of 0.5 has been criticised by Sweeting *et al.* (2004),[33] who suggested the use of alternative correction methods.

4.5.2 PUA responder status

Figure 3. Meta-analysis by ERG of data for PUA responders in pegloticase 8 mg every 2 weeks and placebo groups (trials C0405 and C0406) (Mantel-Haenszel random effects model, with automatic 0.5 correction applied by Review Manager to cells with zero events)

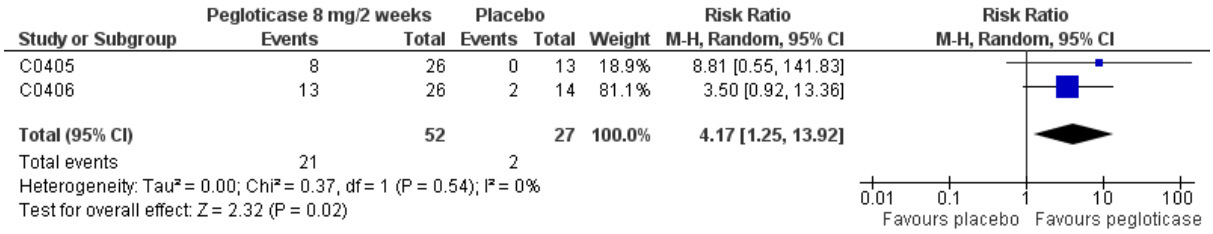


The ERG performed a random effects meta-analysis of the modified intention to treat data (all patients who received at least one study dose) for the primary efficacy endpoint of PUA responder status. The ERG's meta-analysis confirmed the observation made by the manufacturer that PUA response was significantly greater in the pegloticase 8 mg every 2 weeks treatment group versus the placebo group (RR=18.99) (95% CI 2.69, 133.94) (P=0.003). For reference, when a fixed effects model was applied, the combined relative risk was very similar (RR=19.01, 95%CI 2.69 to 134.24).

It was not possible to calculate a relative risk for the simple pooled data utilised by the manufacturer in their submission (eg. risk in group A divided by risk in group B = (a/A) / (b/B)) using a manual uncorrected calculation, since there were zero events in both placebo arms. (However, when the simple pooled data were inputted into Review Manager ([36/85]/[0/43]) and Review Manager applied a correction in response to the zero events in the placebo arms, the relative risk obtained was 37.35 (95% CI 2.35, 549.24).

4.5.3. Complete resolution of tophi

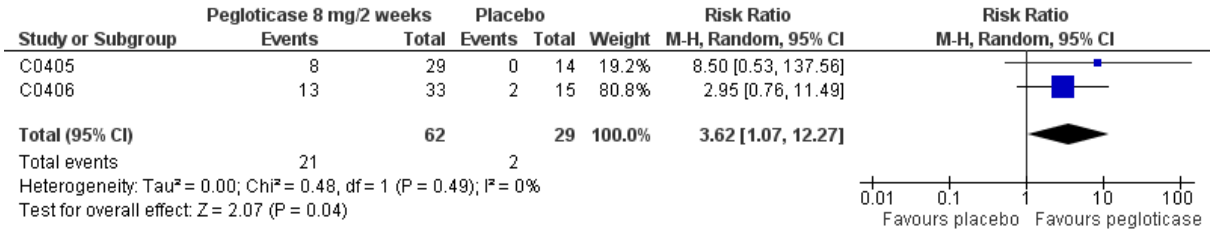
Figure 4. Meta-analysis by ERG of data for complete tophus resolution in pegloticase 8 mg every 2 weeks and placebo groups (based on manufacturer's "tophus evaluable population") (trials C0405 and C0406) (Mantel-Haenszel random effects model, with automatic 0.5 correction applied by Review Manager to cells with zero events) (figure should also be considered Academic in Confidence)



A relative risk of 4.17 was obtained by the ERG, supporting the manufacturer's statement that tophi response was significantly more favourable in the pegloticase 8 mg every 2 weeks treatment arm compared with placebo. However, 95% confidence intervals were relatively wide (and crossed the line of no effect in each individual study). For reference, when a fixed effects model was applied, the combined relative risk was broadly similar (RR=4.57, 95% CI 1.35 to 15.45).

It was possible to calculate a relative risk for the simple pooled data (eg. risk in group A divided by risk in group B = (a/A) / (b/B)) using a manual uncorrected calculation. A relative risk of 5.45 was obtained ([21/52] / [2/27]). Therefore, the uncorrected relative risk of 5.45 manually calculated by the ERG using the manufacturer's simple pooled data was higher than the relative risk of 4.17 generated in the ERG's meta-analysis.

Figure 5. Meta-analysis by ERG of data for complete tophus resolution in pegloticase 8 mg every 2 weeks and placebo groups (based on number of subjects with baseline tophi as reported by Sundy *et al.*, 2011) (trials C0405 and C0406) (Mantel-Haenszel random effects model, with automatic 0.5 correction applied by Review Manager) to cells with zero events) (figure should also be considered Academic in Confidence)



The ERG's meta-analysis generated a relative risk of 3.62, with similarly wide 95% confidence intervals that also overlapped the line of no effect for each individual study. For reference, when a fixed effects model was applied, the combined relative risk was broadly similar (RR=4.04, 95% CI 1.19 to 13.71).

It was possible to calculate a relative risk for the simple pooled data (eg. risk in group A divided by risk in group B = (a/A) / (b/B)) using a manual uncorrected calculation. A relative risk of 4.91 was obtained ([21/62] / [2/29]). As previously, the uncorrected relative risk of 4.91 manually calculated by the ERG using the manufacturer's preferred simple pooling method was higher than the relative risk of 3.62 generated in the ERG's meta-analysis.

Therefore, the relative risk obtained when using the baseline number of patients with tophi (considered by the ERG to be more explicit and reflect the intention-to-treat population), the relative risk was slightly lower than that obtained using the manufacturer's preferred tophus-evaluable population (RR=3.62 vs. RR=4.17).

4.6 Conclusions of the clinical effectiveness section

The ERG and clinical advisors to the ERG were satisfied that all available phase III trials relating to the efficacy and safety of pegloticase in the treatment of gout were included in the submission. The two phase III trials (C0405 and C0406) and open label extension (OLE) study (C0407) were considered by the ERG to be relevant to the decision problem as specified in the scope.

It has been noted earlier in this report that, while two of the clinical advisors to the ERG considered the populations from the two included phase III trials to accurately reflect the population covered by the anticipated licensed indication, a third clinical advisor to the ERG viewed that it was not explicit in the manufacturer's submission (MS) whether trial participants had previously received dose-

optimised xanthine oxidase inhibitors and whether they had failed/been inappropriate for treatment with uricosurics. The ERG agrees that the treatment history of trial participants was not clearly described in the submission. The ERG and clinical advisors to the ERG considered that best supportive care was an appropriate comparator for patients who are refractory to both xanthine oxidase inhibitors and uricosurics or where treatments from these classes of interventions cannot be used due to contraindications or intolerance. The ERG and clinical advisors to the ERG were satisfied that all appropriate outcomes were included in the submission.

The clinical effectiveness evidence included in the submission and subsequent clarification responses demonstrated that pegloticase 8 mg administered intravenously every 2 weeks over 6 months duration in the phase III trials (C0405 and C0406) resulted in a sustained UA response in months 3 and 6 of treatment in just under half (42% in simple pooled analysis) of the modified ITT trial population and also yielded improvements in the majority of secondary outcomes, in particular the rapid resolution of tophi. However, gout flares in the initial months of pegloticase treatment and the occurrence of infusion-related reactions were commonly observed adverse events, with other less frequent adverse events also described. Several cases of anaphylaxis were clearly described in the submission. Since the adverse events data presented in the submission were based on small numbers (due to the relatively small sample sizes of the included studies), the occurrence of adverse events in the post-marketing setting should continue to be monitored.

The clinical effectiveness evidence was based predominantly on the findings from simple pooled analyses of primary and secondary efficacy data from the two included phase III trials. The ERG requested that individual trial and meta-analysed data also be provided, but meta-analyses were not provided and so the ERG conducted exploratory meta-analyses using data for the primary efficacy outcome of PUA response and one of the secondary outcomes, complete tophus resolution. The relative risks for complete tophus resolution calculated manually by the ERG (uncorrected for zero events in a placebo arm) using the simple pooled data appeared to be slightly greater in magnitude than the relative risks calculated using Review Manager (which it should be noted incorporated an automatic correction applied for zero events in a placebo arm). Since the placebo arms of both phase III trials contained zero events for the primary efficacy outcome of PUA response, it was not possible to attempt a comparison of the simple pooled analyses with the meta-analysed data.

Primary efficacy data were based on the measurement of PUA levels, as opposed to SUA levels as specified in the scope, although the manufacturer provided a biochemical justification for the selection of PUA measurements. Whilst PUA response data were clearly reported for the 6 months duration of the phase III trials, the presentation of the evidence base in the submission for long-term efficacy of continued pegloticase treatment was considered by the ERG to be limited. Some limited

and fragmentary evidence was available in the manufacturer's clarification responses and from conference abstracts sourced by the ERG that suggested that, for persistent responders, PUA response and some secondary outcomes, including tophus resolution, may be maintained when pegloticase treatment is continued beyond 6 months. However, importantly, it remained unclear from the submission whether PUA response and other treatment benefits would be maintained over the long-term following the cessation of pegloticase treatment. Clear presentation of such evidence for long-term durability of benefits is considered by the ERG to be important, since these data would be required to support the assumption in the submitted cost-effectiveness model that pegloticase treatment effects can be maintained using urate-lowering therapy following the completion of pegloticase treatment. The impacts of repeated courses of pegloticase 8 mg every 2 weeks on UA levels, secondary outcomes, immunogenicity and adverse events were not clear from the original submission. The lack of evidence for the long-term maintenance of treatment benefits following cessation of pegloticase treatment is also important in light of the limited re-exposure evidence presented, which indicated the potential for the generation of anti-pegloticase antibodies, infusion reactions and loss of efficacy following re-exposure to pegloticase after interruption of treatment.

5. COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Objective and search strategy

A systematic search and review was conducted to address the following question: "What evidence exists for the cost-effectiveness of pegloticase for refractory chronic gout from a UK healthcare perspective?"

The manufacturer states that a comprehensive search was performed to identify the following three types of evidence for a refractory chronic gout patient population:

a) UK economic evaluations for pegloticase

b) The measurement and valuation of health (i.e. utility studies)

c) UK resource utilisation studies (i.e. covering identification, measurement and valuation).

Overall, the searches conducted for the sponsor submission appear satisfactory. A detailed critique of this comprehensive search to identify economic evidence has been described previously in section 4.1.1.

5.1.2 Inclusion/exclusion criteria

The key inclusion criteria for the search covered:

- Any full economic evaluation: cost-utility, cost-effectiveness, cost-benefit, cost-minimisation conducted in a UK specific setting.
- Comparators consisting of best supportive care or placebo
- Adult patients (aged ≥ 18 years) with severe refractory chronic gout who are symptomatic and have failed to normalise SUA with xanthine oxidase inhibitors (allopurinol and febuxostat) at the maximum medically appropriate dose, or for whom these medicines are contraindicated.

The patient population specified were those expected to be covered by the pegloticase marketing authorisation at the time of the search. Whilst this differed slightly from the anticipated licensed indication at the time of submission, the ERG did not consider that this would result in any relevant information being excluded.

5.1.3 Included and excluded studies

No studies were included in the cost-effectiveness review. The search identified one economic evaluation of pegloticase in patients with refractory chronic gout (Wang *et al.,* 2012) [34], but this was not considered relevant due to the non-UK country perspective. The study was also only available in abstract form so contained limited information. Whilst the ERG would agree that this model does not meet the NICE reference case, because it does not take a UK NHS and Personal Social Services (PSS) perspective, the approach taken in this model may be informative and so the ERG have summarised the details from the abstract in Appendix 1. The ERG noted that this analysis assumes retreatment with pegloticase for 6 months every 5 years, uses health states based on flares per year and tophi resolution and not SUA level, and appears to use utility values from a secondary source, although insufficient details are provided to determine the exact source.

5.1.4 Conclusions of the review

The review concludes that the search for economic evaluations of pegloticase yielded no published UK studies in either full paper or conference abstract form relating to the specific target patient population of severe debilitating refractory chronic tophaceous gout. Hence, a *de novo* economic evaluation of pegloticase has been performed. The ERG would agree that no published cost-effectiveness analyses meeting the NICE reference case were identified and therefore a *de novo* economic evaluation was warranted.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Element of health technology assessment	**Reference case**	**Does the submission adequately address the reference case?**
Defining the decision problem	The scope developed by the Institute	The economic model in the original submission didn't adequately address the population who cannot take allopurinol or febuxostat but a revised model was submitted which addressed this limitation.
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes
Perspective on costs	NHS and PSS	Yes
Perspective on outcomes	All health effects on individuals	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes

Element of health technology assessment	Reference case	Does the submission adequately address the reference case?
Synthesis of evidence on outcomes	Based on a systematic review	Short term outcomes based on pooled analysis of phase III RCTs identified by systematic review. Long-term outcomes from indirect evidence identified from systematic review of literature.
Measure of health effects	QALYs	Yes
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Yes for short-term HRQoL. Yes for long-term HRQoL outcomes
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes for short-term trial outcomes Yes for data source used to model long-term HRQoL outcomes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

5.2.2 Model structure

5.2.2.1 Health states

The model structure is described in the MS as being a decision tree coupled to a Markov model, although in practice the whole analysis is captured within the Markov framework without the need for a separate decision tree. Within the pegloticase arm, the first row of the Markov model is used to separate patients into the responder, non-responder and non-completer groups. The following clinical continuation rule is used to define response to pegloticase treatment: "Pegloticase should be discontinued if levels increase to above 360 μmol/L (6 mg/dL), particularly when 2 consecutive levels above 6 mg/dL are observed". The non-completer group is defined as, "patients who are non-persistent to pegloticase treatment." The ERG did not consider this information to be sufficient to determine how these "non-completer" patients would be identified in clinical practice. Each of the responder, non-responder and non-completer groups has a distinct set of health states with no transitions allowed between the groups. For each of these groups, the model has health states defined according to the treatment being given at that time point and the SUA level. In the comparator arm, all

patients receive best supportive care for the duration of the model so the health states are defined solely according to SUA level.

SUA level is captured in the model using four health states: <360 μmol/L (6.0 mg/dL); ≥360 - <480 μmol/L (6.0-8.0 mg/dL); ≥480 - <600 μmol/L (8.0-10.0 mg/dL); and ≥600 μmol/L (10.0 mg/dL). The MS states that health states based on SUA were selected as these were considered to correlate to disease severity, and expected impact on acute gout flares, potential for longer term development of tophi and patient quality of life. The ERG's clinical advisors were satisfied that long-term maintenance of SUA below 360 μmol/L (6.0 mg/dL) could be expected to result in clinically meaningful changes in patient related outcomes, although they noted that the BSR guideline recommends maintaining SUA levels below 300 μmol/L[1]. These health states defined by SUA were also the health states used in a cost-effectiveness analysis of febuxostat which formed part of Ipsen's submission to NICE for TA175.[35]

There is also a death state allowing mortality to be captured within the model. In addition to capturing the distribution of patients across SUA levels, the model also tracks the frequency of flares and the proportion of patients with tophi resolution. The model uses a monthly cycle length for the duration of the 20 year time horizon and does not apply a half-cycle correction.

5.2.2.2 Transition probabilities

The model estimates the distribution of patients across the four SUA levels by assuming a normal distribution around the mean SUA level for each group in the pegloticase arm (responders, non-responders, non-completers) and for the comparator arm population as a whole. This is done for each Markov cycle. So, whilst the model is described as being a Markov model and the structure shown in Figure 7.2 of the MS has arrows showing transitions between the health states, no transition probabilities are used within the model to determine the distribution of patients between the health states defined by SUA level. Transitions to the death state are possible at any time and do not depend on the treatment being given or the patient's SUA level and are therefore the same across the whole population of the model. Transitions between different gout therapies are described below under section 5.2.4.2.

5.2.3 Population

The baseline characteristics of the modelled population are defined according to age (56 years), SUA level (9.6mg/dL) and baseline utility values (0.6). Whilst the source of these values isn't explicitly stated, the MS states that "patient groups were gathered from the two replicate, randomized, double-blind, placebo controlled trials" and refers to baseline characteristics from these trials. The modelled

population is therefore taken to be representative of the population included in these two trials and the baseline characteristics in the model appear consistent with this assumption.

The ERG did have one concern regarding the modelled population, although this concern was addressed when the manufacturer submitted a revised model in response to the clarification letter. The population specified in the scope included both those who are refractory to conventional urate lowering therapies and those in whom conventional urate lowering therapies are contraindicated or not tolerated. However, the treatment sequences used in the model originally submitted by the manufacturer assumed that all patients who respond to pegloticase treatment will progress to maintenance therapy with either allopurinol or febuxostat. This treatment sequence would not be appropriate for those patients in whom conventional urate lowering therapies are contraindicated or not tolerated. The manufacturer submitted a revised model in which these patients progress to best supportive care. The proportion following this alternative treatment sequenced was assumed to be 10%, which is described in the MS as being based on expert clinical opinion. The ERG's clinical advisors felt that 5 to 10% of the population being contraindicated or intolerant would be a reasonable estimate. It should be noted that the proportion of trial participants who were eligible to participate due to either a history of allergy or hypersensitivity or GI intolerance to allopurinol was [redacted] in trials C0405 and C0406 respectively (see Tables 7 and 8 above), suggesting that there were [redacted] patients contraindicated or intolerant to allopurinol in the trials than within the population modelled in the revised basecase analysis. The cost-effectiveness results for this revised basecase analysis which incorporates the alternative treatment sequence for patients in whom conventional urate lowering therapies are contraindicated or not tolerated are summarised in Table 26 in section in 5.2.9.3. The ERG also conducted an exploratory analysis in which the proportion who are contraindicated was set to [redacted], which was the proportion with either a history of allergy or hypersensitivity or GI intolerance to allopurinol across trials C0405 and C0406. The results are reported in Table 37 below.

The ERG were interested to determine the cost-effectiveness of pegloticase in the subgroup of patients who are unable to take maintenance therapy as it would be reasonable to expect that these patients would have different costs and benefits. It should be noted that the model assumes that patients switching to best supportive care have a rapid return of high SUA levels such that the only treatment benefits maintained are those associated with tophi resolution. This may have underestimated treatment benefits in this subgroup if the rise in SUA is more gradual in practice, but this remains uncertain as no data were presented within the submission to show what happens to SUA levels in patients switching to best supportive care after achieving a persistent response to 6 months of pegloticase treatment.

5.2.4 Interventions and comparators

5.2.4.1 Treatment sequences for the intervention arm

The dose of pegloticase in the model was 8 mg administered every two weeks by IV infusion, in line with the draft SPC and decision problem. In addition to drug costs, resource use associated with the IV administration of pegloticase was captured in the model. Finally, patients treated with pegloticase received prophylaxis drugs for gout flares and infusion reactions.

In the model originally submitted patients in the responder group of the pegloticase arm progress from pegloticase treatment, to maintenance therapy and then to best supportive care. This treatment sequence is based on the premise that once low SUA levels (below 360 µmol/L [6mg/dL]) have been established, therapies that were previously ineffective at high SUA levels can now be used to maintain the low levels of SUA achieved in patients who have responded to treatment with pegloticase

Maintenance therapy is assumed to consist of allopurinol for 70% of pegloticase responders and febuxostat for the remaining 30%. The type of maintenance therapy is described in the MS as being, "based on expert opinion from the in-depth interview with an England based clinician involved in the treatment of the target patient population". The ERG's clinical advisors believed that the proportion of pegloticase responders who would receive febuxostat as maintenance therapy would be under 20% and could be as low as 5% in current clinical practice, rather than the 30% assumed in the manufacturer's basecase analysis, although it was also commented that the proportion could increase over-time. The ERG have conducted a sensitivity analysis to explore whether this has a significant impact on the model which can be found in section 5.3.1.

The ERG's clinical advisors thought that it was reasonable to expect patients to move onto maintenance therapy once they had achieved stable low urate levels with pegloticase provided they were not intolerant to or contraindicated for these treatments. However, it should be noted that no data were provided on the efficacy of allopurinol or febuxostat in maintaining low urate levels in the population specified in the decision problem following treatment with pegloticase.

Patients in the non-responder and non-completer groups of the pegloticase arm, who have not succeeded in achieving low levels of SUA, progress from pegloticase treatment to best supportive care. This was considered to be reasonable by the ERG's clinical advisors.

As described earlier, the treatment sequence in which patients progress from pegloticase to maintenance therapy are not appropriate for those patients who are contraindicated to or intolerant of both febuxostat and allopurinol, and therefore the model originally submitted was not considered to be appropriate for this subgroup of the population specified in the decision problem. In response to the

clarification letter, the manufacturer submitted a revised analysis in which pegloticase responders in whom xanthine oxidase inhibitors (both allopurinol and febuxostat) cannot be used, due to either contraindications or intolerance, are assumed to progress directly to best supportive care after finishing the pegloticase treatment course. This change to the model structure was incorporated in the revised basecase analysis in which it was assumed that 10% of the modelled population are contraindicated or intolerant to xanthine oxidase inhibitors, based on expert clinical opinion.

5.2.4.2 Duration of pegloticase treatment

The duration of pegloticase treatment is fixed at 6 months in the responder group, 2 months in the non-responder group and 1 month in the non-completer group with all patients transitioning to the next appropriate therapy at those time points.

The assumption that responders can be identified after 2 months is described in the MS as being "based on company data". Following a request for further data by the ERG, the manufacturer submitted Kaplan-Meier plots for the time to loss of PUA response in the two phase III studies (C0405 and C0406) for the (modified) ITT population. This population therefore includes those classified as non-responders and non-completers in the analysis used to inform the economic model. [redacted] A scenario analysis was presented by the manufacturer in which the duration of treatment for non-responders was varied from 1 to 3 months.

Patients who were classified as non-completers within the two phase III RCTs (C0405 and C0406) were those who did not complete the 6 month treatment course. The reasons for patients becoming non-completers were not described in the original submission and no justification was provided regarding the duration of treatment for non-completers. After a request for clarification on these matters by the ERG, the manufacturer stated that, "the main reason for not completing the treatment course was primarily due to adverse events. In clinical practice, it is likely that AEs or other non-efficacy reasons for discontinuation (e.g. patient dislike of IV administration) would occur within the first month of treatment and hence be identified by the clinician at a routine visit and treatment stopped." However, the ERG was uncertain how non-completers would be identified in clinical practice and when this would be likely to happen. Data on the proportion of non-completers who had withdrawn from pegloticase treatment by one month and the time to treatment cessation for non-completers was requested by the ERG but was not forthcoming with the manufacturer stating, "we are in the process of exploring the availability of this data with the appropriate clinical department within Savient in order to provide a response to this question". Data on the patients discontinuing due to an

adverse event was provided in response to the clarification request and from this it can be seen that [redacted] discontinued due to an adverse event in the 2 weekly dosing arms of C0405 and C0406 trials respectively. Of these the duration of treatment was less than a month in [redacted] patients respectively suggesting that assuming a month of treatment for non-completers may [redacted] treatment costs for pegloticase, although only [redacted] of the 27 non-completers are accounted for in this data. A scenario analysis was presented by the manufacturer in which the duration of treatment for non-completers was varied from 1 to 3 months.

The model assumes that no patient receives treatment with pegloticase beyond 6 months and the maximum number of treatments received is 12. However, combined data from the RCTs (C0405 and C0406) and the open-label extension study (C0407) show that [redacted] A Kaplan-Meier plot on the time to treatment cessation for responders to pegloticase within the two phase III studies (C0405 and C0406), including data from the open-label extension study (C0407), [redacted] Patients enrolled in the open-label extension study (C0407) were allowed to continue pegloticase treatment for a maximum of 30 months (2.5 years) or until the study end-date. Based on these data, the ERG are concerned that that the number of treatments received in clinical practice could be higher than the 6 months assumed in the model. The draft SPC states; "The data for long-term treatment from controlled clinical studies with KRYSTEXXA are limited. This should be considered when the decision is made for a therapy longer than 6 months." The ERG's clinical advisors expected that they would not use the treatment for more than 6 months.

The model assumes that no patient receives a repeat course of pegloticase treatment either after completing the 6 month course or after being classified as a non-responder or non-completer. This was considered by the ERG and their clinical advisors to be a reasonable assumption given that there are limited data on the safety and efficacy of repeat courses of pegloticase. The ERG's clinical advisors had concerns regarding the risk of infusion reactions in patients who are re-exposed to pegloticase due to the development of an immune response to treatment and therefore felt that they would be unlikely to offer repeat courses in clinical practice.

5.2.4.3 Duration of maintenance treatment

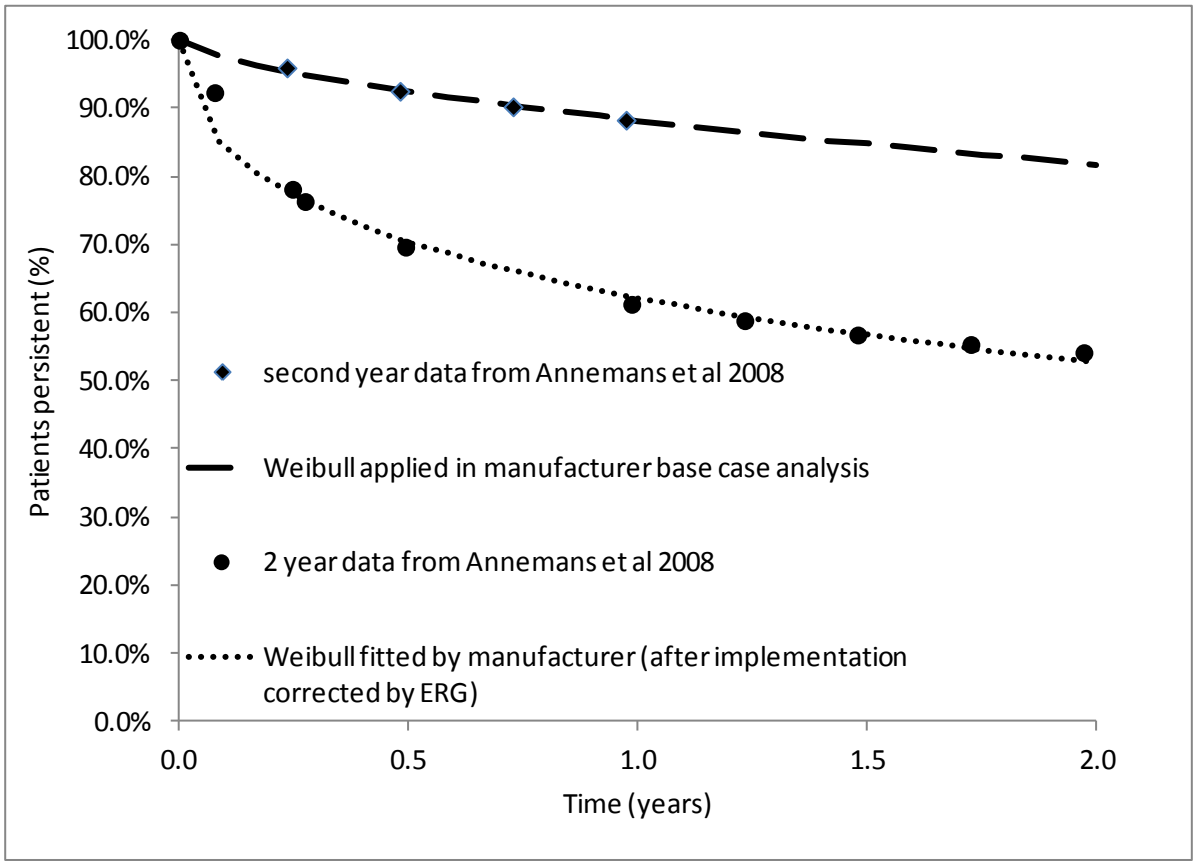
The probability of becoming non-persistent on maintenance therapy, and therefore progressing to best supportive care, is modelled using a constant hazard for febuxostat, and a decreasing hazard for allopurinol. The rate of discontinuation for febuxostat was derived by taking the average proportion

(434/590=26%) who were non-persistent at the end of the 2 year EXCEL trial across the two doses (80 mg/day and 120 mg/day) and assuming a constant hazard (exponential survival curve) to convert this proportion to a monthly rate of 1.3%, which is equivalent to an annual rate of 14%. No data were provided showing how well the exponential curve fitted the actual trial data on non-persistence between the start and end of the EXCEL trial. Results using alternative annual rates of 5% and 15% are presented in a scenario analysis. The model doesn't seem particularly sensitive to this parameter which may be due to the fact that the majority of patients receive maintenance therapy with allopurinol.

The rate of discontinuation for allopurinol was derived by fitting a Weibull survival curve to retrospective 2-year observational data from 7,443 UK patients with chronic gout, of which 89% were receiving allopurinol (Annemans *et al.*, 2008)[4]. In the economic model a Weibull curve was fitted to the second year of data from the study by Annemans *et al.*[4] The reason given for this approach was, "to accurately model long-term persistence (as opposed to persistence from initiation of therapy)". The ERG accept that there may be a higher rate of discontinuation in patients receiving allopurinol for the first time, and this might not be representative of the discontinuation rate in patients receiving allopurinol as a maintenance therapy after pegloticase treatment who will probably have prior experience with allopurinol treatment. However, patients included in the study by Annemans *et al*.[4] were not necessarily receiving allopurinol treatment for the first time at the study index date, as 24.7% were receiving gout preparations prior to the study index date. Figure 6 shows the full 2 year data extracted by the manufacturer from Annemans *et al.*[4] and reported within the spreadsheet model. After a request by the ERG, the manufacturer conducted a sensitivity analysis in which they fitted a Weibull curve (α=0.437, β=66, correlation not stated). However, this revised Weibull curve estimated by the manufacturer was not implemented correctly within the economic model as years were used as the time variable instead of months. The ICER for this sensitivity analysis when using the correct implementation of the revised Weibull curve are given in Table 29. The ERG believe that this revised Weibull curve incorporating the 2 year data from Annemans *et al.*[4] represents a plausible alternative to the Weibull curve applied in the manufacturer basecase.

It should also be noted that there is no direct evidence on persistence with either allopurinol or febuxostat in patients with severe debilitating chronic tophaceous gout who have not responded to or are intolerant to xanthine oxidase inhibitors and who have responded to treatment with pegloticase, i.e the population receiving maintenance therapy within the economic model.

Figure 6 Alternative survival models for persistence on allopurinol



5.2.4.4 Treatments in the comparator arm

Patients in the comparator arm receive best supportive care for the duration of the model. Best supportive care was assumed to consist of standard medical care with NSAIDS, colchicine and corticosteroids but no urate lowering therapy. However, a cost for drug therapy associated with the best supportive care comparator was not included in the economic model within the original submission due to a lack of detail at the time of the submission as to which drugs and dosage are likely to be used. Following a request for further details on the definition of best supportive care, the manufacturer clarified that as part of best supportive care, the following specific drugs may be prescribed:

- NSAID (e.g. Naproxen, 500 mg per day) in about 90% of patients
- Colchicine (e.g. 1000 mg per day) in about 10% of patients
- Corticosteroids (e.g. prednisolone 10-15 mg day) in about 75% of patients.

The MS describes this definition of best supportive care was being based on discussions with a gout clinical expert (Professor of Rheumatology at a North of England treatment centre). As discussed in Section 2, best supportive care was considered to be an appropriate comparator for the population likely to receive pegloticase in clinical practice. Some of the ERG's clinical advisors commented that

the presence of comorbidities in this population may preclude the use of NSAIDs and colchicines. Based on these comments the ERG noted that the usage of these treatments within best supportive care may have been overestimated by the manufacturer.

Costs for these drugs care were incorporated in the manufacturer's revised basecase analysis, submitted in response to the clarification letter. The doses and unit costs (based on BNF prices) applied appeared reasonable and the ERG verified that these costs were applied to all patients receiving best supportive care in both arms of the revised model. Results for this revised basecase analysis can be found in Table 26 below. The ERG did not consider it likely that any over estimation of the treatments used in best supportive would have a significant impact on the cost-effectiveness.

5.2.5 Perspective, time horizon and discounting

A 20 year time-horizon is applied in the basecase and alternative time-horizons of 10 and 40 years are explored in sensitivity analyses. Whilst a life-time horizon could have been justified in this disease area, the sensitivity analysis exploring a 40 year time horizon did not show that the model is particularly sensitive to increasing the time-horizon beyond that used in the basecase.

Costs and benefits have been appropriately discounted at 3.5% and an NHS and PSS perspective has been taken. Alternative discount rates were explored by varying the discount rate for costs and benefits separately from 0 to 6% giving scenarios in which costs and benefits were discounted at different rates. None of the scenarios explored costs or benefits that fall outside of the perspective defined in the reference case.

5.2.6 Treatment effectiveness and extrapolation

5.2.6.1 Treatment effectiveness within the first 6 months

Treatment effectiveness is captured within the model through changes in four patient related outcomes: SUA, quality of life, frequency of flares and tophi resolution. Patient level data were available from the two replicate phase III RCTs (C0405 and C0406) for all four outcomes. The definition of response applied in the economic analysis was based on the following clinical continuation rule: 'Pegloticase should be discontinued if levels increase to above 360 μmol/L (6 mg/dL), particularly when 2 consecutive levels above 6 mg/dL are observed', which is consistent with the advice provided in the draft SPC. However, this clinical continuation rule differed from the definition of response applied in the (modified) ITT analysis of the clinical trials (PUA of above 360 μmol/L [6.0 mg / dL] for ≥80% of the time during months 3 and 6), so additional analyses were performed on the data from these trials to inform the economic model. These analyses also differ from the trials' (modified) ITT analyses as they treat patients who are non-persistent to pegloticase as a separate group rather than treating them as non-responders.

It should also be noted that in the phase III clinical trials, C0405 and C0406, the primary end point was based on PUA, while for the economic model the endpoints were based on SUA as specified in the clinical continuation rule. The ERG requested clarification on the probability of patients being classified as non-responders to pegloticase based on SUA levels when they would have been classified as responders based on plasma uric acid levels and vice versa. The manufacturer stated that SUA would always be spuriously lower than PUA levels making it impossible for patients to be classified as non-responders based on SUA levels who would have been classified as responders based on PUA. They also stated that whilst the opposite form of misclassification was possible, it did not occur within the trial data due to the level of agreement between PUA and SUA and the fact that two values over target (>360 μmol/L) were required for a patient to be classified as a non-responder. The ERG were satisfied with the use of SUA levels to define response within the economic model, given the level of agreement with PUA and the likelihood that SUA levels would be used in clinical practice.

Mean values for SUA, frequency of flares, tophi resolution and quality of life are presented in Tables 7.2, 7.3 7.4 and 7.7 of the MS for the pegloticase responder, pegloticase non-responder and best supportive care (placebo) groups of the two phase III RCTs (C0405 and C0406). No outcomes are presented for the pegloticase non-completer group. It is stated on page 78 of the MS that, "all clinical outcomes measured in the model for the first 6 months (SUA levels, flares, quality of life, and resolution of tophi) were recorded in the clinical trials C0405 and C0406; these were therefore not based on intermediate outcomes." However, when examining the model, the ERG found that whilst the trial data are used as inputs for mean SUA, frequency of flares and tophi resolution within the first 6 months of the model, the values implemented within the model are not those directly obtained from the trials for all groups at all time points, as can be seen in Figures 7 and 8. The efficacy data applied within the first 6 months can be summarised as follows (utility data are summarised in section 5.2.7);

- SUA levels in responders are based on data from the pegloticase arm for the first 6 months and are then maintained at 0.17 (value not sourced) during maintenance therapy. After becoming non-persistent with maintenance therapy they are based on trial data from the pegloticase non-responder group for months 6 to 12 of the model and on the baseline level for the whole trial cohort for the remainder of the model (see Figure 7).
- SUA levels in non-responders are based on data from non-responders in the pegloticase arm of the trials for 2 months and then on data from the placebo arm of the two phase III trials for the remaining 4 months once the patients have progressed to best supportive care (see Figure 7).
- SUA levels in non-completers are based on data from the placebo arm of the two phase III trials for the full 6 months (see Figure 7).

- Frequency of flares in the pegloticase arm is based directly on trial outcomes in the first 6 months for responders receiving pegloticase (see Figure 8)
- Frequency of flares in the pegloticase non-responder group is based on trial data from non-responders for 2 months and then on the SUA level (relationship described in section 5.2.6.2) once the non-responders progress to best supportive care (see Figure 8)
- Frequency of flares in the pegloticase non-completer group is based on trial data from the placebo arm for 1 month and then on the SUA level (relationship described in section 5.2.6.2) once the non-responders progress to best supportive care (see Figure 8)
- Frequency of flares for patients receiving best supportive care in the comparator arm in the first 6 months is derived directly from the trial data (see Figure 8)
- Tophi resolution is assumed to increase linearly over the first 6 months to the level seen at month 6 in the two phase III RCTs.
- The rates of infusion reactions (26%) and vomiting for the pegloticase arm are taken directly from the pooled analysis of the two phase III RCTs but the rates in the best supportive care arm are set to zero.
- The only resource use data based directly on trial outcomes was the incidence of adverse drug effects.

Figure 7 Mean SUA levels for trial data and modelled outcomes

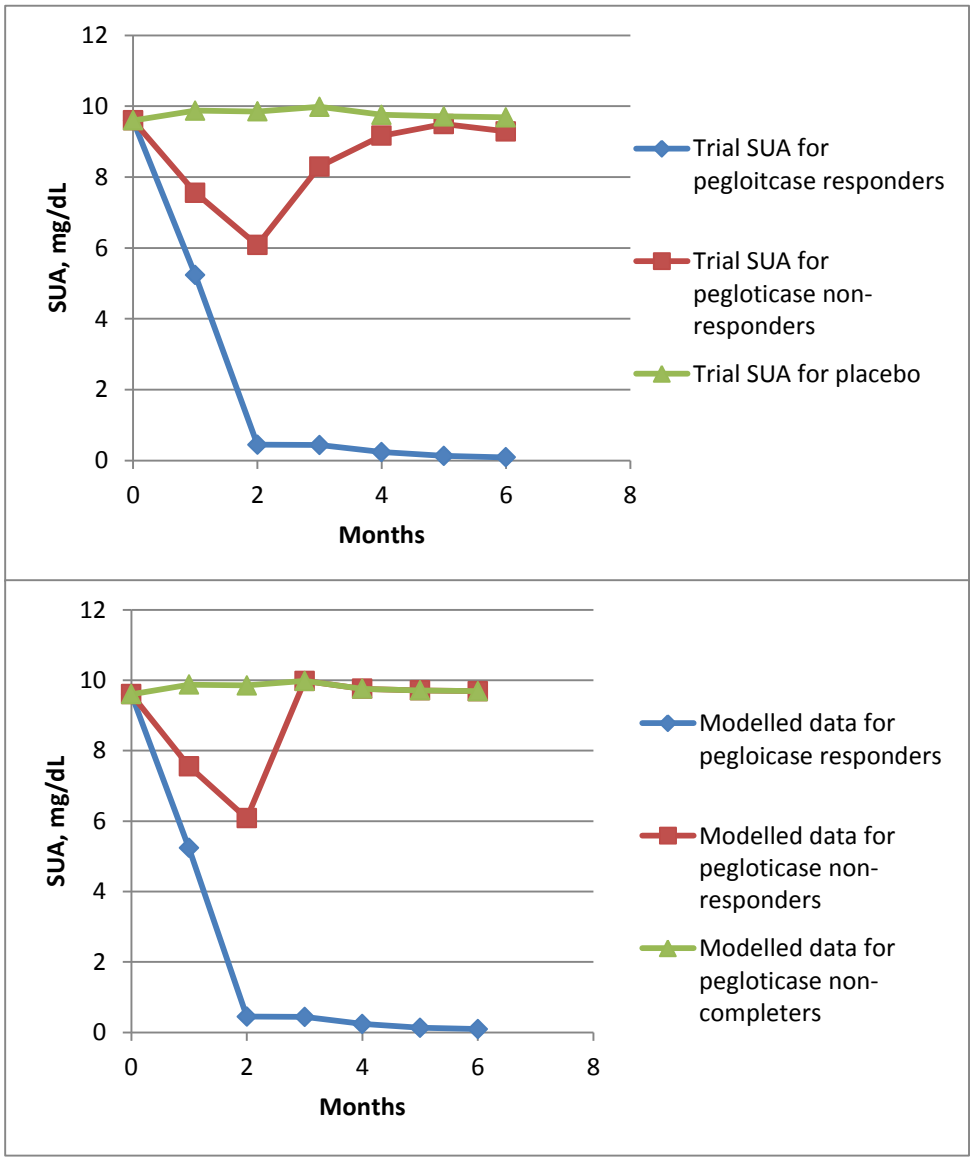
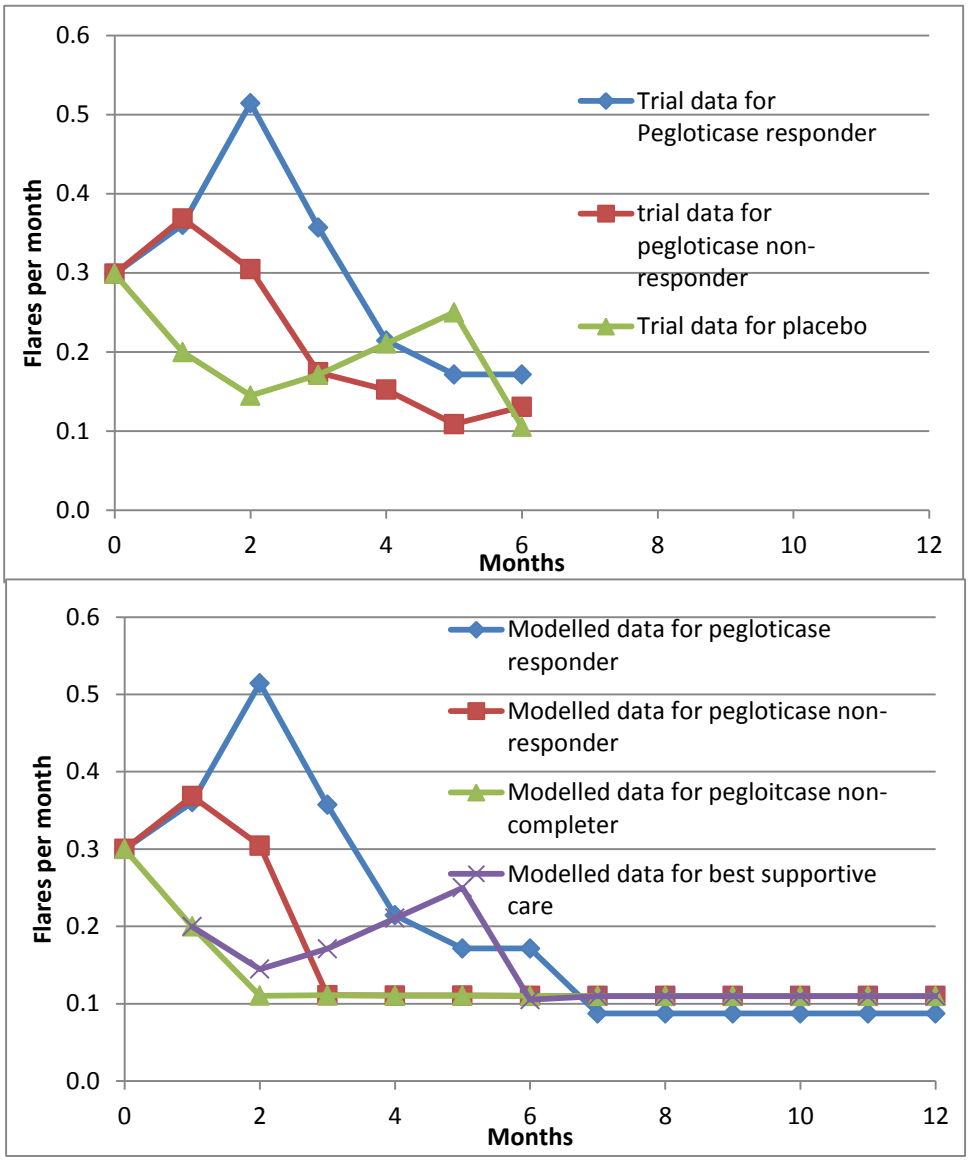


Figure 8 Mean frequency of gout flares for trial data and modelled outcomes



The frequency of flares derived from the SUA level in non-responders and non-completers receiving best supportive care are lower than those observed in non-responders in the trials, as can be seen in Figure 8 above. This may be due to the continued use of pegloticase in these patients within the trials. It is not clear whether 1 or 2 months of pegloticase treatment would be sufficient to result in a higher risk of flares for up to 6 months in non-completers and non-responders respectively. However the rates applied in these groups within the model are lower than those observed even in the placebo arm of the trial. Therefore, flares in the pegloticase arm may have been underestimated in the first 6 months. The frequency of flares in the patients receiving placebo at 6 months are similar to those modelled for best supportive care based on SUA levels at 7 months. However, the frequency of flares predicted at 7 months for pegloticase responders based on SUA levels is lower than that observed at 6 months in the trial data.

The sensitivity analyses presented by the manufacturer in which data from the literature are used to estimate outcomes within the first 6 months and data from the trial are used to estimate outcomes beyond 6 months are not as informative as they may initially appear to be. For example, when using the RCT data to estimate flares beyond the first 6 months, the rates observed in the trial are not applied directly from 6 months. Instead it is assumed that patients with a SUA under target (<360 μmol/L) have the rate of flares observed in pegloticase responders at 6 months and patients with an SUA over target all have the baseline rate of flares observed in the trial which is much higher than the rate observed in the placebo arm, or the non-responder group at the end of the trials. This results in a much higher rate of flares for patients receiving best supportive care in either model arm than was actually observed at the end of the trials and is therefore not considered to be representative of the trial. Similarly, applying data from the literature to model flares within the 6 month trial period is not particularly informative as this data is not appropriate for patients who are responding to pegloticase as an increase in flares is associated with successful urate lowering therapy. This data is already applied to pegloticase non-responders and non-completers. In effect all this sensitivity analysis does is remove any clinically significant difference between flares for patients receiving an active urate lowering therapy and those receiving best supportive care during the first 6 months when one would clinically expect to see this difference.

The ERG would support data from the placebo arm being used to model outcomes in patients who are switched to best supportive care after failure to respond to pegloticase as this better reflects the outcomes that would be expected in clinical practice once the continuation rule is applied than the trial data where no continuation rule was applied. However, the ERG does not believe that a similar justification can necessarily be made for applying best supportive care outcomes in the non-completer group. If these patients demonstrate a persistent response to pegloticase, but do so with fewer treatments than specified in the study protocol, then it would be more accurate to model the treatment effectiveness observed in this group and the average number of doses received in this group.

Alternatively, the manufacturer could have classified each non-completer patient as a non-responder and incorporated their outcomes within the mean result for non-responders. This would have been more in keeping with the modified ITT presented in the clinical effectiveness section of the MS. The ERG requested that a structural sensitivity analysis using this alternative approach be conducted by the manufacturer, but this was not forthcoming. The manufacturer did however clarify their reasons for not using this approach in their basecase, stating that this approach would dilute the observed effectiveness in the non-responder group and inflate the observed effectiveness in the non-completer group (as these two groups are merged). They therefore considered the approach used in the basecase to be “more conservative”, i.e less favourable to pegloticase, than the alternative suggested by the

ERG. Data on trial outcomes for non-completers (mean SUA, number of flares and utility by study month) were requested by the ERG but were not forthcoming. Data were also requested on the time to treatment cessation for non-completers but this was not forthcoming. This makes it difficult to judge if the approach used by the manufacturer was in fact less favourable to pegloticase than classifying non-completers as non-responders.

The ERG conducted a sensitivity analysis in which the proportion of non-completers was set to zero (in practice this was set to $1x10^{-12}$ as a rate of zero caused the model to output errors) and the proportion of responders was set to the rate observed (42%, 95%CI 32 to 54) in the pooled modified ITT analysis from the two phase III RCTs (C0405 and C0406). The results, which can be seen in section 5.3.1, showed that this didn't have a substantial impact on the cost-effectiveness. The ERG would not expect a significant difference in cost-effectiveness when using this approach as the main effect is to re-categorise non-completers as non-responders and these groups have similar outcomes within the model. However, this exploratory analysis is only realistic if the trial outcomes for non-completers were similar to those for non-responders and the average duration of treatment for non-completers was 2 months. In the absence of any data to support these assumptions it remains uncertain whether an alternative modelling approach for handling non-completers would have resulted in a higher or lower ICER.

The ERG noted that the data used to estimate tophi resolution in the economic model (Table 7.4 of the MS) were different from that cited in the clinical effectiveness section of the MS (Table 6.11). This may be partly due to the exclusion of non-completers from the data set used to populate the economic model and partly due to the different criteria used to determine response in these two analyses. It could also be due to different criteria being used to determine the population at risk for this outcome. The denominator is described in Table 6.11 as "no. evaluable patients", whereas in Table 7.4 it is described as "patients with identifiable tophi at baseline". The ERG noted that the data applied in the model was likely to be less favourable to pegloticase than the data reported in the clinical effectiveness section due to the higher rate of tophi resolution in the placebo arm in the data applied in the model.

The ERG also noted that the proportion with tophi resolution from Table 7.4 of the MS are applied to all patients within the model and not to the subgroup with tophi at baseline (only 91/128 patients had tophi at baseline across the pegloticase every 2 weeks and placebo arms of the two phase III trials, C0405 and C0406). This may have overestimated the treatment benefit of tophi resolution and therefore biased the analysis in favour of the pegloticase arm. The ERG conducted a sensitivity analysis in which it was assumed that only 71% of patients have tophi at baseline. To do this they estimated model outputs for the population without tophi at baseline, by setting the proportion with

tophi resolution to100% for all groups at the start of the model. The manufacturer's basecase already implicitly assumes that 100% have tophi at baseline providing model outputs for those with tophi at baseline. They then calculated a weighted average of the outcomes from these two models to estimate the mean for costs and QALYs in a population where 71% have tophi at baseline. It should be noted however, that the proportion of patients receiving pegloticase in clinical practice who have tophi at baseline may be higher than observed in the trials due to the wording of the draft license indication which includes the term "tophaceous gout".

5.2.6.2 Extrapolation of treatment effectiveness beyond 6 months

The model extrapolates the benefits of pegloticase treatment beyond the trial period of 6 months by making assumptions regarding the stability of SUA levels after treatment. In pegloticase responders, it is assumed that the SUA level achieved at the end of 6 months of treatment will be maintained by continued treatment with febuxostat or allopurinol until the patient becomes non-persistent to these maintenance therapies. In patients receiving best supportive care, which includes all patients in the comparator arm and non-responders and non-completers in the pegloticase arm, it is assumed that at 6 months the patient's SUA level returns to the mean baseline level from the two phase III clinical trials (C0405 and C0406). Beyond 6 months, the number of flares is determined by the patient's SUA level based on the data in Table 18. Quality of life is determined by the following three factors; SUA level, whether the patient has experienced tophi resolution and the frequency of flares (see section 5.2.7 for critique of this relationship). Tophi resolution is assumed to be maintained in 100% of responders and 50% of non-responders for the entire time-horizon of the model. Therefore all treatment benefits achieved by pegloticase responders during pegloticase treatment are assumed to be fully maintained for the duration of maintenance therapy and some of the benefits of tophi resolution in both responders and non-responders are maintained for the entire duration of the model.

Table 18 Frequency of flares by SUA state.

SUA (µmol/L) **SUA (mg/dl)**	**≤360** **≤6**	**≥360 - <480** **≥6-<8**	**≥480 - <600** **≥8-<10**	**≥600** **≥10**	**Reference**
Flares (mean±SE)	0.087±0.005	0.099±0.005	0.109±0.006	0.116±0.006	(Febuxostat STA ERG report 2008)

STA=Single Technology Appraisal

In the clinical effectiveness section, on page 63 of the MS, it is stated that "continuation of these benefits beyond six months is supported by the open-label extension study". Whilst in the cost-effectiveness of the MS, section 7.7.1, it is stated that "long-term outcomes were based on the literature; no clinical trial was performed in this period." Further details on outcomes from the OLE study, were requested by the ERG, but as described in section 4, a large amount of anonymised

subject data from the OLE were provided by the manufacturer and it was not possible for the ERG to analyse these within the given timeframe.

In response to a request for clarification the manufacturer stated that the assumption that low SUA levels achieved in the trial can be maintained in the long-term was based on a similar assumption in the manufacturer model submitted for the NICE appraisal of febuxostat. As was reported in the ERG report for TA164 covering the economic evaluation of febuxostat, it was assumed that patients remained in the SUA group and that the percentage of patients with SUA < 360 μmol/L (6 mg/dL) remained relatively constant across time (Stevenson, *et al.* 2008)[36]. This assumption was based on the febuxostat EXCEL trial with follow-up of over 2 years and 145 patients treated with allopurinol (Becker, *et al.* 2007).[37] However, the ERG noted that the population enrolled in the EXCEL trial was not representative of those likely to receive pegloticase in clinical practice, as only patients who achieved SUA levels of less than 6 mg/dL on either allopurinol or febuxostat continued to participate in the EXCEL study long-term and these patients wouldn't be eligible for pegloticase treatment. The population eligible for pegloticase treatment could potentially have more treatment resistant gout and be less likely to maintain SUA levels in the long-term.

Clarification was also requested regarding the methodology used to estimate the relationship between SUA level and mean number of flares per month, including information on the patient population on which the analysis was based and the method used to account for confounding variables. In response the manufacturer stated: "The relationship between SUA level and mean number of flares per month was derived from the ERG report of the HTA submission of febuxostat to NICE (Stevenson *et al.* 2008)[36], and was also reported in the manufacturer submission for febuxostat. …….This is the only known study that provides such data that can be used in economic modelling. Unfortunately, the methodology for estimating this relationship was not described in detail in the ERG report or other publicly available sources of data of the HTA submission." It is therefore difficult for the ERG to critique this evidence. However Stevenson *et al.*[36] made the following comments; "the ERG believes that this is the bivariate analysis and that within this data set there was no significant link between SUA levels and the number of gout flares. However this does not mean that there would be no relationship detected were a bigger or different data set analysed." Whilst the ERG's clinical advisors considered it plausible that SUA levels would be related to the frequency of flares, the ERG consider there to be substantial uncertainty regarding this relationship.

The amount of benefits accrued beyond the trial period is heavily driven by the duration of persistence on maintenance therapy. In addition to the ERG's concerns described above regarding the Weibull model used to extrapolate long term persistence from the Annemans study,[4] it should also be noted that this is indirect evidence and doesn't reflect persistence in patients using maintenance therapy

following pegloticase treatment. The patients included in the analysis by Annemens *et al*. were not selected by gout severity and therefore that population is also unlikely to be representative of the population likely to receive pegloticase in clinical practice.

The absolute treatment benefit estimated by the model is dependent on the mortality rate applied as patients who respond to pegloticase treatment continue to accrue the benefits of achieving a low SUA level either until they become non-persistent to maintenance therapy or they die. The mortality rates applied in the model are described in section 7.10.3 of the MS as being UK specific, but no further details are given in section 7 of the MS. Text within the spreadsheet model itself suggest that the source for mortality data is the East of England Public Health Observatory.[38] Having looked at the data table cited within the model, the ERG understand that the mortality rates are based on Office of National Statistics data for 2001 to 2007 and the rate applied in the model is that for all persons. It is therefore not weighted according to the gender distribution of people with gout, 80% of which are male[4]. This will have underestimated mortality rates, as the male specific rates are higher for all age bands over 55 and the model's starting age is 56. Furthermore, in section 2.3 of the MS it is stated that, "gout is an independent risk factor for all-cause and cardiovascular mortality (Kuo *et al*., 2009).[39]" One would therefore expect the rate of mortality applied in the model to be higher than that for the general population of the UK. The ERG believe that mortality has been underestimated in the model and expect this to result in treatment benefits for pegloticase being overestimated.

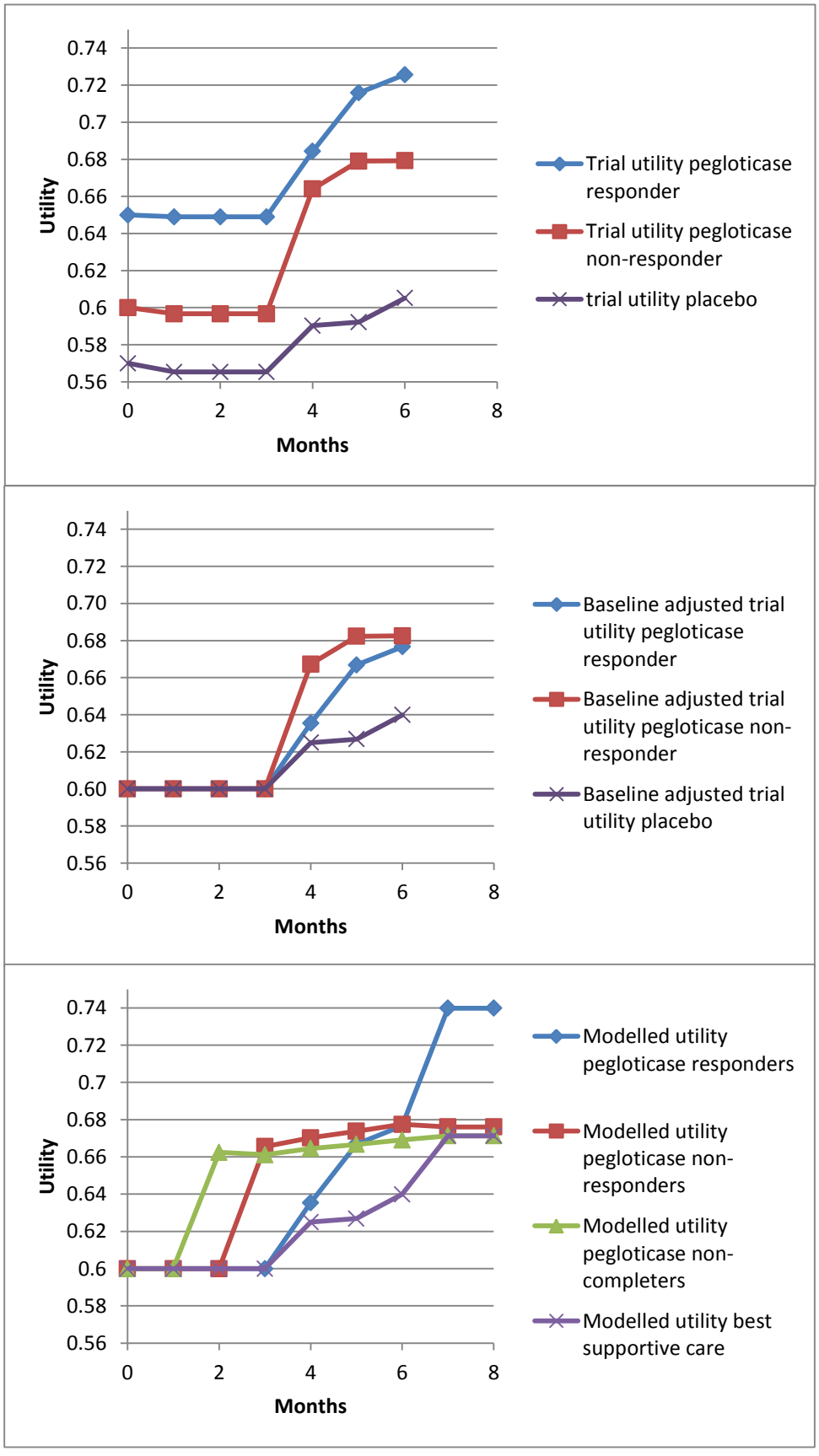
Only one study regarding mortality risk was cited in the MS and this gave an all-cause mortality hazard ratio for gout of 1.46 (95%CI 1.12 to 1.91).[39] The ERG requested that the manufacturer provide further information regarding mortality in the population eligible to receive pegloticase relative to the general population, but were informed by the manufacturer that no published data were available on the mortality rate in severe debilitating chronic tophaceous gout in the UK. In the absence of a systematic review of literature on the hazard ratio for the population eligible to receive pegloticase, the ERG conducted an exploratory analysis in which the mortality risk was doubled to assess whether mortality is a significant drive of cost-effectiveness. The results, which can be found in section 5.3.1 below, show that mortality isn't a significant driver of cost-effectiveness so further effort was not invested to accurately determine the mortality rates for the population likely to receive pegloticase. The manufacturer also provided further sensitivity analyses in which the mortality rates were varied by 10% above and below the general population rates, see Table 29 in section 5.2.10 below, but they also found that this had a marginal impact on the ICER.

5.2.7 Health related quality of life

5.2.7.1 Utility data from trials C0405 and C0406

SF-6D health utility were computed from SF-36 trial data based on the mean scores across all 8 domains of the SF-36, as recently validated by Ara and Brazier (2009)[40] and validated against the EQ-5D. This was considered by the ERG to be an appropriate method of obtaining utility values from the trial given that EQ-5D data were not collected directly from trial participants. The SF-36 has been validated for use in the gout population (Kawata *et al*., 2007)[41]. Mean utility values for the pegloticase responder, pegloticase non-responder and best supportive care (placebo) groups of the two phase III RCTs (C0405 and C0406) are provided in Table 7.7 of the MS and are also shown below in Figure 9. No utility outcomes were provided by the manufacturer for the pegloticase non-completer group. It can be seen from Figure 9 that the baseline differences in mean utility between the pegloticase responder group and the placebo group were of a similar magnitude to the changes in utility achieved by treatment. In order to adjust for these differences within the model, the change from baseline for each group is applied to the mean utility score at baseline which is reported as 0.60. It was noted by the ERG that this value is lower than the baseline SF-6D score in the "pooled population" for the two phase III RCTs (C0405 and C406) of 0.656, given by Strand *et al.,* (2012)[27], although this discrepancy was not noted by the ERG early enough to request clarification from the manufacturer. This may be due to the inclusion of patients from the monthly pegloticase treatment arm of the trials within the figure quoted by Strand *et al.,* (2012)[27], or due to the exclusion of non-completers from the analysis used to population the model. The adjusted values applied in the model are also shown in Figure 9.

Figure 9 Mean utility for trial data, baseline adjusted trial data and modelled outcomes



5.2.7.2 Secondary sources of utility data provided within the submission

The manufacturer states that a systematic search was conducted to identify HRQoL outcomes in refractory chronic gout but no published studies were identified in abstract or full paper form that provided relevant utility data in refractory chronic gout (including severe debilitating refractory chronic gout). Whilst some studies presenting HRQoL outcomes were identified, in general none of these studies presented utility data according to SUA levels as defined in the economic model. Therefore, documentation relating to the NICE and SMC appraisal of febuxostat were also reviewed and these are cited as the source data for information regarding the relationship between flares, SUA and utility given in Table 7.9 of the MS and detailed in Table 19 below.

Table 19 Quality of life values derived from literature

Components of utility calculation (febuxostat SMC report)	
Base utility (mean±SE *)	0.75±0.019
Disutility per SUA state (mean±SE **)	0.034±0.0034
Disutility per flare (mean±SE **)	0.0097±0.00097

* SE assumed to be the same as for utilities in trials C0405 and C0406

** SE assumed to be 10% of the mean

Whilst none of the studies identified in the manufacturer's systematic review of HRQoL literature provide utility values directly applicable to the health states within the model, they do provide some information regarding the strength of the relationship between HRQoL and various measures of disease severity. The paper by Becker *et al.* (2009)[42] provides data on the correlation between baseline clinical measures of gout severity and SF-36 scores in a population with treatment-failure gout similar to the population likely to receive pegloticase under the draft SPC. In this study SUA was correlated strongly with other clinical outcomes but no significant direct association was observed between SUA and HRQoL outcomes. Conversely presence of tophi, number of flares and number of swollen or tender joints were all significantly associated with HRQoL. Hirsch *et al.* (2010)[43] report that a gout specific HRQoL measure was significantly associated with frequency of gout flares and pain between flares, but not SUA level, presence of tophi or the number of joints involved in a flare. An observational study reported by Khanna *et al.* (2010)[44] found that reduction in flares independently predicted improvements in three SF-36 physical scales when adjusting for age, presence of tophi, presence of comorbidities, baseline joint involvement, baseline serum urate and change in serum urate. Baseline SUA also independently predicted improvements in two SF-36 domains and the SF-36 PCS score. Presence of tophi, comorbidities and joint involvement were not independent predictors of improvement in HRQOL in this study. A cross-sectional study reported in abstract form by Khanna *et al.* (2011)[45] found that greater HRQoL burden was associated with higher numbers of flares and the presence of tophi although it is unclear whether these were both independent predictors. These

studies, cited by the manufacturer in their submission, demonstrate that the evidence regarding whether SUA, flares and tophi are all independent predictors of HRQoL in patients with gout is inconsistent between studies. A more rigorous systematic review on this question would be beneficial but was not possible within the timeframe available to the ERG.

5.2.7.3 Utility values applied in the model

It is stated on page 78 of the MS that the quality of life outcomes applied within the first 6 months of the model were recorded in the clinical trials C0405 and C0406. However, when examining the model, the ERG found that whilst the trial data are used as inputs for utility within the first 6 months of the model, the values implemented within the model are not those directly obtained from the trials for all groups at all time points, as can be seen in Figure 9. The assumptions used to implement the trial data can be summarised as follows;

- Utility values from the trial were adjusted to account for baseline differences which favoured the responder and non-responder groups of the pegloticase arm over the placebo arm (see Figure 9).
- Utility levels in pegloticase responders are based on trial data for the first 6 months whilst they continue pegloticase treatment (see Figure 9)
- Utility levels in non-responders are based on data from non-responders in the pegloticase arm of the trials for 2 months and then on SUA levels, frequency of flares and tophi resolution (see Table 20) for the next 4 months whilst the patient receives best supportive care (see Figure 9).
- Utility levels in non-completers are based on data from the placebo arm of the pegloticase arm of the trials for 1 month and then on SUA levels, frequency of flares and tophi resolution (see Table 20) for the next five months whilst the patient receives best supportive care (see Figure 9).
- Utility levels in the comparator arm are based on data from the placebo arm of the trials for 6 months (see Figure 9)

The utility values applied in the model after 6 months (and in some patients before 6 months) are based on a combination of SUA level, frequency of flares and tophi resolution. The utility values applied in the model based on these three factors are shown in Table 20 below. In patients with tophi (i.e those who did not achieve the trial outcome of tophi resolution) the utility decrement per SUA state from Table 19 is applied incrementally for each state above the target (>360 μmol/L). A utility decrement is also applied based on the frequency of flares for each SUA state (given in Table 18) and the disutility per flare given in Table 19. In patients without tophi (i.e those who achieved tophi resolution in the trial), no utility decrement is applied per SUA state leaving just the impact of flares on utility by SUA state. This results in there being a utility gain attributable to tophi resolution which varies from 0.102 in patients with the highest SUA level (>600 μmol/L) to zero in patients with an

SUA level under target (≤360 μmol/L). The average difference between those with and without tophi in patients receiving best supportive care at 1 year is 0.076, based on this group having the distribution of SUA levels observed in the trial population at baseline (9.60mg/dl, SE=0.15mg/dl).

Table 20: Utility values applied in the model by SUA state for people with and without tophi

SUA category (μmol/L)	**≤360**	**>360 ≤480**	**>480 ≤600**	**>600**
Utility in patients with tophi	0.740	0.704	0.669	0.634
Utility in patients wihout tophi	0.740	0.738	0.737	0.736

5.2.7.4 Concerns regarding the application of utility data within the model

It can be seen from Figure 9 that the utility in pegloticase non-responders and non-completers after they switch to best supportive care is higher than the utility in patients receiving best supportive care in the comparator arm. Furthermore it is also higher at some points than the utility in pegloticase responders. This is because the utility levels derived from SUA levels, flares and tophi resolution are higher than those derived directly from the trial data, which generates an unrealistic treatment benefit for non-responders and non-completers receiving best supportive care relative to patients in the comparator arm receiving best supportive care even though the SUA levels were the same. A sensitivity analysis is presented in the MS in which utility values are based on SUA levels and tophi resolution for the entire model population and model duration. This doesn't significantly alter the ICER suggesting that utility gain in the first 6 months is a small factor overall, which appears reasonable given that utility gains in pegloticase responders are extrapolated over a long-period.

The sensitivity analysis which is described as applying the RCT data beyond 6 months is not particularly informative as it applies the utility observed at the end of the trial in responders to all patients with an SUA level under target (<360 μmol/L), and the mean utility from baseline across the whole trial cohort to all patients with an SUA level above target, which is effectively all patients receiving best supportive care. The long-term utility values predicted by this approach for the best supportive care arm are much lower than the baseline adjusted utilities for placebo observed in the trial (0.61 vs 0.64) whilst the values for pegloticase responders are similar to those observed in the trial (0.68 and 0.68). This sensitivity analysis is therefore not considered by the ERG to constitute a fair extrapolation of the utility outcomes from the RCT.

The ERG had concerns that the method for calculating utility from the SUA level, frequency of flares and tophi resolution may result in quality of life improvements being 'double counted' as all three of

the factors used to derive utility are likely to be correlated in an individual. For example, tophi resolution is likely to be correlated with low SUA levels, but the model assumes that the probability of having tophi resolution is the same irrespective of the SUA level achieved and applies a utility benefit for both tophi resolution and low SUA levels. However, the ERG also notes that there are not many instances within the model where this 'double counting' applies in practice as the division of patients into responders and non-responders provides groups which fall largely to one side of the target (360 μmol/L) or the other, such that utility benefits are derived in practice to a large extent from either SUA levels or from tophi resolution and not from both in the same group.

The ERG did not understand why utility was allowed to vary by SUA level in those with tophi but not in those without tophi. If SUA is correlated with symptoms other than tophi and flares, resulting in an additional utility decrement over and above that derived from tophi and flares, it does not seem logical that these symptoms would not affect people without tophi in a similar manner. If tophi resolution is a proxy for low SUA levels, then the model should capture this correlation ensuring that all patients with tophi resolution in the model also have SUA levels under target. This would also avoid the potential for 'double counting' benefits from these two outcomes which is possible when the correlation between these two outcomes is ignored.

There is a similar risk of 'double counting' when capturing both the benefits of flares and lowering the SUA level, as the frequency of flares is assumed to be related to the SUA level within the model and both are treated as independent factors in determining utility. This type of 'double counting' is more problematic in practice as both utility gains are applied to all patients from 6 months and to those patients in the pegloticase arm of the model who receive best supportive care prior to 6 months. The potential for double counting benefits in this manner may have been avoided if the data on the relationship between SUA and utility has been properly adjusted to take into account the frequency of flares as a confounding factor, providing an estimate of the disutility per SUA state in the absence of flares. However, the ERG is not satisfied based on the information provided in the MS that this has been done in the analysis used to generate the utility decrements given in Table 19.

The MS states that the relationship between SUA level and utility in the model beyond 6 months is based on data from the NICE Technology Appraisal of febuxostat (TA164). Limited details have been provided by the manufacturer regarding the methods used to derive this relationship and whether this took into account flares and other potentially confounding factors such as the presence of comorbidities. The data are described on page 86 of the MS as being, "based on a European observational study in chronic gout patients with HRQL/utility measure by EQ 5D and utilities per SUA state derived by regression analysis." It is difficult for the ERG to critique the robustness of these data based on the limited information provided in the MS. However, in the ERG report for

TA164, Stevenson *et al*.[36] made the following comments; "The relationship between SUA level and underlying utility also remains uncertain. Whilst the data appear to suggest that increased SUA levels lead to lower overall utility, the possibility that confounders not collected in the data set could explain this relationship cannot be ruled out." The Committee's concerns regarding the "direct and continuous relationship between utility and serum uric acid concentration" are noted in the Final Appraisal Determination for TA164. In section 4.13 of the FAD it is stated that, "The Committee remained concerned .... that although this relationship was plausible, evidence supporting it was uncertain and not clearly established."

An additional analysis by the ERG group on TA164 was conducted to establish the ICER when assuming no QALY gain associated with the 'chronic utility gain' from lowering SUA levels. This increased the base-case ICER for febuxostat compared with fixed dose allopurinol from £15,000 to £81,000. In section 4.12 of the FAD for TA164 it is stated that, "Although the Committee was persuaded that removal of the 'chronic utility gain' [associated with lowering SUA] would lead to an underestimation of the long-term clinical benefits of febuxostat treatment, it considered that the true base-case ICER, even when compared with fixed-dose allopurinol, would be within a wide range of between £15,000 and £81,000 per QALY gained."

In the light of the approach taken in the febuxostat appraisal, the ERG have also conducted an exploratory analysis in which utility is not dependent on SUA level except through the impact of SUA levels on the frequency of flares. This was done by setting the disutility per SUA state to zero. In the manufacturer's analysis a utility gain for patients without tophi was implemented by applying the utility for patients with SUA levels under target (<360 μmol/L) to all patients without tophi. Therefore when the ERG set the disutility per SUA state to zero, this also removed any benefit of having resolved tophi. On advice from their clinical advisors that tophi resolution is associated with quality of life improvement, the ERG have included the utility gain, from the MS, of 0.076 to all patients with tophi resolution. However, the ERG was also concerned that the baseline utility value of 0.75, which was also taken from the febuxostat appraisal, was not applicable given the severity of gout in this population. The baseline utility for patients with tophi (and without flares) was set to 0.68 which was the utility in non-responders at the end of 6 months. This was considered reasonable given that tophi resolution was achieved in 26% of responders, suggesting that utility values may be even lower in those with tophi. The utility values by SUA for patients with and without tophi under this exploratory analysis are shown in Table 21 below. They vary across SUA states due to the frequency of flares differing across the SUA states. It can been seen that once the utility gain associated with tophi resolution is applied, the utility value for patients with an SUA level under target (<360 μmol/L) and without tophi is slightly higher than that seen at 6 months (utility of 0.73) in pegloticase responders, of whom 62% had tophi resolution.

The manufacturer also supplied a sensitivity analysis removing the relationship between SUA and utility such that utility was based solely on tophi resolution and flares. In their analysis they applied a utility of 0.75 to patients with an SUA under target (360 μmol/L), without flares but with tophi, giving utility values ranging from 0.736 to 0.740 for patients with tophi. They maintained the gain of 0.076 between those with and without tophi giving utility values ranging from 0.813 to 0.816 in those without tophi. These utility values were considered by the ERG to be high in comparison to the utility values achieved within the trials by responders. The results of the manufacturer's sensitivity analysis and the ERG's sensitivity analysis can be found in sections 5.2.10 and 5.3.1 respectively.

Table 21 Utility values by SUA state for the ERG's exploratory analysis assuming that disutility is dependent only on flares and tophi resolution and not directly on SUA.

SUA category (μmol/L)	**≤360**	**>360 ≤480**	**>480 ≤600**	**>600**
Utility in patients with tophi	0.669	0.668	0.667	0.666
Utility in patients wihout tophi	0.745	0.744	0.743	0.742

The ERG are not certain that other factors such as the presence of comorbidities which are correlated with uncontrolled urate levels and the development of tophi have been properly accounted for in the analyses by Khanna *et al.*,(2011)[44] and Khanna *et al.*,(2011)[45] which are used to justify the utility difference between patients with and without tophi. Furthermore, the trial outcome of "tophi resolution" is defined as a "100% decrease in an area of at least one prespecified target tophus without progression or appearance of any new tophus". This means there could be other tophi remaining in patients achieving the trial outcome of "tophi resolution". The HRQoL benefit of this trial outcome may therefore not be equivalent to the HRQoL difference between patients with and without any tophi. The MS also states that their assumptions regarding tophi reformation are "somewhat arbitrary" and "further study from literature or clinical experts regarding this assumption is on-going". In response to the ERG's request for clarification on this point the MS stated that, "we have been conducting further discussions with a key clinical expert who verified that an assumption of 50% reformation is a reasonable basecase assumption and reasonably reflective of that seen in clinical practice in chronic gout (Professor of Rheumatology from a Northern England treatment centre)." However, given that this statement is based on expert opinion alone, the ERG believes that there is considerable uncertainty regarding the long-term maintenance of health benefit achieved through tophi resolution. The ERG therefore conducted an additional sensitivity analysis in which the only HRQoL benefit is that provided by a reduction in gout flares. Although the ERG accept that there is likely to be some benefit attributable to the trial outcome of tophi resolution based on the expert

opinion of the ERG's clinical advisors.

The manufacturer also provided an additional sensitivity analysis, in response to a clarification request, regarding the utility benefit of tophi resolution in which they assumed no utility gain directly attributable to tophi resolution. However, in their sensitivity analysis they kept both the utility gain attributable to gout flares and that attributable to lowering SUA. The results for this sensitivity analysis, which can be found in section 5.10.2, show that the cost-effectiveness results are reasonably sensitive to whether an additional utility gain is attributed to tophi resolution.

5.2.7.5 Comparison of modelled utility against trial data

The difference in mean utilities between the two model arms is greatest at month 4 when it reaches 0.042. This does not appear to be too dissimilar from the difference in utilities between the pegloticase and placebo arms of the trials at 6 months after adjusting for baseline differences (see Table 7.8 of MS which shows 0.68 for both pegloticase responders and non-responders and 0.64 for placebo). These difference in mean utilities between the trial arms within the economic model appear to be modest in the context of the SF-6D values from the two phase III trials (C0405 and C0406) reported by Strand *et al*. (2012) which show a mean improvement from baseline of 0.128 for pegloticase every two weeks and a mean deterioration of 0.008 for placebo (mean changes from baseline are not reported to be statistically significant at p=0.05). This suggests that the model may be underestimating utility gain during the initial 6 months, although it is unclear why there is such a discrepancy between the values reported by Strand *et al.*[27] and those provided in Table 7.7 of the MS. A similar discrepancy was noted in the mean change from baseline for the SF-36 PCS outcomes as noted in section 4. These discrepancies could be due to the exclusion of non-completers from the analysis used to population the model.

5.2.8 Resources and costs

The cost-effectiveness analysis described in the original submission was based on the anticipated price of pegloticase as the final price had not been confirmed at the time of submission. The ERG's report is based on the cost-effectiveness analysis provided in the original submission, but further clarification was sought from the manufacturer regarding the final price. The ERG also requested that the manufacturer provide a set of sensitivity analyses showing the variation in the ICER across the range of prices considered to be plausible by the manufacturer in order to allow the committee to determine the manufacturer's basecase ICER once the final price is confirmed. In response, the manufacturer clarified that the price included in the economic model and submission represents the maximum expected list price but no sensitivity analyses on alternative plausible prices were provided.
The ERG's clinical advisors were satisfied that 3.5 hours was a reasonable estimate of nurse time required for administering pegloticase and monitoring patients to detect and treat infusion reaction.

They was uncertain as to whether any additional pharmacy time would be required and the ERG requested clarification on this matter from the manufacturer. A sensitivity analysis assuming 5 minutes of pharmacy time at a total cost of £2.02 per infusion was subsequently provided by the manufacturer. This had a marginal impact on the ICER, as can be seen in section 5.2.10.

The ERG were satisfied with the justification given for including infusion reactions in the model. However, the basis for the inclusion of vomiting was not considered by the ERG to be explicit. The manufacturer stated that the HRQoL impact of all adverse events are already captured in the economic model, as SF 36 data measured in the trials (C0405 and C0406) are used to model utility outcomes using the SF 6D algorithm. They did not consider that any of the other adverse events, listed in Table 6.17 of the MS, that have a higher incidence for pegloticase than placebo, namely nasopharyngitis (common cold), pruritus (itching) and contusion (bruises), would be expected to have significant impact on patient quality of life or medical resource use. The ERG noted that chest pain was more common in the pegloticase 8 mg every 2 weeks arm of the pooled phase III trials (C0405 and C0406), however exclusion of this adverse event from the model was not justified. The ERG also noted that the rate of infusion reactions applied in the pegloticase arm within the model was based on the pooled analysis of data from C0405 and C0406 without any adjustment made to account for the anticipated reduction in infusion reactions expected as a result of applying the clinical continuation rule (see page 61 of the MS). This may have biased the analysis in favour of best supportive care, although the ERG would expect the impact on the ICER to be marginal.

The ERG was satisfied that the drug costs for maintenance therapy, flare prophylaxis and treatment of adverse events in Table 7.14 of the MS were reasonable and based on current prices from the BNF. With regards to infusion reaction prophylaxis, there appeared to be discrepancy between the drugs used in the trial protocol and those applied in the model. It was stated in the cost effectiveness section (page 94 of the MS) that "gout flare prophylaxis was used in patients treated with pegloticase with either 1 mg/day of colchicine or 500 mg/day of naproxen (50%/50% split between colchicine and naproxen was assumed) for the duration of pegloticase treatment; chlorpheniramine 20 mg IV and methylprednisolone 2000 mg IV drugs per pegloticase infusion." After a request for clarification, the manufacturer confirmed that the prophylaxis drugs applied in the model were those likely to be used in UK clinical practice and these differed from those used in the trial. Two of the ERG's clinical advisors noted that the dose of steroid given as flare prophylaxis within the model may be contraindicated in those patients with cardiac comorbidites but were otherwise satisfied that these treatments represented appropriate flare prophylaxis.

The unit costs for A&E attendance and hospital admission in Table 7.15 are taken from PSSRU Unit Costs (Curtis, 2011)[46] rather than from the Department Health reference costs for a specific HRG

code[47] and are therefore general estimates and not specific to patients with a diagnosis of gout. The ERG was advised by their clinical experts that infusion reactions were unlikely to result in A&E attendance and admission as they would be managed by the staff in attendance on the ward where the infusion is being administered. The model is therefore considered to overestimate the cost of infusion reactions which may have biased the results in favour of best supportive care, although the ERG did not expect the influence of this factor to be significant.

It is stated in the MS that the model assumes that SUA levels are monitored every 3 months in all patients and every 6 weeks in patients receiving pegloticase, although the ERG noted that monthly SUA testing is actually implemented within the model. The model also assumes that patients will receive liver and renal function tests at the start of pegloticase treatment. The draft SPC specifies that SUA levels are measured prior to each infusion and therefore the 6 weekly monitoring incorporated within the model was considered by the ERG to underestimate the additional cost of SUA monitoring associated with pegloticase treatment. The ERG's clinical advisors did not believe that routine SUA testing would be beneficial in patients receiving best supportive care as the test results would be unlikely to result in a change in care and thus the cost of SUA monitoring may have been overestimated in the comparator arm. However, given the low cost of SUA testing cited by the manufacturer, these factors are unlikely to have a significant impact on the ICER. This is supported by the sensitivity analysis on SUA testing provided by the manufacturer which increased SUA testing from once to twice monthly, but which had a marginal impact on the ICER (see Table 29 below). The ERG requested clarification regarding whether the cost of testing included both laboratory and phlebotomy costs, but the manufacturer could not be certain as these costs were also taken from the Ipsen submission[35] for the NICE appraisal of febuxostat where they are simply described as 'unit costs'. The ERG's clinical advisors commented that SUA results would be needed prior to the infusion and therefore expected that a separate phlebotomy appointment would be required. However, the ERG did not believe that the addition of phlebotomy costs would be likely to substantially increase the ICER.

The model originally submitted by the manufacturer did not include a cost for G6PD deficiency testing despite stating that, "all patients at a higher risk for G6PD deficiency should therefore be screened for G6PD deficiency before starting pegloticase" in section 1.12 of the MS. This statement is supported by similar statements in the draft SPC. Further details on the cost of screening for G6PD were requested from the manufacturer who estimated that the cost per patient receiving pegloticase treatment would be £0.43 based on 2% of patients being tested and 10% of those being positive with a cost of £19.23 per test. Incorporation of these costs for G6PD deficiency testing into the economic model did not have a significant affect on the ICER. The ERG were satisfied, after conducting

sensitivity analyses on the proportion receiving tests, that this was not a significant driver of cost-effectiveness.

In the model it is assumed that each year 2% of patients with tophi receive surgery to remove their tophi. The ERG's clinical advisors did not consider surgery to remove tophi to have a place in the current management of gout although they conceded that it does still happen occasionally. The manufacturer was requested to provide further details justifying the applicability of this rate of tophi surgery to current UK practice, but this was simply described as being "based on discussion with UK gout clinicians". The ERG conducted an exploratory sensitivity analysis removing tophi surgery from the model. The results can be found in section 5.3.1. The ICER was only moderately increased suggesting that tophi surgery isn't a significant driver of cost-effectiveness.

The cost of gout flares was based on information presented in the SMC Advice for febuxostat which was limited to an estimate of the mean cost per gout flare.[48] The standard error was not reported in the SMC guidance and therefore had to be estimated by assuming it was 10% of the mean. The cost is described in the MS as being, "derived from the observational study conducted for the febuxostat submissions to NICE and SMC…..and was stated to include the costs of hospitalisation and outpatient visits for a flare." It is difficult for the ERG to critique this evidence based on the limited evidence provided in the MS. This is compounded by the fact that information regarding this cost is marked as commercial in confidence within the Ipsen submission for the febuxostat STA[35] with further details provided by a report which is not in the public domain.[49] Stevenson *et al.*[36] made the following comment on this cost data in the ERG report for the febuxostat STA; "The methodology used to calculate costs were provided in a report that was received, after delay, by [Stevenson *et al.*] and does not appear to be incorrect." We have varied the cost per flare from zero to £500 in a sensitivity analysis to determine whether this parameter is a significant driver of cost-effectiveness. The results which can be found in section 5.3.1, show that overall gout flares are prevented by pegloticase, resulting in a lower ICER when the cost of flares is increased and a higher ICER when the cost is decreased. However, varying this parameter from zero to £500 only resulted in marginal changes in the ICER suggesting that this parameter is not a significant driver of cost-effectiveness within the manufacturer's basecase.

The cost of gout management outside of that related to flares is summarised in Table 7.12 of the MS and in Table 22 below. It is assumed that the cost of gout management is higher in patients with SUA levels above the target (>360 μmol/L) i.e those with uncontrolled urate levels. These data were elicited from a survey of 6 rheumatologists from around the UK whose area of expertise was gout and a further in-depth telephone interview was conducted with a Professor in Rheumatology based in an England treatment centre with experience in the treatment of severe debilitating refractory chronic

tophaceous gout. These costs are applied to all patients within the model regardless of whether they are receiving pegloticase or best supportive care. Based on the same survey of expert opinion, additional rheumatology visits (see Table 23) were also applied to patients treated with pegloticase, although the ERG noted that in practice these costs were only applied within the model to pegloticase responders, and not to those in the pegloticase arm who were classified as non-completers or non-responders. They were also only applied until the pegloticase responder progressed to best supportive care i.e whilst on pegloticase or maintenance therapy. The ERG's clinical advisors commented that most gout care in England and Wales is provided within a primary care setting, with GP visits in patients with an SUA level over target (>360 μmol/L) likely to be higher than the rate shown and rheumatology visits likely to be lower than the rate shown. They commented that patients with uncontrolled urate levels could have high resource use including emergency department visits and hospital admission but that resource use was likely to be related to the number of flares rather than to the SUA level. The ERG requested clarification from the manufacturer regarding the purpose of rheumatology visits in patients with an SUA level over target (>360 μmol/L) and whether this care could not be provided in a general practice setting. The purpose of the rheumatology visits was described in the manufacturer's response as, "assessment of current treatment effectiveness, disease/symptom progression in patients, occurrence of adverse events and use of blood tests". The manufacturer stated that some of these outpatient appointments may be nurse-led rather than consultant-led but that care would still be provided in a secondary care rather than a primary care setting. Two of the ERG's clinical advisors felt that the additional rheumatology visits associated with pegloticase treatment in the years following pegloticase treatment may have been overestimated and considered that 3 visits in the year of treatment and none thereafter would be a reasonable assumption. Although another of the ERG's clinical advisors stated that follow-up in secondary care every 6 to 12 months would be reasonable. The ERG considered that the long-term cost of follow-up in patients after pegloticase treatment may have been overestimated.

Table 22 Resource use per annum for gout management (excluding flares)

Resource use	**SUA<360μmol/dL**	**SUA>360μmol/dL**
Rheumatology visits (all patients regardless of treatment)	0	5
Emergency room visit	0	0.5
Hospital admission	0	0.2
GP visit	2	0

Table 23 Rheumatology visits associated with pegloticase treatment*

Time period	Rheumatology visits per annum* *
Years 0 to 5	3
Years 6 to 10	2
Years 11+	0.5

*applied to pegloticase responders whilst receiving pegloticase treatment or maintenance therapy

**additional to those associated with flares or SUA level

Given that the costs of flares have been separately accounted for within the model, the ERG considered that the costs associated with having SUA levels over target (>360 μmol/L) were probably overestimated in the model. This would have the effect of over inflating the costs of gout management in patients receiving best supportive care. To test the sensitivity of the model to these assumptions on the resource use associated with gout management, the ERG conducted a sensitivity analysis in which the resource use for patients over the SUA target was set equal to that for patients under the SUA target. In addition, the rheumatology visits associated with pegloticase treatment were limited to 3 in year 1 and non-thereafter. The ERG also introduced 2 rheumatology visits for non-responders and non-completers to capture the consultations associated with starting and ending pegloticase treatment. The results, which can be seen in section 5.3.1 below, show that the ICER is sensitive to the resource use attributable to higher SUA levels.

The manufacturer also presented a sensitivity analysis, in response to a clarification request, in which they assumed additional rheumatology visits would be required to start and stop pegloticase treatment in non-responders and non-completers. In this sensitivity analysis, costs were applied for two additional rheumatology visits for each month of pegloticase treatments. This had a marginal affect on the ICER (see Table 29 below for further details).

5.2.9 Cost effectiveness results

5.2.9.1 Basecase deterministic results from the original submitted model

The basecase deterministic costs from the original submitted model are given in Table 24 with a more detailed breakdown of the costs provided in Table 25. From the breakdown of costs, it can be seen that the most significant cost components in determining the incremental cost of pegloticase are the additional drug and administration costs for pegloticase treatment and the reduction in gout management costs, which is driven by the relationship assumed in the model between SUA level and resource use.

Table 24: Deterministic results for the original manufacturer's basecase

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Best supportive care strategy	£23,330	8.940			
Pegloticase strategy	£32,796	9.256	£9,466	0.316	£29,946

Table 25 Summary of predicted resource use by category of cost*

Item	**Cost intervention**	**Cost comparator**	**Increment**	**Absolute increment**	**% absolute increment**
Pegloticase	£11,617	£0	£11,617	£11,617	72.1%
Maintenance phase	£222	£0	£222	£222	1.4%
Best supportive care drug costs	£0	£0	£0	£0	0.0%
Administration	£602	£0	£602	£602	3.7%
Tests	£254	£235	£18	£18	0.1%
Prophylaxis	£280	£0	£280	£280	1.7%
Adverse events	£48	£0	£48	£48	0.3%
Flare costs	£5,167	£5,345	-£177	£177	1.1%
Tophi Surgery	£400	£529	-£129	£129	0.8%
Gout management	£14,205	£17,221	-£3,016	£3,016	18.7%
Total	**£32,796**	**£23,330**	£9,466	£16,110	100%

*adapted from Table 7.22 of the MS

5.2.9.2 Basecase probabilistic results from the original submitted model

The MS presents means and 95% CIs for the incremental costs, incremental QALYs and the ICER. Whilst validating the probabilistic sensitivity analysis, the ERG noted that the Visual Basic macro used to sample the incremental costs and QALYs was re-calculating the spreadsheet between recording the costs and recording the QALY values. In effect this meant that the costs and QALY samples were taken from separate PSA samples, removing any correlation that may exist between incremental costs and QALYs. For this reasons, the PSA results presented in the MS are not reproduced here. The ERG corrected the macro and found that this resulted in a scatterplot on the cost-effectiveness plane which showed some positive correlation between incremental costs and QALYs. The ERG ran 10,000 samples of the PSA and calculated the mean incremental cost and QALYs to be £9,521 and 0.319 respectively, giving an ICER of £29,833 This was done after correcting for the error identified in the Visual Basic macro used to operate the PSA. The mean incremental costs and QALYs from the PSA are within 1% of the deterministic estimates suggesting

that the cost and QALY outputs are a linear function of the model inputs, as would be expected in a model of this design.

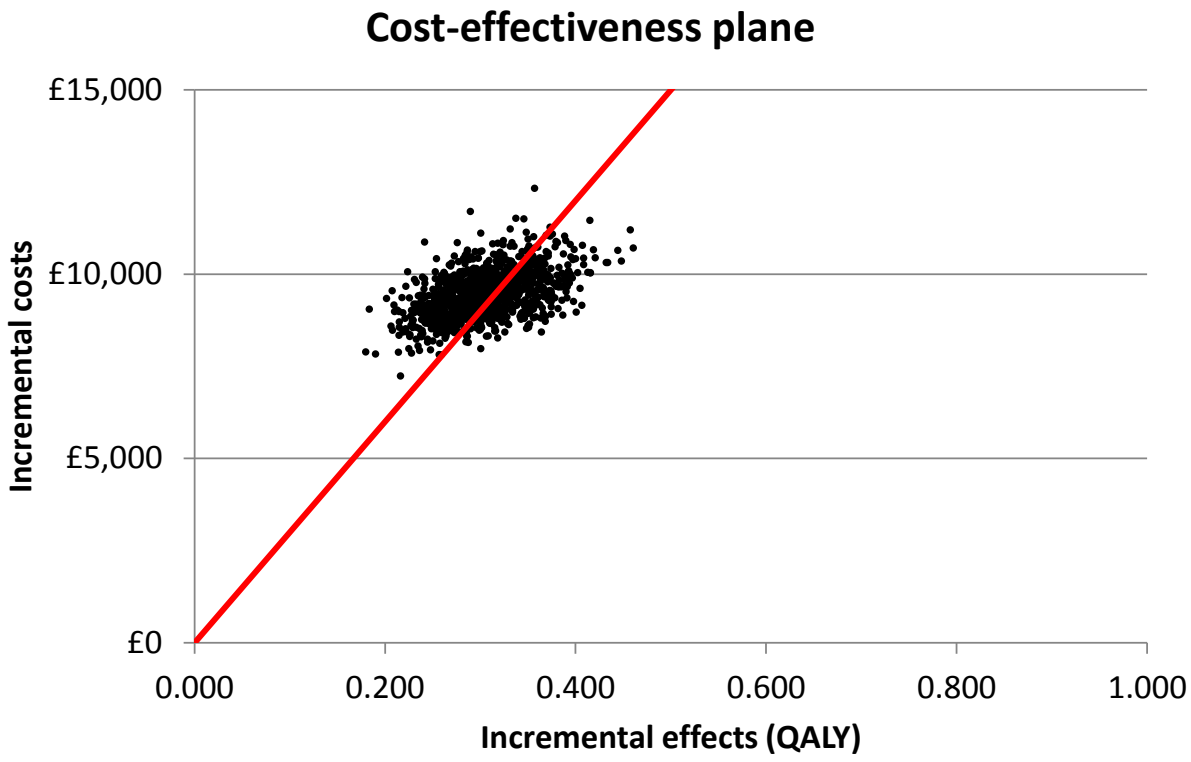
5.2.9.3 Cost effectiveness results for manufacturer's revised basecase

In response to the clarification letter, the manufacturer submitted several additional analyses including a revised basecase analysis which included drug costs for best supportive care and a change to the treatment sequences to allow those pegloticase responders who cannot take maintenance therapy, due to intolerance or contraindications, to progress to best supportive care. The deterministic results for this revised basecase analysis are provided in Table 26. The mean incremental cost and QALYs from 10,000 samples of the PSA (incorporating the ERG's correction to the PSA macro described in 5.2.9.2) were £9,491 and 0.306 respectively, giving an ICER of £31,031. Again the mean incremental costs and QALYs from the PSA are within 1% of the deterministic estimates suggesting that the cost and QALY outputs are a linear function of the model inputs. The scatterplot for 1,000 samples is shown in Figure 10 below.

Table 26 Deterministic results for manufacturer's revised basecase analysis

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£21,919	£24,687	-£2,768	
Total costs	£34,139	£24,687	£9,452	
QALY	9.244	8.940	0.305	£31,027

Figure 10 Probabilistic sensitivity analysis scatter plot for manufacturer's revised basecase* [incorporating ERG's correction of PSA macro]



*line denotes ICER of £30,000 per QALY

5.2.10 Sensitivity analysis

The sensitivity and scenario analyses presented within the MS for the manufacturer's original basecase are summarised in Tables 27 and 28. The deterministic sensitivity analyses showed that the cost-effectiveness of pegloticase was particularly sensitive to changes in baseline SUA, the disutility associated with higher SUA levels and patients' age, as would be expected. Patients with lower SUA levels at baseline have the same probability of response but a smaller change in SUA when achieving an SUA level under target (<360 μmol/L) and therefore a smaller utility gain from responding to pegltoicase. Older patients have a shorter life expectancy over which to accrue benefits from reduced SUA levels. The sensitivity analyses also demonstrate that the disutility associated with higher SUA levels is a significant driver of cost-effectiveness, which is important given that the ERG believe there to be significant uncertainty regarding this relationship. The cost-effectiveness results were also fairly sensitive to changes in the utility value for patients with an SUA level under target and the baseline utility value. Baseline HRQoL is a relatively important factor because it is used to calculate baseline corrected utility values from the trial data which influences QALY gains in the first 6 months of the model and the utility value for patients with a low SUA level influences QALY gains thereafter. The cost-effectiveness results were also moderately sensitive to the parameter values for treatment efficacy and persistence with pegloticase therapy.

The scenario analyses demonstrated the sensitivity of the ICER for several structural changes in the model's clinical pathways. The most sensitive variables were related to the duration patients receive pegloticase and how soon non-responders stop treatment with pegloticase, according to the clinical continuation rule (see Section 7.2.8). The ERG had concerns regarding whether the durations of treatment assumed in the basecase were supported by evidence regarding the actual number of treatments received within the trials and within clinical practice and requested further clarification from the manufacturer on this matter. The scenario analysis in which treatment duration for responders was varied from 1 to 3 months was considered to by the ERG to be a reasonable reflection of uncertainty regarding this parameter given that [redacted] in the modified ITT analysis (in which non-completers were classified as non-responders at the time of treatment cessation). For pegloticase responders, the scenario analysis on treatment duration was not considered to be a reasonable reflection of uncertainty regarding this parameter as [redacted] were observed in the phase III trials (C0405 and C0406) and their OLE study (C0407).

The ICERs were increased to over £50,000 per QALY when assuming no benefits beyond 10 years. From the results presented, it can be inferred that 34% of the discounted QALY gains associated with pegloticase treatment are achieved more than 10 years after treatment. Furthermore, the ERG had concerns regarding the survival model used to extrapolate persistence with allopurinol, and a scenario analysis in which the rate of discontinuation of allopurinol treatment was increased from 12% to 15% per annum resulted in an increase in the ICER from around £30,000 to around £37,000 per QALY. In light of these scenario results, the ERG considers the extrapolation of benefits over such a long time period to be a significant area of decision uncertainty as no direct evidence has been presented by the manufacturer which shows that the SUA levels achieved following response to pegloticase treatment can be maintained by treatment with allopurinol or febuxostat treatment in the long-term.

In response to the clarification letter, the manufacturer submitted a Table of further sensitivity analyses which is reproduced as Table 29 below. In this the two changes that constitute the revised basecase are shown as individual sensitivity analyses on the original basecase and are then combined to produce the revised basecase. Further sensitivity analyses are then presented by my making changes to this revised basecase. It should be noted that the ERG found an error in the implementation of the sensitivity analysis on persistence with maintenance therapy (C9), as described in section 5.2.4.3 above, so Table 29 has been amended to include the ERG's corrected results. It can be seen from Table 29 that the model is particularly sensitive to the relationship between utility and the intermediate model outcomes of tophi resolution and SUA. These relationships have been further explored by the ERG and the results are presented in section 5.3.1 below.

Table 27 Deterministic model results for sensitivity analyses on parameter values (for the original model submitted)

Deterministic analysis	Parameter values			Lower limit			Upper limit		
	Basecase	Lower	Upper	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Baseline characteristics									
Baseline age (years)	56	42	70	£9,322	0.333	£28,007	£9,977	0.257	£38,885
Baseline SUA (mg/dL)	9.6	7.2	12	£10,319	0.164	£62,889	£9,382	0.405	£23,168
Baseline QoL	0.60	0.45	0.75	£9,466	0.349	£27,104	£9,466	0.283	£33,455
Pegloticase effectiveness									
Pegloticase persistence	68%	51%	85%	£8,040	0.242	£33,242	£10,893	0.390	£27,904
Pegloticase effectiveness	60%	45%	75%	£8,681	0.252	£34,458	£10,252	0.380	£26,957
Maintenance therapy									
% allopurinol as maintenance	70%	53%	88%	£9,830	0.309	£31,816	£9,103	0.323	£28,159
Pegloticase									
% infusion reaction	26%	20%	33%	£9,454	0.316	£29,908	£9,478	0.316	£29,984
% vomiting	5%	4%	6%	£9,466	0.316	£29,946	£9,466	0.316	£29,946
Maintenance therapy									
Allopurinol cost (300 mg tablet)	£0.04	£0.03	£0.05	£9,458	0.316	£29,920	£9,475	0.316	£29,972
Febuxostat cost (80 mg tablet)	£0.87	£0.65	£1.09	£9,419	0.316	£29,795	£9,514	0.316	£30,097
Pegloticase administration									

Deterministic analysis	Parameter values			Lower limit			Upper limit		
	Basecase	Lower	Upper	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Nurse time (hours)	3.5	2.6	4.4	£9,316	0.316	£29,470	£9,617	0.316	£30,422
Gout flare prophylaxis	£11	£9	£14	£9,457	0.316	£29,917	£9,476	0.316	£29,976
Infusion reaction prophylaxis	£37	£28	£46	£9,403	0.316	£29,746	£9,529	0.316	£30,146
Resource use costs									
Rheumatologist visit	£132	£105	£146	£9,707	0.316	£30,707	£9,342	0.316	£29,552
GP visit	£30	£23	£38	£9,432	0.316	£29,836	£9,501	0.316	£30,056
A&E visit, not admitted	£106	£84	£123	£9,500	0.316	£30,054	£9,440	0.316	£29,863
A&E visit , if admitted	£147	£101	£171	£9,454	0.316	£29,908	£9,473	0.316	£29,966
Hospital admission	£2,931	£2,070	£3,484	£10,000	0.316	£31,633	£9,124	0.316	£28,863
Tophi surgery	£2,286	£1,822	£2,562	£9,492	0.316	£30,029	£9,451	0.316	£29,897
Flare management	£296*	£222*	£370*	£9,511	0.316	£30,086	£9,422	0.316	£29,806
Long-term outcomes; number of flares per months									
Flares ≤360 mg/dL	0.0874	0.066	0.109	£9,242	0.323	£28,570	£9,691	0.309	£31,388
Flares >360-480 mg/dL	0.0989	0.074	0.124	£9,498	0.315	£30,147	£9,434	0.317	£29,746
Flares >480-600 mg/dL	0.1085	0.081	0.136	£9,588	0.312	£30,715	£9,345	0.320	£29,196
Flares >600 mg/dL	0.1161	0.087	0.145	£9,575	0.313	£30,633	£9,358	0.320	£29,274
Long-term outcomes; utility									
Base utility ≤360 mg/dL	0.75	0.56	0.94	£9,466	0.275	£34,464	£9,466	0.358	£26,475

Deterministic analysis	Parameter values			Lower limit			Upper limit		
	Basecase	Lower	Upper	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Disutility per SUA state:	0.034	0.026	0.043	£9,466	0.246	£38,450	£9,466	0.386	£24,523
Disutility per flare:	0.0097	0.0073	0.0121	£9,466	0.315	£30,061	£9,466	0.317	£29,832

*Added by ERG based on Excel Spreadsheet as not specified in Table 7.24 of submission

Table 28 Deterministic model results for scenarios analysis (for the original model submitted)

Scenario analysis	Parameter source/value			Scenario 1			Scenario 2		
	Base-case	Alternative scenario 1	Alternative scenario 2	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Pegloticase									
Pegloticase course duration	6	5	7	£6,249	0.315	£19,817	£13,159	0.369	£35,655
Evaluation of persistence (months)	1	2	3	£10,682	0.314	£33,969	£11,896	0.313	£38,025
Evaluation of response (months)	2	1	3	£8,434	0.318	£26,556	£10,492	0.315	£33,344
Administration costs	Nurse time[a]	NHS reference[b]		£9,864	0.316	£31,203			
Maintenance therapy									
Non-persistence per year with allopurinol	*Literature*[c]	5%	15%	£9,276	0.322	£28,800	£10,559	0.286	£36,958
Dose of allopurinol (mg /day)	300	600	900	£9,500	0.316	£30,051	£9,533	0.316	£30,157
Non-persistence per year with febuxostat	*Literature*[d]	5%	15%	£9,082	0.331	£27,443	£9,485	0.315	£30,078
Dose of febuxostat (mg /day)	100	80	120	£9,429	0.316	£29,826	£9,504	0.316	£30,066
Short-term outcomes									
Short-term outcomes: flares	RCT[e]	Literature[f]		£9,392	0.316	£29,711			
Short-term outcomes: QoL	RCT[g]	Literature[h]		£9,466	0.319	£29,662			

Scenario analysis	Parameter source/value			Scenario 1			Scenario 2		
	Base-case	Alternative scenario 1	Alternative scenario 2	Incremental costs	Incremental QALYs	ICER	Incremental costs	Incremental QALYs	ICER
Long-term outcomes									
Long-term outcomes: flares	Literature[f]	RCT[e]		£8,540	0.346	£24,646			
Long-term: tophi responders	100%	75%	50%	£9,479	0.295	£32,172	£9,492	0.273	£34,749
Long-term: tophi non-responders	50%	75%	25%	£9,461	0.325	£29,150	£9,471	0.308	£30,786
Long-term outcomes: QoL	Literature[h]	RCT[g]		£9,466	0.294	£32,152			
Time window and discount rates									
Time window (years)	20	40	10	£8,967	0.382	£23,482	£10,463	0.207	£50,482
Discount rate costs	3.5%	0.0%	6.0%	£8,580	0.316	£27,143	£9,884	0.316	£31,267
Discount rate effects	3.5%	0.0%	6.0%	£9,466	0.423	£22,367	£9,466	0.264	£35,885

[a]£92, [b]£152.32, [c]12% in year 1 but decreasing over time, [d]14%. [e]Figure 8, [f]Table 18, [g]Figure 9, [h]Table 20

Table 29: Additional sensitivity analyses provided by the manufacturer after requests for clarification by the ERG [C9 has been corrected by the ERG as an error was identified as described in section 5.2.4.3]

Clarification question	Sensitivity Analysis	Incremental Costs	Incremental QALYs	ICER
-	**Basecase**	**£9,466**	**0.316**	**£29,946**
C2	Xanthine intolerance	£9,746	0.305	£31,993
C3	Include best supportive care costs as per C3	£9,142	0.316	£28,922
-	**Revised base-case (C2+C3)**	**£9,452**	**0.305**	**£31,027**
C9	Alternative source for persistence maintenance therapy	£10,500	0.276	£37,981
C10	Include GP6D screening costs	£9,452	0.305	£31,029
C11	Higher sUA frequency	£9,466	0.305	£31,075
C12	Rheumatologist visit when starting/stopping pegloticase	£9,679	0.305	£31,773
C20	No association between tophi and utility	£9,452	0.217	£43,614
C21	No association between sUA and utility	£9,452	0.245	£38,535
C22	10% higher mortality rate	£9,470	0.303	£31,303
	10% lower mortality rate	£9,433	0.307	£30,751
C26	Include costs for pharmacy time	£9,465	0.305	£31,071

5.2.11 Model validation and face validity check

The MS describes in section 7.8, under the heading "Validation", how the average utility difference between patients with and without tophi resolution who are receiving best supportive care in the model is 0.076 and compares this to values for patients with and without tophi from the literature. As discussed earlier, these values from the literature may not take into account confounding from factors which are correlated to both tophi and utility, such as comorbidities, and may therefore not give a true representation of the difference in health utility achieved by patients who have the trial outcome of tophi resolution. This validation exercise should be interpreted in the light of these concerns.

The ERG validated the model by reproducing selected sensitivity and scenarios analyses and checking that the results changed in the expected manner. No inconsistencies were found with the results presented by the manufacturer. The ERG produced plots of utility, SUA and flare frequency over time for each Markov state and compared these to the data from the trial (see sections 5.2.6 and 5.2.7). They also examined how these plots changed under the various scenario analyses in which the data from the literature is applied to the first 6 months and the data from the trial is applied beyond 6 months.

The ERG also validated the Visual Basic macro used to sample the incremental costs and QALYs by for the PSA by stepping through the code and an error was noted as described in section 5.2.9.2. The ERG also validated the PSA by checking examining all the random numbers sampled within the model to identify which parameters were being varied within the PSA. In doing so they found several occasions where a single random number was being used to sample multiple parameters resulting in 100% correlation between those parameters. This affected the proportion with resolution of tophi and the mean SUA levels, the mean frequency of flares and the mean utility across the three trial data sets used to populate the model (pegloticase responders, pegloticase non-responders and best supportive care) and across multiple time points. There were also a couple of occasions where parameters which might be expected to have some correlation were not correlated within the PSA, such as the shape and scale parameters for the Weibull distribution used to model persistence on allopurinol and the frequency of flares across different SUA levels. Drug costs for allopurinol and febuxostat appear to have been varied in the PSA rather than being fixed at the list price given in the BNF[50]. The PSA does not account for any uncertainty regarding treatment duration or the long-term maintenance of tophi resolution. The uncertainty in gout management costs (which excludes the cost of managing flares) is driven purely by the uncertainty in the unit costs for the individual components rather than uncertainty in the resource use rates. Some parameters that should have been bounded at zero such as the frequency of flares and the mean SUA level were sampled from a normal distribution without any measure taken to prevent the a negative sample. The ERG did not have the resources to spend time

correcting the implementation of the PSA, but they did not consider any of these errors to have significantly biased the ICER.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

These sensitivity analyses have been conducted by making changes to the manufacturer's revised basecase model which incorporates drug costs for best supportive care and appropriate treatment pathways for patients unable to take xanthine oxidase inhibitors due to intolerance or contraindications. Deterministic results are presented as these closely matched the probabilistic results suggesting that the model is linear as would be expected for a model with this structure. Figure 11 summarises the sensitivity analyses conducted by the ERG with detailed results on the individual analyses provided in section 5.3.1. The results from Table 37 could not be included in Figure 11 as they were academic in confidence.

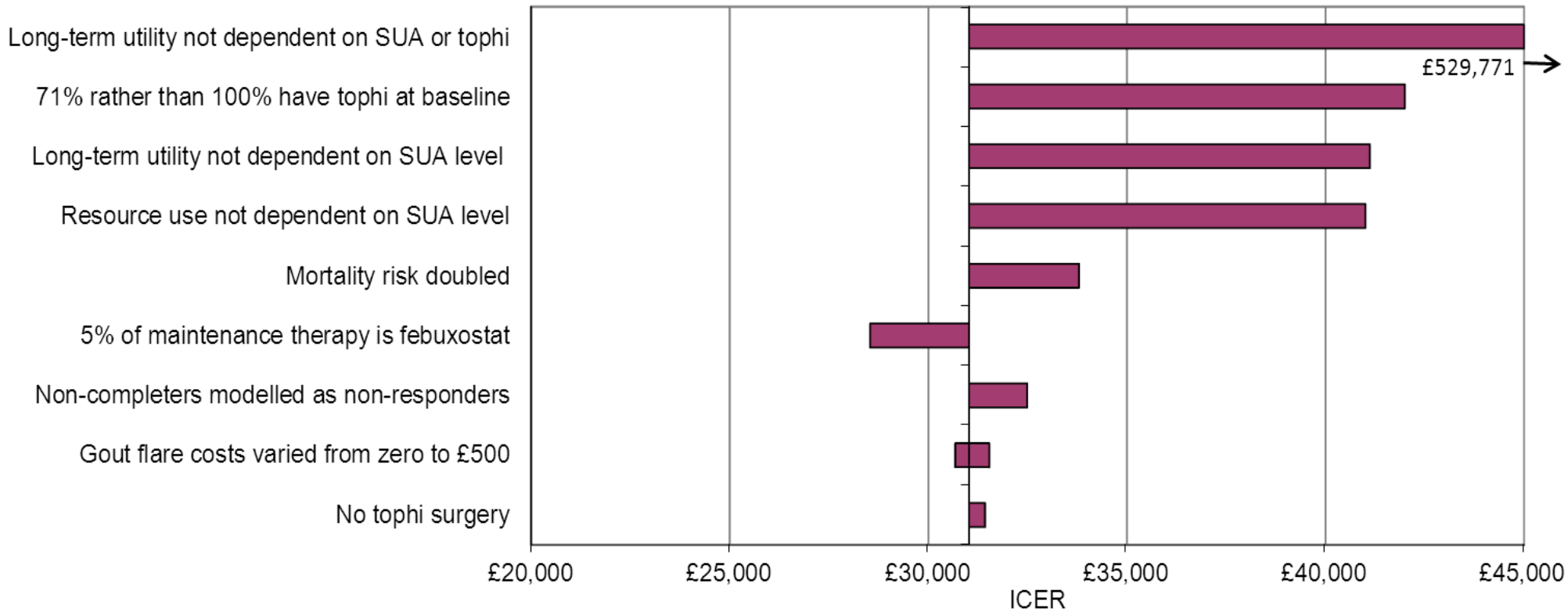
5.3.1 Additional univariate sensitivity analyses

The ERG conducted an exploratory analysis in which the persistence rate was set to 100% and the response rate was set to 42% which was the rate observed in the pooled analysis of the two phase III RCTs (C0405 and C0406) in order to replicate the (modified) ITT analysis. The results in Table 30 below, show that this had little impact on the ICER. However, it should be noted that this exploratory analysis did not remedy the fact that outcomes from non-completers were discarded from the patient level analysis and not used directly within the model to estimate SUA levels, the frequency of flares, tophi resolution or utility within the economic model.

Table 30 Deterministic results for sensitivity analysis using approach used in (modified) ITT to define response

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	£12,911	£0	£12,911	
Drug administration costs	£669	£0	£669	
Other costs	£21,855	£24,687	-£2,832	
Total costs	£35,434	£24,687	£10,748	
QALY	9.270	8.940	0.331	£32,492

Figure 11 Tornado diagram summarising additional sensitivity analyses conducted by ERG



The ERG's clinical advisors believed that the proportion of pegloticase responders who would receive febuxostat as maintenance therapy would be under 20% and could be as low as 5% in clinical practice, rather than the 30% assumed in the manufacturer's basecase analysis. It was also commented that the proportion would be likely to increase over-time. A sensitivity analysis was conducted by the ERG applying the proportion 5% to the basecase deterministic model, to establish whether this factor is a significant driver of cost-effectiveness, and the results are presented in Table 31 below.

Table 31 Deterministic results assuming that 5% of pegloticase responders receive febuxostat.

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£21,423	£24,687	-£3,264	
Total costs	£33,642	£24,687	£8,955	
QALY	9.254	8.940	0.314	£28,535

The ERG was concerned that the mortality rates applied in the model did not reflect the risk of death in the population eligible to receive pegloticase and an exploratory analysis was conducted in which the annual mortality rates applied in the model were doubled. The results, in Table 32 below, show that whilst the ICER is increased when applying higher mortality rates, it is not a particularly important driver of cost-effectiveness.

Table 32 Deterministic results when applying double the annual mortality risk assumed in the basecase

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	£11,608	£0	£11,608	
Drug administration costs	£602	£0	£602	
Other costs	£20,375	£22,961	-£2,586	
Total costs	£32,585	£22,961	£9,624	
QALY	8.594	8.310	0.285	£33,793

The ERG conducted a sensitivity analysis setting the rate of tophi surgery to zero on advice from their clinical advisors that whilst tophi surgery may happen, it should not be part of current gout management. The results, in Table 33 below, show that the ICER increased moderately under this assumption.

Table 33 Deterministic results setting the rate of tophi surgery to zero

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£21,519	£24,158	-£2,639	
Total costs	£33,738	£24,158	£9,580	
QALY	9.244	8.940	0.305	£31,449

As there was limited information presented on the methodology used to derive the cost of gout flare applied in the model, the ERG varied the value from zero to £500 to determine whether it this parameter is a significant driver of cost-effectiveness. The results, summarised in Tables 34 and 35, show that increasing the cost of gout flares, increases the cost savings attributable to pegloticase treatment, but the ICER doesn't vary substantially over the range tested.

Table 34 Deterministic results setting the cost of a gout flare to zero

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£16,729	£19,342	-£2,613	
Total costs	£28,948	£19,342	£9,606	
QALY	9.244	8.940	0.305	£31,534

Table 35 Deterministic results setting the cost of a gout flare to £500

	Pegloticase	Best supportive care	Difference	ICER
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£25,496	£28,370	-£2,874	
Total costs	£37,716	£28,370	£9,345	
QALY	9.244	8.940	0.305	£30,678

The ERG was not satisfied that resource use would be greater in patients with a higher SUA level over and above the difference determined by gout flares. They therefore conducted an analysis in which they set the resource use for patients with an SUA over target (>360 μmol/L) to the same value as applied to those under target. They also reduced the number of rheumatology visits associated with pegloticase treatment to 3 in year 1 and none thereafter but assumed that 2 visits would be required even in those patients who were classified as non-responders or non-completers, giving a net reduction in the costs of rheumatology visits associated with pegloticase. This resulted in lower costs for both model arms, with the pegloticase arm no longer providing a saving in 'other costs' compared to best supportive care. The ICER was increased to £41,000 per QALY as shown in Table 36.

Table 36 Deterministic results when making alternative assumptions regarding resource use

	Pegloticase	Best supportive care	Difference	ICER
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£8,340	£8,067	£273	
Total costs	£20,559	£8,067	£12,492	
QALY	9.244	8.940	0.305	£41,008

The ERG conducted a sensitivity analysis to determine the cost-effectiveness when taking the proportion who are contraindicated or intolerant to xanthine oxidase inhibitors to be the proportion [redacted] who had either a history of allergy or hypersensitivity or GI intolerance to allopurinol across the two phase III trials (C0405 and C0406). As shown in Table 37, this resulted in a increase in the ICER to [redacted] due to the lower long-term benefits assumed in the model for those who cannot take maintenance therapy. However, it should be noted that some of those enrolled in the trials who could not take allopurinol may have been able to take febuxostat, so this probably represents an upper limit on the proportion likely to be contraindicated in clinical practice.

Table 37 Deterministic results when applying the proportion unable to take xanthine oxidase inhibitors within the trial population to the modelled population

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	[redacted]	[redacted]	[redacted]	
Drug administration costs	[redacted]	[redacted]	[redacted]	
Other costs	[redacted]	[redacted]	[redacted]	
Total costs	[redacted]	[redacted]	[redacted]	
QALY	[redacted]	[redacted]	[redacted]	[redacted]

As described in section 5.2.7.4, the ERG conducted an additional analysis assuming that utility benefits are driven solely by the frequency of flares and the resolution of tophi and not directly by the SUA level. Patients without tophi were assumed to have a utility level 0.076 higher than those with tophi resolution. The baseline utility values were also adjusted to give values that better reflected those observed in the trials. The results for this additional analysis are shown in Table 38 below. The QALY benefits are smaller than the manufacturer's basecase analysis, giving an ICER of around £41,118 per QALY. The majority of the QALY benefit in this scenario is being generated by the impact of tophi resolution, as when the difference between those with and without tophi is set to zero (results shown in Table 39), leaving only the affect of flares, the QALY gain decreases to 0.018, giving an ICER of £529,771 per QALY. Whilst the ERG does not consider the scenario with no benefits from tophi resolution to be plausible as discussed in section 5.2.7.4, it is uncertain exactly how much benefit is achieved and maintained by the outcome of tophi resolution recorded in the trial.

Table 38 Deterministic results when making alternative assumptions regarding utility gains

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£21,919	£24,687	-£2,768	
Total costs	£34,139	£24,687	£9,452	
QALY	9.241	9.011	0.230	£41,118

Table 39 Deterministic results when assuming that utility is based solely on flares

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£21,919	£24,687	-£2,768	
Total costs	£34,139	£24,687	£9,452	
QALY	8.895	8.877	0.018	£529,771

The ERG conducted a sensitivity analysis in which it was assumed that only 71% of patients have tophi at baseline. To do this they estimated model outputs for the population without tophi at baseline, by setting the proportion with tophi resolution to100% for all groups at the start of the model. The manufacturer's basecase implicitly assumes that 100% have tophi at baseline, providing model outputs for the population with tophi at baseline. They then calculated a weighted average of the outcomes from these two models to estimate the mean for costs and QALYs in a population where 71% have tophi at baseline. This increased the ICER to £42,000, although it should be noted that the impact of this analysis would be greater if alternative assumptions are made regarding the utility gains from other outcomes such as SUA levels and flares. It should be noted however, that the proportion of patients receiving pegloticase in clinical practice who have tophi at baseline may be higher than observed in the trials due to the wording of the draft license indication which includes the term "tophaceous gout".

Table 40 Deterministic results when 71% of the population have tophi at baseline rather than 100%

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£21,803	£24,533	-£2,730	
Total costs	£34,022	£24,533	£9,489	
QALY	9.412	9.186	0.226	£42,000

5.3.3 Combined sensitivity analysis applying alternative assumptions for both utility and resource use gains associated with SUA levels

The ERG had strong enough concerns regarding the relationship between SUA level and utility and the relationship between SUA level and resource use to conduct a combined analysis removing both these factors from the model. In this combined analysis they set the cost for 'gout management' in patients over the SUA target equal to that for patients under the SUA target. This cost is for 'gout management' over and above the cost of pegloticase treatment, maintenance treatment, best supportive care , management of gout flares and management of adverse events. They also reduced the number of rheumatology visits associated with pegloticase treatment to 3 in year 1 and none

thereafter but assumed that 2 visits would be required even in those patients who were classified as non-responders or non-completers, giving a net reduction in the costs of rheumatology visits associated with pegloticase. In addition to this they set the disutility per SUA to zero and modified the utility values in those without flares to better reflect those observed in the trials and to maintain the difference of of 0.076 observed between patients with and without tophi in the manufacturer's basecase. This combined analysis gave an ICER of £54,345 as shown in Table 41.

Table 41 Deterministic results when combining alternative assumptions regarding utility gains with alternative assumptions regarding resource use

	Pegloticase	**Best supportive care**	**Difference**	**ICER**
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£8,340	£8,067	£273	
Total costs	£20,569	£8,067	£12,492	
QALY	9.241	9.011	0.230	£54,345

5.3.4 Subgroup analysis for patients unable to take maintenance therapy (allopurinol or febuxostat)

It was originally specified in the scope that consideration would be given to subgroup analysis for people who are intolerant of allopurinol or for whom allopurinol is contraindicated. Given that the draft SPC specifies that pegloticase will only be used in adult patients with severe debilitating chronic tophaceous gout who have not responded to or are intolerant to xanthine oxidase inhibitors including febuxostat, the ERG were therefore interested in the cost-effectiveness results for those patients who are intolerant of or contraindicated to both allopurinol and febuxostat. The ICER, presented in Table 42, is based on an adaptation of the manufacturer's revised basecase in which the proportion contraindicated to maintenance therapy was set to 100% and also incorporates the costs of best supportive care added to the revised manufacturer basecase. Given that patient's SUA levels are assumed to increase rapidly upon starting best supportive care, the results for this subgroup may underestimate that benefits of pegloticase if there is a more gradual increase of SUA levels after stopping treatment in clinical practice.

The results for the subgroup who are able to take maintenance therapy are given in Table 43. This is

the same scenario as presented in scenario C3 of Table 29 but more details are provided here.

Table 42 Deterministic results for subgroup who are unable to take maintenance therapy

	Pegloticase	Best supportive care	Difference	ICER
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£24,702	£24,687	£15	
Total costs	£36,922	£24,687	£12,235	
QALY	9.141	8.940	0.201	£60,793

Table 43 Deterministic results for subgroup who are able to take maintenance therapy

	Pegloticase	Best supportive care	Difference	ICER
Technology acquisition cost	£11,617	£0	£11,617	
Drug administration costs	£602	£0	£602	
Other costs	£21,610	£24,687	-£3,077	
Total costs	£33,829	£24,687	£9,142	
QALY	9.256	8.940	0.316	£28,922

5.4 Conclusions of the cost effectiveness section

The submission was considered to be complete with regard to relevant published cost-effectiveness studies. However, several of the data used to populate the *de novo* economic evaluation were sourced from documents related to the NICE and SMC appraisals of febuxostat and insufficient details were provided to allow the ERG to adequately critique the data.

The ERG were concerned that the basecase analysis provided in the original submission did not reflect realistic treatment sequences for the subgroup of patients who are contraindicated to or intolerant to both allopurinol and febuxostat. However, this concern was addressed when the manufacturer submitted a revised basecase analysis, in response to the clarification letter, in which pegloticase responders who are contraindicated to or intolerant to both allopurinol and febuxostat are assumed to progress to best supportive care rather than maintenance therapy. This revised basecase was therefore considered by the ERG to accurately reflect the decision problem specified in the scope. Using this revised basecase analysis, the ERG estimated the cost-effectiveness for the subgroup of patients who are contraindicated to or intolerant to both allopurinol and febuxostat. At £60,000 per QALY, the ICER in this subgroup was substantially higher than the ICER for the subgroup able to take maintenance therapy. This was to be expected given the different assumptions regarding the long-term maintenance of benefits for these two subgroups.

Neither the basecase analysis, provided in the original submission, nor the revised basecase analysis, submitted in response to the clarification letter, are considered by the ERG to represent an unbiased estimate of the technology's ICER. The main area of potential bias was the incorporation of utility gains associated with reductions in SUA levels in addition to utility gains from the reduction in frequency of flares and the resolution of tophi. Exploratory analyses removing the utility gain associated with lowering SUA levels but maintaining the utility gain associated with tophi resolution and reduction in flares resulted in an ICER around £40,000 per QALY. Even this scenario may be considered to be favourable to pegloticase as the ERG believe there to be considerable uncertainty regarding the size of utility benefit attributable to tophi resolution and whether this benefit is maintained in the long-term. The ERG also had concerns regarding the additional resource use attributed to higher SUA levels. A sensitivity analyses exploring alternative assumptions on resource use resulted in an ICER around £40,000 per QALY. The ERG also had concerns regarding the survival curve used to extrapolate persistence with allopurinol. Sensitivity analysis applying a lower rate of persistence resulted in an ICER of £38,000.

The ERG were also concerned that the model structure effectively assumes that all patients have tophi prior to pegloticase treatment whereas only 71% of the trial participants had tophi at baseline. As demonstrated by the ERGs exploratory analyses, the model may overestimate treatment benefits in the trial population. However, the ICER may not be favourable to pegloticase provided treatment with pegloticase is limited in clinical practice to those with tophi, which is likely given the draft indication for pegloticase of severe debilitating chronic tophaceous gout.

The ICER for the ERG's preferred scenario was £54,345. This scenario incorporated the following changes to the basecase; no disutility for higher SUA levels, disutility of 0.076 for patients with tophi versus those without, utility of 0.68 for patients with tophi (and without flares), no increased resource use for higher SUA levels, no additional rheumatology visits for pegloticase treatment after year one, rheumatology visits for starting and stopping treatment in non-responders and non-completers.

The ERG also noted that the model was sensitive to changes in the duration of pegloticase treatment in responders and that the number of doses received in clinical practice could be much higher than the 12 doses (over 6 months) assumed in the model as the mean number of doses for patients enrolled in the open-label extension study was [redacted]. Whilst additional treatments beyond 6 months could be associated with additional clinical benefits, the model already assumes that any benefit achieved in the first 6 months is maintained for the duration of maintenance therapy. It is therefore possible that extending the duration of treatment could increase the ICER as the ratio of cost to benefit for additional doses beyond 6 months would be greater than for the initial six months.
The ERG was also unsure how patients classified as non-completers in the economic model would be identified in clinical practice and how many doses they may receive prior to discontinuing pegloticase treatment. The manufacturer stated that the main reason for not completing the course was due to adverse events and these were likely to occur within the first month. However, data on the timing of treatment discontinuation within the clinical trials were not provided and the ICER was sensitive to the duration of treatment for non-completers in the manufacturer's scenario analysis. Furthermore, no data on SUA, utility and flares for non-completers were provided despite being requested. This made it difficult to say whether assuming best supportive care outcomes for this group was in fact likely to have produced a scenario less favourable to pegloticase.

The ERG also had concerns regarding the extrapolation of benefits beyond the trial period. Whilst there was some evidence available in clarification responses and from conference abstracts that [redacted] there was a lack of evidence supporting the assumption that the SUA levels achieved in pegloticase responders could be maintained in the long-term by treatment with xanthine oxidase inhibitors after cessation of pegloticase treatment.

A key area uncertainty with regards to the cost-effectiveness of pegloticase relates to the lack of certainty regarding the final list price for pegloticase. The manufacturer provided clarification that the price assumed in the MS represents the upper limit and therefore the ICERs may in be lower once the final list price is confirmed. However, this uncertainty makes it impossible for the ERG to provide an

estimate of their most plausible ICER to the committee without the caveat that it is likely to be an overestimate.

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6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Table 44 below summarises the additional economic analyses conducted by the ERG and presents the anticipated direct of travel for several scenarios which the ERG were unable to model due to insufficient data. The ERG conducted meta-analyses of data for PUA response and complete resolution of tophi. As these were considered to be exploratory, the potential impact of these meta-analyses on the ICER has not been estimated.

Scenario 4 is the ERG's preferred scenario with scenario 5 and 6 presenting subgroup analyses for this preferred scenario. Scenarios 7 to 10 explore the impact of making further changes to the ERG's preferred scenario to reflect areas of the economic analysis where there is remaining uncertainty.

Table 44 Impact on the ICER of economic analyses including the ERG's preferred scenario

Scenario number	Scenario description	Incremental costs	Incremental QALYs	ICER
1	Manufacturer's revised basecase	£9,452	0.305	£31,027
2	1 plus ERG's preferred assumptions regarding resource use	£12,492	0.305	£41,008
3	1 plus ERG's preferred assumptions regarding utility gains	£9,452	0.230	£41,118
4	**ERG's preferred scenario (2 plus 3)**	**£12,492**	**0.230**	**£54,345**
Subgroup analysis for ERG basecase				
5	*4 but for subgroup unable to take xanthine oxidase inhibitors*	*£12,698*	*0.202*	*£62,961*
6	*4 but for subgroup able to take xanthine oxidase inhibitors*	*£12,496*	*0.233*	*£53,517*
Sensitivity analysis around ERG basecase for whole population				
7	4 but assuming lower persistence on allopurinol based on 2 year data from Annemans *et al.*[4].	£12,634	0.228	£55,529
8	4 but assuming 3 months treatment in those who are non-persistent with pegloticase	£15,084	0.226	£66,696
9	4 but with a longer duration of pegloticase treatment in responders	Substantial increase	Marginal increase	Increased
10	4 but maintenance therapy unable to maintain low SUA levels	Increased	Decreased	Increased

7. END OF LIFE

Pegloticase does not meet the end of life criteria published by NICE as, although the intervention is anticipated to be indicated for a small patient population, it is not indicated for patients with a short life expectancy and there is no evidence that the intervention offers an extension to life.

8. OVERALL CONCLUSIONS

The ERG and clinical advisors to the ERG were satisfied that all available phase III trials relating to the efficacy and safety of pegloticase in the treatment of gout were included in the submission. The two phase III trials (C0405 and C0406) and open label extension (OLE) study (C0407) were considered by the ERG to be relevant to the decision problem as specified in the scope.

The clinical effectiveness evidence included in the submission and subsequent clarification responses demonstrated that pegloticase 8 mg administered intravenously every 2 weeks over 6 months duration in the phase III trials (C0405 and C0406) resulted in a sustained UA response in months 3 and 6 of treatment in just under half (42% in simple pooled analysis) of the modified ITT trial population and also yielded improvements in the majority of secondary outcomes, in particular the rapid resolution of tophi.

The clinical effectiveness evidence was based predominantly on the findings from simple pooled analyses of primary and secondary efficacy data. The ERG considered that the use of meta-analysis would have been a more robust and transparent method for the combination of the phase III trial data.

Since the adverse events data presented in the submission were based on small numbers (due to the relatively small sample sizes of the included studies), the occurrence of adverse events in the post-marketing setting (including infusion reactions and cases of anaphylaxis) should continue to be monitored.

The presentation of the evidence base in the submission for long-term efficacy of continued pegloticase treatment was considered by the ERG to be limited. Some limited and fragmentary evidence was available in the manufacturer's clarification responses and from conference abstracts sourced by the ERG that suggested that, for persistent responders, PUA response and some secondary outcomes, including tophus resolution, may be maintained whilst pegloticase treatment is continued beyond 6 months. However, importantly, it remained unclear from the submission whether PUA response and other treatment benefits would be maintained over the long-term following the cessation of pegloticase treatment. Clear presentation of such evidence for long-term durability of benefits is considered by the ERG to be important, since these data would be required to support the assumption in the submitted cost-effectiveness model that pegloticase treatment effects can be maintained using urate-lowering therapy following the completion of pegloticase treatment. The impacts of repeated courses of pegloticase 8 mg every 2 weeks on UA levels, secondary outcomes, immunogenicity and adverse events were not clear from the original submission. The lack of evidence for the long-term maintenance of treatment benefits following cessation of pegloticase treatment is also important in

light of the limited re-exposure evidence presented, which indicated the potential for the generation of anti-pegloticase antibodies, infusion reactions and loss of efficacy following re-exposure to pegloticase after interruption of treatment.

The subgroup analysis conducted by the ERG demonstrated that the ICER is substantially higher in patients who are unable to take xanthine oxidase inhibitors as maintenance therapy. In this subgroup who switch to best supportive care after discontinuing treatment with pegloticase, the only long-term treatment benefit is from the maintenance of tophi resolution. This subgroup analysis also demonstrates that the cost-effectiveness of pegloticase treatment is largely dependent on the assumption that xanthine oxidase inhibitors can be used to maintain the benefits of achieving a successful response to pegloticase treatment in the long-term. If SUA levels or tophi resolution cannot be maintained in the long-term, then the ICER for pegloticase therapy compared to best supportive care could be expected to increase substantially. This is supported by the manufacturer's scenario analysis on time-horizon in which reducing the time-horizon of the analysis from 20 to 10 years increased the original manufacturer's deterministic ICER from £29,946 to £50,482 (this analysis used the manufacturer's original model).

Several of the data used to populate the *de novo* economic evaluation were sourced from documents related to the NICE and SMC appraisals of febuxostat and insufficient details were provided to allow the ERG to adequately critique the data. The ERG had particular concern regarding the strength of the evidence used to support the following aspects of the economic analysis:

- the relationship between SUA levels and utility
- the relationship between SUA levels and flares
- the relationship between SUA level and resource use
- the magnitude of utility gain associated with the trial outcome of tophi resolution

The ICER was also sensitive to changes in the survival function used to extrapolate the persistence of patients with allopurinol treatment suggesting that uncertainty regarding the duration of persistence with allopurinol may also be important.

There is also uncertainty regarding the likely cost of pegloticase in clinical practice. The manufacturer is yet to confirm a final price for pegloticase with the cost-effectiveness results being based on an indicative price. The ERG were also concerned that the total number of treatments received in clinical practice could be higher than the number assumed in the economic analysis, suggesting that the ICER may be higher in practice as the clinical benefits may not increase in proportion to the additional cost.

The ICER when using the ERG's preferred assumptions regarding utility gain and resource use is £54,345 in the whole population likely to receive pegloticase. However, it should be noted that this ICER may represent the lower limit of the expected ICER as several other areas of uncertainty which have the potential to increase the ICER were not incorporated into this estimate.

8.1 Implications for research

Further evidence is necessary as to whether benefits of pegloticase are maintained after cessation of pegloticase treatment and whether maintenance therapy with other urate-lowering drugs would be successful in maintaining UA response and other benefits in the long-term. There is also a requirement for further evidence to demonstrate the impact of repeated courses of pegloticase 8 mg every 2 weeks on UA response, secondary outcomes, immunogenicity and adverse events. Clinical advisors to the ERG stated that it would be useful to clinical practice to have further evidence on the impact of pegloticase on renal, hepatic and cardiovascular function and on the effectiveness of pegloticase in patients with renal impairment, with one clinical advisor specifically highlighting moderate to severe renal impairment.

Further research is required to determine whether SUA levels are an independent determinant of utility and resource use in the periods between gout flares. Further research is also required to determine the utility gain attributable to tophi resolution and whether this outcome is maintained in the long-term.

9. APPENDICES

APPENDIX 1

Summary of published cost-effectiveness analysis of pegloticase (Wang *et al.*, 2012)[34]

Population	Refractory chronic gout, with severity subgroups based on flares per year and presence of tophi
Intervention	Pegloticase, assuming 6 months of treatment every 5 years.
Comparator:	Placebo
Time horizon and discounting	3, 5, 10, and 20 years
Discounting	3% discounting for costs and benefits
Structure:	Decision tree representing first 6 months followed by empirical forecasts. Disease progression is modelled by employing a vector autoregression methodology to approximate Markov Chain transition probabilities
Outcomes:	Model tracks flares per year and tophi resolution and cost-effectiveness is reported using ICERs
Efficacy data source	Two replicate, randomized, double-blind, placebo-controlled trials (C0405 and C0406)
HRQoL data source	Utility regression from NHWS (no further details or reference provided)
Resource use data source	Not stated

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