Fostamatinib for treating chronic immune thrombocytopenia [ID1087]

Produced by **Aberdeen HTA Group**

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Contribution of authors

Moira Cruickshank and Mari Imamura summarised and critiqued the company's definition of the decision problem and the methods used for the systematic review of clinical effectiveness evidence reported within the company submission. Neil Scott critiqued the statistical methods and analyses presented in the company submission and checked all the numerical results related to the review of clinical effectiveness evidence. Elisabet Jacobsen and Dwayne Boyers critiqued the cost-effectiveness evidence submitted by the company, checked their economic model, and conducted further scenario analyses. Paul Manson critiqued the methods used for identifying relevant studies and checked the search strategies presented in the company submission. Gavin Preston provided clinical advice during the appraisal. Miriam Brazzelli coordinated all aspects of the appraisal and acted as lead for the clinical effectiveness side of the appraisal. Dwayne Boyers acted as lead for the cost-effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATD	Adult Therapeutic Dose
BID	Bis in die (twice daily)
BNF	British National Formulary
CC	Complications and co-morbidities
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CHMP	Committee for Medicinal Products Human Use
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
EQ-5D	EuroQol - 5 Dimension
ERG	Evidence Review Group
EMA	European Medicines Agency
EPAR	European public assessment report
ERG	Evidence review group
ESD	Early supported discharge
FCE	Finished Consultant Episode
FIT	Fostamatinib for Immune Thrombocytopenia
GI	Gastrointestinal
GPRD	General practice research database
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSCIC	Health and social care information centre
IBLS	ITP Bleeding Score
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage

ITP	Immune thrombocytopenia
IV	Intravenous
IVIg	Intravenous immunoglobulin
KOL	Key opinion leader
LOCF	Last observation carried forward
LY	Life years
LYG	Life years gained
MRS	modified Rankin Score
N/A	Not Applicable
NC	Not Calculable
NR	Not Reported
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OLE	Open-label extension
PAS	Patient access scheme
PSA	Probabilistic sensitivity analysis
PSSRU	Personal social services research unit
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
RTI	Respiratory tract infection
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
THIN	The Health Improvement Network
TPO-RA	Thrombopoietin receptor agonist
TTO	Time trade-off
UK	United Kingdom
WHO	World Health Organisation
WTP	Willingness to pay

1 Executive summary

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

The company (Grifols) provided clinical and cost effectiveness evidence for fostamatinib (Tavlesse®) for the treatment of chronic immune thrombocytopenia (ITP) in adults.

The differences between the decision problem addressed by the company and the final scope issued by NICE are highlighted in Table 1 below.

Table 1 Differences in final scope issued by NICE and decision problem addressed by the company

Parameter	Final scope issued by NICE Decision problem	Decision problem
Population	Adults with chronic immune thrombocytopenia that is refractory to other treatments	The population specified in the NICE final scope reflects the licensed indication for fostamatinib for chronic ITP. The company submission (CS) is for a subset of the licensed population for fostamatinib and focuses on patients who have not had a suitable response to prior therapy including TPO-RA or patients for whom use of TPO-RA is not appropriate. The ERG believes that the narrowing of population definition is relevant to NHS clinical practice.

Parameter	Final scope issued by NICE Decision problem	Decision problem
Comparator(s)	• Splenectomy • Immunosuppressive agents including rituximab (does not currently have a marketing authorisation in the UK for this indication) • Romiplostim • Eltrombopag • Watch and rescue • Cytotoxic agents • Dapsone • Danazol	The company selected 'watch and rescue' as the most relevant comparator. The ERG clinical advisor considers that this does not align with current management of adults with chronic ITP in the UK, as the other comparator treatments specified in the NICE final scope are also all used in clinical practice. The CS did not provide clear evidence about the relative effectiveness of fostamatinib compared with the active comparator treatments listed in the NICE final scope.
Outcomes	The outcome measures to be considered include: • platelet count • response rate • durable response • need for rescue treatments • Use of concurrent treatments • reduction in symptoms (minor and/or severe) • adverse effects of treatment • mortality • health-related quality of life	The outcome of 'use of concurrent treatments' was removed from the decision problem by the company. The ERG considers this reasonable. For 'reduction in symptoms (minor and/or severe)', the only relevant outcome in the CS is bleeding. Health-related quality of life was not reported in the CS and not used in the company's economic model.
Subgroups	Consideration will be given to subgroups of patients: • who have had a splenectomy • for whom a splenectomy is unsuitable If the evidence allows, other subgroups may be identified for whom the technology may be particularly clinically effective. Examples may include: • prior rituximab or • prior TPO-RA use.	No subgroups were specified in the company's decision problem. Of the subgroups mentioned in the NICE final scope, the CS did not report subgroup analysis for patients: • for whom a splenectomy is unsuitable • with prior rituximab.

1.2 Summary of the key issues in the clinical effectiveness evidence

Overall, the ERG considers the methods used to conduct the company's systematic review of clinical effectiveness evidence to be acceptable and in line with current methodological standards [Section 3.1 of this report].

The company conducted a systematic literature review but did not conduct any indirect comparisons or network meta-analysis (NMA) because of a lack of suitable published data due to heterogeneity in factors such as study populations and outcome definitions. However, the ERG believes that this decision has not been adequately justified by the company and notes two recent published reviews in this area that did conduct NMA.

The key clinical effectiveness evidence presented by the company consists of two identically designed, good quality multicentre, phase III RCTs, **FIT1 and FIT2,** that assessed the effects of fostamatinib (N=101) versus placebo (N=49) over a period of 24 weeks. The company also presented the findings of **FIT3**, a 5-year open-label extension study of FIT1 and FIT2 involving a total of 126 participants treated with fostamatinib [Section 3.2.1 of this ERG report]. Instead of conducting meta-analysis, the company presented the results for FIT1 and FIT2 together as a pooled analysis. Endpoints assessed in the pooled analysis of the FIT1 and FIT2 trials included stable platelet response and bleeding.

The study populations of FIT1 and FIT2 were in line with the NICE final scope but broader than those specified in the company's decision problem and included patients who had not undergone prior TPO-RA (53% of the fostamatinib group and 49% of the placebo group) and patients with persistent ITP (6% of the fostamatinib group and 8% of the placebo group). Therefore, the ERG is of the opinion that the data from the FIT1 and FIT2 trials do not suggest a better or worse outcome for fostamatinib treatment in patients with chronic ITP and prior TPO-RA use. Overall, the ERG believes that the study populations are adequate to address the company's decision problem.

As study participants were permitted to receive rescue therapy, the company stated that the placebo groups of FIT1 and FIT2 were equivalent to 'watch and rescue'. The ERG considers these trials to represent a comparison of fostamatinib with rescue therapy as required versus placebo with rescue therapy as required. It notes that rescue therapy was administered in both fostamatinib and placebo groups, although the proportion of participants receiving rescue therapy was lower in the fostamatinib group compared with the placebo group [Section 3.2.1 of this ERG report].

The ERG has some doubts on whether 'watch and rescue' is the most appropriate comparator. In particular, the ERG's clinical expert is of the opinion that the choice of 'watch and rescue' as only comparator does align with the current management of adults with chronic ITP in the UK for whom other treatments among those listed in the NICE final scope are used in clinical practice.

Results of the pooled analysis of FIT1 and FIT2 showed that 18/101 (18%) participants in the fostamatinib group and 1/49 (2%) in the placebo group achieved the primary efficacy endpoint of a stable response (p=0.007, Fisher's Exact Test), defined as a platelet count of ≥50,000/μL on at least four of last six visits (weeks 14-24). For the secondary endpoints, greater numbers of participants in the fostamatinib group than in the placebo group achieved a platelet response at 12 and 24 weeks. The post hoc endpoint of overall response (platelet count of ≥50,000/μL within the first 12 weeks and without rescue medication in this period) was achieved by 43/101 (43%) of participants randomised to fostamatinib and 7/49 (14%) of those randomised to placebo. Most participants across both randomised groups experienced at least one adverse event (AE). Diarrhoea, nausea and hypertension were the most commonly reported AE. Serious AEs were experienced by 13% of fostamatinib participants and 23% of the placebo groups. Two participants died during the study period (one from each randomised group).

1.3 Summary of the key issues in the cost effectiveness evidence

The company's base case ICER (original submission) was £[redacted] per QALY gained at list price. It would appear form the company submitted documentation that a PAS has been agreed at a [redacted] discount from the proposed list price for fostamatinib. However,

analyses at the PAS price have not been reported in the company submission. The ERG identified several errors in the company economic model formulae which were corrected at clarification stage. The company's preferred base case assumptions generate incremental costs (£[redacted]) and incremental QALYs ([redacted]) and an associated ICER of £[redacted] per QALY gained.

The ERG considers the following to represent key issues of uncertainty for decision making:

- The company's submitted economic model compares fostamatinib versus watch and rescue. Several potential alternative comparators that are relevant to the NICE scope have not been included in the economic model (e.g. rituximab and splenectomy). The economic model assumes that UK standard of care for a patient cohort who have chronic ITP and previously failed or were unsuitable for treatment with TPO-RAs is 'watch and rescue'. The economic model does not include any attempt to model other treatments that might be included in the treatment pathway should a patient fail to respond adequately to either fostamatinib or watch and rescue. Such patients would instead be placed on repetitive cycles of rescue therapy for the remaining duration of their life years. The ERG does not consider this reflective of UK standard of care, and the ERG's clinical expert is of the view that very few patients with chronic ITP would be treated repetitively with rescue treatments in UK clinical practice, when other treatments options had not been explored. It is therefore unlikely that the modelled treatment pathway is an accurate reflection of the treatment pathway in UK clinical practice, raising substantial uncertainties regarding cost-effectiveness results.

- The treatment acquisition costs for fostamatinib are based on a pre-defined treatment algorithm regarding dose escalation for early non-responders at 4 weeks, and treatment discontinuation following non-response at 12 weeks. The ERG note that the approach does not take into account the likely variation in treatment practices and prefers the use of the mean daily dosage of fostamatinib, calculated by the company in response to clarification queries.

The ERG also prefers the use of a compliance parameter set to 100%, as non-compliance is already incorporated in the mean dosing.

- The long-term effectiveness (i.e. transitions between platelet count health states) of both watch and rescue and fostamatinib is based on a simple extrapolation of the average transitions observed from the FIT1 and FIT2 clinical trials over the three model cycles up to 12 weeks. However, there is a substantial proportion of missing platelet count data, which raises two issues of uncertainty. First, the sample size to populate transitions is severely diminished and is often based on <10 patients, particularly in the watch and rescue arm where recruited numbers were lower than in the fostamatinib arm. Secondly, it is difficult to fathom the impact on the economic model of the trials' missing data with regard to platelet count. These two issues raise substantial uncertainties regarding both the short and long-term transition probabilities applied in the economic model. The ERG has explored several alternative scenarios to illustrate the impact of uncertainty on the ICER and a judgement is required regarding the most appropriate data to populate the model transitions in the longer term.

- The economic model results are sensitive to the method by which long-term data from the FIT3 OLE study are applied in the economic model to calculate transitions out of the response health state. Loss of a sustained response was defined as any missing data or platelet count $<50x10^9$/L at any measurement time point between months 1 and 24. Different assumptions about how to treat missing data, different assumptions about which state the cohort enter following a loss of response, and different plausible calculation approaches lead to substantially different estimates of the ICER. A judgement call is required regarding the most appropriate approach to calculate longer term loss of response. The ERG notes that future data may become available from the FIT3 study over the longer term that might help address some of these uncertainties.

- The ICER is also sensitive to the long-term treatment acquisition costs of fostamatinib. There is some debate clinically regarding whether it is appropriate to assume a tapering towards a reduction in dose or discontinuation of treatment without detriment to clinical benefits. Whilst such an outcome is clinically plausible, there are no data from the OLE study to support such an assumption. However, the potential to remove treatment costs and continue to gain benefit is an important consideration for decision makers, and even small proportions of patients coming off treatment may have a substantial impact on the ICER.

- There is likely to be substantial variation across the UK with regards to the treatment bundle used for rescue therapy and surgical prophylaxis for chronic ITP patients with low platelet counts. The company's KOL information suggests that only hospital-administered treatments (IVIg, IV methylprednisolone and platelet transfusions) would be used as rescue treatments in the UK. However, the ERG's clinical expert is of the view that other treatments, including oral prednisolone and dexamethasone, which were used in the trials are also appropriate and commonly used in UK clinical practice. A judgement is required regarding the bundle of rescue treatments that is most reflective of UK clinical practice, for use in the economic model.

- The ERG have identified several errors around discounting methods, application of unit costs to rescue therapy and the calculation of mortality risk for the non-responder health state. The net impact of correcting these errors is a substantial increase in the ICER relative to that reported in the company submission.

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred base case ICER incorporates the cumulative impact of the following:

1. Correction of identified model formulae errors regarding application of mortality HRs, discounting formulae, counting of adverse events, calculation

of rescue therapy frequency, calculation of transition probabilities and other minor data inconsistencies.

2. Updating unit costs to 2018/19 values as opposed to inflating from older studies / reference cost sources.
3. Using the mean daily dosage of fostamatinib and assuming a compliance of 100% applied to the mean to inform the treatment acquisition costs of fostamatinib.
4. Amend the bundle of treatments included for rescue therapy in line with the ERG clinical expert's opinion about treatments in UK clinical practice (e.g. including dexamethasone and oral prednisolone within the treatment bundle, in addition to IVIg, IV methylprednisolone and platelet transfusion).
5. Source the cheapest possible unit costs of rescue treatments, making use of generic equivalents where possible and applying dosing in accordance with the ERG's clinical expert opinion regarding dosing.
6. Utilities age adjusted on the model trace and source utilities age adjusted from source literature to the starting age of the model cohort.
7. The use of outpatient bleed probability calculated from a weighted average of splenectomised and non-splenectomised patients as opposed to non-splenectomised only.

The ICER under the set of model assumptions preferred by the ERG is £[redacted] per QALY gained (see Table 2). The corresponding probabilistic ICER is £[redacted], and the probability that fostamatinib and watch and rescue are the most cost-effective strategy at a WTP threshold of £20,000 per QALY gained is 0% and 100% respectively.

Table 2 ICER resulting from ERG's preferred assumptions

	Total costs	**Total QALYs**	**Δ costs**	**Δ QALYs**	**ICER £/QALY**
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has explored the impact of several different scenario analyses on the ICER. Given the correction of several errors, the ERG considers it most appropriate to apply scenario analyses to the ERG corrected / preferred base case ICER to inform decision-making. Scenario analyses are described and justified in Table 24 and results provided in Table 25. A summary of the results of scenario analyses applied to the ERG preferred set of base case assumptions is provided in Table 3.

The ERGs base case ICER is most sensitive to changes in the long term probability of a loss of fostamatinib sustained response, and the exploration of different potential assumptions for a reduction in fostamatinib treatment acquisition costs due to discontinuation of treatment for long-term responders (beyond 1 year). It should be noted that plausible changes in these parameters have a substantial impact on the ICER, but under no scenarios considered does the ICER fall below £30,000 per QALY gained. The same result stands when applying the PAS discount price for fostamatinib (full results of pas price analyses are provided in Appendix 6). The ERG cautions that there remains substantial uncertainty regarding the most plausible base case ICER, but it is likely to be substantially higher than that proposed by the company.

Table 3 Exploratory analyses undertaken by ERG

	Incremental Costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
ERG preferred base case analysis (no PAS)			
Fostamatinib vs. watch and rescue	[redacted]	[redacted]	[redacted]
ERG preferred base case analysis (with PAS)			
Fostamatinib vs. watch and rescue	[redacted]	[redacted]	£143,790
Apply treatment tapering scenario (company preferred application of scenario)			
Fostamatinib vs. watch and rescue	[redacted]	[redacted]	[redacted]
Apply treatment tapering scenario (ERG preferred application of scenario)			
Fostamatinib vs. watch and rescue	[redacted]	[redacted]	[redacted]
Long term loss of fostamatinib response (most favourable to fostamatinib)			
Fostamatinib vs. watch and rescue	[redacted]	[redacted]	[redacted]
Long term loss of fostamatinib response (least favourable to fostamatinib)			
Fostamatinib vs. watch and rescue	[redacted]	[redacted]	[redacted]
Disutility applied to 0 carers for ICH health states			
Fostamatinib vs. watch and rescue	[redacted]	[redacted]	[redacted]
Disutility applied to 2 carers for ICH health states			
Fostamatinib vs. watch and rescue	[redacted]	[redacted]	[redacted]
0% Discount rates applied to costs and outcomes			
Fostamatinib vs. watch and rescue	[redacted]	[redacted]	[redacted]
6% Discount rates applied to costs and outcomes			
Fostamatinib vs. watch and rescue	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: Incremental cost-effectiveness ratio; ICH: Intracranial haemorrhage; PAS: Patient access scheme; QALY: Quality adjusted life year

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for this submission is chronic immune thrombocytopenia (ITP). The company's description of ITP in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is fostamatinib (Tavlesse®).

2.2 Background

Immune thrombocytopenia (ITP) is an acquired immune-mediated disease characterised by increased platelet destruction and thrombocytopaenia, with increased bleeding depending on the degree of thrombocytopaenia.[1-3] The cause of ITP is depletion of platelets by antiglycoprotein autoantibodies via destruction and inhibition of megakaryocyte production of new platelets.[4] Primary ITP is an autoimmune disorder characterised by isolated thrombocytopaenia (i.e. peripheral blood platelet count <100 x 10^9) without any underlying causes or disorders.[2, 3] Most adults with primary ITP follow a chronic course of the disease, defined as lasting for at least 12 months.[2-5] Chronic ITP is the focus of the company submission, as specified in the NICE final scope.

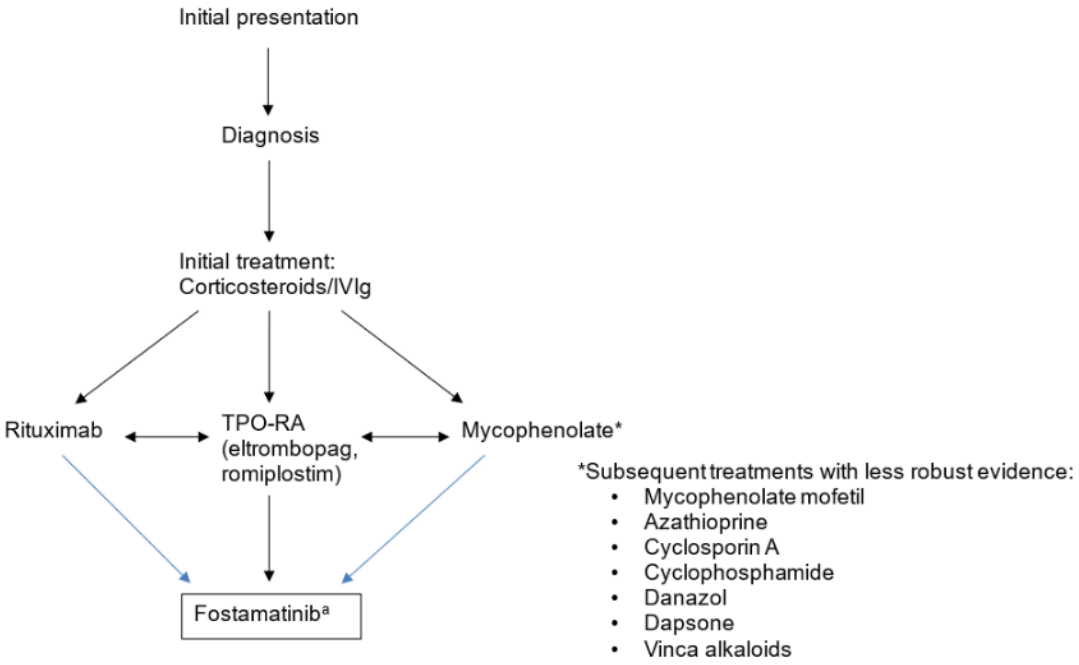
The symptoms of ITP include petechiae, purpura and mucosal bleeding in the urinary tract or in the gastrointestinal or oral cavities, including epistaxis.[6] In addition, people with primary ITP have an increased risk of bleeding, frequently experience fatigue[2, 7] and are faced with physical and psychosocial challenges due to its inflammatory biology and relapse/refractory nature.[4] Quality of life can also be affected, including emotional, functional and reproductive health, and work and social life.[4, 7-9]

The incidence of ITP in adults in Europe is estimated to be between 1.6 to 3.9 cases per 100,000 population per year. Incidence generally increases with age but is generally equal for men and women, with the exception of women in the 30-60 year age group, for whom the prevalence is higher than men.[3,10] Prevalence of ITP has been estimated as 50.3 per 100,000 population, breaking down to 59.3/100,000 for women and 40.7 for men.[11] Estimates of prevalence of chronic ITP have been reported as 20.3/100,000 for the overall population (24.5/100,000 for females and 17/100,000 for males).[12]

There are currently no available clinical or laboratory factors to accurately diagnose primary ITP, with its diagnosis based on clinical expertise and exclusion of other potential causes, involving patient history, physical examination, blood count and analysis of the peripheral blood film.[2,13] Figure 1, Document B of the company submission presents details of the components of a diagnosis of ITP.

The main aim of treatment of ITP is to establish a safe platelet count to, for example, prevent major bleeding.[2] Current treatments for ITP aim to target individual processes in the pathogenesis pathway, either by inhibition of immunological events that encourage destruction of platelets, or inhibit their development (e.g. steroids, intravenous immunoglobulin, anti-D, rituximab) or by encouraging production of new platelets (i.e. TPO-RA). The likelihood of relapse in chronic ITP, or its becoming refractory, is a constant challenge, as there is no cure and current treatments are haphazard in their effectiveness and none consistently result in robust remission (with the exception of splenectomy and rituximab-based treatment in selected circumstances). There is, therefore, a potential therapeutic role for as yet unexplored disease mechanisms in ITP. To that end, the spleen tyrosine kinase (Syk) signaling pathway has emerged as a potential new target for treatment of autoimmune diseases, including ITP.[4, 14]

Fostamatinib is a relatively selective inhibitor of Syk. The major metabolite of fostamatinib (R406) inhibits receptors which have a major role in antibody-mediated cellular responses, thereby reducing platelet destruction.[4,15] The company's proposed positioning for fostamatinib in the clinical care pathway is presented in Figure 1, Document A of the company submission and is reproduced as Figure 1.



[a]fostamatinib is also proposed as a treatment option for patients where use of a TPO-RA is not appropriate.

Light blue arrows indicate that patient must have been treated with a TPO-RA first unless the patient is not appropriate for use of a TPO-RA, for example the blue arrow from rituximab to fostamatinib indicates TPO-RA → rituximab → fostamatinib

Evidence assessed by the International Consensus Report.[13] TPO-RA, thrombopoietin receptor agonist.

Figure 1 Proposed place for fostamatinib in the clinical care pathway (reproduced from Figure 1, Document A of the CS)

The ERG clinical expert considers the company's positioning of fostamatinib to be reasonable and likely to represent clinical practice. The majority of patients will have failed TPO-RA (unless they are not suitable for this treatment, but these patients form a very small group) and these agents should be considered second line therapy. Some, but not all patients may have received mycophenolate, rituximab or other immunosuppressive therapies before or after TPO-RA. There are two TPO-RA in common use (eltrombopag and romiplostim) but others are licensed (with restrictions) but not widely funded (for example, avatrombopag). Patients may have tried eltrombopag and/or romiplostim before fostamatinib.

It should be noted that not all of the second-line drug treatments listed in Figure 1 (azathioprine, ciclosporin A, cyclophosphamide, danazol, dapsone, mycophenolate, rituximab, and vinca alkaloids) are licensed for the treatment of ITP in adults and at present only a limited number of randomised controlled trials (RCTs) have been conducted in

adults.[13] In the UK, rituximab is used as an off-label treatment in patients with ITP and has been assessed by NICE due to its high volume of request.[16]

Presently, there is no single standard treatment pathway for adults with chronic ITP in routine practice in the UK, as noted in previous NICE technology appraisals (TA221 and TA293) for the same indication.[17,18] NICE technology appraisals TA221 and TA293 recommend TPO-RAs (romiplostim and eltrombopag) for adults with chronic ITP whose condition is refractory to standard active treatments and rescue therapies or those who have severe disease and are at a high risk of bleeding that needs frequent courses of rescue therapies.[17, 18]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 4. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 4.

Table 4 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with chronic immune thrombocytopenia that is refractory to other treatments	Adults with chronic immune thrombocytopenia chronic who have not had a suitable response to prior therapy including a TPO-RA, or where use of a TPO-RA is not appropriate.	This population reflects the anticipated positioning of fostamatinib in clinical practice according to clinical experts, and on the basis of the available evidence from clinical trials	The population specified in the NICE final scope reflects the licensed indication for fostamatinib for chronic immune thrombocytopenia (ITP). The company submission (CS) is for a subset of the licensed population for fostamatinib and focuses on adults with ITP who have not had a suitable response to prior therapy including a thrombopoietin receptor agonist (TPO-RA), or patients for whom use of a TPO-RA is not appropriate. The ERG believes that the narrowing of population definition is relevant to NHS clinical practice. The ERG clinical advisor agrees with the clinical expert views elicited by the company that in England fostamatinib would be used after treatment with a TPO-RA in patients that have relapsed or not responded to treatment; or used in patients that are not suitable for treatment with TPO-RAs.[19, 20] The study populations in the clinical evidence submitted by the company (FIT1, FIT2 and FIT3) included all patients who had failed any prior treatment and not only those who had failed prior TPO-RA. The study populations are therefore in line with the NICE final scope and the licensed indication for fostamatinib but broader than those specified in the company's decision problem. The study populations also included patients with persistent (rather than chronic) ITP, who also do not meet the company's or NICE's decision problem. Therefore, the ERG is of the opinion that the data from FIT1 and FIT2 do not suggest a better or worse outcome for fostamatinib treatment in patients with chronic ITP and prior TPO-RA use. Overall, the ERG believes that the study populations are adequate to address the company's decision problem.

Intervention	Fostamatinib	Fostamatinib	Not specified	The intervention described in the company's submission match the intervention described in the final scope. Fostamatinib is administered orally at a starting dose of 100 mg twice daily with dose escalation to 150 mg twice daily after 4 weeks based on platelet count and tolerability, consistent with the Summary of Product Characteristics (SmPC) by the European Medicines Agency (EMA).[15] Fostamatinib is discontinued after 12 weeks if the platelet count does not rise sufficiently to avoid bleeding. According to the EPAR, fostamatinib (Tavlesse®) received a marketing authorization valid throughout the European Union on 9th January 2020 for the treatment of adults with chronic ITP refractory to other treatments and the final European Public Assessment Report (EPAR) was published on 11th February 2020.[15]
Comparator(s)	• Splenectomy • Immunosuppressive agents including rituximab (does not currently have a marketing authorisation in the UK for this indication) • Romiplostim • Eltrombopag • Watch and rescue • Cytotoxic agents • Dapsone • Danazol	• Watch and rescue	Comparison with other therapeutic options typically used in adult patients with chronic ITP who have not had a suitable response to prior therapy including a TPO-RA, or where use of a TPO-RA is not appropriate such as rituximab are hampered by a lack of published evidence. The limited evidence that is available for rituximab is subject to considerable heterogeneity and an	The company selected 'watch and rescue' as the most relevant comparator. Clinical opinion received by the ERG is that the other comparator treatments specified in the NICE final scope are also all used in clinical practice and thus the defined comparator (watch and rescue) does not align with current management of adults with chronic ITP in the UK. The ERG clinical advisor considers that very few people who have clinically symptomatic ITP and therefore would be considered for fostamatinib, are treated with a 'watch and rescue' approach alone. In current clinical practice, it is much more likely that other immunosuppressive therapies such as rituximab, cyclosporin A or mycophenolate would be tried unless all of these have failed already. The CS did not provide any evidence about the relative effectiveness or cost-effectiveness of fostamatinib compared with the active comparator treatments listed in the NICE final scope.

			indirect treatment comparison was not considered feasible. The other treatment options listed as possible comparators are not considered to be supported by robust evidence by latest international guidelines, whilst splenectomy is considered only after failure of medical therapies (Provan et al., 2019)	The company stated that an indirect treatment comparison was not considered feasible, because of a lack of evidence and heterogeneity among studies of the comparators. Upon the ERG's clarification request for the full details of the company's feasibility study (systematic literature review) and complete information about the studies identified for the indirect treatment comparison (clarification question A9), the ERG is of the opinion that the company did not provide detailed evidence to justify that an indirect treatment comparison was not feasible. The evidence submitted by the company (FIT1 and FIT2) used placebo as the comparator for fostamatinib. As study participants were permitted to receive rescue therapy on deterioration of condition, the company stated that the placebo group was equivalent to 'watch and rescue' (e.g., pages 31, 73, 85 of the CS). However, the ERG notes that rescue therapy was administered in both fostamatinib and placebo groups, although the proportion of participants receiving rescue therapy was lower in the fostamatinib group compared with the placebo group. The comparison in the submitted evidence was in effect fostamatinib plus watch and rescue versus placebo plus watch and rescue.
Outcomes	The outcome measures to be considered include: • platelet count • response rate • durable response • need for rescue treatments • Use of concurrent treatments	The outcome measures to be considered include: • platelet count • response rate • durable response • need for rescue treatments • reduction in symptoms	Use of concurrent treatments has been removed from the decision problem. Concurrent treatment was allowed in the fostamatinib trials but had to remain stable to avoid the risk of confounding interpretation of the primary endpoint.	The outcome of 'use of concurrent treatments' was removed from the company's decision problem. The ERG considers this is reasonable because FIT1 and FIT2 permitted stable concurrent treatment in all participants and were therefore not designed to show an effect on reduction of concurrent medication. For the outcome of 'reduction of symptoms (minor and/or severe)' specified in the NICE final scope, the only relevant outcome in the CS was bleeding. The outcome of 'health-related quality of life' specified in the NICE final scope was not reported in the CS. The ERG recognises that quality of life data were measured in FIT1 and FIT2 but were

	• reduction in symptoms (minor and/or severe) • adverse effects of treatment • mortality • health-related quality of life	(minor and/or severe) • adverse effects of treatment • mortality • health-related quality of life		not used in the company's economic model (section B.3.4 of the CS).
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 considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the	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 considered from an NHS and Personal Social Services perspective. The availability of any commercial	N/A	The ERG are satisfied that the framework of economic evaluation (incremental cost per QALY gained over a lifetime horizon from an NHS and PSS perspective) is in line with the NICE scope. A critique of the company's submitted economic evidence is provided in Chapter 4.

	intervention, comparator or subsequent treatment technologies will be taken into account.	arrangements for the intervention, comparator or subsequent treatment technologies will be taken into account.		
Subgroups	Consideration will be given to subgroups of patients: • who have had a splenectomy • for whom a splenectomy is unsuitable If the evidence allows, other subgroups may be identified for whom the technology may be particularly clinically effective. Examples may include prior rituximab or prior TPO-RA use. The availability and cost of biosimilar products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific	Not specified	All subgroups, including prior splenectomies, had a favourable response. Therefore, it was deemed there is no obvious way to subgroup the patient population. Subgroup data has however been included in appendix E, including prior use of a TPO-RA	No subgroups were specified in the company's decision problem. Of the subgroups suggested in the NICE final scope, the CS reported subgroup analysis for patients: • who have had a splenectomy • who had had prior TPO-RA. The CS did not report subgroup analysis for patients: • for whom a splenectomy is unsuitable • who had had prior rituximab.

	treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			
Special considerations including issues related to equity or equality	No special considerations specified	Not specified	Not applicable	The ERG agrees with the company that there are no anticipated equality issues related to fostamatinib.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D.X of the CS. The ERG appraisal of the company's systematic review methods is summarised in Table 5 below.

Table 5 ERG appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Partially	Only details of the MEDLINE search were provided.
Were appropriate bibliographic databases/sources searched?	Yes	
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Only Partially	Eligibility criteria were consistent with the company's decision problem where the only relevant comparator was 'watch and rescue'. The company's systematic review did not include the other active treatment comparators listed in the NICE final scope.
Was study selection conducted by two or more reviewers independently?	Possibly	In Appendix D.1.1, it is stated that two researchers reviewed the titles and abstracts. However, it is not clear whether they worked independently. It is also unclear whether full text papers were reviewed by two researchers working independently.
Was data extraction conducted by two or more reviewers independently?	Yes	See Appendix D.1.1 of the CS.
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	See Section B.2.5 and Appendix D.1.3 of the CS.

Was risk of bias assessment conducted by two or more reviewers independently?	Possibly	One reviewer performed the 'risk of bias' assessment, which was checked by another reviewer (the company response to Question A4 of the clarification document).
Was identified evidence synthesised using appropriate methods?	Possibly	The company did not perform a network meta-analysis including the comparators in the NICE Final Scope. The reasons for this were not fully justified and the ERG is unable to judge whether this was appropriate. They then presented the pooled results of the two identified RCTs (FIT1 and FIT2) as if they were from one trial, on the basis that these studies had identical designs and had previously been reported together.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence (main included studies) using the Centre for Review and Dissemination (CRD) criteria; results are presented in Table 6. The ERG is of the opinion that the company's systematic review of the clinical effectiveness evidence provided sufficient details of FIT1, FIT2 and FIT3, and summarised them appropriately. However, the company did not provide sufficient details of the SLR conducted to identify studies that assessed the relevant comparator treatments, which is considered an omission by the ERG.

Table 6 Quality assessment of the company's systematic review of clinical effectiveness evidence (main trials)

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.1.1 Critique of evidence synthesis methods

The company identified two randomised studies (FIT1 and FIT2) comparing fostamatinib versus control, but no meta-analyses of these studies were performed. Instead, naïve pooling was used to combine them, and the results presented as if they were from a single study. Normally, formal meta-analysis is preferred over simple pooling of studies because of concerns that spurious results may be obtained due to Simpson's paradox if the populations of the studies have different underlying risks.[21] The company's justification was that the two studies had an identical design and their results had already been pooled in the primary results publication.[22] Although the ERG's preference would be to conduct formal meta-analyses, simple pooling is not unreasonable because both studies had an identical design, were conducted at around the same time and had similar baseline characteristics, although the studies were conducted in different geographical areas: FIT1 mainly in North America, Western Europe and Australia and FIT2 mainly in Eastern Europe.

No indirect comparison or network meta-analysis (NMA) is presented in the CS. The only evidence discussed compared fostamatinib with placebo, which the company considered as representative of the comparator specified in NICE's final scope, watch and rescue.

The company acknowledged that fostamatinib could have been compared with other treatments considered in NICE's final scope, including rituximab, cytotoxic agents, dapsone and danazol, which they believe can be used at a similar point in the

treatment pathway, i.e. when there has not been a suitable response to a TPO-RA or when the use of a TPO-RA is not appropriate. Other comparators specified in NICE's final scope included splenectomy, romiplostim and eltrombopag.

They conducted a systematic literature review to identify studies assessing the relevant comparators, but did not provide sufficient information on the results of this review. On page 73 of the submission, the company state that, in the case of rituximab, a NMA including fostamatinib was not feasible because there was limited evidence with considerable heterogeneity. For the other potential comparators, the company again refers to heterogeneity and to the fact that these treatments are not supported by robust evidence from published guidelines.[13]

The ERG requested further details of the company's literature review in order to verify that it was not feasible to conduct an indirect treatment comparison. Details of the search strategy, study flow diagram and references for the 24 identified studies (both RCTs and non-RCTs) and 31 publications were provided by the company at clarification; however, no further details of the actual comparisons and outcomes included in each study or of the feasibility assessment conducted by the company were given. Therefore, the ERG is unable to assess whether the decision not to conduct an NMA is entirely justified. Moreover, the ERG is aware of at least two published NMAs that have been conducted in this topic area.[23, 24]

Arai and colleagues conducted a systematic review and NMA of 12 RCTs of treatments for persistent/chronic ITP.[23] Six treatments (placebo, eltrombopag, avatrombopag, romiplostim, rituximab and rhTPO + rituximab) were included in the network and analyses conducted for several outcomes including overall response to treatment, bleeding and adverse events.

Puavilai and colleagues conducted a systematic review and NMA for adult persistent ITP.[24] Fourteen studies were eligible for inclusion comparing placebo, eltrombopag, romiplostim, rituximab and rhTPO + rituximab and analyses were conducted for outcomes such as platelet response, platelet count, bleeding and SAEs.

Neither of these NMAs included a fostamatinib trial. The results of FIT1 and FIT2 were published in 2018[22] and the search dates for the Arai and Puavilai NMAs were 2017 and 2018, respectively. The ERG notes that these two NMAs include a number of publications that also appear in the list of studies identified by the company's literature review.

The ERG was not able to check each individual study within the timeframe of this appraisal; nevertheless, they believe that, according to the evidence available in the literature, it is likely that the company could have attempted a NMA comparing fostamatinib with at least some of the comparators in NICE's final scope. Although the definition of platelet response would likely vary by study, both published NMAs were able to include this outcome, albeit with slightly different definitions. However, the ERG accepts that there may be considerable heterogeneity between studies and notes that for this appraisal the benefit of a NMA might have been limited by the relatively small number of fostamatinib trials, and therefore by the fact that fostamatinib would have been connected to other treatments in the network only through placebo.

The ERG also notes that no pooled effect sizes (e.g. odds ratios) comparing fostamatinib versus placebo appear to have been used in the economic modelling, which just included group-specific data from FIT1 and FIT2 pooled together.

Overall, the ERG considers the methods used by the company to conduct the systematic review of clinical effectiveness evidence to be acceptable according to current methodological standards. However, the ERG has reservations about the company's feasibility study to support their decision not to conduct an indirect treatment comparison with the active comparator treatments listed in the NICE final scope. The full details of this literature review were not reported in the CS and only a list of references were provided to the ERG, even when further details were requested on clarification. The ERG is of the opinion that additional information provided as part of the company's response was not sufficiently detailed to justify that an indirect treatment comparison or NMA was not feasible.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Based on a systematic literature search, the company identified six potentially relevant fostamatinib studies: FIT1, FIT2, FIT3, NCT00706342, NCT03363334 and NCT04132050 (Table 58, Appendix D of the CS).[25-30] Only the FIT trials were considered in the main CS. No useable published data were identified for NCT03363334 or NCT04132050. No information was provided in the CS about the reason for excluding NCT00706342, but this appears to be a non-randomised Phase II trial. The ERG is not aware of any other relevant fostamatinib publications.

The evidence submitted by the company consists of two Phase III, multicentre, randomised, double-blind, placebo-controlled studies, FIT1 and FIT2,[22] and an open-label extension (OLE) study, FIT3.[31,32] The three studies were administered by the company and investigated the clinical efficacy and safety of fostamatinib (Tavlesse ®, Grifols) for adults with chronic ITP (immune thrombocytopenia). An overview of the study is presented in Tables 3, 4 and 5, Section B.2.2 of the CS. Study methods are summarised in Section B.2.3 and the participant flow of the study is presented in Figures 23 and 24, Appendix D.1.2 of the CS.

FIT1 and FIT2 were two identically designed studies in which participants were randomized in a 2:1 ratio to fostamatinib or placebo for 24 weeks. Randomisation was stratified by baseline platelet count (<15,000/µl or ≥15,000/µl) and prior splenectomy (yes or no). FIT1 enrolled 76 participants (51 on fostamatinib and 25 on placebo), while FIT2 enrolled 74 participants (50 on fostamatinib and 24 on placebo). The company presented FIT1 and FIT2 as a pooled analysis in which a total of 101 participants were assigned to fostamatinib and 49 to placebo.

The study population in both FIT1 and FIT2 was adults with primary persistent or chronic ITP who had failed ≥1 prior therapy for ITP and had ≥3 platelet counts 30,000/µl. Persistent ITP was defined as 3 to 12 months from diagnosis and chronic ITP was defined as lasting for >12 months, in accordance with Rodeghiero et al.[2] (2009). Participants initially received study treatment orally at 100 mg twice daily

(BID) and increased to 150 mg twice daily (or matching placebo) at Week 4 or later if the platelet count remained <50,000/µl and study treatment was well tolerated. Dose could be reduced to 100 mg or 150 mg once daily (QD) if a dose-limiting adverse event occurred. Treatment was discontinued early (after Week 12) due to lack of response defined as platelet count <50,000/µl in general, or <20,000/µl in the case of participants with baseline platelet count <15,000/µl. The former, but not the latter criterion was applied in the economic model. Those participants with a lack of response were considered 'non-responders'.

In both studies, stable concomitant medication consisting of either glucocorticoids, azathioprine or danazol was permitted. 'Rescue' therapy (intravenous [IV] immunogloblin, IV anti-D immunoglobulin G, IV methylprednisolone, oral dexamethasone, or oral prednisone) was administered for participants in either the fostamatinib or the placebo group with platelet count <50,000/µl and meeting specified circumstances (p. 43, Section B.2.3 of the CS). Participants could receive rescue therapy at any time, but those receiving rescue therapy after Week 10 were considered non-responders. On the basis of the rescue therapy provided, the company stated that placebo treatment in FIT1 and FIT2 was equivalent to 'watch and rescue' (page 31, Section B.2 summary; page 73, Section B.2.9; page 85, Section B.2.13, of the CS). However, the ERG notes that rescue therapy was also given to participants assigned to fostamatinib, although the proportion of participants who received rescue medication was lower in the fostamatinib group than in the placebo group (Figure 8, Section B.2.6 of the CS; and Section 3.x of the ERG report).

The FIT3 study was a 5-year, single-arm, open-label extension study of FIT1 and FIT2 involving 126 participants. FIT3 enrolled participants who completed the full 24-week treatment period in FIT1 or FIT2 (responders), and those who had discontinued FIT1 or FIT2 due to lack of efficacy (non-responders) after completing ≥12 weeks of treatment, including at least 4 weeks at a dose of 150 mg BID of study drug (fostamatinib or placebo). The study medicine for all participants was open-label fostamatinib. Responders initiated fostamatinib with the dose and regimen that was effective in achieving a response in either FIT1 or FIT2. Non-responders initiated treatment at 100 mg BID. The FIT3 study completed in March 2020. The most recent interim data analysis was on 8th March 2018, available in the form of an oral abstract

and the company CSR.[27,31] Interim data analysis as of 14th April 2017 is available in a peer-reviewed publication.[32] It should be noted that, although FIT3 is an extension of two other randomised studies, it should not itself be considered as randomised evidence.

The ERG has reviewed the FIT1 and FIT2 studies and has no major concerns about their statistical methodology or conduct.

The quality of the FIT1 and FIT2 studies was assessed by the company and both studies were judged to be at low risk of bias for all domains taken from the ROB2 tool recommended by the Cochrane Collaboration (Section B.2.5, and Tables 60 and 61, Appendix D.1.3, of the CS).[33] The ERG checked the quality assessment of the FIT1 and FIT2 studies from the CS against their original publication and CSRs.[22,25,26] While the ERG noticed some errors for Domains 3, 4 and 5 of Table 61 of the CS, the company's quality assessment was considered by the ERG to be appropriate overall.

Treatment groups in the pooled analysis of FIT1 and FIT2 were well balanced for baseline characteristics including demographics, disease characteristics and prior therapies (Table 9, Section B.2.3 of the CS). Overall, most participants (74.7%, 112/150) were recruited in Europe and the rest from North America and Australia. Of these, 16.7% were recruited in the UK (18 participants on fostamatinib and 7 participants on placebo). The median age of participants was 54 and 53 years for fostamatinib and placebo, respectively. Most participants had chronic ITP (94% for fostamatinib and 92% for placebo) with a median of three prior ITP treatments for both fostamatinib and placebo groups. At baseline, almost half had platelet count <15,000/µl (47% for fostamatinib and 43% for placebo), with a mean platelet count of 16,052 (range 1000-51,000) and 19,818 (range 1000-156,000) for fostamatinib and placebo, respectively. The ERG considers that the population of FIT1 and FIT2 trials is relevant to clinical practice in the UK. However, the ERG notes that those with persistent ITP, who do not meet the company's decision problem, accounted for 6% of the fostamatinib group and 8% of the placebo group in the pooled analysis. Furthermore, patients who had not undergone prior TPO-RA, who also do not meet the company's decision problem, comprise around 50% of the study population (53% of the fostamatinib group and 49% of the placebo group). While this means that the

study population only partially meets the company's decision problem, the ERG clinical advisor agrees with the company's rationale that 'chronic' and 'persistent' ITP definitions may not necessarily impact on clinical decisions or treatment efficacy. Considering that clinical practice and access to TPO-RA vary across countries, the ERG considers the inclusion of patients with prior ITP treatments other than TPO-RA to be acceptable in a clinical trial setting. The ERG also takes into consideration that subsequent subgroup analysis of stable platelet response revealed that fostamatinib performed consistently better than placebo regardless of prior treatment with TPO-RA (Section B.2.7, and Figure 25, Appendix E, of the CS). The ERG is, therefore, of the opinion that the data from the FIT1 and FIT2 trials do not suggest a better or worse outcome for fostamatinib treatment in patients with chronic ITP and prior TPO-RA use. Overall, the ERG believes that the study populations are adequate to address the company's decision problem.

3.2.2 Primary and secondary efficacy endpoints in FIT1 and FIT2

Primary endpoint: FIT1 and FIT2

The primary efficacy endpoint in FIT1 and FIT2 was achievement of a stable platelet response by Week 24, defined as a platelet count of ≥50,000/μL on at least four of the six clinic visits between Weeks 14 and 24, inclusive; participants receiving rescue medication after Week 10 were considered non-responders (and considered for study withdrawal).

The company submission (Document B, page 58) compares the EMA 2014 definition of a platelet response with its own primary efficacy endpoint, stating "the EMA 2014 guidelines define a platelet response as 'any platelet count above 30,000/μL with at least doubling from baseline' and in comparison the primary outcome in FIT1 and FIT2 was considerably more difficult to achieve". The ERG notes that the EMA 2014 defines response as "any platelet count between 30 and 100 x 10^9/L and at least doubling of the baseline count and absence of bleeding".

In FIT1, the primary efficacy endpoint was achieved by 9/51 (18%) participants in the fostamatinib group and 0/25 (0%) participants in the placebo group (Fisher's exact test, p=0.026). In FIT2, the primary efficacy endpoint was achieved by 9/50 (18%) participants in the fostamatinib group and 1/24 (4%) participant in the placebo group

(Fisher's exact test, p=0.15). The pooled analysis of FIT1 and FIT2 showed that a total of 18/101 (18%) of the fostamatinib group and 1/49 (2%) of the placebo group achieved the primary efficacy endpoint. It is worth noting that for this pooled analysis the company reports a 2-sided Fisher's p-value of p=0.0003 but according to the ERG' calculation this should be p=0.007. -

Secondary endpoints: FIT1 and FIT2

Secondary efficacy endpoints in FIT1 and FIT2 were:

- **Achievement of a platelet response** (a platelet count of at least 50,000/μL) at Weeks 12 and 24: At both 12 and 24 weeks, a greater number of participants in the fostamatinib groups of FIT1 and FIT2 had achieved a platelet response. Full results are presented in Section B.2.6, Document B.
- Frequency and severity of bleeding according to the **IT Bleeding Score** (IBLS) over the 24-week study period: The IBLS grades bleeding from 0 (no bleeding) to 2 (marked bleeding). In each trial, mean IBLS scores over 24 weeks were similar in each group.
- Frequency and severity of bleeding according to the **WHO bleeding scale** over the 24-week study period: The scale grades bleeding from 0 (no bleeding) to 4 (debilitating blood loss). In FIT2, scores tended to favour the fostamatinib group while scores in FIT1 tended to favour the placebo group, but there was no clear evidence of a difference.

Post hoc endpoints

The company also presents the following post hoc endpoints:

- Overall response, defined as platelet count ≥50,000/μL within the first 12 weeks without rescue medication in the preceding 12 weeks:
- Onset, magnitude, and durability of platelet effect in primary efficacy endpoint responders:
- Reduction in rescue medication usage:
- Mortality:
- Health-related quality of life (SF-36):

It is worth noting that although SF-36 was assessed, the results were not presented or discussed in the company submission or used in the economic model. Inspection of

the relevant results tables for SF-36 for FIT1 and FIT2 (provided by the company at clarification) showed no statistically significant differences for the majority of domains in change from baseline between the fostamatinib and placebo groups.

Table 7 shows the FIT1 and FIT2 results for the outcomes specified in the decision problem.

Table 7 Summary of FIT1 and FIT2 outcomes specified in the decision problem

	FIT1		FIT2		FIT1 & FIT2 combined	
Outcome	**Fostamatinib (n=51)**	**Placebo (n=25)**	**Fostamatinib (n=50)**	**Placebo (n=24)**	**Fostamatinib (n=101)**	**Placebo (n=49)**
PLATELET COUNT						
Primary outcome: [a]Stable platelet response, n (%)	9 (18)	0 (0)	9 (18)	1 (4)	18 (18)	1 (2)
[b]Platelet response at 12 weeks, n (%)	11 (22)	0 (0)	12 (24)	3 (13)	23 (23)	3 (6)
[b]Platelet response at 24 weeks, n (%)	8 (16)	0 (0)	8 (16)	1 (4)	16 (16)	1 (2)
[c]Platelet count ≥30,000 and ≥20,000 at 12 weeks, n/N (%)	4/25 (16)	0/12 (0)	6/22 (27)	1/9 (11)	10/47 (21)	1/21 (5)
[c]Platelet count ≥30,000 and ≥20,000 at 24 weeks, n (%)	4/25 (16)	0/12 (0)	3/22 (14)	0/9 (0)	7/47 (15)	0/21 (0)
[d]Overall response, n (%)	19 (37)	2 (8)	24 (48)	5 (21)	43 (43)	7 (14)
Platelet count at 12 weeks, median, /µL	36,243 (n=39)	15,955 (n=20)	30,000 (n=47)	21,000 (n=19)[h]	NR	NR

Platelet count at 24 weeks, median, /µL	91,909 (n=11)[i]	NR	74,000 (n=12)	16,000 (n=3)	NR	NR
RESPONSE RATE AMONG FOSTAMATINIB RESPONDERS						
[e]Onset of platelet response, median (range), days	43 (15-73) n=9	N/A	15 (12-56) n=9	N/A	15.5 (12-73), n=18	N/A
Magnitude of platelet response (in fostamatinib responders), median (range)	≥100,000/µL (27,000-204,000) at weeks 18 to 24	N/A	≥100,000/µL (36,000-337,000) at weeks 12-22; 82,000/µL (22,000-367,000) at week 24	N/A	Median 95,000/µL over 24 weeks	N/A
DURABLE RESPONSE IN FOSTAMATINIB RESPONDERS						
[f]Platelet count at 24 weeks, median (range), /µL	≥100,000 (27,000-204,000)	N/A	82,000 (22,000-367,000)	N/A	NR	NR
[g]Duration of platelet response	NR	NR	NR	NR	NR	NR
NEED FOR RESCUE TREATMENTS						

Participants receiving rescue medication before 10 weeks, n (%)	16 (31)	11 (44)	9 (18)	7 (29.2)	25 (24.8)	18 (37)
Participants receiving rescue medication after 10 weeks, n (%)	7 (20)	7 (28)	1 (2)	5 (21)	8 (7.9)	12 (25)
REDUCTION IN SYMPTOMS (MINOR AND/OR SEVERE)						
IBLS score over 24 weeks, mean (SDs not reported)	0.13	0.14	0.04	0.06	NR	NR
WHO bleeding scale score over 24 weeks, mean (SDs not reported)	0.61	0.45	0.26	0.38	NR	NR
MORTALITY						
Mortality, n (%)	0 (0)	1 (4)	1 (2)	0 (0)	1 (1)	1 (2)
Health-related quality of life						
SF-36	Results were available in the CSR but not reported in the company submission as they were not used in the economic mode					

Notes:

[a]Defined as a platelet count of ≥50,000/μL on at least four of the six clinic visits between Weeks 14 and 24, inclusive

[b]Defined as a platelet count of at least 50,000/μL

[c]Among participants with a baseline platelet count <15,000/μL, achievement of a count ≥ 30,000/μL and at least 20,000/μL above baseline

[d]Defined as platelet count ≥50,000/μL within the first 12 weeks without rescue medication in the preceding 12 weeks

[e]Defined as platelet count ≥50,000/μL not occurring within 28 days of rescue medication (in fostamatinib stable responders)

[f]In fostamatinib primary efficacy responders; FIT1 value specified for weeks 18 to 24; FIT2 at 24 weeks

[g]Secondary outcome in FIT3; defined as the time following active treatment when the participant first achieved a platelet count ≥50,000/μL until either: 1) the first of two visits with platelet counts <50,000/μL at least four weeks apart without an intervening visit with a platelet count ≥50,000/μL unrelated to rescue therapy, or 2) rescue therapy, whichever occurred first)

[h]Table 12 of the company submission reports n=9

[i]FIT1 CSR Section 11.4.3 reports 100,000/μL or greater

Subgroup analyses

Subgroups for consideration were specified in the NICE final scope as patients who have had a splenectomy and patients for whom a splenectomy is unsuitable. The company submission reports analyses for the following subgroups in Figure 25, Appendix E of the CS.:

- Age (<median age vs ≥ median age)
- Sex
- Prior splenectomy
- Prior treatment with TPO-RA
- Baseline platelet count (<15,000/μL vs ≥15,000μL)
- Duration of ITP at baseline.

The company states that these subgroup analyses supported the consistency of the efficacy of fostamatinib across subpopulations but that there was no hypothesis testing performed for these analyses. Based on the confidence intervals, there was no clear evidence of subgroup effects for any subgroup.

With regard to the subgroup of participants with a baseline platelet count <15,000/μL (47 randomised to fostamatinib and 21 randomised to placebo in FIT1 and FIT2), the company presents the proportions of those who achieved a count ≥ 30,000/μL or at least 20,000/μL above baseline at weeks 12 and 24.

The FIT1 and FIT2 pooled analysis showed that the endpoint was achieved by 10 of 47 participants (21%) treated with fostamatinib and 1 of 21 participants (5%) who received placebo at 12 weeks; and by 7/47 (15%) and 0/21 (0%) of participants treated with fostamatinib and placebo, respectively, at 24 weeks.

3.2.3 Primary and secondary efficacy endpoints in FIT3

The company also presents the long-term results of FIT3, a non-randomised extension study of FIT1 and FIT2 in which non-responders entered the open label phase.

In FIT3, the primary outcome of achievement of a stable platelet count was analysed in two ways:

- **Stable platelet response including all fostamatinib data (Version 1):** Achievement of a platelet count ≥50,000/μL within 12 weeks of active treatment and maintained for at least 12 months, in all enrolled participants (n=123)
- **Stable platelet response in participants who received placebo in FIT1 and FIT2 and crossed over to receive fostamatinib for the first time (n=44) placebo crossover participants (Version 2):** Achievement of a sustained stable platelet count
    - defined as no two visits, at least four weeks apart, with a platelet count <50,000/ μL, without an intervening visit with a platelet count of ≥50000/μL, unrelated to rescue therapy, within a period of 12 months following initial achievement of the target platelet count

The secondary endpoint in FIT3 was duration of platelet response**.** Primary and secondary outcomes are presented in Table 8 below.

Table 8 Summary of outcomes assessed in FIT3

	FIT3 n (%)
Primary endpoints	
Stable platelet response, n (%)	
Stable platelet response (Version 1): all participants (n=123)	19 (15)
Stable platelet response (Version 2): placebo crossover participants (n=44)	10 (23)
Responders to primary efficacy endpoint Version 1 remaining at month 24, n (%)	14/19 (74)
Secondary endpoint	
Median duration of platelet response (95%CI)	
Participants with a platelet response in first 12 weeks (n=57)	6.1 months (3 to 16)
Responders to primary efficacy endpoint, version 1 (n=19)	38.3 months (16 to 38)

3.2.4 Adverse effects of treatment

The safety population of FIT1 and FIT2 included all participants who received a dose of the study drug (fostamatinib, n=102; placebo, n=48). The methods used to assess safety are reported in Section B.2.10, Document B of the company submission and are considered appropriate by the ERG. In general, the safety profile for fostamatinib is as expected for patients with this clinical condition.

The ERG noted discrepancies in the way adverse events were reported across the company submission and other related publications. For example, Table 17, Document B of the company submission refers to AEs while in the Bussel et al., 2018 publication the identical Table 2 refers to TEAEs.[22] At clarification, the company confirmed that TEAEs were assessed and recorded and stated that *"Figure 13 [of the company submission] does refer to TEAEs and was derived from data in the Bussel [2018] publication from which Table 17 [of the company submission] is taken"*.

Table 9 presents a broad summary of adverse events reported across FIT1, FIT2 and FIT3, as reported in the respective CSRs. In the pooled analysis of FIT1 and FIT2, 85/102 (83%) of participants in the fostamatinib groups and 37/48 (77%) of the placebo groups (data from the respective CSRs; reported in company submission as 36/48) experienced AEs (believed by the ERG to be TEAEs). Serious AEs were more frequent in the fostamatinib group of FIT1 (16%) than FIT2 (10%) but more frequent in the placebo group of FIT2 (26%) than FIT1 (20%). Treatment-related AEs (i.e. those with a possible, probable, or missing causal relationship to study drug) were experienced more frequently by participants in FIT1 (77% and 28% for the fostamatinib and placebo arms, respectively) than in FIT2 (39% and 26%, respectively). Similarly, AEs leading to dose reduction, dose interruption or study drug withdrawal were more frequent in both arms in FIT1 (45% and 24% for fostamatinib and placebo arms, respectively) than in FIT2 (18% and 9%, respectively). Table 18, Document B of the company submission presents details of the specific AEs leading to study drug withdrawal in FIT1 and FIT2. Of the eight (16%) withdrawals in the fostamatinib group of FIT1, two were for gastrointestinal disorders, two for blood and lymphatic system disorders, and one each for alanine aminotransferase increase, chest pain, pneumonia, syncope. There were two (4%) withdrawals in FIT2; one for headache and one for plasma cell myeloma.

The most commonly reported treatment-emergent AEs (TEAEs) in FIT1 and FIT2 (occurring in at least 5% of patients on fostamatinib and at a higher rate than placebo) are reported by severity in Table 17 and Figure 13, Document B of the company submission. The three most commonly reported TEAEs were diarrhoea (31% of fostamatinib group, 15% of placebo group), hypertension (28% and 13%, respectively) and nausea (19% and 8%, respectively).

Table 9 Summary of adverse events reported in FIT1, FIT2 and FIT3

	FIT1		FIT2		FIT3
No of participants (%)	**Fostamatinib (n=51)**	**Placebo (n=25)**	**Fostamatinib (n=51)**	**Placebo (n=23)**	**All Participants (n=123)**
Any AE	49 (96)	19 (76)	36 (71)	18 (78)	95 (77)
Any serious AE	8 (16)	5 (20)	5 (10)	6 (26)	28 (23)
[a]Any treatment-related AE	39 (77)	7 (28)	20 (39)	6 (26)	67 (55)
[b]Any AE leading to dose reduction	5 (10)	1 (4)	5 (10)	0 (0)	NR
[b]Any AE leading to dose interruption	16 (31)	4 (16)	3 (6)	1 (4)	NR
[b]Any AE leading to study drug withdrawal	8 (16)	2 (8)	2 (4)	2 (9)	NR
[b]Any AE Leading to Dose Reduction, Dose Interruption, or Study Drug Withdrawal	23 (45)	6 (24)	9 (18)	2 (9)	36 (29)
Any AE leading to death	0 (0)	1 (4)	1 (2)	0 (0)	2 (2)

Note. Table populated from data in respective CSRs (Table 12-2 in FIT1 and FIT2)

[a]Events with a possible, probable, or missing causal relationship to study drug

[b]For FIT2, one action taken, the most severe one, was reported for each AE, with the following ordering in increasing severity of actions taken: dose interruption, dose reduction, and study drug withdrawal

Table 10 reports common AEs experienced in FIT1 and FIT2 by at least 5% of participants in the safety population of either randomised group. Diarrhoea, nausea and hypertension were among the most commonly reported AEs, in line with the TEAEs reported above. Notably, in FIT2 there was a higher of incidence of nausea in the placebo group (13%) than in the fostamatinib group (8%). In contrast, 29% of the fostamatinib group and 4% of the placebo group in FIT1 experienced nausea. In both FIT1 and FIT2, headache was experienced more frequently among participants who received placebo (24% and 13%, respectively) than fostamatinib (14% and 6%, respectively). The pattern for petechiae across FIT1 and FIT2 was similar: 4% for both fostamatinib arms; 4% and 9% for the respective placebo arms.

Table 10 Adverse events in FIT1 and FIT2 experienced by at least 5% of either treatment group (safety population)

System organ class/ preferred term, n (%)	FIT1		FIT2	
	Fostamatinib (n=51)	Placebo (n=25)	Fostamatinib (n=51)	Placebo (n=23)
Gastrointestinal disorders	**33 (65)**	**9 (36)**	**16 (31)**	**6 (26)**
Diarrhoea	21 (41)	4 (16)	9 (18)	3 (13)
Nausea	15 (29)	1 (4)	4 (8)	3 (13)
Constipation	3 (6)	1 (4)	NR	NR
Abdominal pain	3 (6)	0	NR	NR
Flatulence	3 (4)	0	2 (4)	0
Vomiting	2 (4)	2 (8)	1 (2)	1 (4)
Rectal haemorrhage	0	2 (8)	NR	NR
Investigations	**20 (39)**	**3 (12)**	**NR**	**NR**
Alanine aminotransferase increased	9 (18)	0	NR	NR
Aspartate aminotransferase increased	8 (16)	0	1 (2)	0
Blood pressure increased	3 (6)	1 (4)	2 (4)	1 (4)
Nervous system disorders	**18 (35)**	**9 (36)**	**6 (12)**	**4 (17)**
Headache	7 (14)	6 (24)	3 (6)	3 (13)
Dizziness	9 (18)	4 (16)	NR	NR
Dysgeusia	4 (8)	0	NR	NR
Respiratory, thoracic & mediastinal disorders	**14 (28)**	**9 (36)**	**9 (18)**	**1 (4)**
Epistaxis	9 (18)	4 (16)	6 (12)	1 (4)
Dyspnoea	3 (6)	3 (12)	1 (2)	0
Oropharyngeal pain	1 (2)	2 (8)	NR	NR
Infections and infestations	**17 (33)**	**5 (20)**	**9 (18)**	**5 (22)**
Upper respiratory tract infection	5 (10)	1 (4)	1 (2)	1 (4.3)
Urinary tract infection	3 (56)	0	NR	NR
Bronchitis	NR	NR	3 (6)	0
General disorders & administration site conditions	**12 (24)**	**5 (20)**	**5 (10)**	**0**
Fatigue	6 (12)	1 (4)	NR	NR
Pyrexia	2 (4)	2 (8)	1 (2)	0
Chest pain	4 (8)	1 (4)	2 (4)	0
Vascular disorders	**15 (29)**	**3 (12)**	**9 (18)**	**6 (26)**
Hypertension	13 (26)	1 (4)	7 (14)	3 (13)
Haematoma	NR	NR	1 (2)	2 (9)
Skin & subcutaneous tissue disorders	**11 (22)**	**1 (4)**	**7 (14)**	**4 (17)**
Rash	4 (8)	0	3 (6)	1 (4)

System organ class/ preferred term, n (%)	FIT1		FIT2	
	Fostamatinib (n=51)	Placebo (n=25)	Fostamatinib (n=51)	Placebo (n=23)
Petechiae	2 (4)	1 (4)	2 (4)	2 (9)
Musculoskeletal & connective tissue disorders	**6 (12)**	**4 (16)**	**4 (8)**	**0**
Musculoskeletal pain	0	2 (8)	NR	NR
Blood & lymphatic system disorders	**8 (16)**	**2 (8)**	**5 (10)**	**3 (13)**
Anaemia	2 (4)	2 (8)	1 (2)	0
Thrombocytopaenia	NR	NR	0	3 (13)
Injury, poisoning & procedural complications	**3 (6)**	**1 (4)**	**3 (6)**	**1 (4)**
Contusion	3 (6)	0	3 (6)	0

Serious AEs (SAEs) were experienced in 8/51 (15.7%) and 5/25 (20%) of the fostamatinib and placebo groups, respectively of FIT1, and 5/51 (9.8%) and 6/23 (26.1%) of the respective groups in FIT2. Overall, 13/102 (12.7%) fostamatinib participants and 11/48 (22.9%) of the placebo group experienced SAEs (as reported in the FIT1 and FIT2 CSRs.[25, 26] The company submission and Bussel 2018 publication report 13% and 21%, respectively).[22] The SAEs in the fostamatinib group of FIT1 were: one each of febrile neutropenia, immune thrombocytopenic purpura, thrombocytopenia, retinal tear, diarrhoea, pneumonia, syncope, vaginal haemorrhage and epistaxis. In the placebo group, the SAEs were one each of anaemia, cardiac failure congestive, gastrointestinal haemorrhage, sepsis, menorrhagia, chronic obstructive pulmonary disease and epistaxis. In FIT2, SAEs in the fostamatinib group were one each of bronchitis, contusion, platelet count decreased, plasma cell myeloma, transient ischaemic attack, epistaxis and hypertensive crisis. In the placebo group, the reported SAEs were: three thrombocytopenia, and one each of infection, muscle rupture, menorrhagia and petechiae. The ERG assumes that the larger number of SAEs implies that some participants experienced more than one SAE. There were three withdrawals of study drug in the fostamatinib groups, including one each of non-serious chest pain and syncope, pneumonia and thrombocytopenia.

Overall, the ERG notes that, for several categories of AE, the FIT1 study often had higher rates than FIT2, even though the two studies had an identical design. It is not clear whether this represents differential reporting rates or whether this is a chance finding due to the relatively low number of events.

Comparison of bleeding-related AE incidence between primary efficacy responders and non-responders

In FIT1, bleeding-related SAEs occurred in 2/51 (4%) of the fostamatinib group and 3/25 (12%) of the placebo group. In the placebo group, all of whom were non-responders, 3/25 (12%) experienced bleeding-related SAEs (epistaxis, gastrointestinal haemorrhage and menorrhagia; all resolved or were resolving). In FIT2, bleeding-related SAEs occurred in 2/50 (4%) of participants in the fostamatinib group and 2/24 (8%) of the placebo group. In the placebo group (including 1 responder and 23 non-responders), 2/24 (8%) experienced bleeding-related SAEs (contusion and menorrhagia. The menorrhagia was considered possibly related to the study drug). The pooled analysis showed that 1/18 (6%) of stable responders to fostamatinib and 10/101 (10%) of the fostamatinib group in general experienced moderate/severe bleeding events, as compared to 8/49 (16%) of placebo participants.

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

Indirect or multiple treatment comparisons were not conducted by the company for this appraisal.

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

No indirect comparison analyses were conducted by the company.

3.5 Additional work on clinical effectiveness undertaken by the ERG

None

3.6 Conclusions of the clinical effectiveness section

The key clinical effectiveness evidence for fostamatinib was based on two RCTs of identical design comparing fostamatinib versus placebo, FIT1 and FIT2, and their open label extension study, FIT3. For the purpose of this appraisal, the company pooled the results of FIT1 and FIT2.

The company considered the placebo arms from FIT1 and FIT2 representative of the 'watch and rescue' comparator specified in NICE's final scope. In the opinion of the ERG, these trials represent a comparison of fostamatinib with rescue therapy as required versus placebo with rescue therapy as required.

None of the other comparators specified in NICE's final scope were included in the company's submission. The company argue that an NMA was not feasible due to the lack of published evidence for certain treatments and because of the considerable heterogeneity in the current evidence-base; nevertheless, the ERG feels that inadequate justification for this decision was provided. It also notes that other NMAs have been published in this clinical area, and these have included comparators specified in NICE's final scope such as ritumixab, romiplostim and eltrombopag.

The ERG agrees that the evidence from FIT1 and FIT2 is generally robust and appropriate for consideration in this submission, but notes that no formal meta-analyses were performed and that the economic modelling only made use of group-level data from FIT1 and FIT2 pooled together.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a single systematic review to identify both the clinical and cost-effectiveness evidence base for fostamatinib as a treatment for adults with persistent or chronic ITP. Further details are provided in Appendix D of the CS and a critique is provided in Chapter 3 of the ERG report. The search was not limited by language or date restrictions. The ERG are satisfied that the MEDLINE search strategy provided in Table 54 of the CS and the list of databases searched, detailed in Table 55 of the CS are sufficient to identify any existing economic evaluations of fostamatinib. However, the ERG were unable to replicate all of the company's searches, as details of search strategies for databases other than MEDLINE were not included in the CS.

No studies were identified that evaluated the cost-effectiveness of fostamatinib in the adult population with chronic ITP. The company identified a further nine economic evaluation studies for other chronic ITP treatments. Further details of the identified studies are provided in Appendix 1. None of these studies matched the intended positioning of fostamatinib and none were developed prior to publication of the updated international consensus guidelines document.[13] Therefore, the company developed a *de novo* economic model for the current assessment.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 11 reports the ERGs assessment of the company submission (CS) against the NICE reference case.

Table 11 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	**Yes:** the economic model includes health effects for patients. A disutility was included in the economic model for one carer, applied to the proportion of the cohort who have a severe disability (modified Rankin Scale of 4 or 5) following ICH. Carer disutility was applied for the duration of the remaining life years, regardless of platelet count.
Perspective on costs	NHS and PSS	**Yes:** NHS perspective costs are included. PSS costs, such as social care costs have been included for patients following ICH who have a severe disability and require long-term care, applied as a one-off cost incorporating resource use over 5 years.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	**Yes:** A cost-utility analysis reporting incremental cost per QALY gain for fostamatinib vs. watch and rescue was conducted.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	**Yes:** a lifetime horizon has been applied over 35 years for a starting age 65. The model includes functionality to run a maximum 50-year time horizon. The ERG note that any exploratory analyses that would consider running the model for a cohort <age 50 may not reflect a full lifetime horizon.
Synthesis of evidence on health effects	Based on systematic review	**Partly:** The company conducted a systematic review to determine the clinical effectiveness of fostamatinib. However, the economic model excluded other potentially relevant comparators and the company claimed that an indirect comparison was not feasible (See Section 3.12). The company conducted a systematic review of utilities. However, the company have not provided

		details about how studies were chosen to populate individual model parameters.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Partly:** Health effects were expressed as QALYs. An additional mortality risk was applied to the proportion of the cohort with a severe disability post-ICH and for the proportion of the cohort in the $<30x10^9$/L health state. However, the ERG believes that the HR was applied incorrectly, underestimating the LYGs and QALYs accrued in both arms of the model. It was unclear from the original CS whether the utilities applied in the model were based on responses to the EQ-5D. The company provided a summary table of the utility values used in the model in response to clarification queries. In the majority of cases, EQ-5D data were used where available. However, base case health state utilities were obtained by pooling EQ-5D data from the romiplostim trials with TTO data reported in Szende et al.[34, 35]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	**Yes,** Whilst it is unclear from the CS whether utilities sourced from the literature were based on HRQoL directly reported by patients / carers, inspection of the source studies makes it clear that they were. With regards to carer disutility for patients who are severely disabled following ICH, the disutility applied (-0.162) was sourced from Dewilde et al 2019 collecting data from a cohort of carers for patients that had been hospitalised for ischemic stroke.[36]
Source of preference data for valuation of changes in	Representative sample of the UK population	**Partly:** The original CS was unclear regarding the source of value sets used to generate model utilities. In response to clarification, the company provided a summary table with details of the value sets used, and

health-related quality of life		reported that they were based on several different countries (including the UK, other European countries, US, Canada, China, Japan, and some were not reported). Further inspection of the utility sources indicates that in some cases UK value sets were available from source studies but not applied in the economic model. The base case health state utilities (for different platelet categories) were pooled from the romiplostim trials (EQ-5D) and Szende et al. (UK general population TTO sample).[34, 35] Utilities were not age-adjusted using UK value sets in the model trace for the base case analysis. However, this analysis was provided as a scenario in response to clarification queries.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	**Yes**
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	**No:** Several costs used in the company submission were obtained from old sources, inflated to present day values, when more recent and appropriate NHS reference costs and PSSRU costs were available. Furthermore, several cost parameters for watch and rescue treatment did not use the cheapest possible sources (e.g. generic versions of drugs) to develop treatment acquisition costs for the watch and rescue comparator arm There were several inconsistencies between reported data in the CS, and data included in the economic model and the ERG was not always able to re-produce the unit costs used in the economic model, particularly given insufficient or inaccurate information provided

		regarding the HRGs used to develop the unit costs of bleed events.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	**Yes**, but the ERG notes that the discount rate was not varied in sensitivity analysis. Additionally, the ERG identified an error in the economic model whereby the costs of surgical prophylaxis were not discounted on the Watch and Rescue trace of the model.

Abbreviations: CS, company submission; LYG, life year gains; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome; TTO: Time Trade Off

4.2.2 Model structure

The company submitted a Markov cohort state transition model developed in Microsoft® Excel to determine the cost-effectiveness of fostamatinib plus watch and rescue where required, compared to watch and rescue where required alone.

The model cohort is split into two segments to capture the cost and health-related quality of life (HRQoL) implications for the proportion who have incurred a severe disability post an ICH event and those that have not. There are three health states in each model segment, defined by platelet count categorisation: Non-response, defined as having a platelet count $<30 \times 10^9$/L; partial response defined as having a platelet count between 30×10^9/L and 50×10^9/L, and response defined as having a platelet count $>50 \times 10^9$/L. In each modelled health state, the cohort have a cycle specific risk of ITP bleed events, need for routine health care monitoring, risk of requiring rescue treatment, need for rescue medication for surgical prophylaxis, and risk of mortality that is determined by the platelet count category in which they reside. The cohort also have a risk of adverse events that is directly related to treatment arm of the model, and independent of platelet category.

A hypothetical cohort of 1000 adult patients (mean age 65, 61% male) with chronic uncontrolled ITP enter the model in the non-response health state (normal functioning model segment), based on the assumption that fostamatinib treatment would be indicated by having a platelet count $<30 \times 10^9$/L, and previous failed response to or unsuitability for TPO-RAs. In each 4-weekly model cycle, the cohort transition between the three health states, increasing, decreasing or maintaining their platelet count category according to a set of transition probabilities observed in the FIT1 and FIT2 trials up to 12 weeks for fostamatinib

and placebo (assumed watch and rescue) respectively. Post 12 weeks transitions are extrapolated as the average of the previous 3 cycles with one exception. Longer-term loss of fostamatinib response (i.e. transition out of the >50x10^9/L health state) are obtained from an analysis of the FIT3 OLE study data (see Section 4.2.6 for further details).

The fostamatinib cohort is split into those on and off treatment in each health state. Further details of treatment escalation and stopping rules are discussed in Section 4.2.8 (treatment acquisition costs). The proportion of the cohort who cease treatment (due to failure to achieve a response) cross-over to the watch and rescue arm of the model. The economic model assumed that watch and rescue is the only treatment option for patients who fail to achieve a response to fostamatinib and that patients can have unlimited courses of watch and rescue over the remainder of their life years.

In each model cycle, the cohort are at risk of developing a severe disability post an ICH event, in which case they transition to the "severe disability" model segment. Thereafter, the cohort continue to transition through the platelet count categories following a similar structure and identical transitions probabilities to the normal functioning ITP segment. The proportion of the cohort entering the "severely disabled post ICH" model segment are assumed to have survived an ICH and remain alive with a severe disability defined as a modified Rankin scale (MRS) of 4 or 5. It is assumed that any patients who have an ICH but do not develop a severe disability (i.e. an MRS <4), remain in the normal functionality ITP segment of the model. It is further assumed that severe disability post ICH is permanent; the cohort cannot transition back to normal functionality ITP and thus incur additional life-long costs of health and social care; long-term utility decrements for patients; long-term utility decrements assumed for one full time carer of patients with a severe disability.

The model structure is illustrated in Figure 2 (reproduced from Figure 14 of the CS).

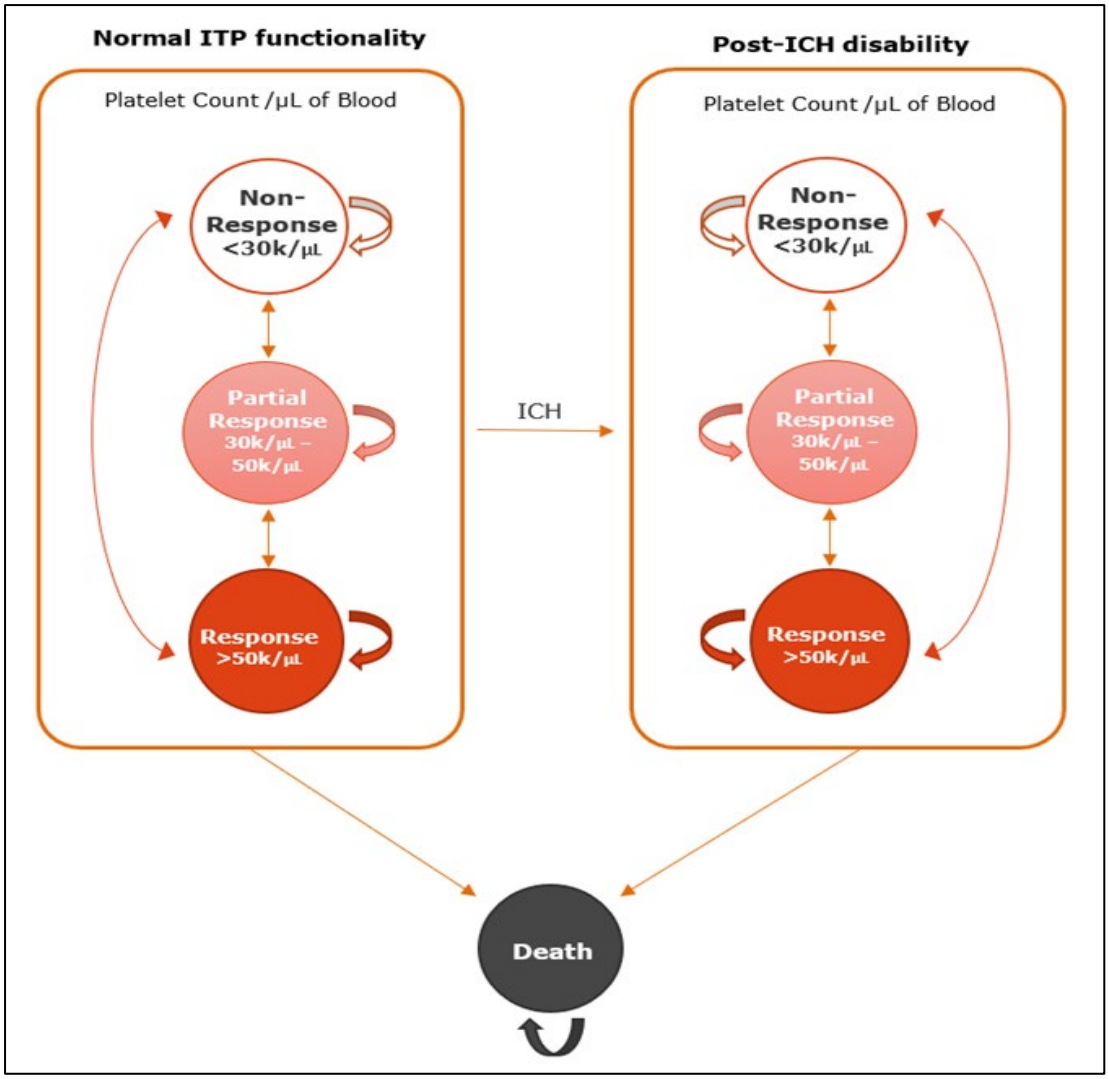


Figure 2 Markov model structure (reproduced from Figure 14 of the CS)

The ERG make the following observations about the company's economic model structure:

First, the ERG are unconvinced about the necessity to split the model cohort into the proportion with and without severe disability following ICH. This event is a rare but serious occurrence. However, the cost and HRQoL implications (for both patients and carers) could have been applied to a proportion of the model cohort in each platelet category health state. This would have simplified the model structure substantially.

Secondly, the assumption that the full proportion of the cohort who develop a severe disability post ICH cannot transition out of this state and thus incur patient and carer disutility for the duration of their life years in the economic model, regardless of platelet count may be questionable. However, the ERGs clinical expert confirms that patients with an MRS score

above 4 are severely disabled and would likely require significant carer time. Whilst their disability might resolve over time, such an occurrence is rare. Given the small proportion of the cohort that enter the ICH health states, the ERG consider any bias small in magnitude.

Thirdly, the ERG are concerned that the company's decision to apply separate health states for platelet categories between 30 x 10^9/L and 50 x 10^9/L, and >50 x 10^9/L adds additional, and potentially unnecessary uncertainty to the trajectory of disease over time. The ERG's clinical expert opinion is that there is little difference in the clinical success for a patient who achieves a platelet count > 30 x 10^9/L and a platelet count >50 x 10^9/L. For a patient who had previously had a platelet count <30 x 10^9/L both outcomes would be considered a success from both a patient and clinician viewpoint, with little difference likely in terms of quality of life, mortality risk, or use of healthcare services. The ERG note that few patients are available from the FIT trials to determine transitions between the 30-50 x 10^9/L and >50 x 10^9/L health states. This is particularly true for watch and rescue, based on the placebo arms of the trials where recruited numbers are fewer than fostamatinib; with even fewer patients in the higher platelet categories to enable robust long-term extrapolation of transition probabilities. The ERG's clinical expert is also of the view that a more informative categorisation of platelet count categories would have been <15 x 10^9/L, 15-30 x 10^9/L and >30 x 10^9/L as it is at the lower platelet counts <15 x 10^9/L where the greatest risk of bleeding events occurs.

Fourthly, the ERG acknowledges the company is positioning fostamatinib as a treatment post failure with TPO-RAs such as eltrombopag or romiplostim or for patients who are unsuitable for these treatments. The ERG consider this positioning reasonable and an accurate reflection of where fostamatinib would be used in UK clinical practice. However, the ERG consider it inappropriate to assume that watch and rescue is the only treatment option available for patients who fail to achieve a response to fostamatinib. The ERG's clinical expert considers it highly unlikely that patients with a low platelet count following failure of fostamatinib would be subjected to an unlimited amount of recurring rescue treatments for the remaining duration of their lives. Several other plausible treatment options exist that could have been included in a treatment pathway model post failure on fostamatinib or watch and rescue (including rituximab, mycophenolate, ciclosporin and splenectomy). The ERG notes that rituximab is not licenced for ITP, but it is used routinely in clinical practice, has demonstrated effectiveness in large RCTs, and forms part of several recommended treatment pathways. The ERG therefore argue that rituximab should have been included as a treatment option in the

economic model. Similarly, the ERG accepts that the use of splenectomy has reduced over time because of the increasing availability of medical therapeutic options, such as TPO-RAs. However, there remains substantial variation in clinical practice around the UK, and some centres still consider splenectomy an appropriate option if other treatments fail and a patient has a consistently low platelet count. For these reasons, the ERG consider the current model structure to be an inaccurate reflection of the treatment pathway for chronic ITP as observed in current UK clinical practice.

4.2.3 Population

The modelled cohort are age 65, 61% male with chronic ITP and a platelet count <30 x 10^9/L who are assumed to have failed or be unsuitable for treatment with TPO-RAs such as eltrombopag or romiplostim. The ERG's clinical expert view is that the approach taken by the company to model fostamatinib post TPO-RA is consistent with how fostamatinib would likely be used in clinical practice.

There are several inconsistencies between the FIT trial population and the characteristics of the modelled cohort, specifically:

- Participants recruited to the trials are at a lower bleeding risk than is likely to be seen in clinical practice. In response to clarification queries, the company clarified that patients were selected for the FIT trials purposely to have a low bleed risk due to ethical concerns about randomising patients with a high bleed risk to a placebo treatment. The ERG accepts this as a legitimate concern but notes that at no point was watch and rescue treatment withheld in the trials, meaning that patients who were at risk of bleeds had access to rescue treatment if needed. On balance, the ERG agrees that the most appropriate population for the model is those that would be most likely to receive the drug in clinical practice. However, the limitations of applying data from a trial population at lower bleed risk to a modelled cohort reflective of clinical practice who are at greater bleed risk introduces uncertainty into the assessment of cost-effectiveness.

- The model starting age (65) is older than the trial population (mean age 54 and 53 pooled across FIT1 and FIT2 in the fostamatinib and placebo arms respectively). This may raise concerns regarding the validity of the adverse events included in the economic model as toxicity associated with both fostamatinib and watch and rescue is likely to increase with

age. The implication is that the adverse event rates included in the economic model, sourced from the FIT trials, may be an under-representation of the true adverse event rates observed in the older, modelled patient cohort. In response to clarification queries, the company clarified that the reason for the lower age group in the trials is that younger patients are less likely to be at a high risk of bleeding. As low bleed risk was a requirement for recruitment into the trials, the mean age is lower than might be observed in clinical practice. The company also provided additional data regarding the rate of adverse events by age from the FIT1 and FIT2 trials. The data show that the probability of at least one moderate or severe AE and / or other infection was: fostamatinib: age <65 (33.8%), age ≥65 (75%) and Placebo: age<65: (29.7%) and ≥65 (36.4%). These data re-enforce the ERG's concerns that adverse events may have been underestimated in the economic model for an age 65 cohort, and that the magnitude of underestimation may have been greater for the fostamatinib as opposed to placebo arms. The ERG is concerned that this issue may bias the ICER in favour of fostamatinib. The magnitude of bias is likely to be small given that most adverse events are of short duration and are assumed resolved with appropriate treatment within a single model cycle.

- The NICE scope suggests that the intended patient population is those with chronic ITP, and the company model is stated to reflect this definition. The ERG note that this is true for the majority of patients enrolled in the FIT1 and FIT2 trials, however a small proportion are noted to have persistent as opposed to chronic ITP. In the FIT trials, 6% of the fostamatinib groups and 8% of the placebo groups had persistent ITP respectively. It is unclear how this would affect cost-effectiveness estimates but it is likely that the magnitude of any biases would be small.

- All modelled patients are assumed to have had previous treatment or be otherwise unsuitable for treatment with TPO-RAs. However, only 47% and 51% in the fostamatinib and placebo groups, pooled across FIT1 and FIT2 had previous TPO-RA treatment. Based on the ERG's clinical expert judgement, it could be reasonable to assume that patients, who had not yet been tried on treatment with TPO-RA, may be more likely to respond than patients with more refractory disease. In such a scenario, the effectiveness of fostamatinib may be over-estimated in the economic model as a result of treatment in a population with more refractory disease than observed in the clinical trials that provide the effectiveness data. The ERG queried this at the clarification stage and

the company provided additional data showing that there were too few patients in each of the platelet count categories to estimate robust transition probabilities using these subgroup data. Furthermore, the ERG notes that the clinical effectiveness subgroup analysis shows no clear differences between those with / without previous TPO-RA treatment in terms of effectiveness. Whilst confidence intervals around the subgroup analyses are wide, indicating substantial uncertainty, the ERG concludes that, on balance and considering the company's response, including the low numbers to inform state transitions, it is reasonable to use the trial data within the economic model. However, the limitations should be acknowledged and it is likely that any bias is the ICER is in favour of fostamatinib.

In summary, the positioning of fostamatinib in the economic model is in line with its likely use in clinical practice. However, several inconsistencies between the trial population and modelled cohort characteristics add uncertainty to the cost-effectiveness estimates that have not been captured in the economic model. It is likely that each of the inconsistencies alone produces only small biases, but taken together could potentially increase the uncertainty substantially.

4.2.4 Interventions and comparators

Intervention: Fostamatinib 100mg and 150mg tablets

The modelled intervention is fostamatinib disodium hexahydrate (Tavlesse®), indicated for the treatment of chronic ITP in adult patients who are refractory to other treatments. Fostamatinib is available as 100mg or 150mg orange film coated tablets. The recommended starting dosage of fostamatinib is 100 mg taken twice daily and the maximum dose is 150mg twice daily. The dosing pathway for fostamatinib used in the economic model is described in Figure 15 of the CS. The cohort starts on the 100mg dose taken twice daily and are re-evaluated at 4 weeks. Responders continue on the 100mg dose for the remainder of their life years, or until a loss of sustained response is observed. Non-responders are escalated to a dose of 150mg taken twice daily and re-evaluated at 12 weeks. Non-responders by 12 weeks have treatment discontinued and enter the watch and rescue arm of the model. Patients who had their dose escalated at 4 weeks and who subsequently respond at 12 weeks remain on the 150mg dose for the remainder of their life years or until a loss of sustained response is observed. Treatment dose reduction or discontinuation is possible if deemed clinically necessary in response to adverse events. The company's base case analysis assumes that

patients remain on the lowest dose that achieved a response for the duration of the model. The ERG's clinical expert agrees that the dosage strategy for fostamatinib is reasonable and broadly reflective of real-world clinical practice use of the drug, though variation is likely and in clinical practice, not all patients would be treated identically.

Comparator: Watch and Rescue

The comparator arm in the economic model is watch and rescue, delivered as required when the platelet count falls and the patient is considered to be at risk of a bleeding event. As reported in Chapter 2, the ERG consider the choice of comparator by the company to be inappropriate, inconsistent with the NICE scope and inconsistent with the treatment pathway for chronic ITP in UK clinical practice. The ERG acknowledges that many treatment options for ITP may not have a specific licence for the disease (e.g. rituximab). However, in practice a treatment such as rituximab would often be considered for a patient who failed to respond to a TPO-RA if they had not been previously treated with that drug. As described in Chapter 3, the ERG is unconvinced that it would not have been possible to conduct an indirect treatment comparison to elicit the relative effectiveness of fostamatinib compared to other treatment options, including rituximab.

In addition to the ERG's concerns about the company's choice of comparator, the ERG raise several concerns about the choice of treatments included for watch and rescue. The company have assumed that only IVIg, platelet transfusion and IV methylprednisolone would be used as rescue treatment in UK clinical practice. This assumption is not based on any published evidence or registry data information; it is inconsistent with the distribution of rescue treatments used in the FIT1 and FIT2 studies and is inconsistent with the ERG's clinical expert opinion with regard to the use of rescue treatment in UK clinical practice. Specifically, the ERG's clinical expert notes that many patients who require rescue treatment, in a non-emergency setting would receive oral prednisolone or dexamethasone. Both treatments are administered orally at home, avoiding the need to attend hospital for administration, and are substantially cheaper alternatives to IV methylprednisolone. Furthermore, the ERG's clinical expert notes that the distribution of rescue treatments used in the FIT1 and FIT2 clinical trials (with the exception of a small proportion of patients receiving anti-D, azathioprine, hydrocortisone and danazol) is more representative of the use of rescue treatment in UK clinical practice than the company's assumptions. Furthermore, the ERG note that it is more appropriate to consider the costs of the closest possible treatment bundle of watch and rescue

therapies to that used in the clinical trials to ensure consistency between cost and effectiveness (transitions through platelet categories) parameters in the economic model.

4.2.5 Perspective, time horizon and discounting

An NHS perspective was adopted for the costs, including the costs of health and social care for the proportion of the cohort with severe disability following an ICH. The ERG is satisfied that the analysis perspective is in line with NICE's reference case. The model was run for a cohort with a starting age of 65 for a time horizon of 35 years until age 100. The ERG considers the lifetime horizon to be appropriate. However, as the model is configured to run for a maximum of 50 years overall, any exploration of starting ages <age 50 should be interpreted cautiously.

Costs and QALYs were discounted by 3.5% per annum in the model, which is consistent with the NICE reference case. However, the company have not provided any sensitivity analysis around this source of methodological uncertainty. The ERG therefore vary the annual discount rate between 0% and 6% for costs and QALYs in scenario analyses. Furthermore, the ERG noted an error in the company's economic model where the costs of surgical prophylaxis were not discounted on the watch and rescue arm of the model, biasing the ICER in favour of fostamatinib. The ERG have corrected this error in Section 6.3.

4.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness is based on the 4-weekly cycle specific transitions between platelet response states obtained from the FIT1 and FIT2 trials up to week 24 (cycle 6), extrapolation of the FIT trial data over the longer-term, and 24-month data from FIT3 for the loss of fostamatinib response (transitions out of the $>50x10^9$/L health state). Lower platelet counts are associated with an increased risk of bleeding events (sourced from the romiplostim trial and Allen et al. 2016), an increased need for rescue therapy (informed by data from FIT1 and FIT2), increased contact with health professionals to monitor the patient's ITP (obtained from clinical expert opinion sought by the company) and an increased mortality risk (obtained from the literature). The key drivers of life-year and QALY gains within the model are the hazard ratio (HR) of mortality applied to the proportion of the cohort with a platelet count $<30 \times 10^9$/L, the potential for fostamatinib to generate a sustained long term response and assumptions about the long term extrapolation of transition probabilities in the model.

Treatment response (transition probabilities)

Transitions over the first 24 weeks

Cycle specific transition probabilities between the health states over the first 24 weeks (6 cycles) of treatment were derived from transition count data observed in the FIT1 and FIT2 trials, for both fostamatinib (intervention arm in the trials) and 'watch and rescue' (placebo arm in the trials). The transition count and probability data are provided in Table 12 below (obtained from the company submitted excel model file).

Table 12 Transition count data from FIT1 and FIT2

Fostamatinib					**Placebo**				
Baseline - week 4					**Baseline - week 4**				
	<30	**30-50**	**>50**	**Total**		**<30**	**30-50**	**>50**	**Total**
<30	61 (68%)	17 (19%)	12 (13%)	90	**<30**	32 (76%)	10 (24%)	0 (0%)	42
30-50	6 (55%)	4 (36%)	1 (9%)	11	**30-50**	2 (50%)	2 (50%)	0 (0%)	4
>50	0 (0%)	1 (100%)	0 (0%)	1	**>50**	0 (0%)	1 (100%)	0 (0%)	1
total	67	22	13	102	**total**	34	13	0	47
week 5 - week 12					**week 5 - week 12**				
	<30	**30-50**	**>50**	**Total**		**<30**	**30-50**	**>50**	**Total**
<30	33 (66%)	10 (20%)	7 (14%)	50	**<30**	21 (78%)	4 (15%)	2 (7%)	27
30-50	6 (29%)	7 (33%)	8 (38%)	21	**30-50**	5 (45%)	5 (45%)	1 (9%)	11
>50	0 (0%)	4 (31%)	9 (69%)	13	**>50**	0 (NC)	0 (NC)	0 (NC)	0
total	39	21	24	84	**total**	26	9	3	38
week 13 - week 24					**week 13 - week 24**				
	<30	**30-50**	**>50**	**Total**		**<30**	**30-50**	**>50**	**Total**
<30	2 (67%)	1 (33%)	0 (0%)	3	**<30**	0 (NC)	0 (NC)	0 (NC)	0
30-50	1 (33%)	1 (33%)	1 (33%)	3	**30-50**	0 (NC)	0 (NC)	0 (NC)	0
>50	1 (7%)	1 (7%)	12 (86%)	14	**>50**	0 (0%)	0 (0%)	1 (100%)	1
total	4	3	13	20	**total**	0	0	1	1

*<30: <30 x 10^9/L; 30-50: 30 x 10^9/L to 50 x 10^9/L; >50: >50 x 10^9/L; NC: Not Calculable.

The ERG would like to highlight the low number of patients available from the FIT trials to inform some of the transition counts (often only informed by 1 patient, especially in the placebo arm). In particular, the ERG note that there is a substantial proportion of missing data at the relevant time points to calculate transitions. The ERG caution that the high proportion of missing data raises uncertainty regarding the true transitions for the economic model, as it is unclear whether those with missing data would improve, reduce, or maintain their platelet counts. Whilst the ERG acknowledges that some missing data are inevitable, this issue increases uncertainty for the population of important model parameters. The uncertainty is magnified further because the data are used to extrapolate transitions over the full lifetime horizon of the model (for all but the loss of sustained fostamatinib response). The ERG therefore notes that the long-term magnitude of relative effectiveness of fostamatinib vs.

watch and rescue is uncertain. The direction of any biases are unclear, but are potentially of substantial magnitude.

The low numbers to inform some transitions necessitated the company to make several assumptions where it was not possible to derive transition probabilities from the data. For example, in the watch and rescue arm, there was no data to inform transitions between the >50 x 10^9/L and other health states beyond week 5. Therefore, the company assumed a relative risk (RR) of 0.9 would apply to the transition probabilities relative to the available data for fostamatinib. The company did not describe or justify the assumed RR in any of the documentation provided. The approach taken appears to be inconsistent with the company's stated approach on page 98 of the CS, which was to apply *"...the probability of moving between health states from a more severe health state was assumed to be the same probability of moving between health states from the next best health state, a conservative assumption."* The ERG agrees that the stated approach would be appropriate in the absence of available data and have amended the company's economic model to reflect this.

Extrapolation beyond 24 weeks

Tables 30 and 31 in the CS describe the transition probabilities post week 24. Post 24 weeks, the base case transition probabilities were calculated as an average of the transitions in the previous periods for the watch and rescue arm. The company submitted economic model also provides the functionality to use last observation carried forward instead, excluding the transitions between baseline and week 4, but the CS did not consider the impact of that scenario on cost-effectiveness results.

A similar approach was taken for the fostamatinib arm for all transitions, except transitions out of the >50 x 10^9/L health state. The company interpreted this parameter as a loss of sustained response, which was estimated using data available from the FIT3 OLE study. The loss of response was calculated by identifying the number of fostamatinib patients in the FIT 3 study who had a response at month 1 that still had a response at all follow up time points up to 24 months (i.e. 6,12,18,24). At 1 month, 20 patients had a response and at 24 months, 7 patients still had a response. This equated to 35% of initial responders who maintained that response consistently until 24 months. Patients with a platelet count <50 x 10^9/L or with missing data at any one time point were classed as non-responders. The loss of response was then extrapolated over the longer term using an exponential function, to calculate the average

loss of response per cycle (4.47%). Half were assumed to transition from response health state to partial response health state and the remaining half to the non-response health state. Furthermore, the proportion of the cohort who transition out of the >50 x 10^9/L health state are assumed to come off treatment due to a loss of effectiveness and thereby transition to the watch and rescue arm of the model for the remainder of their life years. The ERG queried the appropriateness of using different methodological approaches to extrapolate long-term effectiveness across the different model arms. The ERG considers the company's response to clarification to be reasonable and are satisfied with the approach taken.

The ERG also notes that the company's approach to calculating loss of treatment response on fostamatinib from the FIT3 data is conservative, by assuming that patients with one missing follow up time point between months 1 and 24 are non-responders. There is substantial uncertainty underpinning the most appropriate long-term extrapolation approach in the economic model. The ERG notes that the company have not sufficiently explored the impact of alternative assumptions on the ICER and have thus provided several additional scenario analyses for the committee's consideration (See Section 6.3). The ERG further notes that additional data may become available over the longer term (up to 5 years) from the FIT3 OLE study that may help to reduce some of the uncertainties regarding the long-term sustained response of fostamatinib.

Finally, the ERG converted all the transition rates to transition probabilities for application on the model trace, correcting a minor error in the probability calculations on the 'Data Sheet' tab of the model. The ERG's corrections resulted in a revised set of transition probabilities presented Appendix 2. The transition probabilities for remaining in a health state were higher in the ERG's preferred approach than in the company's approach.

In summary, the model predicts that the watch and rescue arm spend 66% of their life years gained in the <30 x 10^9/L health states compared to 61% in the fostamatinib arm. This is because of better response data for fostamatinib and because patients are more likely to achieve and maintain a response on fostamatinib than on watch and rescue.

Survival (transitions to the death state)

Mortality in the economic model is dependent on platelet category and presence or absence of a severe disability following an ICH. For the proportion of the cohort with normal ITP

functionality (i.e. those without a severe disability post ICH), and a platelet count ≥30 x 10^9/L, mortality is assumed equal to UK general population all-cause mortality rates, obtained from the UK lifetables. A platelet count <30 x 10^9/L and severe disability post-ICH were assumed to have an additional mortality risk of HR=1.60 obtained from Schoonen et al. 2009[37] and H=2.02 obtained from Gonzales-Perez et al. 2013[38] over the general population all-cause mortality respectively. The HR of having both a low platelet count and severe disability post ICH (i.e. in the 'Severe disability post ICH, <30 x 10^9/L' health state) was 3.23 obtained by multiplying the HR for the two states together. Both mortality HRs were obtained from UK studies.

Schoonen et al. 2009 is a retrospective UK population-based study using the General Practice Research Database (GPRD) including all patients with at least one diagnostic code related to ITP that were first diagnosed between 1990–2005 (i.e. incident ITP) followed up for a median of 3.4 years.[37] The study reported the HR of death among all incident ITP patients as 1.60, 95% CI (1.3 to 1.9) compared to age and sex matched controls. The study does not specify the platelet count categories to which the HR applies but the company have assumed that it applies only to those in the platelet count <30 x 10^9/L health state. It is unknown what proportion of participants in the source study actually had a platelet count <30 x 10^9/L, yet the HR is applied in the economic model only for those in the <30 x 10^9/L health state. The ERG raises two concerns with this approach. First, it could be argued that the excess mortality applies to all patients with ITP, regardless of platelet count, including those who had a successful treatment. If this is the case, it would be more appropriate to apply the HR across all platelet count categories. Secondly, it could be argued that the HR for patients who reside in the <30 x 10^9/L health state could be much higher than that reported in the source study. The first issue generates a bias in favour of fostamatinib. The second issue may generate a bias against fostamatinib. The overall magnitude and direction of bias is unclear.

Gonzales et al. 2013 was a study using the UK THIN database which contains medical records by primary care physicians from more than 500 general practices in the UK, with a mean age of 70.8.[38] The HR obtained from this study represents the excess mortality in patients 1 year after haemorrhagic stroke compared to those not experiencing the event. The ERG accept that the company chosen source for the additional mortality risk associated with stroke post ICH is appropriate. However, the ERG are concerned that the overall mortality HR (=3.23) in the 'severe disability post ICH, <30 x 10^9/L' health state may be

overestimated. This is because the two HRs are applied multiplicatively, assuming independence of mortality risk between severe disability post ICH and due to low platelet counts. This is unlikely to be true as the additional mortality risk of a low platelet count is likely confounded with the additional mortality risk following ICH, given that a major cause of ICH is low platelets in the context of this assessment. Whilst the ERG are unaware of any robust data to inform the incremental mortality risk associated with ICH for patients with low (<30 x 10^9/L) platelet count, it is worth noting that any bias is likely to favour fostamatinib.

The ERG have identified an error in the application of HRs to generate cycle specific probabilities of transition to the death state in the model. Cells E121: S121 on the clinical inputs tab in the company submitted economic model file calculated the cycle specific mortality probability. The formula applied was:

p2 = 1-EXP(-(p1^(1/HR),

where p2 is the cycle specific mortality in for example the <30 x 10^9/L health state; p1 is the annual all-cause general population mortality and HR represents the mortality HR for p2 vs. p1 obtained from the literature. However, the correct formula is:

p2 = 1-(EXP(-(-(LN(1-p1))*HR))),

The corrected formula would convert the probability to a rate as suggested by the company, in accordance with Briggs et al. 2006[39], and would then multiply that rate by the appropriate HR before re-converting to a 4-weekly cycle specific probability. An alternative implementation of the formula: where p2 = 1 – ((1-p1)^HR) would also be an appropriate approximation, but without the conversion between rates and probabilities. The impact of this error is a substantial reduction in the mortality probability for the proportion of the cohort in the lowest platelet count category, and those with severe disability post ICH. For example, in the non-response <30 x 10^9/L health state, cycle 1, the probability of death was 0.0116 (using the company's approach) while using the ERG's approach the equivalent probability of death was 0.0013. This correction results in the modelled life years increasing from ~5-6 life years to ~12 life years, more in line with other NICE submissions in the ITP population (for example in TA221).[17]

Another ITP related economic evaluation (Allen et al. 2016) took a different approach to the added mortality risk in the ITP population.[40] They assumed that there was an added mortality risk associated with hospitalisation for severe bleed (mortality rate was 1.7% for other bleed (coagulation disorder), 4.6% for GI bleeding and 13.2% for ICH). The company's clinical expert opinion was that a mortality risk associated with hospitalisation of ITP related severe bleeds (as done in Allen et al. and TA221) is not the only added mortality risk in the ITP population (response to clarification question B6). They argued that according to Schoonen et al. 2009, 13% of deaths were due to bleeding and 17% were due to infection.[37] From ERGs inspection of the paper, 75 out of 139 deaths in the ITP population a plausible cause of death could be identified. Of the 75 deaths, 10 were due to bleeding (13%), 14 deaths were due to infectious disease (19%), and for the remaining deaths it could not be concluded whether this was due to bleeding/infection. The ERG accepts the company's reasoning for not just applying a mortality HR for bleeding events only as there may be other reasons for the increased mortality rate such as from infection.

Probability of severe bleed events

The company included a risk of severe bleeding events. This is an additional risk to people with ITP. The bleeding risks were obtained from the placebo arm in the romiplostim trials (Gernsheimer et al. 2010)[41] for those with a platelet count of <30 x 10^9/L and from Allen et al. 2016[40] (where the bleeding risks from the eltrombopag studies (RAISE[42] and EXTEND[43]) for those with a platelet count of >50 x 10^9/L was used. A linear interpolation between the two points (<30 x 10^9/L and >50 x 10^9/L) was assumed for the 30-50 x 10^9/L platelet count health state.

The bleeding rates in the romiplostim trials were considered quite high by the ERGs clinical expert compared to other studies with a larger sample of ITP patients.[44-46] In the first year of the model for the watch and rescue arm, the predicted bleed event rate was approximately 1.4 and for the fostamatinib arm the predicted bleed event rate was approximately 1.1 (ERG calculation in the CS excel model file). This is about two to three times higher than the equivalent bleed event rate observed in Altomare et al. 2016 for chronic ITP patients aged over 65.[45] This was a large retrospective cohort study looking at administrative medical claims data on ITP patients in the US. However, the ERG have not identified a study that reports the risk of bleeding by platelet threshold needed for the model or the bleeding risk by

platelet count for a particularly refractory population who have failed multiple previous treatment options..

The ERG make the following observations regarding the bleeding event data used in the economic model:

A) Using data from two different sources to populate bleed event risks across different platelet counts generates some uncertainty regarding the true incremental impact of changing platelet count on the risk of bleed events. Without any formal assessment of study comparability, the use of different sources may bias results from the economic model.
B) The risk of inpatient cranial bleeds (for the <30 x 10^9/L platelet level health state) was based on 2 out of 41 patients in the romiplostim trials having a cranial bleed (resulting in a 4-weekly probability of 0.008). The small sample size adds additional uncertainty;
C) The risk of a GI bleed and inpatient other bleeds (for the <30 x 10^9/L platelet level health state) was assumed to be equal with probability data based on 1 patient out of 41 patients in the romiplostim trials that had a GI bleed (resulting in a monthly probability of 0.004).
D) A further uncertainty in the bleeding risks is that the company assumed a linear interpolation between the low (<30 x 10^9/L) and high (>50 x 10^9/L) platelet count health states for the 30-50 x 10^9/L platelet count health state. This may not be the case, since severe bleeding is very uncommon in patients with platelet count ≥30 x 10^9/L.[46] Neunert et al. 2015 also suggested that there is no a clear relationship (e.g. linear) between the risk of bleeding and platelet count.[47]
E) The ERG consider the risk of an outpatient bleed (0.0280) in the >50 x 10^9/L health state inappropriate because it was based on the non-splenectomised group in the romiplostim trials, and not on the weighted average across the splenectomised and non-splenectomised groups. Using the weighted average approach results in an average 4-weekly probability of 0.0492. The weighted average is more appropriate to maintain consistency with the proportion of patients who are splenectomised / non splenectomised in the FIT1 and FIT 2 studies.
F) The risk of severe disability post ICH was 0.001 (=7.9%+5.5% / 0.008 where the 7.9% and 5.5% were the proportion with MRS 4 and 5 respectively). This was based on a study by Rodriguez-Castro et al. 2019, using data from 961 ICH patients with

outcome data at 3 months post ICH (obtained from registry data of patients admitted to a stroke unit in Spain).[48] The ERG consider the company's approach to calculating the risk of severe disability post ICH to be reasonable.

Probability of adverse events

For the original CS, adverse event data for fostamatinib and watch and rescue were obtained from the FIT trials and placebo arm of the romiplostim trial used in TA221 respectively.[17] At the clarification stage, the company updated their adverse event data in the economic model by obtaining the incidence of adverse events of any severity experienced by ≥ 5% of participants from FIT1 and FIT2 for both fostamatinib and watch and rescue (Table 16 and Table 17 in clarification response to question B8). The ERG identified and corrected some minor discrepancies between the adverse event data reported in the response to clarification queries, used in the economic model, and the clinical study report. The ERG have applied the data as reported in the CSR directly in the economic model. Furthermore, to explore the potential impact of counting bleeding events under bleed and adverse events, the ERG has conducted a scenario analysis removing epistaxis and petechiae from the list of adverse events included in the model. Table 13 describes the adverse events and cycle specific probabilities (with the ERG's corrections in brackets).

Table 13 Treatment related adverse events used in the economic model

	Fostamatinib (n=102)	Placebo (n=48)	Fostamatinib cycle probability [A]	Placebo cycle probability [A]
Diarrhoea	30	7	0.056	0.026
Hypertension	20	4	0.036	0.014
Nausea	19	4	0.034	0.014
Alanine amino-transferase increased	9	0	0.015	0.000
Alspartate amino-transferase increased	8 (ERG: 9)	0	0.013 (ERG: 0.015)	0.000
Dizziness	9	4	0.015	0.014
Epistaxis[B]	15	5	0.026	0.018
Upper RTI	8 (ERG: 6)	1 (ERG:2)	0.013 (ERG: 0.010)	0.003 (ERG: 0.007)
Urinary tract infection	3	0	0.005	0.000
Abdominal pain	3	0	0.005	0.000
Fatigue	6	1	0.010	0.004
Pyrexia	2 (ERG: 3)	2	0.003 (ERG: 0.005)	0.007
Headache	10	9	0.017	0.034
Rash	7	1	0.012	0.004
Chest pain	4 (ERG: 6)	1	0.007 (ERG: 0.010)	0.004
Anaemia	2 (ERG: 3)	2	0.003 (ERG: 0.005)	0.007
Contusion	6	0	0.010	0.000
Petechiae[B]	2	2	0.003	0.007

Abbreviations: ERG: Evidence Review Group; RTI: Respiratory tract infection

[A] Includes ERG correction applied to the AE probabilities by first converting the 24-week probabilities to rates, which allows for a calculation of the 4-weekly cycle specific probabilities.

[B] The ERG conduct a scenario analysis setting the probability of epistaxis and petechiae adverse events to 0

4.2.7 Health related quality of life

The FIT1 and FIT2 studies did not collect EQ-5D data and so it was not possible to develop health state utility values that would fit the NICE reference case from data collected within the trials. SF-36 survey data were collected in the trials, but deemed inappropriate for inclusion in the model because a) the trial population is not comparable to the population in the economic model (See Section 4.2.3). Furthermore, the company argued that because less than 25% of patients responded to the SF-36 questionnaires, there was insufficient data to generate robust SF-6D health state utility values. In addition, no difference was found in the SF-36 outcome data that were collected between fostamatinib and placebo.[25, 26] The ERG considers it unfortunate that these data were not available from the trials, but accepts the company's justification for not utilising the trials' quality of life outcome data in the economic model.

Therefore, the company conducted a joint systematic literature review to identify cost, resource use and quality of life data for inclusion in the economic model. The search strategy is reported in Appendix I, Table 66. The company identified 15 studies, listed and summarised in Appendix H, Table 62 of the CS. Three studies were considered relevant for use in the economic model (Allen et al. 2016, Szende et al. 2010 and Iskedijan et al. 2012).[34, 40, 49] These studies informed the utilities associated with gastrointestinal bleed, inpatient other bleed, rescue event, outpatient bleeds and intracranial haemorrhage. The ERG are content with the company's search for utilities related to ITP. However, the methods used to source other utility values (e.g. for the ICH health states, carer disutility and disutilities associated with adverse events) were not described in the CS.

A summary of the utilities used in the economic model was presented in Table 36 of the original CS and updated by the company at clarification stage (in response to clarification question B9) with a) revised adverse event (and hence adverse event disutility) data, and b) details of the utility measurement (e.g. EQ-5D) and value set applied for each source.

Table 14 describes the company preferred utility values (as revised in response to clarification queries) and the ERG preferred alternative utility values, where different from the company's sources / data. The ERG notes that there were some inconsistencies between the company submitted documentation and the utilities applied in the model (the utilities

applied in the model are reported in brackets where different from the documentation). The ERG assumes that utilities in the model are correct.

The ERGs justifications for using an alternative utility values and sources are as follows:

- The pooled utility value applied by the company for the response, partial response and no platelet response health states (without bleeds) was pooled from the romiplostim trials, (using EQ-5D) and from Szende et al. 2010 (using TTO).[34] Since the use of EQ-5D data is more compatible with the NICE reference case, the ERG prefer the romiplostim trial utility values that were reported in TA221.[17]
- The ERG are concerned that some utilities may be at risk of double counting quality of life impact of events in the model. The company applied a disutility of a rescue event of 0.181 (associated with no bleed). However, the health state utility values in health states non-response <30 x 10^9/L, partial response 30-50 x 10^9/L, and response >50 x 10^9/L are based on those with no bleed. To avoid the potential for double-counting, the ERG therefore prefer to exclude the disutility from a rescue event.
- The company used a Chinese study using Chinese population-based time trade-off (TTO) model for the disutility associated with hypertension (=0.0575). The ERG prefer Sullivan et al 2011 (Supplementary Table 3) using a UK value set (=0.0375).[50] Both were using EQ-5D data.
- For the disutility of nausea and fatigue, the company sourced the study by Hagiwara et al. 2019. [51] The company used the Chinese value set. The ERG prefer using the UK value set which was reported in the same study in the appendices (eTable 3).
- For the disutility of anaemia, the company applied a disutility from severe anaemia. However, patients could experience mild anaemia instead of severe anaemia. The same source reports a disutility from mild anaemia and the ERG prefer to take an average of the two disutilities (0.12+0.32 / 2 = 0.220).

Table 14 Utility values used in the economic model

	Company used utility value	ERG preferred utility value (if different)	ERGs preferred utility source
Non-response <30 x 10^9/L	0.800	0.762	Base case: Romiplostim trials as per TA221[17]
Partial response 30-50 x 10^9/L	0.800	0.762	Base case: Romiplostim trials as per TA221[17]
Response >50 x 10^9/L	0.835	0.794	Base case: Romiplostim trials as per TA221[17]
Severe disability post ICH <30 x 10^9/L	0.330	--	
Severe disability post ICH 30-50 x 10^9/L	0.330	--	
Severe disability post ICH >50 x 10^9/L	0.330	--	
Disutility associated with adverse events of chronic immune thrombocytopenia			
Intracranial Haemorrhage	0.766 (excel model file: 0.769)	--	
Gastrointestinal Bleed	0.354 (excel model file: 0.357)	--	
Inpatient Other bleed	0.354 (excel model file: 0.357)	--	
Rescue Event	0.181 (excel model file: 0.184)	0	Assumed zero to avoid risk of double counting disutility of rescue event, low platelet health state and bleed events
Outpatient Bleed - <30 x 10^9/L	0.072 (excel model file: 0.075)	--	

	Company used utility value	**ERG preferred utility value (if different)**	**ERGs preferred utility source**
Outpatient Bleed - >50 x 10^9/L	0.070 (excel model file: 0.073)	--	
Carer disutility			
Carer disutility – Severe disability post ICH <30 x 10^9/L	0.162		
Carer disutility – Severe disability post ICH 30-50 x 10^9/L	0.162		
Carer disutility – Severe disability post ICH >50 x 10^9/L	0.162		
Disutility associated with adverse reactions – Fostamatinib & 'Watch and Rescue'			
Diarrhoea	0.044		
Hypertension	0.058	0.038	Sullivan et al 2011 (Supplementary Table 3)[50]
Nausea	0.062	0.054	Hagiwara et al. 2019 (UK value set, eTable 3)[51]
ALT increased	0.050		
AST increased	0.050		
Dizziness (with a fall)	0.120		
Epistaxis	0.026		
Upper RTI[A]	0.037		
Urinary Tract Infection	0.019		
Abdominal pain	0.069		
Fatigue	0.049	0.056	Hagiwara et al. 2019 (UK value set, eTable 3)[51]

	Company used utility value	ERG preferred utility value (if different)	ERGs preferred utility source
Pyrexia	0.110		
Headache	0.140		
Rash	0.002		
Chest pain	0.039		
Anaemia	0.320	0.220	Matza et al. 2015 (average of the disutility of mild anaemia and severe anaemia)[52]
Petechiae	0.002		

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; RTI: Respiratory tract infection; ICH: Intracranial Haemorrhage

[A] There was a minor typo in the CS regarding the utility source for Upper RTI, rash and chest pain. The company sourced Sullivan et al. 2006,[53] however, the ERG found that the utility values were actually obtained from Sullivan et al. 2011.[50]

In addition to the ERG's preferred utilities applied above, the ERG conduct a further scenario analysis to explore the impact on utilities and the ICER of assuming a similar approach to assigning proportions of people with severe disability post ICH who are MRS 4 / MRS5 to that used for the calculation of costs. The consistent approach assumes that 7.9% had MRS 4 and 5.5% had MRS 5 sourced from Rodriguez-Castro 2019.[48] This is slightly different to the approach taken by the company for utility calculation, based on 495 patients having MRS 4 and 285 patients having MRS 5. The ERG note the impact on the ICER is minimal.

At the clarification stage the ERG requested that the utility values be age and sex adjusted. In response to clarification question B9, the company normalised the base utilities (health state utilities) to the baseline age in the model (aged 65) and allowed the utility applied in the model traces to age adjust over each subsequent model cycle, thereby allowing utilities to reduce as the cohort ages. This was provided as a scenario analysis in the clarification letter. In addition, the ERG believe that all source utilities should have been age adjusted to the start age of the model cohort, given that multiple utility sources are used to parameterise the economic model, with each source deriving data from cohorts with different baseline

characteristics. The ERG have therefore age and sex adjusted all the source utilities used in the economic model.

4.2.8 Resources and costs

Treatment acquisition costs

Fostamatinib

Fostamatinib is administered as an oral tablet, taken twice daily, in either a 100mg or 150mg dose depending on the patient's response to treatment. The list price of fostamatinib is £3,090 and £4,635 per 60-unit pack of 100mg and 150mg respectively. The ERG note that the company refer to a patient access scheme, where a simple discount of [redacted] on the proposed list price is proposed, but the impact of the PAS price on the ICER was not explored in the CS. Therefore, for the remainder of this report, all treatment acquisition costs are calculated at list price. A full set of ERG analyses at the proposed PAS price are provided in Appendix 6 for completeness.

Each 4-weekly model cycle therefore consists of 56 administrations of fostamatinib. The cohort are modelled to receive 100mg for 4 weeks (the first cycle), after which point the patient is reviewed. If a response has been achieved (defined as achieving a platelet count of 30 x 10^9/L or above), the patient remains on a 100mg regimen. Non-responders are modelled to receive an increased dosage of 150mg for cycles 2 and 3. If they are still a non-responder after 12 weeks, treatment is stopped and no further fostamatinib treatment costs are incurred. Responders at 12 weeks to the 150mg dose remain on that dose for the remainder of their time on treatment. The company have not modelled any further escalation of dosage beyond 150mg. The ERGs clinical expert considers this reasonable, as there is currently insufficient evidence to assess the benefit-risk trade-off of further dosage increases. If a patient fails to respond to the 150mg dose, they would have their treatment stopped and an alternative treatment approach would be used going forward.

In response to clarification queries, the ERG requested further detail with regards to mean dosages of fostamatinib observed in the clinical trials and a discussion of how they compare against the treatment algorithm applied in the economic model. This information, together with alternative cycle specific treatment acquisition costs is reported in Table 15. No additional administration costs are required as the treatment is taken at home. The ERG clinical expert considers this reasonable.

Table 15 Alternative treatment acquisition costs for the economic model

	Company base case approach used in economic model.		ERG preferred treatment acquisition costs	
	Mean dosage on treatment	**Cycle specific cost on treatment**	**Mean dosage on treatment**	**Cycle specific cost on treatment**
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2-3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4+	[redacted]	[redacted]	[redacted]	[redacted]

Notes: Data on average treatment acquisition costs are for those on treatment.

Treatment acquisition costs are further adjusted for the compliance observed in the FIT1 and FIT2 trials (i.e. 96%). The ERG questions the appropriateness of further adjusting for compliance to reduce treatment acquisition costs for two reasons. First, the ERG notes that the mean daily dosage is already higher in the trials than the mean dosage observed through the application of the treatment escalation and cessation rules applied in the economic model. As there is likely to be some variation in clinical practice across treating clinicians and patient specific factors, it may be more appropriate to consider the trial estimates directly. The ERG notes that these data already implicitly include an adjustment for compliance. Therefore, the ERG considers it inappropriate to adjust for compliance in an analysis using the mean dosage data. The ERG prefers the use of the mean dosage provided in response to clarification queries, with a 100% compliance for the calculation of treatment acquisition costs in the model. This approach is also more consistent with the comparator Watch and Rescue strategy where it is assumed that compliance is equal to one. The cumulative impact of using the mean dosage of fostamatinib and setting the compliance parameter to 1 is a modest increase in the company's base case ICER.

The company's base case model assumes that there would be no long-term treatment tapering, that is, treatment would not be discontinued for long-term sustained responders. However, the model includes functionality to apply a sensitivity analysis where 40% of patients in the response states (all platelet counts of 30 x 10^9/L or above) could be weaned from treatment over time, whilst still maintaining long-term benefit. The ERG's clinical

expert confirms that when a sustained response in platelet count is achieved, as with other treatments for ITP, it is likely that fostamatinib can be tapered to stop in some but not all patients. There is some evidence with other drugs that this is due to the re-development of peripheral immune tolerance to platelets in patients who have a sustained high platelet count. This prevents the immune mediated destruction of platelets which is the main pathophysiological mechanism in ITP and allows sustained remission from ITP without ongoing therapy. Therefore, it is relevant to consider a scenario where a proportion of patients who have a long-term response may eventually be removed from fostamatinib treatment and that there is thus some merit in the company's sensitivity analysis.

However, whilst such tapering is clinically plausible, accurately determining the proportion of patients who would be tapered to stop, the proportion who would be tapered onto a reduced dosage, and the proportion who would remain on their full treatment dosage is difficult. Such an analysis would be associated with substantial uncertainty, particularly given that there is no evidence of the effect of treatment tapering from the FIT3 open label extension study.

The ERG's clinical expert considers it more plausible that such a treatment weaning would occur in those with a higher platelet count only, therefore it may be more plausible to apply the treatment weaning in a proportion of the cohort who have achieved a platelet count of $>50x10^9$/L only. The ERG view is that the company approach to modelling treatment tapering is conservative and may introduce a bias against fostamatinib. The magnitude of any bias is unclear, given that there is no evidence to suggest what proportion of patients can come off long-term treatment without detriment to clinical benefit. The ERG therefore accepts the conservative approach taken for the company base case analysis is appropriate. The ERG considers an alternative exploratory scenario analysis, where treatment weaning is applied to a proportion of the cohort with a platelet count $>50x10^9$/L would be appropriate to illustrate the uncertainty in this model parameter.

In summary, the ERG's preferred approach to calculating the treatment acquisition costs for fostamatinib is to use the mean data from the trial regarding dosing, a compliance parameter of one, and in line with the company base case to assume no treatment tapering over time for sustained responders. The company and ERG preferred assumptions regarding the calculation of treatment acquisition costs are compared in Table 16. The impact of moving to the ERG's preferred assumptions is a modest increase in the ICER.

Table 16 Fostamatinib treatment costs (company vs. ERG preferred assumptions)

Parameter	Company base case assumption	ERG preferred base case assumption	ERG scenario analysis
Average dosage of Fostamatinib per cycle	According to proposed treatment escalation and cessation	Based on mean dosage from the FIT1 and FIT2 trials	N/A
Compliance	96%	100%	N/A
Treatment tapering for sustained response beyond 1 year	None	None	40% of patients achieving a platelet count of >50 x 10^9/L removed from treatment after 1 year [A]

[A] Note, the company provided a scenario analysis where 40% of patients achieving a platelet count of >30 x 10^9/L would come off treatment after 1 year. The ERG considered a threshold of >50 x 10^9/L would be more appropriate for this scenario analysis.

Watch and Rescue (frequency of rescue events)

The following assumptions apply to the risk of requiring rescue therapy for a rescue event: A) all patients who have a falling platelet count receive rescue treatment regardless of model arm; and B) the cost of a course of rescue treatment (including types of medication and average dosage applied) is independent of both treatment arm and platelet count. Therefore, differences in rescue treatment costs are driven by the proportion of the modelled cohort in each health state at a point in time. The greater the proportion in the lowest platelet count state, the greater the rescue medication costs applied in the model.

The frequency of rescue events are pooled across the FIT1 and FIT2 trials by platelet count health state. Inspection of the CSR data indicates that the company may have calculated the frequency of rescue events using numbers of people who experienced an event over the trial, rather that the number of actual events, thereby potentially under-estimating the frequency of rescue events across the health states. The ERG has recalculated the frequency of rescue

events using the event data from the trials. However, as the ERG does not have access to the raw data from the FIT1 and FIT2 studies, it was necessary to assume that the number of events per person was equal across the different platelet count health states (reported as 1.7 and 1.3 for fostamatinib and placebo respectively after 10 weeks in the CSRs) and then averaged across study arms for application in the model. It is likely that with access to the raw data, the company can improve the accuracy of this analysis, as it would be reasonable to assume that the number of events per person increases for lower platelet count health states. The company and ERG preferred calculations are compared in Table 17.

Table 17 Alternative approaches to calculating frequency of rescue events

Health state	Company preferred frequency of rescue treatment per cycle, based on expert opinion	ERG alternative frequency of rescue treatment per cycle based on trial data from FIT1 and FIT2.
<30 x 10^9/L	5.5%	7.8%
30-50 x 10^9/L	1.7%	2.6%
>50 x 10^9/L	0.7%	1.2%

The impact of adopting the ERG's preferred assumption is a small reduction in the ICER for fostamatinib compared to watch and rescue.

Watch and Rescue (treatment bundle)

The company have consulted KOLs about what rescue treatments are used for a patient requiring rescue in UK clinical practice. However, the information provided by the company lacks clarity about the number of clinicians consulted, variation in the approach taken across different regions or variation in the approach to treating individual patients. For example, it is assumed that the distribution of treatments is the same for all patients whether they require rescue for low platelets or require surgical prophylaxis. Similarly, all patients receive the same treatment regardless of platelet count, once they require rescue. The company have assumed that all steroid use is intravenous, but this is inconsistent with the rescue medication used in the trial. The ERG's clinical expert opinion is that oral prednisolone and

dexamethasone, both used in the FIT trials, but excluded from the company treatment bundle for rescue events would be used frequently as rescue medication and as surgical prophylaxis for minor procedures in UK clinical practice.

In response to a clarification query on this issue, the company provided a revised proportion on treatment using information from the FIT1 and FIT2 trials, but again restricted the treatment bundle to only include patients receiving IVIG, IV methylprednisolone and platelet transfusion. These are the most expensive rescue treatments to deliver and only account for about 40% of all rescue medication used in the clinical trials. The ERG believes that the approach taken overestimates the cost of rescue medication, which likely biases the ICER in favour of fostamatinib.

The ERG have consulted the clinical study reports and consider it more appropriate to apply the treatment bundle used in the trials (where relevant to UK clinical practice) in order to calculate the average cost of treating a rescue event. The ERG's clinical expert has reviewed the rescue medications used in the trials and identified those that are used in UK clinical practice. The company preferred and revised ERG distributions of rescue treatments considered for use in the economic model are provided in Table 18 below for comparison. The proportions receiving each treatment are scaled up to reflect that a patient may receive more than one treatment during a rescue event. It is important to note that this parameter has an important impact on the ICER, but is highly uncertain, and clinical practice is likely to vary substantially around the UK.

Table 18: ERG assessment of the relevance of FIT1 and FIT2 trial rescue treatments to UK practice and dosage

Rescue medications sourced from CSRs	Company original submission (based on expert opinion)[C]	Company response to clarification, scenario analysis (obtained from FIT trial data)[C]	ERG preferred treatment bundle			ERG preferred dosage (based on clinical expert opinion)
			Pooled across trial arms[A]	Relevant to UK clinical practice (Y/N)?[B]	Treatment distribution - UK clinical practice [D]	
Danazol (oral)	--	--	2 (2%)	N	--	--
Platelets (IV)	20% x 1.0	11% x 1.1	4 (3%)	Y	3.31% x 1.21	1.5 adult platelet pools
Dexamethasone (oral)	--	--	15 (11%)	Y	12.40% x 1.21	40mg/day for 4 days
hydrocortison	--	--	2 (2%)	N	--	--
Methylprednisolone (IV)	100% x 1.0	11% x 1.0	10 (8%)	Y	8.26% x 1.21	10mg/KG/day over 2 days
Prednisolone (oral)	--	--	17 (13%)	Y	46.28% x 1.21	1mg/KG over 2 weeks
Prednisone	--	--	35 (26%)	Y (as prednisolone)	--	--
prednisone acetate	--	--	4 (3%)	Y (as prednisolone)	--	--
Anti - D	--	--	0 (0%)	N	--	--
Imm unoglobulin G human (IV)	100% x 1.1	86% x 1.593	2 (2%)	Y	29.75% x 1.21	1g/kg
Immunoglobulin Human normal	--	--	30 (23%)	Y (as IVIg)	--	--
Immunoglobulins	--	--	5 (4%)	Y (as IVIg)	--	--
Azathioprine	--	--	7 (5%)	N	--	--

Abbreviations: CSR: Clinical study report; ERG: Evidence Review Group; IV: Intravenous; N: No; Y: Yes

[A] Note that probabilities add to more than 1 because more than treatment may be used per rescue event. Data are from Table 14.3.12 of the CSRs

[B] Each treatment in the bundle assessed for relevant to UK clinical practice by the ERG's clinical expert advisor.

[C] All treatment shares multiplied by upwards to account for the potential for more than one dosage of any treatment to be given per rescue event.

[D] For the ERG analysis, all treatments were multiplied by 1.21 in the economic model to reflect the potential for more than one treatment to be used per rescue event in the absence of more detailed data about treatment bundle combinations from the CSRs.

Watch and Rescue (unit costs of treatment)

The unit costs of watch and rescue treatments used in the company's economic model are described in Table 40 of the CS. The ERG has several concerns about the sources of unit costs used in the economic model:

A) The company used the average unit cost across a range of different platelet pack sizes to deliver the required dosage for rescue treatment. In response to a clarification query from the ERG, the company subsequently revised their cost calculation to reflect the minimum cost approach to reach the required dosage.

B) The ERG note that the company have not used the lowest cost produce available to obtain the required IVIg dosage required for rescue medication. The ERG prefer the lowest feasible unit cost obtained from the BNF to make up the required dosage.

The ERG's preferred base case analysis assumes that the lowest cost approach to making up the required dosages is applied. Table 19 compares the ERG and company preferred unit costs of rescue medication.

Table 19 ERG vs. Company preferred unit costs of rescue therapy

Item	Co. preferred unit cost	Co source	ERG preferred unit cost	ERG source
Platelet pool unit cost	£224.11	2013/2014 costs inflated to 2020 values based on old NHSBT price lists[54]	£211.26	2020/21 NHSBT price list, cost per unit of platelets pooled (1ATD), item code: BC045[55]
IVIG 1g/kg	£1020/20g pack	BNF 2020[56]: Flebogamma DIF 20g/400ml solution for infusion (Grifols UK Ltd)	£836 / 20g pack	BNF 2020[56]: Gammaplex 20g/400ml solution for infusion vials (Bio Products Laboratory Ltd)
IV methyl-prednisolone	Minimum cost to make up required dose from: 40mg (£1.58); 125mg (£4.75); 500mg (£9.60); 1000mg (£17.30)[A]	BNF 2020[57]	Minimum cost to make up required dose from: 40mg (£1.58); 125mg (£4.75); 500mg (£9.60); 1000mg (£17.30)[A]	BNF 2020[57]
Prednisolone	N/A	N/A	£1.90 / pack (cost per course: £5.70)	BNF 2020[58] (assume 3 packs of pevanti 10mg size 30, unit cost £1.90 per package to deliver a total dosage of 1mg per kg over up to 2 weeks.
Dexamethasone	N/A	N/A	£6.84 / pack (cost per course: £13.68)	BNF 2020[59] (assumes a dosage of 40mg per day over 4 days = 160mg dose requirement, made up from 2 packs of 50 tables (2mg) generating total tab dose of 200mg @6.84 per package.; Dexamethasone 2mg tablets (Alliance Healthcare (Distribution) Ltd)

Abbreviations: ATD: Adult Therapeutic Dose; BNF: British National Formulary; IV: Intravenous; IVIG: Intravenous Immunoglobulin; NHSBT: NHS Blood and Transplant

[A] Note that the company original submission applied the average of these unit costs.

Bleed event costs

The costs of severe bleed events are described in Table 44 of the CS. There were several inconsistencies between information reported in the CS, response to clarification queries and included within the respective economic models. Specific issues included: A) insufficient detail with regards to the HRG codes used; B) inconsistencies between the HRG codes included in the company submission and those used in the economic model; C) HRG codes that were inconsistent with HRG code descriptors provided and D) insufficient or incorrect details regarding the setting of care (e.g. day case, inpatient non-elective short stay, inpatient non-elective long stay or outpatient). For these reasons, it was not possible for the ERG to replicate the unit costs of bleed events used in the economic model. Table 20 below compares the ERG's preferred unit costs of bleeding events, based on the descriptions provided by the company and in consultation with the ERG's clinical expert with those preferred by the company (either from the CS or response to the clarification letter).

Table 20 ERG and company preferred unit costs of bleed events

Bleed event	Co. preferred unit cost, 2018 values (inflated to 2019 values)	ERG preferred unit cost (2019 values)	ERG source description
Outpatient bleed	£441.75 (£449.26)	£361.80	NHS reference costs 2018-19, average unit cost for a day case procedure, weighted by activity across currency codes FD03F, FD03G and FD03H (GI bleeds without intervention)[60]
GI bleed	£3,474.70 (£3,533.76)	£2,992.13	NHS reference costs 2018-19, average unit cost for non-elective long stay admissions, weighted by activity across currency codes FD03A to FD03E (All GI bleed codes with single or multiple intervention, all CC scores)[60]
ICH	£5,204.00 (£5,292.45)	£4,098.84	NHS reference costs 2018-19, average unit cost for non-elective long stay admissions, weighted by activity across currency codes AA23C to AA23G (Haemorrhagic Cerebrovascular disorders, all CC scores) [60]
Inpatient other bleed	£2,082.00 (£2,117.39)	£1,217.89	NHS reference costs 2018-19, average unit cost for non-elective short stay admissions, weighted by activity across currency codes FD03B and FD03E (GI bleed codes with single or multiple intervention, low CC scores only)[60]

Abbreviations: CC: Complications and co-morbidities; GI: Gastrointestinal; ICH: Intracranial haemorrhage

Adverse event costs

The costs of adverse events are provided in Table 47 of the CS. The ERG consider these costs to be reasonable.

Surgical prophylaxis costs

The company additionally assume that all patients attending all hospital procedures will require surgical prophylaxis if they have a platelet count < 30 x 10^9/L. Whilst the ERG agrees that it is appropriate to consider rescue treatment for patients with a low platelet count, there are several concerns with the approach taken by the company:

- It is assumed that all procedures and interventions reported by HSCIC under hospital admitted patient care activity, including non-invasive diagnostic procedures will require prophylaxis. The ERG's clinical expert has reviewed the list of activities reported in the source data and identified procedures that would and would not require prophylaxis in clinical practice. Approximately 71% of procedures in the over 65 population would be deemed as requiring surgical prophylaxis. The full list of procedures deemed to require prophylaxis are reported in Table 31, Appendix 3 for information.

- The company's analysis assumes that all patients requiring surgical prophylaxis will be provided with the same dosage and bundle of rescue treatments used for an active rescue event. The ERG's clinical expert considers this to be inappropriate, stating that most patients will receive one course of treatment only, and treatment would likely be with either IVIG for major surgery or oral prednisolone for minor surgery. The ERG have assumed that surgery at the following sites is generally considered major: Nervous system, Endocrine system and breast, lower digestive tract, other abdominal, heart, artery and vein, bones skull, bones other, miscellaneous. And surgery at the following sites would generally be considered minor: Eye, Ear, Respiratory tract, upper digestive tract, mouth, urinary, genital tract, skin, soft tissue, diagnostic. The ERG accepts that there may be exceptions to this rule, but feel that, on balance the approach provides a reasonable estimate of the proportion of patients who would likely receive oral prednisolone (56%) and IVIG (44%) for surgical prophylaxis.

The ERG have implemented the described changes and note that the ERG preferred approach leads to a significantly reduced cost of surgical prophylaxis compared to the company's

preferred approach. When combined with the ERG's preferred unit cost assumptions for rescue treatment, in particular IVIg, the impact on costs is even greater. The ERG considers the company's approach to over-estimate the costs of surgical prophylaxis by a substantial margin, generating a moderate bias in the ICER in favour of fostamatinib, given the greater use of rescue treatment and longer time in the $<30 \times 10^9$/L health sate.

Routine management costs for ITP

Details of the resource use for routine management and follow up of ITP patients (Haematologist consultation, blood tests, biochemistry) were obtained from clinical expert opinion. The main contributor to these costs is the number of consultations with a haematologist. The ERG notes that it is unclear how many clinical experts were consulted or what the range of opinion was regarding the frequency of consultation. The ERG notes that because the frequency of consultations is assumed to be platelet count dependent, the number of consultations per week/month/year has a moderate impact on the ICER. The ERG considers the impact of a less intensive follow up strategy, informed by the ERG's own clinical expert on costs in the model.

The ERG also notes that the unit cost of a haematologist consultation is obtained in 2013 values and inflated to 2019 values in the model. The ERG prefers the use of a unit cost sourced directly from 2019 NHS reference costs. The ERG notes that the ERG's approach generates a unit cost per visit of £173, compared to £176.90 using the company's approach. The impact on the ICER is therefore minimal.

Resource use associated with acute stroke care was obtained from the Sentinel audit report, 2016. The ERG considers the report to be comprehensive in terms of resource use data reported and is therefore a generally suitable source from which to develop the costs of stroke care. Whilst the report was published in 2016, it makes use of 2014 NHS reference costs. However, the company assumed the source values were in 2016 values and therefore inflated the wrong figures to present day values. Furthermore, the ERG consider it inappropriate to use inflation indices, when up to date national average unit costs are readily available. The ERG has therefore re-costed acute stroke care by updating the unit costs provided in the Sentinel report using up to date national average unit costs. The company's preferred total cost of acute stroke care was £9,012, whereas the ERG's preferred cost is £8,622. Details of the ERG's vs. the company's costing approach are provided in Appendix 4. Given the rarity of the acute stroke event, the impact on the ICER is minimal.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

Markov model traces are provided in Appendix J1.1 (Figures 28 and 29 of the CS). Disaggregated costs: Treatment cost, Rescue treatment cost, cost of surgical prophylaxis, other health state costs and adverse event costs are reported for each arm of the model in Table 75 of the CS. Total health state QALYs and total health state costs are reported by model arm in Tables 73 and 74 of the CS respectively. The ERG notes that disaggregated costs were not provided by platelet count health state.

The original company submission included several errors in relation to model calculation formulae and sourcing of model input parameters. Some of these errors favoured fostamatinib, whilst others favoured watch and rescue. The company corrected errors identified by the ERG at the clarification stage. The cumulative impact of these corrections and revised company assumptions was a small increase in the ICER from £[redacted] to £[redacted]. However, the ERG notes that the company's preferred base case ICER does not incorporate all the requested changes by the ERG in response to the clarification letter. Furthermore, additional errors were identified post-clarification and these are discussed in Chapter 6.

Table 21 below indicates the company's original and revised post-clarification queries ICER.

Table 21 Company preferred base-case results

	Total Costs (£)	Total LYG	Total QALY	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Original base case							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised base case post-clarification (deterministic)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised base case post-clarification (probabilistic)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figures 3 and 4 illustrate the scatter plot of simulations from the PSA and CEAC for the company's preferred assumptions respectively.

Figure 3 Incremental cost-effectiveness scatter plot for company's preferred base case (re-produced from Figure 3 of the company response to clarification)

Figure 4 CEAC for company's preferred base case (re-produced from Figure 4 of the company response to clarification)

5.2 Company's sensitivity analyses

All further analyses described in this section are implemented using the company's updated model base case in response to clarification queries. The company conducted several deterministic analyses by varying model input parameters within the bounds of their confidence limits or +/- 20% if confidence interval data were not available. The results of the one-way sensitivity analyses are provided in the tornado diagram in Figure 5 based on a WTP threshold of £30,000 per QALY gained.

Figure 5 Tornado diagram illustrating one-way sensitivity analyses conducted by the company (reproduced from Figure 2 of the company response to clarification)

The tornado diagram shows that the company's base case ICER is most sensitive to the treatment cost of fostamatinib, the probability of a loss of response to fostamatinib over time, and the HR of mortality in the <30 x 10^9/L platelet group.

Company conducted scenario analyses

Whilst the ERG accepts that the tornado analysis is useful in understanding the most important model parameters, it does not fully describe the impact of key modelling uncertainties on the cost-effectiveness results. The ERG notes that the company's original submission included only one scenario analysis to explore the impact of key uncertainties around model assumptions. That scenario analysis explored the impact on the ICER of assuming that 40% of fostamatinib patients with a platelet count >30 x 10^9/L could come off treatment after 1 year and still maintain the clinical benefits of the drug. The impact was a modest decrease in the ICER. The ERG notes that the company have not re-produced this analysis using their revised preferred base case and it is therefore included in Chapter 6. Scenario analyses provided in response to the ERG's clarification queries are provided in Table 22.

Table 22 Company conducted scenario analyses in response to clarification

	Total Costs (£)	Total LYG	Total QALY	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Revised base case post-clarification (deterministic)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Using an average of early phase transitions to project future fostamatinib transitions							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply age-adjusted health state utilities to the model trace							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply trial-based probabilities of watch and rescue, assuming only IVIG, platelets and IV methylprednisolone would be used in UK clinical practice							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: Incremental cost-effectiveness ratio; IV: Intravenous; LYG: Life years gained; QALY: Quality adjusted life year

The company's base case ICER was most sensitive to scenario analyses conducted around the longer-term extrapolation of transition probabilities in the economic model. In general, the ERG note that the company have not conducted adequate scenario analyses to determine the impact of key modelling assumptions on the ICER. The impact is that the range of ICERs presented fail to demonstrate the true range of uncertainty in the ICER.

5.3 Model validation and face validity check

The company submission states that the economic model has undergone thorough internal and external validation and that the clinical structure and modelling assumptions were

validated as part of an advisory panel. The company supplied the minutes of those advisory panel meetings and the ERG are satisfied that the clinical assumptions used in the model are a fair representation of the meeting minutes. The ERG notes that the key opinion leader information sought to inform the modelling assumptions was based on a small sample of clinical experts (5 at the first advisory board, 2 at the second, with one clinical expert attending both meetings). The ERG note that there may still be variation in practice across the UK that was not captured at these advisory boards. For example, the ERG's clinical expert highlights the variation in the use of splenectomy and rituximab as important considerations that are not included in the economic model. Details of internal validity checks on the model outputs have not been provided.

The ERG identified several formulae errors in the company's originally submitted economic model as well as several inconsistencies between the model and submitted documentation. The ERG raised these issues in the clarification letter. The ERG are satisfied that the identified errors were corrected in the revised economic model and are not discussed further here.

The ERG have re-checked the company's revised economic model in response to clarification queries. Several further model errors were identified using the black-box checklist described by Tappenden and Chilcott 2014[61] (Table 23) and through additional face validity and random formulae checks conducted by the ERG. The impact of correcting the identified modelling errors was a substantial increase in the company's base case ICER. Several additional errors in sourcing of data parameters to populate the model were also identified. The impact of correcting these issues on the ICER is described further in Section 6.3.

Table 23 Black box' verification checks conducted on the company submitted model in response to clarification queries

Model component	Model test	Unequivocal criterion for verification	Issues identified
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	No issues identified on the model trace formulae. However, the ERG identified a formula error in the application of HRs to the severe disability health states and <30 x 10^9/L states that affected both arms of the model. The implication was a substantial under-estimation of life year and hence QALY gains for both arms of the economic model. The implication of correcting this error is a substantial increase in the ICER.
	Sum expected health state populations at any model time-point (state transition models)	Total probability equals 1.0	No further issues identified
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	No further issues identified
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	No further issues identified
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	No further issues identified
Cost estimation	Set intervention costs to 0	ICER is reduced*	No further issues identified
	Increase intervention cost	ICER is increased*	No further issues identified
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	The costs of rescue medication applied for surgical prophylaxis were not discounted or half cycle corrected on the 'Watch and Rescue' Markov trace. The implication of correcting this error is a moderate increase in the ICER.
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	No further issues identified

Model component	Model test	Unequivocal criterion for verification	Issues identified
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range 0\x \1, samples from lognormal distribution lie in range x[0, etc.)	No further issues identified
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	Due to a formula error on the fostamatinib model trace, adverse events were not counted beyond year 25 for the fostamatinib arm of the model, but are counted for the full model time horizon in the watch and rescue arm. The implication of correcting this error is a small increase in the ICER for fostamatinib.
	Amend value of each individual model parameter*	ICER is changed	No further issues identified
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	No further issues identified
ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year * Note this assumes that the parameter is part of the total cost function and/or total QALY function			

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG have undertaken several different exploratory and sensitivity analyses to illustrate the impact of variation in different plausible assumptions on the ICER. Table 24 describes each of the analyses undertaken, together with a justification for each. Further details of changes to the economic model to enable these analyses are provided in Appendix 5. All changes reported in this Chapter are applied using the list price for fostamatinib. A set of analyses using the proposed PAS price are provided in Appendix 6.

Table 24 ERG justification for additional exploratory and sensitivity analysis

Parameter/Analysis	Company base case assumptions	ERG preferred analysis / exploratory analysis conducted	Justification for ERG's assumption	ERG report section
Changes that contribute to the ERG's preferred base case analysis (reported in Table 25)				
Corrections applied to the economic model calculations / formulae / data sourcing				
Costs of rescue treatment for surgical prophylaxis costs on the watch and rescue trace	Not discounted or half-cycle corrected	Discounting and half cycle correction applied	Discounting should be applied across all costs in both arms of the model	5.3
Data input on QoL inputs sheet	Not referencing the relevant cells	Referencing the relevant cells	Minor correction to the formula, improving the accuracy of the QoL data inputs.	Appendix 5, Table33
Counting of adverse events on the fostamatinib model trace	Counted for 25 years	Counted for full 35-year time horizon.	The ERG prefers application of adverse event risks for the full duration of the time horizon to ensure consistency with the application on the W&R trace.	Appendix 5, Table 33
Cycle specific mortality calculation formula (application of mortality HR for platelet counts <30 x10^9/L & for severe disability post ICH states	p2 = 1-EXP(-(p1^ (1/HR) [A]	p2 = 1-(EXP(-(-(LN(1-p1))*HR)))[A]	The ERG has amended the formulae to ensure correct application of the mortality HR	4.2.6 & 5.3

Parameter/Analysis	Company base case assumptions	ERG preferred analysis / exploratory analysis conducted	Justification for ERG's assumption	ERG report section
Frequency of rescue events	Calculated using the number of people who had a rescue event	Calculated as the number of rescue events, assuming a mean number of events per person from the CSRs [B]	The ERG's approach accounts for the fact that some patients had more than 1 rescue event over the duration of the trials [B]	4.2.8, Table 17
Reported numbers of adverse events	Applied as per response to clarification document	Revised to match data in CSR	The ERG prefers correction of several minor discrepancies in the reporting of adverse event numbers to ensure consistency between economic model and CSR.	Appendix 5, Table 33
4-weekly probability of adverse events	Cycle specific probabilities calculated by direct manipulation of probability data	Convert to rates, then manipulate and then convert back to 4-weekly cycle specific probabilities	The ERG believes it is more technically correct to convert to rates before manipulation into cycle specific probabilities	Appendix 5, Table 33
Transition probability calculations	1. Applied as rates to the model trace 2. In absence of data assumes RR of	1. Applied as probabilities to the model trace	1. Probabilities as opposed to rates should be applied to the model traces	4.2.6 & Appendix 5, Table 33

Parameter/Analysis	Company base case assumptions	ERG preferred analysis / exploratory analysis conducted	Justification for ERG's assumption	ERG report section
	transition (W&R vs. Fostamatinib) from high to low platelet counts is 0.9	2. Assumes transitions are equal to the transitions between the next worse states where data are available	2. The ERG applies the assumption specified in the CS which is more appropriate than an arbitrary RR	
Remaining probabilities reported over a time horizon other than 4-week cycle specific	Conversion of probabilities from reported time horizon to cycle-specific time applied directly to probability data	Probabilities converted to rates before manipulation and then converted to 4-weekly cycle specific probabilities.	The ERG believes it is more technically correct to convert probabilities to rates before manipulation into cycle specific probabilities	Appendix 5, Table 33
ERG preferred cost assumptions and data				
Unit cost sources for bleeding events, haematologist consultation, acute stroke care and stroke rehabilitation	Various sources that refer to NHS reference costs from various years (e.g. 2013/14 or 17/18) and to 2019 (stated as 2020) values[62]	Apply updated 2018/19 NHS reference costs directly	The ERG considers it more appropriate to use the most up to date NHS reference cost data available (NHS reference costs 2018-19).[60]	4.2.8

Parameter/Analysis	Company base case assumptions	ERG preferred analysis / exploratory analysis conducted	Justification for ERG's assumption	ERG report section
Fostamatinib treatment acquisition costs	The company calculate costs according to a defined treatment algorithm.	Calculate costs based on the mean dose observed from the trials.	The ERG considers the mean dose from the FIT trials to be more appropriate for costing and more in line with the likely variation in dosing that might be observed in clinical practice.	4.2.8
Fostamatinib treatment compliance	96% (as per FIT1 and FIT2)	100%	Given that the ERG prefers the use of the mean dose (which already accounts for compliance), the ERG does not consider it necessary to further adjust for compliance	4.2.8
Distribution of different types of rescue therapy	Based on KOL opinion:	Based on rescue treatments used in FIT1 and FIT2 that the ERG's clinical expert considers relevant to UK clinical practice.	The ERG considers it more appropriate to use the available data from FIT 1 and FIT 2 clinical study reports to identify the rescue treatments used. ERG's clinical expert reviewed the treatments and identified those that would be used in UK clinical practice (including oral prednisolone and dexamethasone). [C]	4.2.8, Table 18

Parameter/Analysis	Company base case assumptions	ERG preferred analysis / exploratory analysis conducted	Justification for ERG's assumption	ERG report section
Unit costs of rescue therapy	Various, including use of branded alternatives	Consistent use of cheapest approach / use of treatment to generate required dosage	The ERG considers it more appropriate to use the cheapest cost sources available from the BNF	4.2.8, Table 19
Source of information to inform rescue therapy dosing	KOL input	ERG clinical expert opinion	ERG prefer to apply the dose suggested by ERG clinical expert opinion.	4.2.8, Table 18
Proportion of patients in the $<30x10^9$/L health state requiring rescue treatment for surgical prophylaxis	All procedure listed on the Hospital Admitted patient Care Activity report would require surgical prophylaxis.	Some less invasive listed procedures such as diagnostic imaging would not require surgical prophylaxis.	ERG clinical expert opinion was that not all procedures listed would require surgical prophylaxis.	4.2.8 & Appendix 3, Table 31
Use of rescue medication and dosage for surgical prophylaxis	Assumed to be the same average cost as treatment for a rescue event	55% treated with one course of oral prednisolone (assumed minor procedure); 45% treated with one course of IVIg (assumed major procedure)	ERG clinical expert reviewed the Hospital Admitted Patient Care Activity 2018-19 document and identified clinical sites where surgery would most commonly be considered as minor (treated with oral prednisolone) or major (treated with IVIg).	4.2.8 & Appendix 3, Table 31
Utilities				

Parameter/Analysis	Company base case assumptions	ERG preferred analysis / exploratory analysis conducted	Justification for ERG's assumption	ERG report section
Age adjust utilities on model trace	Not applied in preferred base case (only as a scenario)	Apply age adjustment	Best practice methodology[63]	4.2.7
Utility input data	Various	Various	ERG have updated utility sources to use utilities in line with the NICE reference case wherever possible. This includes using EQ-5D data from the Romiplostim trials is in line with the NICE reference case as opposed to pooling with Szende et al. based on TTO data.[34]	4.2.7, Table 14
Age/sex adjustment of utility input values to model cohort start age / sex.	No age/sex adjustment	Age/sex adjust all utility input values	Best practice methodology[63]	4.2.7
Probability of outpatient bleeding				
Probability of outpatient bleeding	Allen et al. 2016, based on the non-splenectomised group[40]	Weighting the two probabilities from Allen et al.[40] (for the splenectomised and non-splenectomised group) according to the	The weighted average across splenectomised and non-splenectomised groups is more appropriate to keep the consistency with the proportion of patients who are splenectomised and	4.2.6

Parameter/Analysis	Company base case assumptions	ERG preferred analysis / exploratory analysis conducted	Justification for ERG's assumption	ERG report section
		proportion splenectomised and non-splenectomised in FIT 1 and FIT 2.	non-splenectomised in the FIT1 and FIT 2 trials.	
Changes that contribute to the ERG's additional <u>exploratory</u> analyses (reported in Table 26)				
Long term treatment effectiveness of fostamatinib scenario analyses				
Fostamatinib treatment tapering	No long-term tapering	40% of the cohort with a response (>50 x 10^9/L) could be weaned off treatment over time while keeping the benefit of treatment	To explore the uncertainty surrounding the fostamatinib long term treatment benefit, as it may be plausible for patients to come off treatment while remaining successful (although there is no evidence to support this)	4.2.6, 4.2.8
Loss of response to fostamatinib in the long term	Loss of response calculated from the FIT3 OLE study, using data between months 1-24, assuming missing data are a loss of response and applying a 50/50 split for transition	Explore various single and combinations of assumptions including using month 6-24 data, assuming missing data are classed as responders, and using FIT3 data directly to	The company assumptions surrounding fostamatinib loss of response data in the long term is highly uncertain. It is important to explore the impact of varying these assumptions on the ICER	4.2.6

Parameter/Analysis	Company base case assumptions	ERG preferred analysis / exploratory analysis conducted	Justification for ERG's assumption	ERG report section
	from >50x10^9/L to <30 x10^9/L and 30-50 x10^9/L states respectively.	populate the split of transitions from >50x10^9/L to <30 x10^9/L and 30-50 x10^9/L states respectively.		
Other scenario analyses surrounding QoL and adverse events				
Carer disutility in the severe disability post ICH state (no. of carers assumed)	One carer	Vary between 0-2 carers	To explore the sensitivity of the ICER to the company's application of carer disutility in the model.	4.2.7
Probability that severe disability is MRS 4 or MRS 5 for utility calculation purposes [D]	0.32 (different approaches for cost and outcome parameters)	0.33 (similar approach for cost and outcome parameters)	To explore the impact of ensuring consistent approach taken for obtaining MRS probability for outcomes and costs parameters	4.2.7
Bleed related adverse events (epistaxis and petechiae)	Epistaxis and petechiae are included as adverse events	Remove bleed related adverse events (epistaxis and petechiae) from adverse event data	There is a risk of double-counting since epistaxis and petechiae could also be bleed events.	4.2.6
Methodological scenario analyses				
Discount rate for costs and QALYs	3.5% per year	0% per year 6% per year	To explore the impact of the discount rate on the ICER	4.2.5

[A] where p2 is the cycle specific mortality probability for example in the <30 x 10^9 /L health state; p1 is the all-cause general population mortality and HR represents the mortality HR for p2 vs. p1 obtained from the literature. An alternative acceptable formula that would generate similar results would have been p2 = 1 – ((1-p1)^HR).

[B] Note that the ERG have calculated the mean number of rescue events per patient across the trial arms. Sufficient data were not available from the CSRs to calculate this parameter separately for each platelet count category (model health state).

[C] Whilst the ERG's preferred approach attempts to account for the fact that a proportion of patients may receive more than one rescue therapy in an event (calculated by the ERG from the CSRs as 1.21 on average), there was insufficient information available to the ERG to identify which treatments were used in combination.

[D] Note that in the company base case analysis, the probability of MRS 4 was calculated as 495/(495+285), source unclear. For the ERG preferred analysis, the probability of MRS 4 was calculated as 5.5%/(7.9%+5.5%) as per Rodriguez-Castro et al. 2019 (consistent with the approach taken for apportioning costs to MRS 4/ MRS5).[48]

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Section 6.3 below describes the impact of additional scenario analyses undertaken by the ERG on the ICER. Given that several corrections were made to the economic model, the ERG did not consider it helpful for decision-making to apply scenarios to the company submitted base case results.

6.3 ERG's preferred assumptions

The ERG's preferred base case ICER incorporates the cumulative impact of the following:

1. Correction of identified model formulae errors regarding application of mortality HRs, discounting formulae, counting of adverse events, calculation of rescue therapy frequency, calculation of transition probabilities and other minor data inconsistencies.
2. Updating unit costs to 2018/19 values as opposed to inflating from older studies / reference cost sources.
3. Using the mean daily dosage of fostamatinib and assuming a compliance of 100% applied to the mean to inform the treatment acquisition costs of fostamatinib.
4. Amend the bundle of treatments included for rescue therapy in line with the ERG clinical expert's opinion about treatments in UK clinical practice (e.g. including dexamethasone and oral prednisolone within the treatment bundle, in addition to IVIg, IV methylprednisolone and platelet transfusion).
5. Source the cheapest possible unit costs of rescue treatments, making use of generic equivalents where possible and applying dosing in accordance with the ERG's clinical expert opinion regarding dosing.
6. Utilities age adjusted on the model trace and source utilities age adjusted from source literature to the starting age of the model cohort.
7. The use of outpatient bleed probability calculated from splenectomised and non-splenectomised patients as opposed to non-splenectomised only.

The cumulative impact of each individual change (described in Table 24 above) to generate the ERG's preferred ICER is reported in Table 25. The deterministic and probabilistic ICER under the set of model assumptions preferred by the ERG is £[redacted] and £[redacted] per QALY gained respectively.

Table 25 Cumulative impact of ERG preferred assumptions on the ICER

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Company submissions							
Company preferred base case analysis (original submission)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company preferred base case analysis (revised submission following clarification)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correction of model errors							
Apply discounting and half cycle correction to surgical prophylaxis costs on the watch and rescue trace							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correction of data input on QoL inputs sheet							

	Total Costs (£)	**Total LYG**	**Total QALYs**	**Incremental Costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correction to apply the costs of adverse events for the full 35 year time horizon on the fostamatinib trace							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correction to formula for application of mortality HR							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correction to calculation of rescue event frequency (accounting for the fact that any person may have more than 1 rescue event)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correction to the reporting of adverse events to ensure consistency with FIT1 / FIT2 clinical study reports							

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correction to formula applying the 4-weekly probability of adverse events							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG correction to transition probability calculations and applying assumptions consistent with the company submission where data do not exist to populate a transition							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG corrections of all other cycle specific probabilities to ensure that data are converted to rates before manipulation							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG preferred data and assumptions (Costs)							

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Updated unit costs of bleeding events, haematologist consultation, acute stroke care and stroke rehabilitation to use 2019 NHS reference cost values where available							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use mean dosage of fostamatinib from trials to determine treatment acquisition costs							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume compliance parameter =100%, given that mean dosage is applied							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply ERG preferred distribution of rescue therapy (sourced from FIT1 and FIT2 trials), including treatments such as dexamethasone and oral prednisolone							

	Total Costs (£)	**Total LYG**	**Total QALYs**	**Incremental Costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply ERG preferred rescue medication unit costs, applying lowest cost approach from BNF to attain required dosage							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply ERG preferred dosing for rescue medication (based on ERG clinical expert opinion)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply ERG preferred proportion of admitted patient procedures that would require surgical prophylaxis (based on ERG clinical expert opinion)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Apply ERG preferred use of rescue medication and dosage for surgical prophylaxis, based on assumptions about which procedures are most commonly minor (oral prednisolone) or major (IVIg)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG preferred data and assumptions (utilities)							
Age adjust utilities on the model trace							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply ERG preferred utility input data							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age adjust utility input sources							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Other parameters / adjustments							
ERG preferred outpatient-bleeding data (weighted of splenectomised / non-splenectomised patients) from Allen et al.[40]							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG preferred base case analyses							
Deterministic							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 6 Scatter plot of cost-effectiveness plane using ERG preferred base case ICER (Reproduced directly from Company submitted economic model)

Figure 7: Cost-effectiveness acceptability curve using ERG preferred base case ICER (Reproduced directly from Company submitted economic model)

Table 26: Scenario analyses applied to the ERG preferred base case analysis

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
ERG preferred base case analysis (no PAS)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term treatment tapering scenarios (base case: none)							
Apply treatment tapering scenario (company preferred application of scenario)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply treatment tapering scenario (ERG preferred application of scenario)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long term loss of fostamatinib response (Base case: Time-points: 1-24m; Missing data: Response loss; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: assume 50/50)							
Time-points: 1-24m; Missing data: Response loss; Transitions to <30 / 30-50: FIT3 data							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time-points: 1-24m; Missing data: Response sustained; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: 50/50							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time-points: 1-24m; Missing data: Response sustained; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: FIT3 data							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time-points: 6-24m; Missing data: Response Lost; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: 50/50							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time-points: 6-24m; Missing data: Response Lost; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: FIT3 data							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time-points: 6-24m; Missing data: Response Sustained; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: 50/50							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time-points: 6-24m; Missing data: Response Sustained; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: FIT3 data							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume long-term fostamatinib extrapolation is equal to the average of previous cycles that used data from FIT1 and FIT2.							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility assumptions (base case: disutility applied for 1 carer for ICH states)							
Disutility applied to 0 carers for ICH health states							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutility applied to 2 carers for ICH health states							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other analyses							
Remove bleed related adverse events (Epistaxis and Petechiae) from adverse event data to reflect that they may be captured within Bleeding event model parameters							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Re-weighting the MRS utilities based on 7.9% with MRS 4 and 5.5% with MRS 5 (Rodriguez-Castro 2019; Dewilde et al. 2019)[36, 48]							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methodological uncertainty							
0% Discount rates applied to costs and outcomes							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6% Discount rates applied to costs and outcomes							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 Conclusions of the cost effectiveness section

The company's base case ICER (original submission) was [redacted] increasing to [redacted] per QALY gained following response to clarification queries. The ERG has corrected several errors in the model formulae calculations that lead to a substantial increase in the ICER compared to that generated using the company submitted model. However, the ERG concludes that even after correction of modelling errors, there remains substantial uncertainty regarding the most plausible base case ICER for decision-making.

The ERG considers the following to represent key issues of uncertainty:

- The economic model assumes that UK standard of care for a patient cohort who have chronic ITP and previously failed or were unsuitable for treatment with TPO-RAs is 'watch and rescue'. The model assumes that no other treatment options, such as rituximab, splenectomy or others would be considered. The approach is in inconsistent with the ERG's understanding of the treatment pathway where all possible treatment options will be exhausted. The ERG therefore considers it unlikely that the modelled treatment pathway is an accurate reflection of the treatment pathway in UK clinical practice.

- The true treatment acquisition costs for fostamatinib are an important determinant of cost-effectiveness and it is unclear what dosage would be more appropriate in real-world clinical practice (mean dosage from the trial or following a strict treatment algorithm as per the company preferred assumptions)

- Long-term effectiveness (transition probabilities) is based on a small sample, with substantial proportion of missing data obtained up to 12 weeks from the FIT1 and FIT2 studies and extrapolated based on a simple average over the model lifetime horizon. The long-term loss of fostamatinib response, based on two-year data from FIT3 is sensitive to assumptions about the calculation approach. Overall, the ERG considers there to be substantial residual

uncertainty regarding the longer-term treatment effectiveness for both arms of the economic model.

- There is likely to be substantial variation across the UK concerning the treatment bundle used for rescue therapy and surgical prophylaxis for chronic ITP patients with low platelet counts. This adds further uncertainty to the most plausible estimate of the ICER

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8 Appendices

Appendix 1 Details of the company's search for ITP studies assessing comparator treatments and for economic evaluations (other than Fostamatinib).

Search strategies for comparator treatments

The company provided details of the search strategies used to identify studies assessing comparator treatments other than fostamatinib at clarification. Although comprehensive in identifying ITP and appropriate publication types, the systematic review reported in section A9 of the company's clarification response is limited by using only drug names as text words to identify comparator treatments, rather than using database index terms to identify classes of drugs. Repeating the company's search with drug classes (monoclonal antibodies, immunosuppressive agents, sulfones, and thrombopoietin receptor antagonists) in Ovid MEDLINE finds an additional 80 results that may be relevant for the scope of this appraisal. Similar differences would be expected for the other sources searched for the systematic review of clinical evidence.

Search strategies for economic evaluations

The company identified 9 studies evaluating the cost-effectiveness of treatments for chronic ITP, other than fostamatinib. The company did not provide sufficient details to replicate the search. It is unclear whether these studies were identified as part of a systematic search or not. However, the identified studies may still be informative for developing the economic model structure and sourcing of parameter data.

Two of the studies evaluated treatments that would be considered 1st line treatments in the UK, and 7 of the studies were of treatments considered as 2nd line treatments (e.g. TPO-RAs) for chronic ITP in the UK. Furthermore, 2 of the studies were UK studies that evaluated the cost-effectiveness of TPO-RAs. Due to the company's positioning of fostamatinib is for those who are refractory to or unsuitable for TPO-RAs, the economic evaluations captured in the review do not match the population in the economic model. Furthermore, none of the economic models were developed after the updated international consensus guidelines document was published (Provan et al.

2019),[13] and therefore, a completely new model was required for the assessment of fostamatinib.

Table 27 Included studies in the systematic review of economic evaluations

Study, year	Perspective	Population	ERG: Relevance to decision problem?	ERG: Relevance to population of economic model?
'Intravenous Immunoglobulin for Treatment of Idiopathic Thrombocytopenic Purpura: Economic and Health Service Impact Analyses', 2008[64]	Canadian publicly funded health care system	Chronic ITP with platelet count <20 x 109/L	No	No, the model structure may be relevant however it is set in Canada and not the UK. Furthermore, the treatment options for chronic ITP (IVIg and Prednisone) in this assessment would only be considered 1st line treatments in the UK and not relevant. The inclusion of splenectomy as a treatment option for those who fail medical treatment may be of relevance to this submission. However, the transition from medical management to splenectomy was not considered in the company submission. This is because splenectomy is not used as frequently anymore in the UK according to the company's clinical expert opinion.
Xie et al., 2009[65]	Same as above.	Same as above.	No	Same as above.
Boyers et al., 2012[66]	UK NHS	Chronic ITP with platelet count <30 x 109/L	No	No, the assessment is of Elthombopag, which is considered a 2nd line treatment in the UK. Whereas the company position Fostamatinib as 3rd line treatment, i.e. for those where TPO-RA is unsuitable or refractory.
Lee et al., 2013[67]	Irish healthcare system	Chronic ITP splenectomised patients who are refractory to other treatments (e.g. corticosteroids, IVIg), and as second-line treatment for adult non-splenectomised patients where surgery is contra-indicated.	No	No, the assessment is of Romiplostin and Elthombopag which is considered a 2nd line treatment in the UK. Whereas the company position Fostamatinib as 3rd line treatment, i.e. for those where TPO-RA is unsuitable or refractory.
Parrondo et al., 2013[68]	Spanish health care payer	Chronic ITP	No	No, the perspective of the analysis was that of Spain, not the UK. Furthermore, the assessment is of TPO-RA treatments which is considered a 2nd line treatment in the UK. Whereas the company position Fostamatinib as 3rd line treatment, i.e. for those where TPO-RA is unsuitable or refractory.

Study, year	Perspective	Population	ERG: Relevance to decision problem?	ERG: Relevance to population of economic model?
Allen et al., 2016[40]	UK NHS	Splenectomised patients with cITP who are refractory to other treatments (e.g. corticosteroids and IVIg) and 2) non splenectomised patients with cITP who are refractory to other treatments (e.g. corticosteroids and IVIg) and in whom splenectomy is contraindicated.	No	No, the assessment is of TPO-RA treatments which is considered a 2nd line treatment in the UK. Whereas the company position Fostamatinib as 3rd line treatment, i.e. for those where TPO-RA is unsuitable or refractory.
Tremblay et al., 2018[69]	US payer	cITP who had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.	No	No because was conducted using US payer perspective and the assessment is of TPO-RA treatments which is considered a 2nd line treatment in the UK. Whereas the company position Fostamatinib as 3rd line treatment, i.e. for those where TPO-RA is unsuitable or refractory.
Pettigrew et al., 2013[70]	Canadian societal	Chronic ITP	No	No, the assessment is conducted from a Canadian perspective, and evaluates Romiplostin which is considered a 2nd line treatment in the UK. Whereas the company position Fostamatinib as 3rd line treatment, i.e. for those where TPO-RA is unsuitable or refractory.
Chiche et al., 2014[71]	French payer	Chronic ITP	No	No, the assessment is conducted from a French payer perspective, and evaluates Romiplostin and Rituximab which are considered a 2nd line treatments in the UK. Whereas the company position Fostamatinib as 3rd line treatment, i.e. for those where TPO-RA is unsuitable or refractory.

Appendix 2 ERG adapted transition probabilities

Table 28 ERG adapted transition probabilities for fostamatinib up to week 24

Baseline -> Week 4						
	Non-response <30x10^9/L	**Partial response 30-50 x10^9/L**	**Response >50 x10^9/L**	**Severe disability post ICH <30x10^9/L**	**Severe disability post ICH 30-50 x10^9/L**	**Severe disability post ICH >50 x10^9/L**
Non-response <30x10^9/L	67.7%	18.9%	13.3%	0.1%	0.0%	0.0%
Partial response 30-50 x10^9/L	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%
Response >50 x10^9/L	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%
Severe disability post ICH <30x10^9/L	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%
Severe disability post ICH 30-50 x10^9/L	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Severe disability post ICH >50 x10^9/L	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
Week 5 - Week 12						
	Non-response <30x10^9/L	**Partial response 30-50 x10^9/L**	**Response >50 x10^9/L**	**Severe disability post ICH <30x10^9/L**	**Severe disability post ICH 30-50 x10^9/L**	**Severe disability post ICH >50 x10^9/L**
Non-response <30x10^9/L	82.1%	10.5%	7.3%	0.1%	0.0%	0.0%
Partial response 30-50 x10^9/L	15.5%	63.2%	21.3%	0.0%	0.0%	0.0%
Response >50 x10^9/L	0.0%	16.8%	83.2%	0.0%	0.0%	0.0%
Severe disability post ICH <30x10^9/L	0.0%	0.0%	0.0%	82.2%	10.6%	7.3%
Severe disability post	0.0%	0.0%	0.0%	15.5%	63.2%	21.3%

ICH 30-50 x10^9/L						
Severe disability post ICH >50 x10^9/L	0.0%	0.0%	0.0%	0.0%	16.8%	83.2%
Week 13 - Week 24						
	Non-response <30x10^9/L	**Partial response 30-50 x10^9/L**	**Response >50 x10^9/L**	**Severe disability post ICH <30x10^9/L**	**Severe disability post ICH 30-50 x10^9/L**	**Severe disability post ICH >50 x10^9/L**
Non-response <30x10^9/L	87.3%	12.6%	0.0%	0.1%	0.0%	0.0%
Partial response 30-50 x10^9/L	12.6%	74.7%	12.6%	0.0%	0.0%	0.0%
Response >50 x10^9/L	2.4%	2.4%	95.1%	0.0%	0.0%	0.0%
Severe disability post ICH <30x10^9/L	0.0%	0.0%	0.0%	87.4%	12.6%	0.0%
Severe disability post ICH 30-50 x10^9/L	0.0%	0.0%	0.0%	12.6%	74.7%	12.6%
Severe disability post ICH >50 x10^9/L	0.0%	0.0%	0.0%	2.4%	2.4%	95.1%

Table 29 ERG adapted transition probabilities for watch and rescue up to week 24

Baseline -> Week 4						
	Non-response <30x10^9/L	**Partial response 30-50 x10^9/L**	**Response >50 x10^9/L**	**Severe disability post ICH <30x10^9/L**	**Severe disability post ICH 30-50 x10^9/L**	**Severe disability post ICH >50 x10^9/L**
Non-response <30x10^9/L	76.1%	23.8%	0.0%	0.1%	0.0%	0.0%
Partial response 30-50 x10^9/L	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%
Response >50 x10^9/L	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%
Severe disability post ICH <30x10^9/L	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%
Severe disability post ICH 30-50 x10^9/L	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Severe disability post ICH >50 x10^9/L	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
Week 5 - Week 12						
	Non-response <30x10^9/L	**Partial response 30-50 x10^9/L**	**Response >50 x10^9/L**	**Severe disability post ICH <30x10^9/L**	**Severe disability post ICH 30-50 x10^9/L**	**Severe disability post ICH >50 x10^9/L**
Non-response <30x10^9/L	88.4%	7.7%	3.8%	0.1%	0.0%	0.0%
Partial response 30-50 x10^9/L	26.1%	69.2%	4.7%	0.0%	0.0%	0.0%
Response >50 x10^9/L	26.1%	69.2%	4.7%	0.0%	0.0%	0.0%
Severe disability post ICH <30x10^9/L	0.0%	0.0%	0.0%	88.5%	7.7%	3.8%
Severe disability post	0.0%	0.0%	0.0%	26.1%	69.2%	4.7%

ICH 30-50 x10^9/L						
Severe disability post ICH >50 x10^9/L	0.0%	0.0%	0.0%	26.1%	69.2%	4.7%
Week 13 - Week 24						
	Non-response <30x10^9/L	**Partial response 30-50 x10^9/L**	**Response >50 x10^9/L**	**Severe disability post ICH <30x10^9/L**	**Severe disability post ICH 30-50 x10^9/L**	**Severe disability post ICH >50 x10^9/L**
Non-response <30x10^9/L	88.4%	7.7%	3.8%	0.1%	0.0%	0.0%
Partial response 30-50 x10^9/L	26.1%	69.2%	4.7%	0.0%	0.0%	0.0%
Response >50 x10^9/L	26.1%	26.1%	47.7%	0.0%	0.0%	0.0%
Severe disability post ICH <30x10^9/L	0.0%	0.0%	0.0%	88.5%	7.7%	3.8%
Severe disability post ICH 30-50 x10^9/L	0.0%	0.0%	0.0%	26.1%	69.2%	4.7%
Severe disability post ICH >50 x10^9/L	0.0%	0.0%	0.0%	26.1%	26.1%	47.7%

Table 30 ERG adapted transition probabilities beyond 24 weeks

Fostamatinib						
	Non-response <30x10^9/L	**Partial response 30-50 x10^9/L**	**Response >50 x10^9/L**	**Severe disability post ICH <30x10^9/L**	**Severe disability post ICH 30-50 x10^9/L**	**Severe disability post ICH >50 x10^9/L**
Non-response <30x10^9/L	80.80%	13.46%	5.63%	0.09%	0.01%	0.01%
Partial response 30-50 x10^9/L	13.69%	70.40%	15.86%	0.01%	0.04%	0.01%
Response >50 x10^9/L	2.24%	2.24%	95.53%	0.00%	0.00%	0.00%
Severe disability post ICH <30x10^9/L	0.00%	0.00%	0.00%	85.90%	12.06%	2.04%
Severe disability post ICH 30-50 x10^9/L	0.00%	0.00%	0.00%	13.40%	71.63%	14.97%
Severe disability post ICH >50 x10^9/L	0.00%	0.00%	0.00%	2.24%	2.24%	95.53%
Watch and rescue						
	Non-response <30x10^9/L	**Partial response 30-50 x10^9/L**	**Response >50 x10^9/L**	**Severe disability post ICH <30x10^9/L**	**Severe disability post ICH 30-50 x10^9/L**	**Severe disability post ICH >50 x10^9/L**
Non-response <30x10^9/L	85.8%	11.1%	3.0%	0.092%	0.0%	0.0%
Partial response 30-50 x10^9/L	26.1%	69.2%	4.7%	0.0%	0.0%	0.0%
Response >50 x10^9/L	26.1%	26.1%	47.7%	0.0%	0.0%	0.0%
Severe disability post ICH <30x10^9/L	0.0%	0.0%	0.0%	88.5%	7.7%	3.8%
Severe disability post ICH 30-50 x10^9/L	0.0%	0.0%	0.0%	26.1%	69.2%	4.7%

Severe disability post ICH >50 x10^9/L	0.0%	0.0%	0.0%	26.1%	26.1%	47.7%

Appendix 3 Surgical prophylaxis

Table 31 List of procedures (admitted patient care) for which rescue treatment would be required as surgical prophylaxis

A Nervous System (A01-A84)	Appropriate (Y/N)	Type of prophylaxis (prednisolone for minor / IVIg for major surgery)
A1 Tissue of brain (A01-A11)	Y	IVIg
A2 Ventricle of brain and subarachnoid space (A12-A22)	Y	IVIg
A3 Cranial nerves (A24-A36)	Y	IVIg
A4 Meninges of brain (A38-A43)	Y	IVIg
A5 Spinal cord and other contents of spinal canal (A44-A57)	Y	IVIg
A6 Peripheral nerves (A59-A73)	Y	IVIg
A7 Other parts of nervous system (A75-A84)	Y	IVIg
B Endocrine System & Breast (B01-B41)		
B1 Pituitary and pineal glands (B01-B06)	Y	IVIg
B2 Thyroid and parathyroid glands (B08-B17)	Y	IVIg
B3 Other endocrine glands (B18-B25)	Y	IVIg
B4 Breast (B27-B41)	Y	IVIg
C Eye (C01-C90)		
C1 Orbit (C01-C08)	Y	Prednisolone
C2 Eyebrow and eyelid (C09-C23)	Y	Prednisolone
C3 Lacrimal apparatus (C24-C29)	Y	Prednisolone
C4 Muscles of eye (C31-C37)	Y	Prednisolone
C5 Conjunctiva and cornea (C39-C51)	Y	Prednisolone
C6 Sclera and iris (C52-C65)	Y	Prednisolone
C7 Anterior chamber of eye and lens (C66-C77)	Y	Prednisolone
C8 Retina, other parts of eye and anaesthetics (C79-C90)	Y	Prednisolone
D Ear (D01-D28)		
D1 External ear and external auditory canal (D01-D08)	Y	Prednisolone
D2 Mastoid and middle ear (D10-D20)	Y	Prednisolone
D3 Inner ear and eustachian canal (D22-D28)	Y	Prednisolone
E Respiratory Tract (E01-E98)		
E1 Nose (E01-E11,E64-E66)	Y	Prednisolone
E2 Nasal sinuses (E12-E17)	Y	Prednisolone
E3 Pharynx (E19-E28)	Y	Prednisolone
E4 Larynx (E29-E38)	Y	Prednisolone
E5 Trachea and bronchus (E39-E52, E67)	Y	Prednisolone
E6 Lung and mediastinum (E53-E63)	Y	Prednisolone
E7 Non operations on lower respiratory tract (E85-E98)	Y	Prednisolone
F Mouth (F01-F63)		
F1 Lip (F01-F06)	Y	Prednisolone
F2 Tooth and gingiva (F08-F20)	Y	Prednisolone
F3 Tongue and palate (F22-F32)	Y	Prednisolone
F4 Tonsil and other parts of mouth (F34-F43)	Y	Prednisolone
F5 Salivary apparatus (F44-F58)	Y	Prednisolone
F6 Other Dental (F63)	Y	Prednisolone
G Upper Digestive Tract (G01-G82)		
G1 Oesophagus including hiatus hernia (G01-G25)	Y	Prednisolone

A Nervous System (A01-A84)	**Appropriate (Y/N)**	**Type of prophylaxis (prednisolone for minor / IVIg for major surgery)**
G2 Stomach pylorus and general upper gastrointestinal tract endoscopy (G26-G48)	Y	Prednisolone
G3 Duodenum (G49-G57)	Y	Prednisolone
G4 Jejunum (G58-G67)	Y	Prednisolone
G5 Ileum (G68-G82)	Y	Prednisolone
H Lower Digestive Tract (H01-H70)		
H1 Appendix (H01-H03)	Y	IVIg
H2 Colon (H04-H32)	Y	IVIg
H3 Rectum (H33-H46)	Y	IVIg
H4 Anus and perianal region (H47-H70)	Y	IVIg
J Other Abdominal Organs - Principally Digestive (J01-J77)		
J1 Liver (J01-J17)	Y	IVIg
J2 Gall bladder (J18-J26)	Y	IVIg
J3 Bile duct (J27-J53)	Y	IVIg
J4 Pancreas (J54-J68)	Y	IVIg
J5 Spleen (J69-J72)	Y	IVIg
J6 Pancreas (J73-J77)	Y	IVIg
K Heart (K01-K78)		
K1 Wall septum and chambers of heart (K01-K24)	Y	IVIg
K2 Valves of heart and adjacent structures (K25-K38)	Y	IVIg
K3 Coronary artery (K40-K51)	Y	IVIg
K4 Other parts of heart and pericardium (K52-K78)	Y	IVIg
L Arteries and Veins (L01- L99,O01-O05,O15,O20)		
L1 Great vessels and pulmonary artery (L01-L13)	Y	IVIg
L2 Aorta (L16-L28)	Y	IVIg
L3 Carotid cerebral and subclavian arteries (L29-L39)	Y	IVIg
L4 Abdominal branches of aorta (L41-L47)	Y	IVIg
L5 Iliac and femoral arteries (L48-L63)	Y	IVIg
L6 Other arteries (L65-L72)	Y	IVIg
L7 Veins and other blood vessels (L73-L99)	Y	IVIg
L8 Overflow arteries and veins (O01-O05, O15,O20)	Y	IVIg
M Urinary (M01-M86)		
M1 Kidney (M01-M17)	Y	Prednisolone
M2 Ureter (M18-M33)	Y	Prednisolone
M3 Bladder (M34-M49)	Y	Prednisolone
‡ M4 Outlet of bladder and prostate (M51-M71)	Y	Prednisolone
M5 Urethra and other parts of urinary tract (M72-M86)	Y	Prednisolone
‡ N Male Genital Organs (N01-N35)		
‡ N1 Scrotum and testis (N01-N13)	Y	Prednisolone
‡ N2 Spermatic cord and male perineum (N15-N24)	Y	Prednisolone
‡ N3 Penis and other male genital organs (N26-N35)	Y	Prednisolone
P Lower Female Genital Tract (P01-P32)		
‡ P1 Vulva and female perineum (P01-P13)	Y	Prednisolone
P2 Vagina (P14-P32)	Y	Prednisolone
Q Upper Female Genital Tract (Q01-Q57)		
‡ Q1 Uterus (Q01-Q21)	Y	Prednisolone
‡ Q2 Fallopian tube (Q22-Q41)	Y	Prednisolone
Q3 Ovary and broad ligament (Q43-Q57)	Y	Prednisolone

A Nervous System (A01-A84)	Appropriate (Y/N)	Type of prophylaxis (prednisolone for minor / IVIg for major surgery)
R Female Genital Tract Associated With Pregnancy Childbirth & Puerperium (R01-R43)		
R1 Fetus and gravid uterus (R01-R12)	Y	Prednisolone
R2 Induction and delivery (R14-R27)	Y	Prednisolone
R3 Other obstetric (R28-R34)	Y	Prednisolone
R4 Obstetric scans and studies (R36-R43)	N	N/A
S Skin (S01-S70)		
S1 Skin or subcutaneous tissue (S01-S63)	Y	Prednisolone
S2 Nail (S64-S70)	Y	Prednisolone
T Soft Tissue (T01-T99)		
T1 Chest wall pleura and diaphragm (T01-T17)	Y	Prednisolone
T2 Abdominal wall (T19-T31,T97-T99)	Y	Prednisolone
T3 Peritoneum (T33-T48)	Y	Prednisolone
T4 Fascia ganglion and bursa (T50-T62)	Y	Prednisolone
T5 Tendon (T64-T74)	Y	Prednisolone
T6 Muscle (T76-T83)	Y	Prednisolone
T7 Lymphatic tissue (T85-T96)	Y	Prednisolone
U Diagnostic Testing & Rehabilitation (U01-U54)		
U1 Diagnostic Imaging (U01-U21)	N	N/A
U2 Diagnostic tests (U22-U40)	Y	Prednisolone
U3 Rehabilitation (U50-U54)	N	N/A
V Bones & Joints Of Skull & Spine (V01-V68)		
V1 Bones and joints of cranium, face and jaw (V01-V21)	Y	IVIg
V2 Bones and joints of spine (V22-V68)	Y	IVIg
W Other Bones & Joints (W01-W99,O06-O10,O17-O19,O21-O27,O29)		
W1 Complex reconstruction of hand and foot (W01-W04)	Y	IVIg
W2 Bone (W05-W36)	Y	IVIg
W3 Joint (W37-W99)	Y	IVIg
W4 Overflow other bones and joints (O06-O10, O17-O19, O21-O27, O29,O32)	Y	IVIg
X Miscellaneous Operations (X01-X97)		
X1 Operations covering multiple systems (X01-X27)	Y	IVIg
X2 Miscellaneous operations (X28-X68)	Y	IVIg
X3 Specified Drug therapy (X70-X98)	N	N/A

Abbreviations: IVIg: Intravenous Immunoglobulin; N/A: Not Applicable;

Appendix 4 Acute stroke care costs.

Table 32 ERG vs. Company preferred approaches to costing of an acute stroke event

Item	ERG interpretation	ERG assessment of definition	Unit cost reported	Year reported	Correct year	ERG preferred unit cost for model	Year	ERG source
Ambulance	*See treat and convey, national average*	*Appropriate*	233/case	2016	2014	258/case	2019	PSSRU Unit costs of health and social care[72]
CT scan	NHS reference costs 2013-2014 RA08A, adult CT one area, no contrast, direct access, age 19+	Appropriate	91/case	2016	2014	78/case	2019	NHS reference costs 2018/19[60] - code RD20A (Computerised Tomography Scan of One Area, without Contrast, 19 years and over) - direct access
Thrombolysis	NHS reference costs 2013-2014 YR23B (day-case); Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4	Appropriate	875/case	2016	2014	1050/case	2019	NHS reference costs 2018/19[60] - code YR23B (Computerised Tomography Scan of One Area, without Contrast, 19 years and over) - direct access; Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4
Acute stroke unit	Average cost per day of a short stay (weighted average of code AA35A-F) *ERG note: not actually*	Cost of a short stay non-elective procedure is appropriate	649/day	2016	2014	£4,751/case	2019	The ERG prefers the use of per case costing taking the weighed average of HRG codes AA35 (a-f), non elective Long stay, weighted across different

	cost per day but rather cost per short stay total							CC scores according to FCEs. The ERG considers the company's approach of costing a full short stay + an additional 18.5 days calculated from a straightforward division of the tariff that in itself couldn't be replicated by the ERG to be inappropriate.
Stroke Unit*	NHS reference costs 2013-2014- average per day cost in non-elective long-stay stroke patient AA35A-F	Not appropriate to cost a short and long stay under the same HRG code. Would be more appropriate to just cost a full event for a non-elective stroke, weighted average across all the appropriate FCE activity	233/day	2016	2014			
Average length of stay	Sentinel 2010 report		19.50			N/A		ERG prefers per case rather than per day costing for the stroke event.
Overall cost per event			£9012			£8,622		

Abbreviations: CC: Complications and co-morbidities; ERG; Evidence Review Group; FCE; Finished Consultant Episodes; HRG; Healthcare Resource Group; N/A: Not Applicable; NHS: National Health Service

Appendix 5 ERG changes to the company submitted economic model

Table 33 ERG changes to the company submitted economic model – corrections and preferred approaches

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
Changes to probability parameters							
Transition probabilities - correction	Data Store	AE120-AH161	**1)** For 'watch and rescue', the company assumed a relative risk of 0.9 would apply to the transition probabilities relative to the available data for fostamatinib. **2)** Transitions were not converted from rates to probabilities for application in the model	The company did not describe or justify the assumed RR in any of the documentation provided.	**1)** Implement the company stated approach as per page 98 of the CS assuming missing transition probabilities are equal to the probability of moving between health states from the next best health state for which data are available **2)** Rates to cycle specific probabilities for application in the model.	N/A	To improve consistency of model and submitted company documentation and to ensure correct methods for converting probabilities over different time frames are applied.
Cycle specific probability of surgery - correction	Data Store & Cost Inputs	Data Store I11-111 & Cost Inputs D-AM234	4/52.143*annual probability of surgery	N/A	Formulae for converting annual probability to monthly probability: p2 = 1-(EXP(-(-(LN(1-p1))*4/52.143))), where p1 is the annual probability.	Briggs et al. 2006[39]	Correction of calculation approach.

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
Probability of outpatient bleed	Quality of Life Inputs & Cost Inputs	Quality of Life Inputs J64-J65, J67-68 & Cost Inputs U159-X160, U162-X163	0.028	Allen et al. 2016,[40] based on the non-splenectomised group	0.0492	Allen et al. 2016,[40]	Average of splenectomised and non-splenectomised from Allen et al. weighted according to proportions of splenectomised / non-splenectomised patients in the FIT1 and FIT2 studies. [40]
Proportion receiving surgical prophylaxis	Data Store	D173-AB174 & A625-AG752	All procedures listed in the Hospital Admitted patient Care Activity report	Hospital Admitted patient Care Activity report, NHS Digital	All procedures requiring prophylaxis based on ERG expert opinion (excludes some diagnostic testing procedures)	Hospital Admitted patient Care Activity report, NHS Digital	ERG clinical expert suggested that not all procedures listed in the report would require surgical prophylaxis.
4 weekly cycle specific probability of adverse events - correction	Data Store	P589-Q606	(n/(24 weeks*N))*4 weeks	N/A	1-EXP(-(-(LN(1-(n/N))/24 weeks)*4 weeks))	N/A	To ensure correct methods for converting probabilities over different time frames are applied.
Mortality risks	Clinical Inputs	E121-S770	p2 = 1-EXP(-(p1^(1/HR), where p2 is the cycle specific mortality;	Not reported	p2 = 1-(EXP(-(-(LN(1-p1))*HR))), where p2 is the cycle	Briggs et al. 2006 [39]	To correct the formulae, the ERG converted the

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
			p1 is the all-cause general population mortality and HR represents the mortality HR for p2 vs. p1 obtained from the literature.		specific mortality; p1 is the all-cause general population mortality and HR represents the mortality HR for p2 vs. p1 obtained from the literature.		probability to a rate as suggested by the company, in accordance with Briggs et al. 2006,[39] and then multiplied that rate by the appropriate HR before re-converting to a probability.
Changes to utility parameters							
Health state utility input values obtained from the literature (age and sex adjustment)	Quality of Life Inputs & Data Store	Quality of Life Inputs H19-20, E26-28, H39-68 , D82-120, & Data Store C757-L789	The company normalised the base utilities to match the baseline age (65) in the model.	Ara and Brazier 2010[73]	All utility sources age and sex adjusted to the model cohort start age	Ara and Brazier 2010[73]	To ensure that all source utilities used in the model are age / sex adjusted to the starting age of the model cohort.
Minor correction of formula on QoL inputs sheet	Quality of Life Inputs	F93 & F98, D115 & D120	Hard coded, not referencing the relevant cell.	N/A	Refencing the appropriate cell	N/A	Correction of formulae.

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
Utility: Non-response <30x10^9/L	Quality of Life Inputs	E26	0.8 (pooled data from 2 sources)	Romiplostim (EQ-5D) and Szende et al. (TTO)[35, 41]	0.762 (single source)	Romiplostim (EQ-5D) [35]	EQ-5D data is more consistent with the NICE reference case.
Utility: Partial response 30-50x10^9/L	Quality of Life Inputs	E27	0.8 (pooled data from 2 sources)		0.762 (single source)		
Utility: Response >50x10^9/L	Quality of Life Inputs	E28	0.84 (pooled data from 2 sources)		0.794 (single source)		
Disutility from hypertension (adverse event)	Quality of Life Inputs	D83 & D105	0.0575	Zhang et al. 2017[74]	0.0375	Sullivan et al 2011 (Supplementary Table 3)[50]	UK value set
Disutility from nausea (adverse event)	Quality of Life Inputs	D84 & D106	0.062	Hagiwara et al. 2019[51]	0.054	Hagiwara et al. 2019 (UK value set, eTable 3) [51]	UK value set
Disutility from fatigue (adverse event)	Quality of Life Inputs	D92 & D114	0.049	Hagiwara et al. 2019[51]	0.056	Hagiwara et al. 2019 (UK value set, eTable 3)[51]	UK value set

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
Disutility from anaemia (adverse event)	Quality of Life Inputs	D97 & D119	0.32 (based on the disutility of severe anaemia only)	Matza et al. 2015	0.220 (based on the average disutility of mild anaemia (0.12) and severe anaemia (0.32))	Matza et al. 2015	The ERG prefer to take the average disutility of having mild and severe anaemia given that both mild and severe AEs were modelled.
Adverse events - correction	Data Store	I-J593, I-L596, I-J600, I603-J604	N/A	N/A	N/A	N/A	Correction to adverse events to match the clinical study reports
Treatment acquisition dose	Cost Inputs	D28-L30	Cycle 1: [redacted] on 100mg BID (model average: [redacted]).	Dosing applied following defined treatment algorithm regarding dose escalation and discontinuation	Cycle 1: [redacted]	Applying the mean dose from FIT 1 and FIT 2	Mean dose is more appropriate for costing purposes
			Cycle 2-3: [redacted] on 100mg BID and [redacted] on 150 mg BID (model average: [redacted])		Cycle 2-3: [redacted]		
			Cycle 4+: [redacted] on 100mg BID and [redacted] on 150mg BID (model average: [redacted])		Cycle 4+: [redacted]		
Rate of compliance	Cost Inputs	F32	96% (treatment acquisition cost adjusted for compliance observed in the trials)	Bussel et al., 2018.[22]	100%	company clarification response document	Mean dose accounts for the treatment compliance.

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
Cost of rescue treatment (cost per unit)							
Intravenous immunoglobulin	Cost Inputs	H42:45 & F43-J43	£1020/20g pack	BNF 2020[56]: Flebogamma DIF 20g/400ml solution for infusion vials (Grifols UK Ltd)	£836 / 20g pack	BNF 2020[56]: Gammaplex 20g/400ml solution for infusion vials (Bio Products Laboratory Ltd)	Cheapest available approach to costing IVIg from the BNF
Platelet transfusion	Cost Inputs	H54-K55	£224.11	2015 costs inflated to 2020 values, based on old NHSBT price lists[54, 75]	£211.26 (cost per units of platelets pooled (1 ATD), item code: BC045)[55]	2020/21 NHSBT price list[55]	More appropriate to use up to date unit cost directly as opposed to inflating old values
Oral prednisolone	Cost inputs	C57-K58	Not included	N/A	£1.90 per pack (Total cost per course: £5.70); Assumes 3 packs of Pevanti 10mg size 30, unit cost £1.90 per package to deliver a total dosage of 1mg per kg over up to 2 weeks.	BNF 2020[58]	ERG clinical expert opinion suggests that oral prednisolone is an appropriate rescue treatment for use in UK clinical practice

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
Dexamethasone	Cost inputs	C60-K61	Not included	N/A	£6.84 (Acquisition cost: £13.68) Assumes a dosage of 40mg per day over 4 days = 160mg dose requirement, made up from 2 packs of 50 tables (2mg) generating total tab dose of 200mg at £6.84 per package.; Dexamethasone 2mg tablets (Alliance Healthcare (Distribution) Ltd)	BNF 2020[59]	ERG clinical expert opinion suggests that dexamethasone is an appropriate rescue treatment for use in UK clinical practice
Cost of surgical prophylaxis	Markov Trace (watch and rescue)	AT9-658 & AW9-658	Company preferred surgical prophylaxis costs equal to the costs of a rescue event	Company KOL input	Company preferred surgical prophylaxis costs calculated assuming oral prednisolone for minor procedures and IVIg for major procedures.	ERG clinical expert opinion input	The ERG believe that the ERG's clinical expert opinion is more reflective of UK clinical practice
Cost of surgical prophylaxis - correction	Markov Trace (watch and rescue)	AW9-658	No discount rate/half-cycle correction was applied to the cost of surgical prophylaxis on the watch and rescue trace.	N/A	Discount the cost of surgical prophylaxis on the watch and rescue arm and apply half-cycle correction.	N/A	ERG correction of calculation error
Rescue treatment dosage							

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
Distribution of different types of rescue therapy	Cost Inputs	Cost Inputs D69-74, I69-74, D89-94 & I89-94	IV Immunoglobulin: 1.00 x 1.1 IV methylprednisolone: 1.00 x 1 Platelet transfusion: 0.20 x 1 Oral Prednisolone: 0.00 Dexamethasone: 0.00 *Proportions scaled up to account for more than one dose of treatment per event (alternative values provided at clarification)	Co. interpretation of relevance of FIT1 and FIT2 rescue treatments to UK clinical practice	IV Immunoglobulin: 0.2975 IV methylprednisolone: 0.0826 Platelet transfusion: 0.0331 Oral Prednisolone: 0.4628 Dexamethasone: 0.1240 *further multiplied by 1.21 to account for potential of multiple treatments per event	ERG interpretation of relevance of FIT1 and FIT2 rescue treatments to UK clinical practice	ERG clinical expert opinion suggests that oral prednisolone and dexamethasone are appropriate rescue treatments for use in UK clinical practice
Platelet transfusion (first unit) Platelet transfusion (subsequent units)	Cost Inputs	D54-E55, E71-F72, D81-82	8 platelet pools, size 2.78x10^9--> 2 platelet pools / 6 hours for 24 hours Note: alternative values provided at clarification not used in base case model)	NHS document, blood components and guidance for their clinical use - treatment pathway for patients with ITP, 2020[76]	1-2 adult platelet pools.	ERGs clinical expert opinion	The company's dosage reflects an unusual scenario (described in the company source as for acute emergency treatment), a management of severe / life threatening bleeding. A lower dose is likely more generalisable to clinical practice.

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
IVIg	Cost inputs	E69-F69 & E89-F89	1g/KG	Based on KOL sought by the company.	1g/KG	ERGs clinical expert opinion	ERGs clinical expert opinion
IV methyl-prednisolone	Cost inputs	D48-G51, E70-F70, D80 & E90-F90	1g/day for 3 days	Based on KOL sought by the company.	10mg/kg per day for 2 days = 10*77.95*2 = 2g	ERGs clinical expert opinion	ERGs clinical expert opinion
Oral prednisolone	Cost Inputs	D58-E58, E73-F73, E93-F93,	Not included	N/A	1mg/KG taken over 1-2 weeks	ERGs clinical expert opinion	ERGs clinical expert opinion
Dexamethasone	Cost Inputs	D61-E61, E74-F74 & E94-F94	Not included	N/A	40mg per day over 4 days	ERGs clinical expert opinion	ERGs clinical expert opinion
Frequency of rescue events calculation	Data Store	H184-I196	Calculated using mean number of people experiencing an event	Table 14.5.1.1 of CSRs	Calculated using mean number of events	Table 14.5.1.1 of CSRs	More appropriate to use the mean number of rescue events because a patient can experience more than 1 rescue event.
Treatment unit cost for bleeding events							

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
Outpatient bleed	Cost Inputs	E158-G158	£441.75 (inflated to 2019: £449.26)	NHS reference costs 2017/2018[62]	£361.80 (Assumes average unit cost for a day case procedure, weighted by activity across currency codes FD03F, FD03G and FD03H (GI bleeds without intervention)	NHS reference costs 2018-19[60]	More appropriate to use the most up to date NHS reference cost.
GI bleed	Cost Inputs	E165-G165	£3474.7 (inflated to 2019: £3533.76); based on HRG codes: FD3A and C Gastrointestinal bleed with Multi- and single interventions (all CC scores). Mean of these	NHS reference costs 2017/2018.[62]	£2,992.13; based on average unit cost for non-elective long stay admissions, weighted by activity across currency codes FD03A to FD03E (All GI bleed codes with single or multiple intervention, all CC scores)	NHS reference costs 2018-19[60]	More appropriate to use the most up to date NHS reference cost.
ICH	Cost Inputs	E172-G172	£5,204.00 (inflated to 2019: £5,292.45); based on HRG codes AA23C and B - Haemorrhagic Cerebrovascular Disorders with CC Score 14+ and 10-13	NHS reference costs 2017/2018.[62]	£4,098.84; based on average unit cost for non-elective long stay admissions, weighted by activity across currency codes AA23C to AA23G (Haemorrhagic Cerebrovascular disorders, all CC scores)	NHS reference costs 2018-19[60]	More appropriate to use the most up to date NHS reference cost.

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
Inpatient other bleed	Cost Inputs	E179-G179	£2082.00 (inflated to 2019: £2117.39); based on weighted average of FD3A and C GI bleed with Multi- and single interventions, and without interventions (low CC score).	NHS reference costs 2017/2018[62]	£1,217.89; Based on average unit cost for non-elective short stay admissions, weighted by activity across currency codes FD03B and FD03E (GI bleed codes with single or multiple intervention, low CC scores only)	NHS reference costs 2018-19[60]	More appropriate to use the most up to date NHS reference cost.
Haematologist consultation	Cost Inputs	E186-G186	£159.65 (inflated to 2019: £176.90); Based on code 303 Clinical Haematology, Consultant led: First Attendance Non-Admitted Face to Face	NHS reference costs 2017/2018. [62] and NICE TA293 2013[18]	£173; Based on consultant led outpatient consultation, service code: 303, haematology, consultant led)	NHS reference costs 2018-19[60]	More appropriate to use the most up to date NHS reference cost.
Unit cost of stroke acute care							
Ambulance	Data Store	D253-F253	£246.99	Sentinal Stroke National Audit 2016[77]	£258/case	NHS reference costs 2018-19[60]	ERG considers it more appropriate to use the most up to date unit costs and to apply full HRG cost per event as opposed to developing costs using cost per day.
CT scan	Data Store	D254-F254	£96.46*		£78/case		
Thrombolysis	Data Store	D255-F255	£927.53		£1050/case		
Acute stroke unit / day	Data Store	D256-F256	£687.97		£4,751/case		
Stroke unit / day	Data Store	D257-F257	246.99*				
Costs of stroke rehabilitation (£/hour)							

Item	Tab	Cell (ERG model)	Company preferred approach / parameter value	Company reference	ERG preferred approach / parameter value	ERG reference	ERG justification for amendment
Occupational therapy	Data Store	D264	£74; based on HRG code A06A1 , community health services occupational therapist with adult one to one, per visit	NHS reference costs 2013-2014	£83; based on HRG code A06A1 , community health services occupational therapist with adult one to one, per visit	Updated NHS reference costs 2018/19[60]	ERG considers it more appropriate to use the most up to date unit costs.
Physiotherapist	Data Store	E264	£52	NHS reference costs 2013-2014 WF01B (Actually A08A1)[78]	£63	Updated NHS reference costs 2018/19[60]	
Speech and Language	Data Store	F264	£84	NHS reference costs 2013-2014 A13A1[78]	£107	Updated NHS reference costs 2018/19[60]	
Psychotherapy	Data Store	G264	£61	ESD Psychologist per hour (PSSRU 2014)[79] - assume 1 hour of time required per patient	£99.50	PSSRU 2019.[72] Band 8C £90, D £109 clinical psychologist consultant	

*Incorrectly obtained from the source. (Reported as 2016, but actually 2014 values)

Abbreviations: ATD: Adult Therapeutic Dose; BID: bis in die (twice daily); BNF: British National Formulary; CC: Complications and comorbidities; CS: Company Submission; EQ-5D: EuroQol - 5 Dimension; ERG: Evidence Review Group; ESD: Early Supported Discharge; FIT: Fostamatinib for Immune Thrombocytopenia; GI: Gastrointestinal; HR: Hazard Ratio; ICH: Intracranial Haemorrhage; IV: Intravenous; IVIg: Intravenous Immunoglobulin; ITP: Immune Thrombocytopenia; KOL: Key Opinion Leader; mRS: modified Rankin Scale; N/A: Not Applicable; NHS: National Health Service; NHSBT: NHS Blood and Transplant; QoL: Quality of Life; PSSRU: Personal Social Services Research Unit.

Appendix 6 Cost-effectiveness analyses using the company's proposed PAS price

Table 34 below reproduces Table 22 (Chapter 5) of the ERG report, implementing the same analyses but using the company's proposed PAS price discount for fostamatinib.

Table 34 Company conducted analyses using PAS price (applied individually)

	Total Costs (£)	Total LYG	Total QALY	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Revised base case post-clarification (deterministic)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,255
Using an average of early phase transitions to project future fostamatinib transitions							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,841
Apply age-adjusted health state utilities to the model trace							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,464
Apply trial-based probabilities of watch and rescue, assuming only IVIG, platelets and IV methylprednisolone would be used in UK clinical practice							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,109

Table 35 Cumulative impact of ERG preferred assumptions on the ICER (using PAS price)

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Company submissions							
Company preferred base case analysis (original submission)							
Watch and Rescue	NR	NR	NR	NR	NR	NR	NR
Fostamatinib	NR	NR	NR	NR	NR	NR	NR
Company preferred base case analysis (revised submission following clarification)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,255
ERG correction of model errors							
Apply discounting and half cycle correction to surgical prophylaxis costs on the watch and rescue trace							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,097
ERG correction of data input on QoL inputs sheet							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,098

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
ERG correction to apply the costs of adverse events for the full 35 year time horizon on the fostamatinib trace							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,099
ERG correction to formula for application of mortality HR							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£76,366
ERG correction to calculation of rescue events (accounting for the fact that any person may have more than 1 rescue event)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£71,197
ERG correction to the reporting of adverse events to ensure consistency with FIT1 / FIT2 clinical study reports							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£71,438
ERG correction to formula applying the 4-weekly probability of adverse events							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£72,130

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
ERG correction to transition probability calculations and applying assumptions consistent with the company submission where data do not exist to populate a transition							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£82,850
ERG corrections of all other cycle specific probabilities to ensure that data are converted to rates before manipulation							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£80,408
ERG preferred data and assumptions (Costs)							
Updated unit costs of bleeding events, haematologist consultation, acute stroke care and stroke rehabilitation to use 2019 NHS reference cost values where available							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,629
Use mean dosage of Fostamatinib from trials to determine treatment acquisition costs							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£97,261

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Assume compliance parameter =1, given that mean dosage is applied							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£103,491
Apply ERG preferred distribution of rescue therapy (sourced from FIT1 and FIT2 trials), including treatments such as dexamethasone and oral prednisolone							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£123,995
Apply ERG preferred rescue medication unit costs, applying lowest cost approach from BNF to attain required dosage							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£125,574
Apply ERG preferred rescue medication dosing for rescue medication (based on ERG clinical expert opinion)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£125,913

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Apply ERG preferred proportion of admitted patient procedures that would require surgical prophylaxis (based on ERG clinical expert opinion)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£126,672
Apply ERG preferred use of rescue medication and dosage for surgical prophylaxis, based on assumptions about which procedures are most commonly minor (oral prednisolone) or major (IVIg)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£125,787
ERG preferred data and assumptions (utilities)							
Age adjust utilities on the model trace							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£131,592
Apply ERG preferred utility input data							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£138,743

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Age adjust utility input sources							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£140,951
Other parameters / adjustments							
ERG preferred outpatient-bleeding data (weighted of splenectomised / non-splenectomised patients) from Allen et al.							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£143,790
ERG preferred base case analyses							
Deterministic							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£143,790
Probabilistic							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£164,792

Table 36 Exploratory analyses applied individually to ERG preferred base case analysis using PAS price

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
ERG preferred base case analysis (with PAS)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£143,790
Long term treatment tapering scenarios (base case: none)							
Apply treatment tapering scenario (company preferred application of scenario)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£105,853
Apply treatment tapering scenario (ERG preferred application of scenario)							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£119,407
Long term loss of fostamatinib response (Base case: Time-points: 1-24m; Missing data: Response loss; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: assume 50/50)							
Time-points: 1-24m; Missing data: Response loss; Transitions to <30 / 30-50: FIT3 data							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£145,886

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time-points: 1-24m; Missing data: Response sustained; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: 50/50							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£121,397
Time-points: 1-24m; Missing data: Response sustained; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: FIT3 data							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£122,337
Time-points: 6-24m; Missing data: Response Lost; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: 50/50							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£135,797
Time-points: 6-24m; Missing data: Response Lost; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: FIT3 data							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£134,836
Time-points: 6-24m; Missing data: Response Sustained; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: 50/50							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£115,345

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Time-points: 6-24m; Missing data: Response Sustained; Transitions to <30 x 10^9/L / 30-50 x 10^9/L: FIT3 data							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£114,994
Assume long-term fostamatinib extrapolation is equal to the average of previous cycles that used data from FIT1 and FIT2.							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£164,284
Utility assumptions (base case: disutility applied for 1 carer for ICH states)							
Disutility applied to 0 carers for ICH health states							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£159,423
Disutility applied to 2 carers for ICH health states							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£130,950

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Other analyses							
Remove bleed related adverse events (Epistaxis and Petechiae) from adverse event data to reflect that they may be captured within Bleeding event model parameters							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£142,515
Methodological uncertainty							
0% Discount rates applied to costs and outcomes							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£115,456
6% Discount rates applied to costs and outcomes							
Watch and Rescue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Fostamatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£163,677