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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Review

Dasatinib for the first-line treatment of chronic myeloid leukaemia (part review of TA251) [ID1014]

The following documents are made available to the consultees and commentators:

1. **CDF committee meeting slides** prepared by NICE project team

2. **Company submission – dasatinib (part review of TA251) [ID1014]** from Bristol Myers Squibb

3. **Patient group, professional group and NHS organisation submission** from:
   - **CML Support Group**
   - **Leukaemia CARE**
   - **NCRI-ACP-RCP**
   - **The Royal College of Pathologists**

4. **Expert personal perspectives** from:
   - **Clinical expert**, nominated by the Royal College of Physicians
   - **Patient expert**, nominated by the CML Support Group

5. **Evidence Review Group report** prepared by the Decision Support Unit

6. Evidence Review Group report – **factual accuracy check & ERG responses**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Handouts for the public

Dasatinib for treatment of chronic myeloid leukaemia

Cancer Drug Fund rapid reconsideration of TAs 241 and 251
29 September 2016

- Evidence Review Group: Decision Support Unit
- Company: Bristol-Myers Squibb

Chronic myeloid leukaemia (CML)

- Myeloproliferative disorder of pluripotent haemopoietic stem cells caused by chromosomal translocation
- Approx 95% of people have a “Philadelphia chromosome” with a fusion oncogene called BCR-ABL which produces a overactive tyrosine kinase
- Approx 560 - 800 new cases per year in UK (c.2660 prevalent cases in England and Wales)
- Slowly progressive – 3 phases:
  - chronic phase
  - accelerated phase
  - blast crisis (transformation)

Dasatinib

- Oral agent
- 100mg a day for first-line CML
- 140mg a day for imatinib-resistant CML
- Tyrosine kinase inhibitor
- Marketing authorisation for the treatment of ‘adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia in the chronic phase’ and ‘adult patients with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate’.

Previous appraisals (1)

- TA 251: Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of CML
  - Standard dose imatinib and nilotinib were recommended for the first line treatment of people with chronic phase CML
  - **Dasatinib not recommended** as it was similar in efficacy to nilotinib but more expensive (due to nilotinib PAS)
  - Dasatinib was either dominated by nilotinib or ICERs > £300,000/QALY gained versus imatinib in Assessment Group's scenarios

Previous appraisals (2)

- TA 241: Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML, and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance
  - Nilotinib was recommended for second-line treatment of chronic or accelerated phase CML
  - High-dose imatinib was dominated and not recommended
  - **Dasatinib not recommended**; committee considered estimated ICERs were higher than acceptable for the NHS, and were highly likely to be above the figures suggested
  - Committee agreed no good evidence to distinguish clinically between dasatinib and nilotinib; conclusion supported by the clinical specialists

Appraisal timeline

- TA 241 (Second-line) published 13th January 2012
- TA 251 (First-line) published 25th April 2012
- Full economic analysis submitted for rapid reconsideration (March 2016)
  - On advice from NICE – abbreviated submission with a cost-minimisation analysis was resubmitted (May 2016)
- **Company says:** “cost-minimisation analysis appropriate as original submission concluded that nilotinib and dasatinib had similar clinical effectiveness profiles”

Company clinical evidence

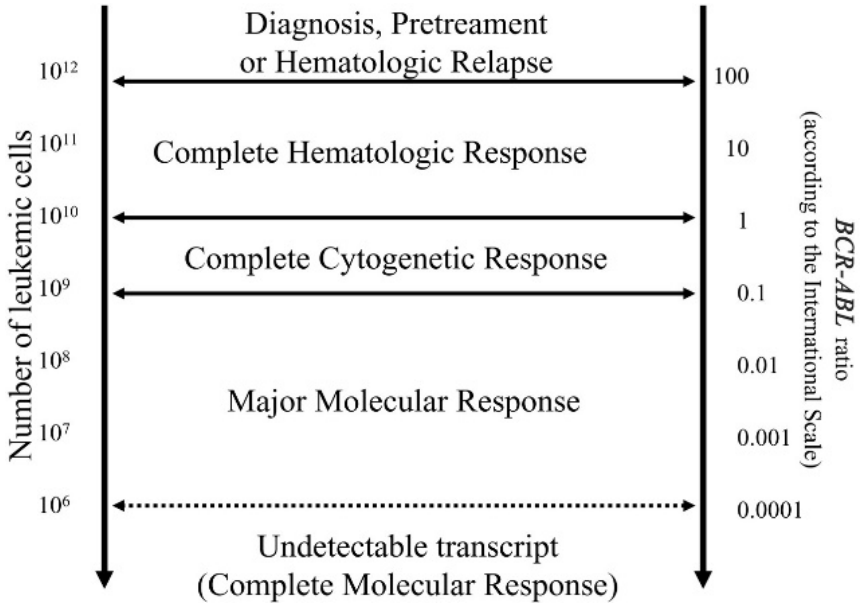
- Additional follow-up data of trials presented in original submission
- Surrogate outcomes used to predict long-term clinical effectiveness
- Systematic literature review / network meta-analysis of indirect comparisons

DSU concludes:

- “no new data that would change the conclusions that there is insufficient evidence to distinguish between dasatinib and nilotinib treatment”

Surrogate outcomes

- Complete Cytogenetic Response (CCyR) and Major Molecular Response (MMR) outcomes used
- TA251 – 4.3.8: “Committee accepted…that people with either a complete cytogenetic response or major molecular response after 12 months experienced better long-term survival”



Overview of indirect comparisons (1st line)

Study	Therapy	Probability of response by 12 months	
		CCyR	MMR
Oxford Outcomes 2013 – MTC (BMS-sponsored)	Dasatinib 100mg	77.1% (67.2–85.3)	51.1% (43.9–58.5)
	Nilotinib 600mg	77.7% (64.8–87.7)	58.7% (49.6–67.5%)
	Nilotinib 800mg	75.3% (61.0–86.1)	57.8% (48.7–66.8)
Abacus 2016 – NMA (BMS-sponsored)	Dasatinib 100mg	XXXX	XXXX
	Nilotinib 600mg	XXXX	XXXX
	Nilotinib 800mg	XXXX	XXXX
PenTAG 2012 – MTC	Dasatinib 100mg	82.3 (SE:0.020)	44.0 (SE: 0.027)
	Nilotinib 600mg	81.7 (SE: 0.019)	46.0 (SE: 0.026)
Analysis Group 2014 – NMA (Novartis-sponsored)	Dasatinib 100mg	-	44.8% (35.2–54.5)
	Nilotinib 600mg	-	55.2% (9.5–60.9)
Analysis Group 2011 – MAIC (Novartis-sponsored)	Dasatinib 100mg	83.4% (NR)	45.9% (NR)
	Nilotinib 600mg	80.9% (NR)	56.8% (NR)
Analysis Group 2015 – MAIC (Novartis-sponsored)	Dasatinib 100mg	-	45.9% (NR)
	Nilotinib 600mg	-	56.1% (NR)

CCyR: complete cytogenetic response; MMR: Major Molecular Response; MAIC: matching-adjusted indirect comparison; NMA: network meta-analysis; MTC: Mixed-treatment comparison

Adverse events (1st line)

- new 60 month time-point from the DASISION study
- serious adverse events higher in dasatinib compared to imatinib
- TA251 – 4.3.9: “although dasatinib and nilotinib were associated with different adverse effects, tolerability was similar between both drugs”

	12 months follow-up		60 months follow-up	
	Dasatinib	Imatinib	Dasatinib	Imatinib
Neutropenia (Grade 3 & 4)	20.9%	20.2%	XXXX	XXXX
Thrombocytopenia (Grade 3 & 4)	19.0%	10.1%	XXXX	XXXX
Anaemia (Grade 3 & 4)	10.1%	7.0%	XXXX	XXXX
Pleural effusion (All grades)	10.1%	0.0%	28.3%	0.8%

Naïve Comparison at 24 months (2nd line)

Study	Therapy	Achieved response		Survival	
		CCyR	MMR	OS	PFS
Chronic phase CML					
CA180-034	Dasatinib 140mg OD	50.3%	38.2%	94%	75%
START-R[a]	Dasatinib 70mg BD	43.5%	28.7%	NR	86%
NCT00109707	Nilotinib 800mg	44%	27.9%	87%	64%
Accelerated Phase CML					
CA180-035	Dasatinib 140mg OD	32.3%	-	63.4%	51.0%
Le Coutre (2012)	Nilotinib 800mg	21%	-	70%	33%
Blast Phase CML					
CA180-035 (Myeloid)	Dasatinib 140mg OD	XXXX	XXXX	XXXX	XXXX
CA180-035 (Lymphoid)	Dasatinib 140mg OD	XXXX	XXXX	XXXX	XXXX

CCyR: complete cytogenetic response; MMR: Major Molecular Response; OS: Overall survival; PFS: progression-free survival; OD: once-daily; BD: bi-daily

[a]START-R only assessed people with imatinib resistance (not intolerance) - previous AGs had identified a number of methodological limitations and a high level of asymmetric crossover

Company cost evidence

- Cost-minimisation analysis against imatinib and nilotinib
  - takes into account a proposed simple patient access scheme (PAS) – a discount of XXX from list price
- The Company says:
  - ensures that nilotinib and dasatinib are comparable in costs
  - when dasatinib and nilotinib discounts are applied, dasatinib can be considered to be cost saving versus nilotinib
  - significant advantages to the NHS in the availability of dasatinib, where evidence suggests efficacy comparable to nilotinib, with a lower acquisition cost

Cost-minimisation results (non-PAS)

- Both dasatinib and nilotinib are supplied with a PAS which are commercial in confidence
- For illustration purposes an analysis has been provided comparing the list prices of the treatments

Intervention	Monthly cost (£)	Incremental cost of dasatinib (£)
first-line CML treatment		
Dasatinib 100mg	£2,541.49	N/A
Imatinib 400mg	£1,863.26	£678.23
Nilotinib 600mg	£2,644.64	-£103.15
second-line CML treatment		
Dasatinib 140mg	£2,541.49	N/A
Imatinib 600mg[a]	£2,794.86	-£253.37
Imatinib 800mg[a]	£3,726.48	-£1,184.99
Nilotinib 800mg	£2,644.64	-£103.15

[a]High dose imatinib was assessed but not recommended for second-line CML in TA 241

Cost-minimisation results (PAS)

- The company inferred a PAS discount of XXX for nilotinib

Intervention	Monthly cost (£)	Incremental cost of dasatinib (£)
first-line CML treatment		
Dasatinib 100mg (PAS)	£XXXX	N/A
Imatinib 400mg	£1,863.26	£XXXX
Nilotinib 600mg (inferred PAS)	£XXXX	£XXXX
Nilotinib 600mg (PAS)	Confidential	Confidential
second-line CML treatment		
Dasatinib 140mg (PAS)	£XXXX	N/A
Imatinib 600mg[a]	£2,794.86	£XXXX
Imatinib 800mg[a]	£3,726.48	£XXXX
Nilotinib 800mg (Inferred PAS)	£XXXX	£XXXX
Nilotinib 800mg (PAS)	Confidential	Confidential

[a]High dose imatinib was assessed but not recommended for second-line CML in TA 241

DSU critique of cost evidence

DSU noted:

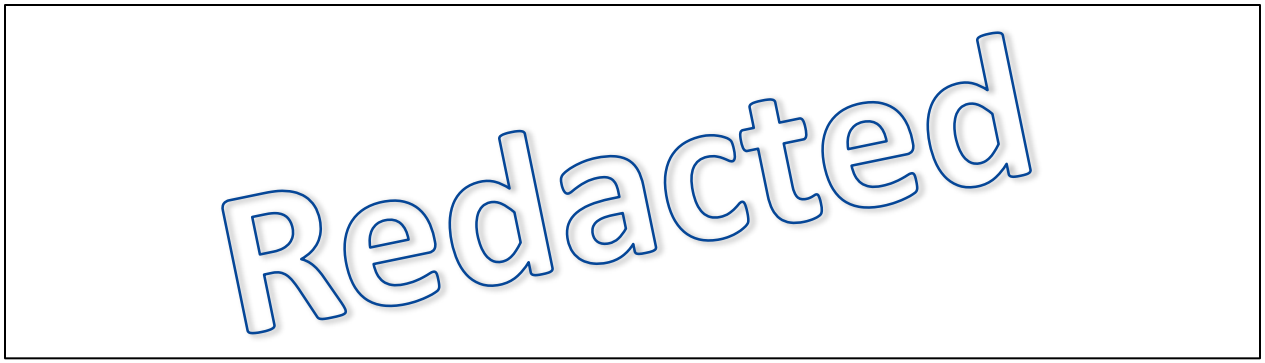
- Cost-minimisation analysis requires equivalence of all health outcomes and treatment costs other than drug acquisition
- New sequence of treatments may become clinically relevant – for example:

Imatinib →	nilotinib →	dasatinib →	SCT/HU
Imatinib →	dasatinib →	nilotinib →	SCT/HU
Nilotinib →	dasatinib →	imatinib →	SCT/HU
Dasatinib→	nilotinib →	imatinib →	SCT/HU

DSU review of uncertainty

- 1st line serious adverse events higher for dasatinib than imatinib
- mean treatment duration differs in original AG model for 1st line CML – imatinib: 7.1yrs; dasatinib: 7.8yrs; nilotinib: 9.0yrs
- non-significant differences in relative efficacy of dasatinib and nilotinib
- relationship between survival and surrogate outcomes uncertain

Submitted analysis



DSU assessment of evidence

- full cost-effectiveness analysis with probabilistic sensitivity analysis would be required to identify and quantify any significant uncertainty

Key issues for consideration

- Are the assumptions in the cost-minimisation analysis appropriate?
  - Is it plausible that dasatinib is not significantly different to nilotinib?
- Are there any other factors that should be taken into account?

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Single technology appraisal

Dasatinib (Sprycel®) for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase

Company evidence submission

August 2016

File name	Version	Contains confidential information	Date
		Yes/no	

Contents

Tables and figures

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Abbreviations

AE	Adverse events
AIC	Akaike Information Criterion
ALL	Acute lymphoblastic leukaemia
AlloSCT	Allogenic stem cell transplant
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
AP	Accelerated phase
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
BCR-ABL	BCR (breakpoint cluster region) and ABL (Abelson) fusion protein
BNF	British National Formulary
BP	Blast phase
cCCyR	Confirmed complete cytogenetic response
CCyR	Complete cytogenetic response
CDF	Cancer Drugs Fund
CHR	Complete haematological response
CI	Confidence interval
CML	Chronic myeloid leukaemia
CMR	Complete molecular response; decrease of 4.5 log below the standard baseline
CP	Chronic phase
CrI	Credible intervals
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ELN	European LeukemiaNet
ESMO	European Society for Medical Oncology
FFS	Failure-free survival
FISH	Fluorescence in situ hybridisation
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HRQoL	Health-related quality-of-life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
INR	International normalized ratio
ITT	Intent-to-treat
LY	Life year
MAIC	Matching-adjusted indirect comparison
MCyR	Major cytogenetic response
MI	Myocardial infarction
MIMS	Monthly Index of Medical Specialities
MMR	Major molecular response; decrease of 3.0 log below the standard baseline
$MR^{3.0}$	Major molecular response; decrease of 3.0 log below the standard baseline
$MR^{4.0}$	Decrease of 4.0 log below the standard baseline
$MR^{4.5}$	Complete molecular response; decrease of 4.5 log below the standard baseline
MTA	Multiple Technology Appraisal
NICE	National Institute for Health and Care Excellence

NMA	network meta-analysis
OD	Once daily
OR	Odds ratio
OS	Overall survival
PAS	Patient access scheme
PCR	Polymerase chain reaction
PCyR	Partial cytogenetic response
PenTAG	Peninsula Technology Assessment Group
PFS	Progression-free survival
Ph+	Philadelphia chromosome positive
PSA	Probabilistic sensitivity analysis
PTT	Partial thromboplastin time
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RFS	Relapse-free survival
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
TFS	Transformation-free survival
TA	Technology Appraisal
TKI	Tyrosine kinase inhibitors
ULN	Upper limit of normal
WBC	White blood cell

1. Executive summary

1.1 Statement of decision problem

NICE has previously assessed the use of dasatinib, nilotinib and imatinib for the treatment of newly diagnosed chronic myeloid leukaemia (CML) as part of TA251.[1] Currently, the NICE pathway specifies use of imatinib and nilotinib as the recommended first-line tyrosine kinase inhibitors (TKIs), and nilotinib as the recommended second-line TKI.[2]

Previous NICE appraisals have reviewed the clinical effectiveness evidence for dasatinib versus nilotinib and imatinib. During the undertaking of TA251, the Appraisal Committee concluded that the available evidence suggests that dasatinib and nilotinib provided superior clinical benefit, as measured by surrogate outcome measures, to standard-dose imatinib in the first-line treatment of people with chronic phase CML.[1] The Appraisal Committee also concluded from indirect comparisons that dasatinib and nilotinib could be considered equally as effective in treating newly diagnosed CML.[3] However in this appraisal, nilotinib was made available to the NHS at a discounted price, which enabled the Committee to approve nilotinib for use in this setting.

Given the evidence that dasatinib and nilotinib demonstrate comparable efficacy, the dasatinib PAS has been designed to [redacted]. A dasatinib PAS discount of [redacted] has been applied, which we believe is comparable to that of nilotinib, as inferred from publically available incremental cost-effectiveness ratio (ICERs) in previous health technology assessments (HTAs).[1,4-6] When dasatinib and nilotinib discounts are applied, dasatinib can be considered to be [redacted] versus nilotinib and imatinib. Thus, there are significant advantages to the NHS in the availability of dasatinib, where evidence suggests efficacy is higher than imatinib and comparable to nilotinib, [redacted].

1.2 Description of the technology being appraised

Table 1. Technology being appraised

UK approved name and brand name	Dasatinib (Sprycel®)
Marketing authorisation/CE mark status	Dasatinib received marketing authorisation on 20 November 2006 for the treatment of adult patients with CML or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy including imatinib mesilate.[7] Subsequently, the licensed indication for dasatinib was extended on 6 December 2010 to include the treatment of adult patients with newly diagnosed Ph+ CP CML.[8]
Indications and any restriction(s) as described in the summary of product characteristics	Dasatinib (Sprycel®)[7] is indicated for the treatment of adult patients with: • Newly diagnosed Ph+ CML in CP. • CP, AP or BP CML with resistance or intolerance to prior therapy including imatinib mesilate. • Ph+ ALL and lymphoid blast CML with resistance or intolerance to prior

	therapy. This submission focuses on the use of dasatinib for the treatment of adult patients with newly-diagnosed Ph+ CP CML. For clarity, the use of dasatinib for the treatment of adult patients with CML who are resistant or intolerant to prior therapy is considered within a separate submission.
Method of administration and dosage	The recommended starting dose for CP CML is 100 mg dasatinib once daily, administered orally[7]

1.3 Administration and costs of the technology

Table 2. Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	20 mg, 50 mg, 80 mg, 100 mg and 140 mg film-coated tablets[7]	
Acquisition cost (excluding VAT) *	List price: £2,504.96	MIMS[9]
	[redacted]	[redacted]
Method of administration	Oral[7]	
Doses	The recommended starting dose for chronic phase CML is 100 mg dasatinib once daily, administered orally[7]	
Dosing frequency	Once-daily[7]	
Average length of a course of treatment	Not applicable	
Average cost of a course of treatment	Not applicable	
Anticipated average interval between courses of treatments	Not applicable	
Anticipated number of repeat courses of treatments	Not applicable	
Dose adjustments	Dose escalation[7] In clinical studies in adult CP CML patients, dose escalation to 140 mg once daily was allowed in patients who did not achieve a haematological or cytogenetic response at the recommended starting dose. Dose reduction[7] Guidelines for dose adjustments to allow management of adverse reaction are specified in the SPC, and include reductions to 80 mg and 50 mg.	
Anticipated care setting	It is anticipated that dasatinib therapy would be initiated by a specialist.	

CML: chronic myeloid leukaemia; CP: chronic phase; MIMS: Monthly Index of Medical Specialities; PAS: Patient Access Scheme; SPC: Summary of Product Characteristics.

Table 3. The decision problem

	Final scope issued by NICE*	Decision problem addressed in the company submission	Rationale if different from the final NICE scope*
Population	Adults with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia in the chronic phase.	Adults with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia in the chronic phase.	Not applicable
Intervention	Dasatinib (Sprycel®)	Dasatinib (Sprycel®)	Not applicable
Comparator (s)	The interventions will be compared with each other, in line with their marketing authorisations.	Imatinib (Glivec®) and nilotinib (Tasigna®)	Not applicable
Outcomes	The outcome measures to be considered include: • event-free survival • progression-free survival • time to progression • overall survival • response rates: cytogenetic, molecular and haematological • time to treatment failure • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • Progression-free survival • Time to progression • Overall survival • Response rates: cytogenetic, molecular and haematological • Adverse effects of treatment	Available clinical data is presented where available.
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.	Cost-comparison analysis predicated on the clinical conclusions drawn during TA251 and the finding that these conclusions remain unchanged.	Not applicable
Subgroups to be considered	If evidence allows, the appraisal will consider subgroups based on people with and without genetic mutations.	None	Not applicable
Special considerations including issues related to equity or equality	None specified in previous scope.	None	Not applicable

* Scope issued by NICE unavailable at time of submission preparation. Decision problem addressed in the company submission is based on the final scope issued for TA251.[1]

1.4 Summary of the clinical effectiveness analysis

During the undertaking of TA251, the Appraisal Committee concluded that the available evidence suggests that dasatinib and nilotinib provided superior clinical benefit, as measured by surrogate outcome measures, to standard-dose imatinib in the first-line treatment of people with chronic phase CML.[1] The Appraisal Committee also concluded from indirect comparisons that dasatinib and nilotinib could be considered equally as effective in treating newly diagnosed CML.[3] However, a Patient Access Scheme (PAS) discount was made available for nilotinib but not for dasatinib; this enabled the Committee to approve nilotinib for use in this setting.[1] Evidence presented within this submission supports these conclusions.

Several clinical trials have demonstrated that patients receiving dasatinib have significantly superior clinical outcomes compared with those receiving imatinib, with more patients achieving cytogenetic and molecular responses.[9] Additionally, these responses are achieved earlier in dasatinib-treated patients, and are highly durable.[10] Although there are no trials directly comparing dasatinib and nilotinib, indirect comparisons broadly confirm NICE TA251 conclusions that dasatinib and nilotinib could be considered equally as effective in treating CML.[3]

Dasatinib is well-tolerated;[11] as shown in Table 9, the majority of drug-related adverse events (AEs) were grade 1–2 in severity and occurred within the first 12 months.[9, 10] As with all TKIs, the main AEs were haematological; while the incidence of grade 3–4 neutropenia was comparable between the groups, grade 3–4 thrombocytopenia and anaemia events were more frequent in the dasatinib arm. Of the non-haematological AEs occurring in at least 10% of patients, most occurred less frequently among patients receiving dasatinib than those receiving imatinib, including nausea, vomiting, muscle inflammation, rash and fluid retention.[9]

Pleural effusions are known to be associated with dasatinib treatment,[11, 12] and these were reported more frequently in patients receiving dasatinib.[9] However, these events were commonly low grade and can be managed in the majority of cases without the requirement for treatment discontinuation.[9, 11, 12] Additionally, occurrence of pleural effusion does not appear to affect attainment of cytogenetic and molecular responses, with high rates reported at both 12 and 60 months of follow-up.[9, 10]

In addition, dasatinib demonstrates a reassuring cardiovascular safety profile. A recent pooled analysis concluded that in the dasatinib global clinical trial populations (CML, Ph+ ALL and castration-resistant prostate cancer), the rate of cardiovascular ischaemic events was not higher than expected when compared with comparator CML or prostate cancer populations.[13] This is in contrast with the known cardiovascular safety signal associated with other TKI treatments.

In summary, patients receiving dasatinib have significantly superior clinical outcomes compared with those receiving imatinib, and dasatinib and nilotinib can be considered equally as effective, in treating newly diagnosed CML. No new data has been identified to change the conclusions drawn by the Appraisal Committee during TA251.

1.5 Summary of the cost-effectiveness analysis

Based on the above, a cost-comparison analysis versus imatinib and nilotinib is presented, noting that versus imatinib this is highly conservative due to the demonstrated superiority of dasatinib versus imatinib. Savings of up to [redacted] per patient are anticipated, driven by the [redacted] of dasatinib versus both imatinib and nilotinib.

2. Health condition and position of the technology in the treatment pathway

CML is a myeloproliferative disorder characterised by increased production of granulocytes in the blood and bone marrow,[1,10] diagnosed in 624 patients in England during 2013.[11] CML has three phases: CP, AP and BP.[1] During CP, patient symptoms are often mild and non-specific, including fatigue, weight loss, night sweats, anaemia, a feeling of 'fullness' and a tender lump on the left side of the abdomen caused by enlargement of the spleen. Around 90% of CML is diagnosed during the CP, and the duration of this phase can vary between patients. CML may then progress to AP, which is characterised by more rapid disease progression and immature blast cells proliferate in the blood and bone marrow. As the patient enters BP, blast proliferation rapidly increases, and life expectancy is reduced to around 3–6 months.[1]

More than 90% of patients presenting with CML possess the Philadelphia chromosome (i.e. Ph+): a genetic abnormality caused by a reciprocal translocation between chromosomes 9 and 22, resulting in the fusion of the *BCR* and *ABL* genes and expression of the constitutively active tyrosine kinase, BCR-ABL.[1,10] The presence of the BCR-ABL protein gives rise to aberrant activation of cell signalling pathways, which are associated with changes in growth factor dependence, proliferation and apoptosis and cell adhesion, resulting in hyperproliferation of granulocytes.[12] TKIs targeting BCR-ABL signalling pathways have had a profound impact on the treatment of CML, dramatically changing survival outcomes to the point where the life expectancy of patients is nearly equivalent to that in the general population.[13-15]

Current clinical guidelines from European Society for Medical Oncology (ESMO) and European LeukemiaNet (ELN) both recommend that patients with newly diagnosed CP CML receive either imatinib, nilotinib or dasatinib as a first line therapy.[13,16,17]

The efficacy of CML treatments can be evaluated using the haematological, cytogenetic and molecular responses. The precise definition of these responses, as specified by ELN guidelines, is provided in Table 4, and the relationship between the different responses, the number of leukaemic cells and the expression of BCR-ABL transcripts is depicted in Figure 1.

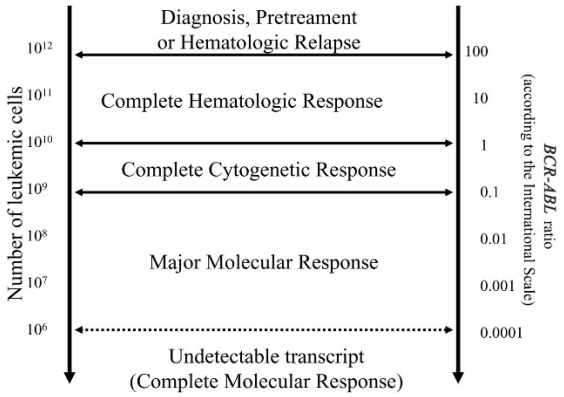

Figure 1. Approximate relationship between response, number of leukaemic cells, and the level of BCR-ABL transcripts; figure from European LeukemiaNet guidelines[18]

Table 4. European LeukemiaNet definition of CML responses[13,18]

Response		Criteria
Complete haematological response (CHR)		Platelet count <450 × 10^9/l; white blood cell count <10 × 10^9/l; differential without immature granulocytes and with less than 5% basophils; non-palpable spleen
Cytogenetic response	Complete (CCyR)	0% Ph+ cells, of at least 20 bone marrow metaphases
	Partial (PCyR)	1%-35% Ph+ cells, of at least 20 bone marrow metaphases
	Major (MCyR)	Either CCyR or PCyR response achieved
Molecular response*	$MR^{3.0}$ (3 log reduction or major response [MMR])	BCR-ABL expression of ≤0.1%
	$MR^{4.0}$ (4 log reduction)	Detectable disease with <0.01% BCR-ABL or undetectable disease >10,000 ABL transcripts
	$MR^{4.5}$ (4.5 log reduction) or complete response [CMR])	Detectable disease with <0.0032% BCR-ABL or undetectable disease in cDNA with >32,000 ABL transcripts
*Molecular response: assessed according to the International Scale (IS) as the ratio of BCR-ABL transcripts to ABL transcripts, or other internationally recognised control transcripts; expressed and reported as BCR-ABL% on a log scale, where 10%, 1%, 0.1%, 0.01%, 0.0032%, and 0.001% correspond to a decrease of 1, 2, 3, 4, 4.5, and 5 logs, respectively, below the standard baseline		

As described in Table 5, NICE has previously assessed use of dasatinib, nilotinib and imatinib for the treatment of CML (TA251).[1] . During the undertaking of TA251, the Appraisal Committee concluded that the available evidence suggests that dasatinib and nilotinib provided superior clinical benefit, as measured by surrogate outcome measures, to standard-dose imatinib in the first-line treatment of people with chronic phase CML.[1] The Appraisal Committee also concluded from indirect comparisons that dasatinib and nilotinib could be considered equally as effective in treating newly diagnosed CML.[3] However, , a Patient Access Scheme (PAS) discount was made available for nilotinib but not for dasatinib; this enabled the Committee to approve nilotinib for use in this setting.[1] Currently, the NICE pathway specifies use of imatinib and nilotinib as the recommended first-line TKIs, and nilotinib as the recommended second-line TKIs.[2]

It is recommended that the TKI choice must take into account tolerability and safety, as well as patient characteristics, particularly age and comorbidities.[13] This gives clinicians the opportunity to tailor the CML treatment to the individual patient based on their expert opinion, particularly in the context of optimising adherence, avoidance of AEs and providing a treatment with the deepest response that is proven to be the most rapid and durable. However, only imatinib and nilotinib have been recommended by NICE following health

technology assessment, reducing the therapeutic options available to optimise the treatment pathway and achieve the best outcomes for the patient.

Dasatinib provides clinical benefits that are superior to those provided by imatinib and comparable to those provided by nilotinib. This resubmission details a conservative cost-comparison analysis, taking into account the availability of a dasatinib PAS, where dasatinib results in cost savings, driven by lower acquisition costs, versus nilotinib and imatinib.

Table 5. Relevant health technology assessments in the UK

Intervention	HTA body	ID	Date	Indication	Advice
Dasatinib	SMC	370/07[19]	2007	Treatment of adults with CML with resistance or intolerance to prior therapy including imatinib	Restricted recommendation, superseded by NICE TA241
		371/07[20]	2007	Treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy.	Not recommended
	NICE	TA241[5]	2012	Treatment of imatinib-resistant CML and treatment of people with CML for whom imatinib has failed because of intolerance	Not recommended
		TA251[1]	2012	First-line treatment of CML	Not recommended
	AWMSG	1407[21]	2008	Treatment of adults with Ph+ ALL and lymphoid blast CML with resistance or intolerance to prior therapy.	Not recommended
		1307[22]	2008	Treatment of chronic, accelerated or blast phase CML	Restricted recommendation, superseded by NICE TA241
		1211[23]	2012	Treatment of adult patients with newly diagnosed Ph+ CML in the chronic phase	Not recommended, superseded by NICE TA251
Imatinib	NICE	TA241[5]	2012	Treatment of imatinib-resistant CML	Not recommended
		TA251[1]	2012	First-line treatment of CML	Recommended for newly diagnosed patients with Ph+ CP CML
		TA70[24]	2003	Treatment of CML	Recommended for first line treatment of Ph+ CP, AP and BP CML, or for imatinib-naïve patients who present in CP but progress to AP or BP
Nilotinib	SMC	440/08[6]	2008	Treatment of chronic phase Ph+ CML in adult patients resistant to or intolerant of at least one prior therapy including imatinib	Restricted recommendation, superseded by NICE TA241
		709/11[4]	2011	Treatment of adult patients with newly diagnosed Ph+ CML in the chronic phase	Recommendation, superseded by NICE TA251
	NICE	TA241[5]	2012	Treatment of imatinib-resistant CML and treatment of people with CML for whom imatinib has failed because of intolerance	Recommended for Ph+ CP or AP CML if imatinib resistant or intolerant
		TA251[1]	2012	First-line treatment of CML	Recommended for newly diagnosed patients with Ph+ CP CML
	AWMSG	3714[25]	2015		Recommended as an option for use within NHS Wales

ALL: acute lymphoblastic leukaemia; AP: accelerated phase; AWMSG: All Wales Medicines Strategy Group; BP: blast phase; CML: chronic myeloid leukaemia; CP: chronic phase; NICE: National Institute for Health and Care Excellence; Ph+: Philadelphia chromosome positive; SMC: Scottish Medicines Consortium

3. Clinical effectiveness

Key points

Direct evidence from randomised controlled trials (RCTs): versus imatinib

- All four available RCTs (DASISION, S0325, NORD CML006 and SPIRIT-2) demonstrate that dasatinib is significantly superior to imatinib in terms of cytogenetic and molecular response.

Indirect evidence from indirect comparisons: versus nilotinib and imatinib

- For the majority of indirect comparisons and endpoints in newly diagnosed CP CML:
    - Dasatinib is significantly more efficacious than imatinib 400 mg/day.
    - There is no significant difference between dasatinib and nilotinib.

These data are supportive of the conclusions drawn during TA251.

Previous NICE appraisals have reviewed the clinical effectiveness evidence for dasatinib versus nilotinib and imatinib. During the undertaking of TA251, the Appraisal Committee concluded that the available evidence suggests that dasatinib and nilotinib provided superior clinical benefit, as measured by surrogate outcome measures, to standard-dose imatinib in the first-line treatment of people with chronic phase CML.[1] The Appraisal Committee also concluded from indirect comparisons that dasatinib and nilotinib could be considered equally as effective in treating newly diagnosed CML.[3]

A systematic literature review (SLR) was conducted to identify additional studies that could inform a comparison of dasatinib versus nilotinib and imatinib as first-line treatments for CML (see Appendix 1).

As in TA251, evidence to support the comparative efficacy of dasatinib versus imatinib for the treatment of newly-diagnosed patients with CP CML is derived primarily from DASISION: an open-label, randomised, multicentre phase III trial of dasatinib versus imatinib in the treatment of patients with newly diagnosed Ph+ CP CML.[26]

Additionally, supportive evidence is available from the following randomised controlled trials (RCTs):

- SWOG S0325: an open-label, randomised, phase IIb study of imatinib or dasatinib for previously untreated patients with CP CML.[27]
- NORD CML006: an open-label, randomised, multicentre phase II trial comparing dasatinib versus imatinib in patients with newly diagnosed CP CML.[28]
- SPIRIT-2: a phase III, prospective, randomised comparison of imatinib versus dasatinib in patients with newly diagnosed CP CML.[29]

Results at 12 and 60 months from DASISION are discussed in brief below; all novel clinical evidence since TA251 is included in Appendix 2, including real-world data retrospectively comparing outcomes in patients with CML receiving dasatinib, nilotinib and imatinib.

Systematic literature review results were also used to inform a network meta-analysis of dasatinib, nilotinib and imatinib. [redacted]

Table 6: Relative treatment effect: odds ratios for CCyR and PCyR by 12 months

[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

Several indirect comparisons have been conducted in order to inform comparative effectiveness decisions regarding dasatinib versus nilotinib.[30-34] However, many of these studies did not undertake an SLR in order to inform the comparison, or did not provide details of such a comparison.[32-34] Further, the majority of studies used only the pivotal studies DASISION and ENESTnd to inform the comparison. The most recent SLR available[30] was updated to identify recent publications relevant to this comparison, and an NMA was undertaken.

Six additional published indirect comparisons have been identified: one independent mixed treatment comparison conducted by Firwana et al (2015)[35]; one NMA conducted by Oxford Outcomes Ltd (sponsored by Bristol-Myers Squibb Pharmaceuticals Ltd)[30]; one mixed-treatment indirect comparison conducted by the Peninsula Technology Assessment Group (PenTAG)[31] as part of NICE TA251[1]; one NMA conducted by Analysis Group (sponsored by Novartis Pharmaceuticals Corporation)[32]; and two matching-adjusted indirect comparisons conducted by Analysis Group (sponsored by Novartis Pharmaceuticals Corporation)[32,34]. An overview of these studies and outcomes of interest (CCyR and MMR by 12 months) are provided in Table 7.

The available evidence from the clinical trials, indirect comparisons and real world data demonstrate that outcomes in newly diagnosed CML patients are superior following dasatinib or nilotinib treatment compared with imatinib treatment.[30-35] Additionally, evidence available from the indirect comparisons suggests that dasatinib and nilotinib are similarly effective for the treatment of CML in newly diagnosed patients. These conclusions are in line with those of the NICE Appraisal Committee during TA251.[1,3]

Table 7. Overview of published indirect comparisons

Study	Year	Methodology	Studies included	Therapies	CCyR by 12 months		MMR by 12 months	
					Probability of response % (95% CrI)	OR (95% CrI)	Probability of response % (95% CrI)	OR (95% CrI)
Firwana et al (2015)[35]	2015	SLR and mixed treatment comparison	DASISION ENESTnd BELA EPIC S0325	Imatinib Dasatinib Nilotinib Bosutinib Ponatinib	NR		NR	
Oxford Outcomes[30]*	2013 (SLR conducted 2011)	SLR and NMA	DASISION Baccarani[36] German CML Study IV ENESTnd S0325 Cortes[37] SPIRIT	Dasatinib 100 mg	77.1% (67.2–85.3)	2.16 (1.23–3.5)	51.1% (43.9–58.5)	2.09 (1.55–2.78)
				Imatinib 400 mg	62.4% (reference)	Reference	33.6% (Reference)	Reference
				Imatinib 800 mg	70.1% (62.1–76.9)	1.45 (0.99–2.01)	48.1% (43.1–53.1)	1.84 (1.50–2.24)
				Nilotinib 600 mg	77.7% (64.8–87.7)	2.41 (1.11–4.29)	58.7% (49.6–67.5%)	2.87 (1.95–4.11)
				Nilotinib 800 mg	75.3% (61.0–86.1)	2.06 (0.95–3.73)	57.8% (48.7–66.8)	2.76 (1.88–3.98)
PENTAG[31†]	2012	Mixed-treatment indirect comparison	DASISION ENESTnd	Nilotinib 600 mg vs dasatinib	NR	1.09 (0.61–1.92)	NR	1.28 (0.77–2.16)
				Nilotinib 800 mg vs dasatinib	NR	0.95 (0.54–1.67)	NR	1.24 (0.74–2.08)
				Imatinib	68.3 (SE: 0.020)	NR	24.6 (SE: 0.018)	NR
				Dasatinib	82.3 (SE:0.020)	NR	44.0 (SE: 0.027)	NR
				Nilotinib 600 mg	81.7 (SE: 0.019)	NR	46.0 (SE: 0.026)	NR
Analysis Group NMA[32]	2014	SLR (no details provided) and NMA	DASISION ENESTnd S0325	Dasatinib	NR	NR	44.8% (35.2–54.5)	NR
				Imatinib	NR	NR	26.7% (22.0–32.0)	NR
				Nilotinib 600 mg	NR	NR	55.2% (9.5–60.9)	NR
Analysis Group MAIC[34]	2011	MAIC	DASISION ENESTnd	Dasatinib	83.4% (NR)	NR	45.9% (NR)	NR
				Imatinib (DASISION)	66.5% (NR)	NR	26.9% (NR)	NR
				Imatinib (ENESTnd)	71.5% (NR)	NR	28.1% (NR)	NR
				Nilotinib 600 mg	80.9% (NR)	NR	56.8% (NR)	NR
Analysis Group MAIC[33]	2015	MAIC	DASISION ENESTnd	Dasatinib	NR	NR	45.9% (NR)	NR
				Imatinib (DASISION)	NR	NR	28.1% (NR)	NR
				Imatinib (ENESTnd)	NR	NR	26.5% (NR)	NR
				Nilotinib 600 mg	NR	NR	56.1% (NR)	NR

CCyR: complete cytogenetic response; CrI: credible interval; OR: odds ratio; MAIC: matching-adjusted indirect comparison; MMR: major molecular response; NMA: network meta-analysis; NR: not reported; SLR: systematic literature review.
* Includes data for endpoints achieved at or by 12 months
† Rate of CCyR reported by 12 months; rate of MMR achieved at 12 months; odds ratio presented within Table 18; probability presented within Tables 38 and 38.

3.1 DASISION

DASISION was an open-label, multinational, randomised phase III trial evaluating dasatinib versus imatinib in patients with newly diagnosed CP CML.[26,38-45] Patients were stratified according to the Hasford risk scale and randomised in a 1:1 ratio to the dasatinib or imatinib treatment groups. Treatment allocation was not masked.[38]

Patients were considered eligible if they fulfilled the following criteria:[38]

- Adult patients (at least 18 years of age).
- Ph+, CP CML newly diagnosed by bone marrow cytogenetic studies within 3 months prior to study entry, where CP was defined as:
  - <15% blasts
  - <20% basophils
  - <30% blasts plus promyelocytes in peripheral blood and bone marrow
  - a platelet count of ≥100×10^9/l
  - absence of extramedullary disease, with the exception of hepatosplenomegaly
- No prior treatment for CML except for anagrelide or hydroxycarbamide (also called hydroxyurea).
- Eastern Cooperative Oncology Group (ECOG) performance status 0–2.
- Adequate hepatic function, defined as: total bilirubin less than or equal to twice the upper limit of normal range (≤2 x ULN); and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN.
- Adequate renal function, defined as serum creatinine ≤3 x ULN.

Patients were randomly assigned to receive either dasatinib, administered orally at a dose of 100 mg once daily (with or without food) or imatinib, administered orally at a dose of 400 mg once daily (with food).[38] Patients continued to receive the assigned study therapy until disease progression or development of unacceptable toxic effects.

The primary endpoint was confirmed CCyR (cCCyR) by 12 months after the initiation of treatment, defined as CCyR (described below) documented on two consecutive assessments at least 28 days apart.[38] Patients who had a first assessment of CCyR at 12 months that was confirmed on a second assessment thereafter were considered to have had a cCCyR by 12 months.[38]

[redacted] More patients in the imatinib group discontinued due to disease progression or treatment failure (10.9% in the dasatinib group versus 14.0% in the imatinib group), while more patients receiving dasatinib discontinued due to intolerance (16.3% dasatinib versus 6.6% imatinib). [redacted] while the median average daily dose was 99 mg for dasatinib and 400 mg for imatinib.[46]

The baseline data were well balanced between the two treatment groups.

The rate of cCCyR within 12 months was significantly higher in patients receiving dasatinib versus those receiving imatinib (77% versus 66%; p = 0.007), meeting the primary endpoint.[38] Similarly, the rates of CCyR and MMR within 12 months were significantly higher in the dasatinib group, as

described in Table 8. By 60 months, MMR was still significantly superior in the dasatinib group versus the imatinib group, [redacted]

[redacted]

Table 8. Efficacy responses in newly diagnosed CP CML patients in DASISION study[38,46,47]

	Dasatinib N=259	Imatinib N=260	p-value
Primary endpoint			
cCCyR rate within 12 months	199 (77%)	172 (66%)	0.007
Secondary and tertiary endpoints			
cCCyR rate at any time*	[redacted]	[redacted]	[redacted]
MMR rate at any time*	198 (76%)	167 (64%)	0.0021
Rate of CCyR within 12 months	[redacted]	[redacted]	[redacted]
Rate of PCyR within 12 months	[redacted]	[redacted]	[redacted]
Rate of MMR within 12 months	119 (46%)	73 (28%)	< 0.0001
Time to cCCyR: Hazard ratio (95% CI)*	[redacted]		[redacted]
Time to cCCyR: Median (months)*	[redacted]	[redacted]	[redacted]
Time to MMR: Hazard ratio (95% CI)*	[redacted]		[redacted]
Time to MMR: Median (months)	[redacted]	[redacted]	[redacted]
PFS at 60 months*	[redacted]	[redacted]	[redacted]
OS at 60 months*	91%	90%	[redacted]

CI: confidence interval; cCCyR: confirmed complete cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response; OS: overall survival; PCyR: partial cytogenetic response; PFS: progression-free survival; NR: not reported.
* 60-month follow-up data

[redacted]

Table 9 summarises the AE profile of dasatinib versus imatinib after 12 months and 60 months follow-up.

[redacted]Within the dasatinib group, this was most commonly due to pleural effusion (15 [5.8%] patients versus 1 [0.4%] patient in the imatinib group), pulmonary hypertension (6 [2.3%] patients versus none in the imatinib group) and drug-related cytopenias (5 [1.9%] patients versus 4 [1.6%] in the imatinib group).[46]

At the 60-month follow-up, a total of 52 patients (26 in each treatment group) had died since study initiation, of which 8 (3.1%) in the dasatinib group and 5 (1.9%) in the imatinib group occurred within 30 days of the last dose of therapy.[46] However, there were no further deaths attributed to the study drug in either treatment group.

[redacted]

[redacted]

After 60 months of follow-up, treatment-related pleural effusion was observed in 73 (28.3%) dasatinib-treated patients and 2 (0.8%) imatinib-treated patients; however, this was grade 3–4 in only 7 (2.7%) of dasatinib-treated patients.[46] Management of treatment-related pleural effusions in the dasatinib group most commonly involved dose interruption (45/73 [61.6%]) or reduction (30/73 [41.1%]); however, treatment discontinuation was required in 15 patients. Additionally, patients were often prescribed diuretics (34/73 [46.6%]), corticosteroids (23/73 [31.5%]), or both (20/73 [27.4%]). Therapeutic thoracentesis was required in 9 (12.3%) dasatinib-treated patients with drug-related pleural effusion. However, pleural effusion did not impair the ability of patients to obtain a response; 71 (95.9%) achieved a cCCyR, 61 (82.4%) achieved an MMR, and 37 (50.0%) achieved a CMR.[46]

Table 9. Summary of drug-related adverse event profile in the DASISION study[46,47]

	12 months				60 months*			
	Dasatinib (n=258)		Imatinib (n=258)		Dasatinib (n=258)		Imatinib (n=258)	
	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4	All	Grade 3-4
Drug-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38 (14.7)	[redacted]	28 (10.9)
Diarrhoea	45 (17.4)	1 (0.4)	45 (17.4)	2 (0.8)	[redacted]	[redacted]	[redacted]	[redacted]
Headache	30 (11.6)	0	27 (10.5)	0	[redacted]	[redacted]	[redacted]	[redacted]
Skin rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	15 (5.8)	1 (0.4)	25 (9.7)	0	[redacted]		[redacted]	
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	11 (4.3)	0	5 (1.9)	0	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	12 (4.7)	0	26 (10.1)	0	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	15 (15.8)	0	30 (11.6)	0	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related Fluid Retention	50 (19.4)	2 (0.8)	109 (42.2)	2 (0.8)	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	26 (10.1)	0	0	0	73 (28.3)	7 (2.7)	2 (0.8)	0
Superficial oedema	23 (8.9)	0	92 (35.7)	1 (0.4)	[redacted]	[redacted]	[redacted]	[redacted]
Other fluid-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pericardial effusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary hypertension	[redacted]	[redacted]	[redacted]	[redacted]	12 (4.7)	[redacted]	1 (0.4)	[redacted]
Congestive heart failure/cardiac dysfunction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory Abnormalities								
Absolute neutrophil count (neutropenia)	168 (65.6)	53 (20.7)	149 (58.0)	52 (20.2)	[redacted]	74 (28.7)	[redacted]	61 (23.7)
Haemoglobin (anaemia)	231 (90.2)	26 (10.2)	216 (84.0)	17 (6.6)	[redacted]	34 (13.2)	[redacted]	23 (8.9)
Platelets (thrombocytopenia)	181 (70.7)	49 (19.1)	160 (62.3)	27 (10.5)	[redacted]	56 (21.7)	[redacted]	37 (14.3)
ALT	112 (43.8)	1 (0.4)	84 (32.7)	3 (1.2)	129 (50.4)	2 (0.8)	111 (43.2)	4 (1.6)
AST	84 (32.8)	1 (0.4)	76 (29.6)	2 (0.8)	112 (43.8)	2 (0.8)	102 (39.7)	3 (1.2)
Total bilirubin	40 (15.6)	3 (1.2)	39 (15.2)	0	50 (19.5)	3 (1.2)	48 (18.7)	0

AEs: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

* 12-month follow up AE terms were coded and grouped by system organ class using Medical Dictionary for Regulatory Activities (MedDRA) version 12, while 60-month follow-up terms used MedDRA version 13.1. Some terms were remapped for the purpose of complying with regulatory guidance for reporting adverse reactions, and avoiding exhaustive lists of every reported AE, including those that were minor, commonly observed in the absence of drug therapy, or not plausibly related to drug therapy.

4. Cost-comparison

Key points

- Dasatinib is expected to be associated with cost savings of between [redacted] and [redacted] per patient per month

The available evidence demonstrates that dasatinib is associated with superior outcomes to imatinib in CML patients. Based network meta-analysis and indirect comparison, it can be suggested that outcomes are comparable between dasatinib and nilotinib. This is in line with conclusions of the NICE Appraisal Committee during TA251.[48]

Based on the conclusion of comparable efficacy between dasatinib and nilotinib, and notwithstanding the demonstrated superiority of dasatinib versus imatinib across all identified head-to-head studies, the economic evaluation presented will be a simplified cost-comparison analysis, based on the assumption of equivalent efficacy and safety across all three TKIs. This analysis takes into account a PAS discount for dasatinib, which has not previously been available. Given the evidence that dasatinib and nilotinib demonstrate comparable efficacy, the dasatinib PAS has been designed to ensure these two treatments are of comparable cost.

4.1 Intervention technology and comparators

Intervention:

- Dasatinib: 100 mg once-daily

Comparators:

- Imatinib: 400 mg once-daily
- Nilotinib: 300 mg twice-daily

4.2 Cost inputs

4.2.1 Treatment costs and dosing estimates

Unit costs of dasatinib, imatinib and nilotinib are summarised in Table 10, obtained from MIMS[9] and the British National Formulary (BNF)[49]. Monthly costs applied in the analysis are presented in Table 11, along with dosing assumptions and sources. All TKIs are assumed to be administered at licensed dose, based on median dose administered in pivotal studies[38,50] and to ensure that costs represent clinically feasible doses.

Please note, this submission takes into account PAS availability for dasatinib and nilotinib, described below, which reduces unit costs from those described in Table 10 and Table 11.

Table 10. Unit costs of common medications used in the treatment of CML[9,49]

Intervention	Unit Dose	Pack description	Pack price
Dasatinib (Sprycel®)	100 mg	30-tab pack	£2,504.96
	140 mg	30-tab pack	£2,504.96
Imatinib (Glivec®)	100 mg	60-tab pack	£918.23
	400 mg	30-tab pack	£1,836.48
Nilotinib (Tasigna®)	150 mg	112-cap pack	£2,432.85
	200 mg	112-cap pack	£2,432.85

Table 11. Treatment costs and dosing estimates

Intervention	Assumed dose	Source of dose assumption	Cost	Source of cost
Monthly costs				
Dasatinib	100 mg once daily	SPC[7]	£2,541.49	MIMS[9]
Imatinib	400 mg once-daily	SPC[51]	£1,863.26	MIMS[9]
Nilotinib	300 mg twice daily	SPC[52]	£2,644.64	MIMS[9]

4.2.2 Patient Access Schemes

A PAS is available for both dasatinib and nilotinib. The discount available in the nilotinib PAS is confidential, and as such is unavailable for use in this evaluation. Given the evidence that dasatinib and nilotinib demonstrate comparable efficacy, the dasatinib PAS has been designed to ensure [redacted]. A dasatinib PAS discount of [redacted] has been applied, which we believe is [redacted] to that of nilotinib, as inferred from publically available incremental cost-effectiveness ratio (ICERs) in previous health technology assessments (HTAs).[redacted]

4.2.3 Resource use and adverse event-related costs

As the assumption underpinning the analysis is that dasatinib, nilotinib and imatinib are comparable in terms of health outcomes, it follows that, with the exception of drug acquisition costs which are described above, all other resource utilisation, including that required for management of adverse events, would also be comparable. As such, there is no need to consider additional costs, as they will offset each other when comparing treatment strategies.

4.3 Results

Results of the analyses are presented in Table 12. The cost-comparison analysis demonstrates that treatment with dasatinib is likely to result in a cost-saving approach to CML therapy when compared to imatinib and nilotinib. The estimated cost savings are expected to be between [redacted] and [redacted] per patient per month when using dasatinib.

Table 12. Cost comparison results

Intervention	Monthly cost (£)	Incremental cost of dasatinib (£)
Dasatinib	[redacted]	[redacted]
Imatinib	£1,863.26	[redacted]
Nilotinib	£2,644.64	[redacted]

4.4 Interpretation and conclusions of economic evidence

Dasatinib is not a new treatment: originally licensed in 2006, its efficacy and safety profile is well established. Evidence presented in this submission supports the conclusions drawn by NICE during TA251, that dasatinib is associated with superior outcomes versus imatinib in CML patients and that there is minimal difference in efficacy between dasatinib and nilotinib in this setting. However, nilotinib was made available to the NHS at a discounted price, and this enabled the Committee to approve nilotinib for use in this setting.

Following a cost-comparison analysis versus nilotinib, savings of up to [redacted] per patient per month are anticipated with the use of dasatinib when a PAS is applied. This is due to the [redacted] of dasatinib compared to imatinib and nilotinib at expected doses. **There are significant advantages to the NHS in the availability of dasatinib, where evidence suggests efficacy comparable to nilotinib, with [redacted].**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

TA251- Dasatinib for the first-line treatment of chronic myeloid leukaemia

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

The template without any addition by respondents is 6 pages in length, we assume the reference to 10 pages is in addition to the 6 pages.

NB: Reference is made in this submission to the recently published FAD for TA 299 which has a guidance publication date after that of this submission.

Although we acknowledge and accept that until the publications date (24th August) its contents remain confidential we feel secure in referring to its contents here because this document will remain confidential until after that date.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: The Chronic Myeloid Leukaemia Support Group (CMLSg)

Your position in the organisation: [redacted]

Brief description of the organisation:

CMLSg is the only UK registered charity (Reg No 1114037) with a sole focus on CML. It is patient lead with its Director and three of our Trustees being CML patients. Because of the rarity of CML (incidence is around 1 case per 100,000), CMLSg operates primarily, but not exclusively, online. Our objective is to offer support, information and advocacy to CML patients and those that care for them so that they can, after treatment, resume a life as close as possible to that lived before diagnosis.

In addition to obtaining funding from the public and to avoid any inference of bias, we are careful to seek funding from all companies that have licensed drug based treatments (Tyrosine Kinase Inhibitors or TKIs) for CML.

Our annual audited accounts are available via the Charity Commission website.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

2.1 The use of TKIs has transformed outcomes for CML patients over the last 15 years. CML has moved from being an acute condition with a high mortality rate to a chronic, long term condition for the overwhelming majority of patients most of whom can anticipate a life expetancy near to the norm.

2.1 For these patients, living with the condition revolves around the management of side effects that accompany any drug based treatment. Side effects can vary from patient to patient, can vary over the course of a treatment with a particular TKI and differ between TKIs over the course of an invidual's treatment.

2.2 For those patients unable to obatin an optimal response to the TKIs that are routinely avaiable in the NHS in England, the search for a TKI that can do so brings with it understandable anxiety and stress given that CML, without an effective treatment, remains a malignant condition. This anxiety is shared by those that care for them.

2.3 Given the well documented high risks involved, all patients are fearful of the only non TKI treatment routinely available, Stem Cell Transplantation (SCT), and would regard it as a treatment of last resort after all TKIs have been either considered or deployed as treatments.

2.3.1 For those for whom an SCT would be considered, a number would not qualify either because a matched donor cannot be located before the disease progresses, or their clinical profile disqualifies SCT as an option.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

3.1 Given the invariably fatal outcome if left untreated, it is axiomatic that the primary outcome most important to patients is survival.

3.2 Should an optimal response be obtained following treatment with a TKI that is either routinely available in the NHS in England or via some other NHS access route (for example for a medicine reimbursed via the Cancer Drugs Fund), securing a quality of life similar to that present before disease onset is the next most important priority for patients.

3.3 Third would be a resumption of public life by the patient within their social networks and community including employment if applicable which, given the median age at diagnosis is around 55, is a relevant consideration.

3.4 For carers, the greater the distance travelled along this three stage continuum the better, since this brings successive decreases in the caring burden placed upon them.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

3.5 Currently three TKI treatments are licensed for first line use of the five that are available (ie licensed) for CML treatment. Two, of these three, first line treatments are routinely available in the NHS in England with NICE recommending both (standard dose) imatinib and nilotinib in first line (TA 251) with dasatinib being the third.

3.6 By far the most pervasive treatment in first line is first generation imatinib. Clinicians working in the NHS in England have had over a decade of experience of using imatinib as a first line treatment as have clinicians treating patients elsewhere. A very recent estimate from a leading clinician is that some 90% of newly diagnosed patients receive imatinib as a first treatment in the NHS in England (June 2016 FAD TA 299: section 4.2). Approximately 60% of these patients would be expected to obtain an optimal response following imatinib use (*'Which TKI? An embarrassment of riches for chronic myeloid leukemia patients'* T. Hughes & D. White - American Society of

Haematology Education Programme 2013: 168-75. doi:10.1182/asheducation-2013.1.168).

3.7 Second generation nilotinib is more potent than imatinib and it is unsurprising that newly diagnosed clinical trial patients obtained a faster and deeper response than those patients randomised to imatinib. However there is a lack of evidence of their being any significant difference between the two drugs in terms of either progression free, or overall, survival (*'Initial choice of therapy among plenty for newly diagnosed chronic myeloid leukemia'* D. Marin - American Society of Haematology Education Programme 2012: 115- 121 doi:10.1182/asheducation-2012.1.115).

3.7.1 In addition there is a *'small but important incidence of more serious side effects'* amongst patients treated with nilotinib with these being *'arterial thrombotic events'* and *'poor diabetic control'*. (*'Cancer Drugs Fund and CML: an unhappy alliance'* Professor J. Apperley in the online only, Oncology Central November 2015)

3.7.2 Nilotinib also has, as Marin (above reference) notes, an exacting posology with a twice daily 'before and after' fasting requirement. TKI treatments are daily and for life for the overwhelming majority of the population on treatment. Given the median age (around 55) of the patient population and the success of TKI treatments in securing survival, decades long time-on-treatment would be a reasonable expectation for newly diagnosed patients. Maintenance of an optimal response that ensures survival is dependent on strict adherence to a TKI treatment regime since there is evidence that loss of response is related to poor adherence. Although the study that reached this conclusion was restricted to patients treated with imatinib the concluding sentence noted *'Unfortunately, the relatively poor adherence to imatinib that we have described in this article may apply equally to patients receiving second-generation tyrosine kinase inhibitors.'* (*'Adherence Is the critical factor for achieving Molecular Responses in patients with Chronic Myeloid Leukemia who achieve Complete Cytogenetic Responses on Imatinib*' Marin et al Journal of Clinical Oncology 2381-2388 Vol 28 No 14 May 2010)

3.7.3 When the factors noted in 3.7.1 and 3.7.2 are considered together, the pervasive use of imatinib as a first TKI treatment is understandable. However as also noted in 3.6, some 40% of patients are unable to achieve an optimal response, be that one based on tolerance or resistance, following imatinib treatment. The availability of dasatinib,as an alternative licensed TKI option for first line use, is therefore welcomed by clinicians and patients.

3.7.4 Despite a negative recommendation from NICE (TA251 - 2012) the committee '*...concluded that there was insufficient evidence to distinguish between dasatinib and nilotinib in terms of clinical effectiveness.'* (4.3.7 TA 251)

3.7.5 The Committee also *'... concluded that the available evidence suggests that dasatinib and nilotinib provided superior clinical benefit, as measured by surrogate outcome measures, to standard-dose imatinib in the first-line treatment of people with chronic phase CML*.' (4.3.6 TA 251)

3.8 A plausible proposition, taking together the points raised in sections 3.5 to 3.7.5 above, would be that there is a rationale for a preference of dasatinib over nilotinib and imatinib as a first line treatment should the strategic objective be a fast and durable response and if there are no comorbidity issues present likely to contraindicate its use.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)

- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

(i) For those patients able to secure an optimal response, the principal benefit of dasatinib treatment is that of long term survival with a reasonable anticipation of a life lived to near life expectancy.

(ii) For those patients for whom dasatinib represents a well tolerated treatment option and assuming an optimal, durable response has been obtained, the enjoyment a high quality of life as a result of their treatment would be a reasonable expectation.

(iii) As a second generation (2G) TKI, the response obtained with first line dasatinib would be faster and deeper compared to first generation imatinib in first line assuming a patient was not resistant to dasatinib.

(iv) The TKI other than imatinib current recommended by NICE for routine use in first line, nilotinib, has an exacting pre use, twice daily, fasting requirement. Many, but not all, patients find this regime presents compliance challenges. This is especially applicable for patients with busy working lives and in particular those whose work schedules are subject to fluctuation and variation over which they have little control.

(v) Dasatinib is effective, or more effective, in its action against certain mutations (and ineffective against others). Considerable variation exits as to which mutations each of the TKIs are effective against.

(vi) For some patients, dasatinib represents the only TKI they are both not resistant to and are able to tolerate as a treatment. For them, dasatinib represents resolution to an unmet need.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

See above for the particular sub groups of the overall CML patient population described.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

Differences can exist amongst sub group populations most distant to those described above although, very importantly, not amongst those with an understanding of the patient profile dependent variation in individual TKI clinical effectiveness. In short what works for some may not work for all where the 'what' refers to a family of TKI treatments.

4. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

A key concern is the achievement of an optimal response. It follows that the greater the number of TKIs of proven clinical effectiveness (together with an acknowledgement of the variation in effectiveness across the patient population) there are that are available, the greater the possibility of obtaining an effective response assuming the TKI is well tolerated.

Please list any concerns patients or carers have about the treatment being appraised.

The principal concern uppermost amongst the patient population would be the problem of pleural effusion following dasatinib treatment. This is the most public of the known treatment challenges although there is widespread

acknowledgement that is not an inevitable treatment side effect or that this is the sole side effect.

What is less known are the much developed and improved measures deployed in mitigation.

That said, dasatinib would not present a prudent treatment of first choice for a patient with an existing bronchial condition.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

5. *Patient population*

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Given the unusual nature of the Rapid Reconsideration process and the burden of its Committee's workload we wish to avoid any repetition. Therefore please see our responses to Section 4 from which it is possible to easily deduce our response to this section.

6. *Research evidence on patient or carer views of the treatment*

Is your organisation familiar with the published research literature for the treatment?

☐ Yes ☐ No, we will leave a response to his section to the clinical experts who will probably wish to discuss the emerging results of the SPIRIT 2 Clinical Trial.

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in

the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

7. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

8. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

8.1 Dasatinib treatment is innovative in so far as it has been proven to be a clinically effective treatment for a sub group of the CML patient population who are either resistant to or are unable to tolerate all other licensed TKIs.

8.1.1 It is not innovative in the sense that it represents a step change in approaches to the treatment of CML.

Are there any other issues that you would like the Appraisal Committee to consider?

8.2 The Committee will no doubt be aware of NHS England's (NHSE) proposals published earlier this year (and circulated for public consultation) entitled *'A Clinical Commissioning Policy Statement for dasatinib for the 1st line treatment of CML and 2nd line treatment of imatinib resistant CML.'*

8.2.1 One part of the Background section (2) of the NHSE document recounts the evaluation, access and recent research history of dasatinib. The section closes with this sentence:

'This policy statement has been developed because dasatinib is a recognised clinically effective treatment for CML which is now also cost effective to the NHS'

8.2.2 Section 3 alludes to what is presumably a recent (post NICE TA s 241 & 251 of 2012) agreement between the manufacturer and NHSE on the *'likely price of care*' for patients treated with dasatinib in the NHS with the outcome that NHSE now regards the treatments the proposals describe as *'affordable*'.

8.2.3 If so, alignment is obtained with NICE guidance (for both 1st and 2nd line treatment) with the implication being that the part of the guidance (1st line) covered by this Rapid Reconsideration should proceed to a positive recommendation with the necessary *'commercial in confidence discount'* Patient Access Scheme (PAS) rendered a formality by DH rather than be subject to consideration.

8.2.4 In this sense this Rapid Reconsideration takes on a similar formality like quality since it would not be logically consistent for 'affordability' status to have been granted without the same status being granted for 'cost effectiveness'. This does not extend to 'cost effectiveness' being accepted yet 'affordability' being contested.

9. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

(i) Following negotiations with the manufacturer, it appears dasatinib is now accepted by NHSE as a 1st line treatment for CML that is both clinically effective and cost effective. It is also a treatment judged as affordable and it follows that the treatment represents an effective use of NHS resources. The Committee should therefore logically arrive at a positive recommendation for its routine use in the NHS in England.

(ii) Newly diagnosed patients in England able to obtain a well tolerated, optimal response following treatment, for example those randomised to the dasatinib arm of the SPIRIT 2 trial, have long recognised dastainib to be a clinically effective treatment. They will welcome its addition to existing routine first line NHS treatments and the consequent redundancy of the necessity of a clinician making an ICDFR for first line use or the necessity of failing either imatininb or nilotinib on the grounds specified in order to obtain access to dasatinib as a subsequent 2nd line treatment.

(iii) Since second generation (2G) TKIs (including dasatinib) are proven to deliver a faster, deeper response than first generation imatinib we welcome the addition a a second generation TKI as a first line treatment should the Committee make a positive recommendation.

(iv) We welcome the move towards the European wide specialist clinician consensus a postive recommendation would contribute to.
(v) Should the recommendation be positive, we also recognize the small contribution made towards delivering the Secretary of State's ambition that cancer survival rates in England (and the devolved nations) should match those obtained in equivalent EU member states.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

Dasatinib for the first-line treatment of chronic myeloid leukaemia (part review of TA251)

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
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- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Leukaemia CARE

Your position in the organisation: [redacted]

Brief description of the organisation:

Leukaemia CARE is a national blood cancer support charity – founded in 1967 and first registered with the Charity Commission in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. We support people affected by leukaemia, lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, myelodysplastic syndrome, myeloproliferative disorders and aplastic anaemia.

Our database currently holds over 19,000 records. This includes patients, carers, healthcare professionals etc.

Leukaemia CARE offers this care and support through our head office, based in Worcester and a network of volunteers all around the United Kingdom. Care and support is offered over seven key areas:

- 24-hour CARE Line (including a Nurse Advisor)
- Live chat (currently office hours only)
- Support groups
- Patient and carer conferences
- One-to-one phone buddy support
- Cancer campaigning and patient advocacy
- Information and booklets

Since its inception our CARE-Line has taken many thousands of calls from patients, their carers, family and friends. Our website provides extensive information on all aspects of the blood cancer journey, running from diagnosis to what happens when treatment stops and includes emotional effects of a blood cancer and help for those caring for a patient. Our focus is purely on information and support for everyone affected by a diagnosis of blood cancer. See: http://www.leukaemiacare.org.uk

Leukaemia CARE also works with other charities and policy/decision makers to campaign for the rights of all patients affected by a blood cancer to have access to and receive the best possible treatment and care when they need it.

Organisational Funding:

Over 85% of our total funding comes from our own fundraising activities and those of our volunteers. This includes a wide range of activities – such as legacies, community events, marathons, recycling campaigns etc. Leukaemia CARE receives funding from a wide range of pharmaceutical companies, but in total those funds do not exceed 15% of our annual income. Any funds received from the pharmaceutical industry are received and dispersed in accordance with the ABPI Code of Practice and the Leukaemia CARE code of practice. Our Code of Practice is a commitment undertaken voluntarily by Leukaemia CARE to adhere to specific policies that regulate our involvement with the pharmaceutical industry.

A copy of our code of practice is available at:

http://www.leukaemiacare.org.uk/resources/code-of-practice

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Chronic myeloid leukaemia (CML) is a rare, chronic form of leukaemia. There are over 650 people diagnosed in England and Wales each year. It is slightly more common in men than women and, as with most blood cancers it is more prevalent in people over the age of 60.

Common symptoms include “fatigue”, “pain”, frequent infections (for example a “persistent cough”), “bruises”, abdominal discomfort, fever, aching joints and bones, feeling weak and breathless, “night sweats”, unusual bleeding and unexplained “weight loss”. Many patients with CML have few or even no symptoms at the time they are diagnosed, as CML is often discovered following a routine check-up or a blood test for another condition. There are three types of staging for CML; chronic, accelerated and blast. Symptom burden varies, often depending on the stage of the disease but most patients will experience some or all of these symptoms as the disease progresses.

“I finally realised something was wrong when I started bruising; huge bruises on my legs that just didn’t make sense.”

Being diagnosed with CML can be “scary” and often leaves patients feeling “numb” or “helpless” - this is sometimes magnified because patients often haven’t heard of the rare condition. Patients will often experience a range of emotional thoughts following a diagnosis and will require support. Patients have to contend with the psychological and emotional side effects of a cancer diagnosis as well as an often profound symptom burden.

“When I was diagnosed, it was like I had been hit by a truck.”

“I was stressed and scared my poor husband and parents to death.”

Such feelings do not remain with the patient alone but causes a “ripple effect” felt by their carers and families. Any improvement in access to treatment for

CML will therefore have a wider beneficial impact than just the patient group in question.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

From a patient perspective, the most important treatment outcomes will include survival (both progression and overall) and an improved quality of life (e.g. improved symptom control and reduced side effects).

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The standard treatment for CML is a tyrosine kinase inhibitor (TKI). First-line treatment options for chronic myeloid leukaemia patients include:

- imatinib (Glivec®)
- nilotinib (Tasigna®)

Imatinib is the most commonly used TKI to treat CML in the first instance. Its introduction into clinical practice transformed patient outcomes and overturned the historic median survival of 2 to 3 years (following a CML diagnosis) – meaning many patients could live a normal life span following their diagnosis. However approximately one-third of imatinib-treated patients with newly diagnosed CML (chronic phase) have inadequate responses or do not experience long term benefit from the drug. These mainly occur in the first three years of treatment, demonstrating a need for a more durable option.

"Some of the side effects weren't nice: constantly upset stomach, bone pains and tiredness."

"The most important thing was getting up in the morning, fighting through the side effects and getting to work. Leaving the house became a problem and I had to keep a multitude of drugs with me (paracetamol, ibuprofen, imodium,

amongst others) to ensure I could function. It was quite an anxious time as I could never know when I would have an attack of side effects."

As a result, a second generation of TKIs was developed. Following the demonstration of its clinical superiority to imatinib in clinical trials, nilotinib was also recommended as a first-line therapy to treat patients with CML. Although dasatinib demonstrates similar (positive) results as nilotinib, its tendency to be less susceptible to certain "mechanisms of resistance observed with imatinib treatment" is advantageous and as such, it should be routinely available to newly diagnosed CML patients.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

As with nilotinib, dasatinib showed clinical superiority over imatinib and clinical trials demonstrated that complete cytogenetic and major molecular responses occurred faster in patients treated with dasatinib, opposed to imatinib. Furthermore, data indicated that the results were durable.

For patients that respond, they will expect to live as near normal a life as possible. It will enable people to keep going with day to day activities (e.g. work, education, caring for children/ grandchildren etc.) This is key to the

psychological health of these patients and their families as their condition no longer dominates their whole life. Although some adverse events were recorded, dasatinib was generally well tolerated and non-haematological events (including rash, vomiting and nausea) occur less for patients treated with it. This could lead to an improved quality of life for patients.

It's worth noting that such benefits would not only be beneficial to the patient but would also have a wider impact on any carers and family. As such, it is key that access to dasatinib for CML patients is maintained.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Dasatinib has a different chemical structure to imatinib and as such it is less susceptible to most known mechanisms of imatinib resistance.

Furthermore, some TKIs cannot be taken due to co-morbidities and adverse effects so this provides a further option for patients unsuitable for the alternative options (imatinib and nilotinib). For example nilotinib may not be appropriate for patients with diabetes, because of its twice daily fasting requirement. In comparison dasatinib is usually taken once a day (with or without food), so is more convenient for patients and could minimise some adherence issues.

The combination of its durability, tolerability and its more convenient administration mechanism means it would be a clinically effective, convenient first line therapy option for newly diagnosed CML patients.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

N/A

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:
• aspects of the condition that the treatment cannot help with or might make worse

- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Whilst imatinib is both clinically effective and well tolerated (due to its mild toxicity) for most, some patients become resistant to it or are unable to tolerate its side effects. Furthermore, second generation TKIs such as dasatinib have a much higher potency and appear to yield quicker, more durable responses than the older TKI, indicating a need to expand access to currently available treatment options. As such, an increase in recommended comparator options would be a welcome shift for patients in this setting.

Please list any concerns patients or carers have about the treatment being appraised.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Patients who are unsuitable for the currently available treatment options.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☑ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

N/A

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

N/A

9. Other issues

Do you consider the treatment to be innovative?

☑ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

As the first targeted therapies for CML, we consider all tyrosine kinase inhibitors (TKIs) to be innovative. TKIs (including dasatinib) have transformed the treatment of CML from a fatal disease into a chronic condition with normal life expectancy for those that respond to treatment. As previously discussed, dasatinib has a different chemical make up to its comparator treatment option imatinib. We therefore consider it to be an innovative treatment.

Are there any other issues that you would like the Appraisal Committee to consider?

N/A

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Chronic myeloid leukaemia (CML) is a rare, chronic form of leukaemia. Being diagnosed with CML is “scary” and patients will often experience a range of emotional thoughts following a diagnosis, as well as having to cope with their symptom burden, which means they often require support.

- Common symptoms include “fatigue”, “pain”, frequent infections (for example a “persistent cough”), “bruises”, abdominal discomfort, fever, aching joints and bones, feeling weak and breathless, “night sweats” , unusual bleeding and unexplained “weight loss”.

- The development of TKI’s have transformed the outlook of CML patients, broadening treatment options to include life prolonging drugs that allow patients a good quality of life.

- Dasatinib has been shown to have superior clinical effectiveness over comparator option imatinib, causing higher rates of cytogenetic and major molecular responses. It also offers an alternative option for those unsuitable for the currently available treatment options.

- Dasatinib has a favourable safety profile, demonstrating side effects deemed generally manageable. As such, dasatinib in the first-line setting patients a convenient, effective treatment that could offer more durable responses in a shorter time frame, improve their overall patient experience.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA251- Dasatinib for the first-line treatment of chronic myeloid leukaemia

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted], RCP registrar submitting on behalf of:

Name of your organisation: NCRI-ACP-RCP

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA251- Dasatinib for the first-line treatment of chronic myeloid leukaemia

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

In order for chronic myeloid leukaemia (CML) patients to be treated with the highest quality of care and not to offer a sub-standard level of management, inferior to many other European countries, impacting on patient outcome and quality of life, TKIs should be used within their licensed indications. Dasatinib first line therapy should be available for the same indications that NICE approved nilotinib. Since the concept of first line second generation TKI use has already been approved and recognised by NICE (in the case for nilotinib), this appraisal will focus on the differential benefits of dasatinib first line. As NICE has already approved up-front second generation TKI use, this concept will not be expanded on in this submission.

Modern management of CML within the NHS is with tyrosine kinase inhibitor (TKI) therapy, directed by haematologists. There are three TKIs licensed first line for CML: imatinib and the second generation drugs: dasatinib and nilotinib. Bosutinib is undergoing trial for first line therapy at present. CML is a tri-phasic disease comprising of chronic, accelerated and often terminal blast phase.

<u>Chronic and accelerated phase CML</u>

Only imatinib, and the second generation drug nilotinib are approved for first line therapy for CML in chronic and accelerated phase by NICE.

<u>Blast phase CML</u>

With the exception of nilotinib, all other TKIs are licensed for the more aggressive and highly refractory blast phase of CML. It is essential that physicians have access to more potent drugs than imatinib for effective treatment of more advanced phase CML. The availability of only imatinib for blast phase CML is a very serious issue that

has hampered treatment of advanced phase CML and needs to be urgently corrected.

There should not be a significant geographical variation, as therapy follows the recommendations published and updated by the European LeukaemiaNet. Both the European ELN guidelines and the NCCN American guidelines clearly recommend all licensed TKIs for first line therapy and do not discriminate between them. Similarly, there should not be a difference in opinion between specialists as most accept the recommendations outlined by the ELN. However, there is no availability of dasatinib in Scotland.

Alternatives to NICE approved first line TKIs have been clinical trials. In the UK, the SPIRIT-2 NCRI study (now completed) compared first line imatinib with first line dasatinib; the commercial Avillion sponsored CML study (now completed) compared first line imatinib with Bosutinib, and the next NCRI study will compare first line imatinib against first line dasatinib or nilotinib (SPIRIT-3- due to open mid/end 2016).

Although nearly 80% of patients will achieve clinical responses on imatinib, after 8 years of therapy, only half of these patients will still be receiving imatinib due to failure of the drug due to resistance or intolerance. More patients will achieve faster and more potent clinical responses on second generation drugs (nilotinib/dasatinib) up front, but these may also be associated with side-effects effects of therapy, causing patients to discontinue for intolerance rather than resistance. The benefit of giving 2nd generation TKIs upfront is the advantage of earlier responses reducing the risk of progression to advanced phase CML. There is a significant reduction in progression to advanced phase CML in the first 2 years compared to imatinib.

Patients with chronic phase CML can be stratified according to their risk of progression by their Sokal risk score. Patients with a high Sokal score are traditionally predicted to have a worse outcome and these patients should have the opportunity to be treated with a more potent 2nd generation drug upfront. Patients in advanced phase need to be treated more aggressively upfront to prevent disease progression, and these patients should have access to 2nd generation drugs up-front.

The advantage of a deeper response is that more patients will become eligible to stop TKI medication in the future. Only patients that have achieved deep molecular responses (Complete molecular response (4-4.5 log reduction, quantitative PCR for BCR-ABL of < 0.01% on the International scale (IS)) are currently eligible for stopping studies. Trials of stopping TKI are also in place for patients in a major molecular response (MMR, quantitative PCR of < 0.1% on the IS). Far greater number of patients achieve MMR and CMR on 2nd generation drugs, such a dasatinib. More patients will therefore be able to stop their TKI medication which has a considerable impact not only for health-economic considerations, but will also spare patients any long-term side-effects of therapy.

The true comparator of dasatinib first line, would be first line nilotinib. First line nilotinib has a number of practical issues- it needs to be given twice a day, with a 3 hour fast for each medication, which has issues with drug compliance.
Nilotinib also has a distinct side-effect profile:

-aggravates diabetes
-causes glucose intolerance leading to 25% of patients having indices within the diabetic range within 5 years of nilotinib therapy
-increases the cholesterol levels in patients
-is associated with cardio-vascular (CV) thrombotic events, which by definition are irreversible. These arterial side-effects are more prevalent in patients with pre-existing CV risk factors.

Despite the requirement to prevent progression and to attempt to achieve deeper molecular responses on 2nd generation drugs on order to stop future TKI therapy, all haematologists would avoid giving at CV risk patients nilotinib. A preference for the NICE approved 2nd generation TKI approach upfront would be an alternative 2nd generation TKI in order not to inflict an arteriothrombotic event to a patient already at risk of developing this event.

Dasatinib is not known to be associated with conventional arteriothrombotic events, typically myocardial infarction, stroke and peripheral arterial occlusive disease.

Patient groups that would be specifically discriminated against if 1st line dasatinib were not available and nilotinib alone remained, would be patients with:
-diabetes
-CV disease
-those with CV risk factors

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The technology would be very easy to use, as it would be similar to current management of TKI therapy, with no additional clinical requirements. Haematologists have been very familiar with the use of dasatinib first line in the context of the national SPIRIT-2 study, pre nilotinib NICE first line approval. The management of patients on dasatinib would follow ELN recommendations in a straightforward fashion.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The monitoring and testing would be equivalent to the current practice of all other TKIs with no formal additional tests required. Like nilotinib, dasatinib is a more potent TKI and increases the chance of discontinuing life-long TKI therapy, although this is a subject being evaluated in clinical trials.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA251- Dasatinib for the first-line treatment of chronic myeloid leukaemia

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The technology under clinical trial conditions does reflect that of clinical practice. This has now been validated in many independent reviews of standard first line 2nd generation TKI therapy in CML management. The most important outcome is to achieve the expected CCyR with minimal toxicity. Achievement of CCyR is a surrogate marker of survival, and predicts long-term outcome. Additional surrogate markers include achievement of MMR, which is termed a 'safe haven' due to its association with a lack of progression. The achievement of MMR and CMR in greater numbers on dasatinib allows for stopping TKI therapy.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Most side-effects on dasatinib are low-grade, easily manageable, and importantly reversible. The incidence of pleural effusion on dasatinib is much lower when dasatinib is given first line, rather than second line and is usually in the order of 10-20%. Pleural effusions are importantly reversible, and it is a frequent observation that the better responding patients develop a pleural effusion allowing for dose reduction. Side-effects of therapy as with all TKIs are dose dependent. Adverse events that were not highlighted in clinical trials include an 0.2-0.6% incidence of pulmonary arterial hypertension from the BMS pharmacovigilance database. As with other adverse events, this improves on drug withdrawal. Haematologists are very aware of the dasatinib spectrum of side-effects and their management.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

As dasatinib has been licensed for some time, and indeed prior to nilotinib, the clinical evidence remains equivalent to that of published clinical trials.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology

appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The delivery of care would not change. Haematologists would be able to improve and more specifically treat their patients according to their Sokal risk score and co-morbidities. Importantly they would not be placing their patients at risk of worsening co-morbidities. NHS staff already have experience with dasatinib and have enrolled patients in the SPIRIT-2 national trial, comparing first line dasatinib with imatinib.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

By approving this technology, NICE would only enhance opportunity and reduce the impact on patients with particular co-morbidities as out-lined above.

In order for NICE to fully achieve its goal for the pursuit of equality this Appraisal needs to incorporate the use of dasatinib for first line for <u>all</u> phases of CML.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

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Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

Your name: [redacted]

Name of your organisation: Royal College of Pathologists
Are you (tick all that apply):

√ a specialist in the treatment of people with the condition for which NICE is considering this technology?

√ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

√ an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
Consultant Haematologist at Imperial College

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA251- Dasatinib for the first-line treatment of chronic myeloid leukaemia

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

Chronic myeloid leukaemia (CML) is a triphasic disease characterised by the presence of the Philadelphia chromosome which itself contains the fusion oncogene BCR-ABL1. This gene encodes a dysregulated tyrosine kinase with enhanced auto-phosphorylation. The majority of patients (>90%) present in the relatively stable chronic phase (CP) but without treatment the disease progresses to a terminal blast crisis (BC), usually through an intermediate stage known as acceleration. CML-BC is uniformly fatal with a life expectancy of less than 5 years. The true incidence of CML in the UK is unknown but is probably just less than 1 per 100,000 population per annum. However, the prevalence of the disease has increased considerably in recent years because of the highly significant improvements in treatment.

The prognosis of CML has changed so dramatically since 2000 that the majority of patients now have a normal life expectancy and this is solely due to the introduction of the tyrosine kinase inhibitors (TKI) that target the causative oncoprotein, Bcr-Abl1. The first of these was imatinib (1999), followed by the second generation agents (2GTKI) dasatinib (2006), nilotinib (2007) and bosutinib (2010), and most recently the third generation drug (3GTKI), ponatinib. All the TKI rapidly normalise the blood count (complete haematological remission-CHR) in patients presenting in chronic phase. It also induces a considerable reduction in tumour load as evidenced by the loss of cells containing the Philadelphia chromosome when the bone marrow was examined by conventional chromosome analysis. This state is known as complete cytogenetic remission (CCyR) and is achieved in approximately 75% of patients after 18 months of treatment with imatinib, but more rapidly and in a higher percentage of patients treated initially with dasatinib or nilotinib. 40-60% of patients achieve a greater reduction in tumour load as indicated by the detection of the RNA encoding BCR-ABL1 only by highly sensitive molecular methodology (RT-PCR). This state is known as major molecular remission (MMR). In approximately 5% of patients the RT-PCR for BCR-ABL1 becomes negative indicating complete molecular remission (CMR).

Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be?

Practice across the UK is largely uniform as it is determined by drug availability through previous NICE apprasals. Outside the context of a clinical trial, most patients presenting in CP are treated with imatinib although nilotinib is also available in the UK and is often used for patients with poor prognostic features at diagnosis (using the Sokal/Hasford/EUTOS prognostic scores for CP).

For patients who present in advanced phase the only available drug is imatinib: this is not the drug of choice. For those presenting in accelerated phase, some have an excellent chance of responding as well as patients presenting in chronic phase, and

should be offered the most potent drug so as to optimise the chance of response and minimise the risk of progression to blast crisis. For those presenting or progressing to blast crisis, the central nervous system is a sanctuary site for residual disease and should be treated with a drug capable of crossing the blood brain barrier: the nly TKi that can do this is dasatinib.

Excellent guidelines have been provided by an expert consensus group from the European Leukemia Net (ELN), first published in 2006 with revisions in 2009 and 2013. A further update is in preparation. These guidelines permit any of imatinib, dasatinib and nilotinib as first line treatment and set out milestones for response (which by definition include both depth of response and the time to that response).

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The ability of the first of the 2GTKI, dasatinib and nilotinib, to durably rescue 50% of patients who were resistant to and/or intolerant of imatinib, led logically to phase III studies of their use in newly diagnosed patients. DASISION randomised patients to imatinib 400mg daily or dasatinib 100mg daily and ENESTnd randomised patients to imatinib 400mg daily or one of two doses of nilotinib, 300mg bd or 400mg bd. Both studies reported 12 month data in the New England Journal of Medicine confirming that each of the 2GTKI had superiority over imatinib in terms of rates of complete cytogeneic and major molecular remissions. This had the immediate effect of changing the treatment of newly diagnosed patients to one or other of the 2GTKI in many centres across the world. This approach has been tempered somewhat by the more recent findings of serious adverse events in a proportion of patients, such that the choice of drug now takes into consideration the diagnostic risk score and pre-existing co-morbidities.

The six year data from ENESTnd have been presented at major international haematology meetings and confirm earlier findings. 82% of patients remain on nilotinib 300mg bd, 65% on the higher dose and 80% on imatinib. 78% of patients on nilotinib achieved MMR compared to 61% on imatinib. The proportion of patients achieving MR4.5 (the depth of remission compatible with trials of stopping therapy) is 55% on either dose of nilotinib compared to 33% on imatinib.

The five year data form DASISION show similar results with 76% and 64% reaching MMR at 5 years on dasatinib and imatinib respectively. The rates of MR4.5 at 5 years were 42% f0r Dasatinib and 33% for imatinib. Very few patients have lost MMR and none have lost a 4.5 log reduction in tumour load. Dasatinib was equally well tolerated as imatinib so concerns about excess toxicities appear unfounded. The data confirm the expected superiority of 2GTKI over imatinib in the first line setting. Early concerns about tolerability appear unfounded and indeed both trials have very good data to suggest that the incidence of grade ¾ toxicity falls with time, such that very few patients developed toxicity in the second year. Both studies show a decrease in the rate of disease progression in the first two years of the 2GTKI compared to imatinib and we would expect this eventually to be reflected in survival.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA251- Dasatinib for the first-line treatment of chronic myeloid leukaemia

A major problem in designing trials in CML is that the survival is so good with first line imatinib (as patients failing this will receive a 2GTKI or a transplant and be salvaged) that many years will have to elapse before a survival advantage can be demonstrated. Thus it is important to consider surrogate marker such as CCyR amd MMR rates. In addition, although progression to advanced phase is now a rare event in CML, the ability of the 2GTKI to reduce this rate in the first two years is very important, as these patients cannot be rescued through salvage therapy.
In summary I am in favour of both drugs being available for upfront treatment of newly diagnosed patients.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

There are a number of prognostic scores that can be applied to patients in chronic phase at diagnosis, i.e. Sokal, Hasford and EUTOS. Despite the Sokal and Hasford scores being developed for patients on busulphan and hydroxycarbamide respectively, all the risk scores are applicable to patients in the TKI era. Patients who fall into the higher/highest category have an increased risk of progressing to advanced phase. Since the risk of progression on TKI is largely restricted to the first two years of diagnosis, it is logical to offer these patients the most potent drugs as early as possible in their disease course.

Recently at least two countries with access to good national cancer registries have reported that younger patients (<25 years) seem to have more aggressive disease and are more likely to develop progressive disease. Since this is also the group that have the best outcome form allogeneic stem cell transplantation, it makes sense to offer these the most potent treatment from diagnosis. If they fail to respond to upfront 2GTKI they can then be referred for early transplant.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Specialist clinics in secondary or tertiary care, staffed by consultant haematologists and supported by clinical nurse specialists. Many patients who are responding well and whose medical team follow the ELN guidelines can be managed in secondary care. Others who are failing to respond adequately should be referred to a tertiary care centre with expertise in the management of difficult situations.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

See above. As far as I am aware the TKI are always used for their licensed indications.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA251- Dasatinib for the first-line treatment of chronic myeloid leukaemia

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Excellent guidelines have been provided by an expert consensus group from the European Leukemia Net (ELN), first published in 2006 with revisions in 2009 and 2013. A further update is in preparation. These guidelines permit any of imatinib, dasatinib and nilotinib as first line treatment and set out milestones for response (which by definition include both depth of response and the time to that response). There are similar guidelines from the US National Comprehensive Cancer Network.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

As indicated above, the majority of patients with CML will enjoy a near-normal life expectancy if we can achieve deep responses and long-term drug tolerability. Attention should be paid to rigorous molecular monitoring at 3 monthly intervals to ensure that patients continue to respond well and to initiate alternative treatment if they should show evidence of failure of treatment

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The majority of patients should expect receive the TKI on a daily basis for life. At present a small proportion of patients have been able to discontinue treatment after several years. This proportion will increase. First, those patients who have been treated long enough to be offered the opportunity to stop treatment, are those who responded well to imatinib, because if they had poor responses, the other drugs were not yet available. This would have included not only patients in who imatinib was ineffective but also those who could not tolerate the drug long-term. Now, we can recognise the patient with a lower chance of responding to imatinib, as early as 3-6 months after initiation of treatment and by prescribing the alternative TKI, can give these patients deep responses and eventually offer them an opportunity to stop. Patients who were unable to tolerate imatinib long-term now change to a more acceptable agent and will eventually achieve deep responses: some of these will also be offered an opportunity to stop. Second the chance of achieving deep and durable responses is higher if nilotinib or dasatinib are used as initial therapy (the first line study on bosutinib is currently underway and it is possible that similar results will emerge) and the expectation is that more of patients with very deep response will be offered a trial of stopping treatment.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA251- Dasatinib for the first-line treatment of chronic myeloid leukaemia

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Although the most important outcomes of any cancer therapy are overall survival and disease free survival, these studies are virtually impossible to do in CML now. The survival is now so good, that the numbers of patients to be included in the studies would be very large and the duration of the trial would be very long. Such studies are not attractive to funders and the treatment algorithm has usually changed long before the trial ends. The outcome of most recent studies were measured in terms of CCyR, MMR and MR4.5. These are surrogate markers of survival and appear to be highly predictive.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The side effects of all the TKI tend to fall within the same spectrum of disorders,but each drug has a particular side effect profile that is not (or rarely) seen with the others. Some of the more serious side effects have emerged only with time and remarkably, imatinib remains the safest of all, despite use now extending to 18 years. Examples of more serious side effects include arterial thrombotic events, hypertension, induction of diabetes and poor control of pre-existing diabetes with nilotinib, pleural effusions and pulmonary arterial hypertension with dasatinib, hepatitis with bosutinib and arterial thrombotic events, hypertension and pancreatitis with ponatinib. This results in the not uncommon position of trying to choose a drug according to the pre-existing co-morbidities of the patient. Giving nilotinib or ponatinib to a long-tern smoker with hypertension and a history of ischaemic heart disease is likely to result in further medical problems, as is giving dasatinib to a patient with pre-existing chronic obstructive airways disease or bosutinib to a patient with cirrhosis. There is no doubt that the TKI have saved the lives of patients with CML but are beginning to result in additional disease burden that could be avoided with better initial drug selection. Of course there will be patients in whom the best drug in terms of efficacy is not the best drug in terms of co-morbidity but at this stage, the decision will be based on a careful evaluation of the risk-benefit.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a

judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Data relating to the front line use of dasatinib in the commercial phase II and II studies have been extensively reported. Data from the UK NCRI CML Working Party Spirit-2 study of dasatinib vs imatinib for newly diagnosed patients has been reported in international meetings and is being prepared for submission for publication. Over 800 patients were randomised in over 145 centres across the country. At 2 years 70% of patients remained on dastanib and 61% on imatinib. The 2 year follow up confirmed a significant difference in the rates to MMR between dasatinib at 58% and imatinib at 46%. Furthermore the rates of MR4.5 at 2 years were 20% on Dasatinib and 14% on imatinib.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

UK physicians are particularly familiar with the use of dasatinib in CML in first and subsequent line settings. The UK NCRI CML Working Party SPIRIT 2 study was a 1:1 randomised study of imatinib vs dasatinib for newly diagnosed patients. Over 800 patients were randomised in over 145 centres across the country. At the time of the study dasatinib was also available for patients who had failed (through resistance or intolerance) imatinib and/or nilotinib. There is therefore considerable experience in the use of dasatinib.

No additional resources or education would be necessary, especially if patients who have failed more than two TKI were to be referred to a specialist CML centre. Providing appropriate access to dasatinib according to its licensed indications would make the management of UK patients straightforward and logical.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular

protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

At present the only drug available for imatinib resistance and intolerance is nilotinib. Because of the associated thrombosis and hyperglycaemia, nilotinib should not be given as first-line therapy to any patient with pre-existing risk factors for these conditions. This means that many patients with CML are not necessarily discriminated against but are exposed to unnecessary risks. Furthermore, as outlined above, patients who present in advanced phase disease or in chronic phase with high risk scores, or who are young and present in chronic phase, should all be considered for a 2GTKI at diagnosis. This would result in any patient in this situation who had risk factors for thrombosis and/or diabetes, being considered for imatinib rather than nilotinib which would put them at risk of early progression. Dasatinib should be available for these patients and others who prefer a once daily rather than a twice daily drug regimen.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Dasatinib for the first-line treatment of chronic myeloid leukaemia (part review of TA251) ID1014

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by NCRI-RCP-ACP and consequently I will not be submitting a personal statement.

Name: .....[redacted].....

Signed: .....

Date: .....23/8/16.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Patient/carer expert statement

Dasatinib for the first-line treatment of chronic myeloid leukaemia (part review of TA251) ID1014

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: [redacted]
Name of your nominating organisation: CML Support
Do you know if your nominating organisation has submitted a statement?

☐ Yes

Do you wish to agree with your nominating organisation's statement?

☐ Yes

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes

- a carer of a patient with the condition?

☐ No

- a patient organisation employee or volunteer?

☐ Yes

Do you have experience of the treatment being appraised?

☐ Yes

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

Most patients who live with CML do so with great success. In general, I am one of those lucky ones. Life goes on.

However, though life goes on, it's not quite the same as before. For me, I get side-effects which from speaking with other patients are pretty common. I am easily fatigued to the point I cannot work a 5-day week. I get joint and muscle pain, which can hinder some aspects of my life. For my day-to-day life this means that I have to manage my energy levels more carefully than most people do which means sometimes saying "no" to things I'd really like to do.

I know through chatting with other less fortunate patients that I am "lucky". I respond well to treatment. Others do not respond to any TKI adequately, and face a much more difficult path, and others have the enormous benefit, which we did not have some time back, that when one TKI doesn't work, or isn't tolerated, another is.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

The primary treatment outcome I want, and I think most patients would desire would be achieving a major molecular response to leukaemia. This is highly correlated to long-term survival. The reasons why this is the primary outcome I want does not require much explanation.

I am pleased that after commencing dasatinib I reached MMR.

Now that I am in MMR, with long-term survival looking good, I want to return as close as possible to my previous standard and quality of life before diagnosis. Successfully returning to work (only part time) was incredibly important to me as our work is something that so many of us find self-defining to an extent. I want to have an active life including exercise and ability to socialize with friends and family. For the most part, I can do this when I want to by being careful how hard I work and managing my energy levels carefully.

I'm a relatively young patient and another outcome that is critical to me is around family planning. Not just the ability to conceive and for my wife to hold a pregnancy to a safe and successful conclusion for both baby, mother and me - but to have confidence in treatment to allow for long term forward family planning.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

Please see the CMLSg submission

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)

- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

- Survival
- High quality of life
- Convenience of tablet form
- Non reliance on clinical setting to take treatment
- Ability to return to work and active personal life
- For most people, relatively low grade side effects

Please explain any advantages that you think this treatment has over other NHS treatments in England.

- Different side effect profile (both major and minor side effects) to other available treatments
- Lack of fasting requirement which can be a significant barrier to compliance
- Once a day schedule
- Potentially deeper response than other available treatments

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

From talking with other patients I'm aware of differences of opinion amongst some patients about the demands placed upon them by a treatment regime that is based on a 'daily dose for life' protocol where a lack of adherence presents real clinical challenges. Some find this very onerous whereas others

adapt their lifestyles easily to it. A patient's particular perspective is likely to affect decision making on issues like, for example, dose reduction and especially cessation. I know some patients who may be candidates for cessation / reduction are quite happy to apply an "if it's not broke, don't fix it" strategy, whereas others who experience deeper side-effects would be very keen to reduce / stop their drugs.

I know of younger patients, those of working-age and in busy careers find the fasting associated with some TKI drugs very burdensome. It interferes strongly with a good quality of life and where they have jobs that have irregular and unpredictable working hours and commitments it presents a real challenge to adherence. This was one of my primary concerns when I was required to stop taking imatinib and switch to a second-generation TKI.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

- TKI treatment is generally non-curative, which is disadvantageous from a physical and mental health wellbeing perspective

- Side effect management remains a considerable issue for many patients

- Treatment may cause irreversible side effects for some patients – e.g. cardiac events

Please list any concerns you have about the treatment being appraised.

- The side effect profile of dasatinib is different to other TKIs and therefore it may be disadvantageous to come patients, but advantageous to others.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

- None known.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

- Patients who have failed other available TKIs either due to a clinically poor outcome, or an unacceptable side effect profile may find dasatinib is a successful treatment option for them

- Patients with an active lifestyle, who work shift work or have an otherwise unpredictable schedule may benefit greatly compared to a TKI which requires a fasting schedule. A fasting schedule with an unpredictable schedule can have a significant impact on medical compliance.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

- Assuming that the potential inclusion of dasatinib is in addition to currently available TKIs there is no group of patients who would be disadvantaged by its introduction.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations

from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

- Those attempting to conceive a child (mother or father) are impacted by current CML treatment. It is my understanding that dasatinib does not offer any benefit over other available treatment, therefore there is not an equality issue with regard to this group.

- No other issues are apparent

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

Dasatinib has a different molecular structure to other treatments available. This can help reduce or eliminate side effects for patients, compared to another treatment. It may also help patients develop a faster and deeper response to disease, with potential for deescalating dosage or even attempting treatment withdrawal completely with a successful outcome.

Dasatinib may work for a patient where other TKIs have failed, which may save a patient's life. From that patient's perspective that is about as innovative as things get.

Is there anything else that you would like the Appraisal Committee to consider?

Though I am aware that there is some emerging evidence to suggest that patients who exhibit a very deep response to TKIs can attempt to stop taking them, and for some of those patients CML does not return to previous levels, in general TKIs are a non-curative treatment to CML.

A bone marrow transplant is a curative option for CML patients who can find a donor. However, this is generally not an attractive option to CML patients

except those who have failed to respond to all TKIs. A bone marrow transplant has mortality rates that are unfavorable when compared to TKI therapy. Even when a bone marrow transplant is highly successful, as the Anthony Nolan Foundation put it, “a bone marrow transplant patient is a patient for life” just as most TKI patients are TKI patients for life it’s clear that CML patients are patients for life. TKIs have a less challenging therapy profile compared to traditional chemotherapy and bone marrow transplant in the first instance.

Since TKI is an oral chemotherapy it is a treatment option that is easy for patients to take whilst going about their normal life. The mortality profile is favourable compared to a bone marrow transplant and long-term problems associated with traditional chemotherapy, radiation and a bone marrow transplant such as kidney problems to not generally present with TKI usage. TKI therapy is a considerably more predictable therapy choice for patients with high quality outcomes expected and experienced by most patients.

Not every patient performs well on each TKI, which is why it is important that a variety of TKIs are available to treat patients to get the best therapeutic and quality of life response possible to their leukaemia.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Dasatinib can help some patients achieve a deeper and faster disease response
- Side effect profiles of all TKIs differ. By having more options, there is more chance to treat patients with acceptable side effects and therefore increased quality of life
- The use of this treatment over some other available treatments eliminates the need to fast for long periods and therefore helps medical compliance
- The addition of another more powerful second generation TKI to join, nilotinib, the other member of that class as a first line treatment would

reflect a more modern, upgraded approach to CML treatment comparable to that obtained in other similar countries.

- Much is made of patients being able to choose the treatments most suited to their individual requirements. This extends beyond side effects, frequency, dosage etc to a whole treatment, holistic package which is, for TKIs for CML and for most patients, for life. Having three rather than two entry level treatments adds considerably to a choices list.

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CANCER DRUGS FUND RAPID REVIEW OF:

DASATINIB FOR TREATING IMATINIB-RESISTANT CHRONIC MYELOID LEUKAEMIA AND FOR PEOPLE FOR WHOM TREATMENT WITH IMATINIB HAS FAILED BECAUSE OF INTOLERANCE

(PART REVIEW OF NICE GUIDANCE TA 241)

&

DASATINIB FOR THE FIRST-LINE TREATMENT OF CHRONIC MYELOID LEUKAEMIA

(PART REVIEW OF NICE GUIDANCE TA 251)

REPORT BY THE DECISION SUPPORT UNIT

1st September 2016

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk

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This report should be referenced as follows:

Rothery C. Cancer Drugs Fund rapid review of dasatinib for treating imatinib-resistant chronic myeloid leukaemia and for people for whom treatment with imatinib has failed because of intolerance (part review of TA241) & dasatinib for the first-line treatment of chronic myeloid leukaemia (part review of TA251). Centre for Health Economics, University of York, 2016.

Use of confidential data

Any ‘commercial in confidence’ data provided by the company, and specified as such, is highlighted in blue and underlined in the review. Any ‘academic in confidence’ data provided by the company, and specified as such, is highlighted in yellow and underlined in the review.

EXECUTIVE SUMMARY

Background

The National Institute for Health and Care Excellence (NICE) is reconsidering cancer drugs currently funded through the Cancer Drugs Fund (CDF). As part of this process, dasatinib (Sprycel®) for the treatment of chronic myeloid leukaemia (CML) with resistance or intolerance to prior imatinib treatment (part review of NICE Guidance TA 241) and dasatinib for the first-line treatment of CML (part review of NICE Guidance TA 251) is being rapidly reviewed. For this report, the NICE Decision Support Unit (DSU) has adopted the role of an Assessment Group (AG) and provides a critique of the company's submission for the use of dasatinib in the first- and second-line settings.

In 2011, a Final Appraisal Determination (FAD) was issued for a Multiple Technology Appraisal (MTA) indicating that dasatinib was not recommended as a cost-effective use of National Health Service (NHS) resources for the treatment of CML with resistance or intolerance to prior imatinib treatment (TA 241). However, NICE did recommend nilotinib for this indication, while high-dose imatinib was not recommended. The committee concluded that there was no evidence to distinguish between the clinical effectiveness of dasatinib and nilotinib but, with a Patient Access Scheme (PAS) in place for nilotinib, treatment with dasatinib and high-dose imatinib were dominated by nilotinib (i.e. more costly with same or less effects). The committee concluded that the incremental cost effectiveness ratio (ICER) for nilotinib compared with hydroxycarbamide was likely to be less than £31,300 per quality-adjusted life year (QALY) gained.

In 2012, a FAD was issued for a MTA indicating that dasatinib was not recommended as a cost-effective use of NHS resources for the first-line treatment of CML (TA 251). However, NICE did recommend both nilotinib and standard-dose imatinib for this indication. The committee concluded that there was insufficient evidence to distinguish between the clinical effectiveness of dasatinib and nilotinib but, with a Patient Access Scheme (PAS) in place for nilotinib, treatment with first-line nilotinib followed by second-line imatinib dominated first-line treatment with dasatinib followed by either imatinib or nilotinib. The ICER for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib was estimated to be £11,000 per QALY gained. The committee concluded that nilotinib represented a cost-effective first-line treatment for CML. The committee also recognised the

proven long-term record of safety and efficacy for imatinib and concluded that standard-dose imatinib should also be an option for first-line treatment of CML.

The company's new submission

For this rapid review of appraisals TA 241 and TA 251, the company presented a PAS which consists of a discount on the list price of dasatinib along with additional evidence to support the conclusions drawn in the appraisals about the clinical effectiveness of dasatinib compared to nilotinib and imatinib.

The company performed a systematic literature review to identify studies assessing treatments for adults with CML who are resistant or intolerant to prior therapy and for treatment of newly diagnosed CML. The company presented additional follow-up data of trials comparing dasatinib and imatinib. No trials directly comparing dasatinib and nilotinib were identified in either the first- or second-line setting. The company indicated that a network meta-analysis (NMA) comparing dasatinib, nilotinib and imatinib in the second-line setting was not possible due to a lack of control arm studies for nilotinib and a lack of equivalent follow-up periods or endpoints reported. The company presented results from a NMA for the surrogate outcomes of complete and partial cytogenetic response in the first-line setting. The company concluded that the available evidence suggests that dasatinib and nilotinib are similarly effective, and offer superior outcomes compared with imatinib, in newly diagnosed CML. The company also concluded that no new data had been identified to change the conclusions drawn in TA 241 that there is limited evidence to distinguish between dasatinib and nilotinib treatment for resistance to prior imatinib therapy.

The company presented a simple cost comparison analysis of dasatinib, nilotinib and imatinib based on an assumption of equivalent efficacy and safety across all three interventions in the first- and second-line setting. The company's analysis takes account of the new PAS discount on the list price of dasatinib. The company concludes that there are significant advantages to the NHS in the availability of dasatinib, where evidence suggests efficacy is higher than that of imatinib and comparable to nilotinib [redacted].

DSU critique of the company's new submission

No new evidence has been presented by the company that changes the conclusions drawn in TA 241 and TA 251 regarding the relative efficacy and safety of the interventions. The evidence base for first- and second-line treatment of CML remains uncertain and relies on the use of surrogate outcomes to predict survival. The presentation of results from a longer follow-up has not resolved this uncertainty. The DSU concludes that there is insufficient evidence to distinguish between dasatinib and nilotinib for the treatment of chronic or advanced phase CML.

The cost comparison undertaken by the company is a cost-minimisation analysis (CMA). The company has assumed that all health outcomes (surrogate outcomes, adverse event rates, progression-free survival, overall survival and treatment duration) are equivalent between dasatinib, nilotinib and imatinib. Therefore, with the exception of drug acquisition costs, all other resource use and costs are equal. In doing so, the company has implicitly assumed that there is no uncertainty in health outcomes and costs, which means that there is no value to the collection of additional efficacy data to distinguish between dasatinib and nilotinib – a conclusion not supported by the uncertain evidence base. The company has also implicitly assumed that health outcomes are not only equivalent for first-line treatments but also equivalent for subsequent lines of therapy. A simple CMA will only hold when treatment strategies with the same number of lines of therapy are compared against each other.

The DSU concludes that, under the assumption of equivalence of outcomes for dasatinib and nilotinib, the NHS would be indifferent between dasatinib and nilotinib for the treatment of imatinib-resistant or imatinib intolerance chronic phase CML. Dasatinib and nilotinib are expected to dominate high-dose imatinab (i.e. less costly and more effective) in the second-line setting. The DSU concludes that there is considerable uncertainty surrounding the assumption of equivalence of outcomes for dasatinib, nilotinib and imatinib for first-line treatment of chronic phase CML. A full probabilistic cost-effectiveness analysis would be required to quantify this uncertainty and to assess the relative cost-effectiveness of the interventions when dasatinib is offered with a PAS discount to its list price.

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TABLES

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ABBREVIATIONS

AG	Assessment Group
CCyR	Complete cytogenetic response
CDF	Cancer Drugs Fund
CHR	Complete haematologic remission
CI	Confidence interval
CMA	Cost minimisation analysis
CML	Chronic myeloid leukaemia
DSU	Decision Support Unit
FAD	Final Appraisal Determination
HU	Hydroxyurea
ICER	Incremental cost-effectiveness ratio
MCyR	Minor cytogenetic response
MMR	Major molecular response
MTA	Multiple Technology Appraisal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PAS	Patient access scheme
PCyR	Partial cytogenetic response
PenTAG	Peninsula Technology Assessment Group
PFS	Progression free survival
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
SCT	Stem cell transplantation
SHTAC	Southampton Health Technology Appraisal Centre

1. INTRODUCTION

The National Institute for Health and Care Excellence (NICE) is currently in the process of re-considering cancer drugs that were previously funded through the current Cancer Drugs Fund (CDF) following appraisal by NICE that did not result in a recommendation. This reconsideration entails a rapid review of the companies' resubmissions to determine whether these drugs now represent a cost-effective use of National Health Service (NHS) resources and if not, whether they should continue to be used within the revised CDF.

The NICE Decision Support Unit (DSU) has been commissioned to review the company submissions for (i) the reconsideration of dasatinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) in people for whom treatment with imatinib has failed because of intolerance (part review of NICE Guidance TA 241 [1]); and (ii) the reconsideration of dasatinib for the first-line treatment of chronic myeloid leukaemia (part review of NICE Guidance TA 251 [2]). These two applications of dasatinib were originally considered in separate Multiple Technology Appraisals (MTAs). The first of these appraisals considered dasatinib, high-dose imatinib and nilotinib for adults in whom CML is resistant to treatment with standard-dose imatinib or in adults who have imatinib intolerance [1]. This appraisal was conducted in 2010 to 2011 with the Final Appraisal Determination (FAD) issued in August 2011. NICE did not recommend dasatinib for the treatment of chronic, accelerated or blast-crisis phase CML in adults with imatinib intolerance or whose CML is resistant to treatment with standard-dose imatinib. However, NICE did recommend nilotinib for this indication, while high-dose imatinib was not recommended. Following the NICE recommendations the company for dasatinib, Bristol-Myers Squibb, made an Appeal against the FAD in September 2011. The Appeal Panel was convened in November 2011 but all grounds for appeal were dismissed.

The second MTA considered dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of CML [2]. This appraisal was conducted in 2011 to 2012 with the FAD issued in March 2012. NICE did not recommend dasatinib for the first-line treatment of chronic phase Philadelphia-chromosome-positive CML. However, NICE did recommend both nilotinib and standard-dose imatinib for this indication. Dasatinib was subsequently added to the CDF.

In the scope of these rapid reviews, new evidence is generally not permitted unless an exception has been granted by NICE. For this reconsideration, the company has presented a new Patient Access Scheme (PAS) which consists of a discount on the list price of dasatinib. The company has also presented additional evidence to support the conclusions drawn in TA 241 and TA 251 about the clinical effectiveness of dasatinib. Two separate company submissions have been received for the reconsideration of dasatinib in a first- and second-line setting:

I. Dasatinib for the treatment of adult patients with chronic, accelerated or blast phase chronic myelogenous leukaemia with resistance or intolerance to prior therapy including imatinib mesile – Part review of TA 241 [3];
II. Dasatinib for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia in the chronic phase – Part review of TA 251 [4].

The DSU has been asked by NICE to provide a critical evaluation of the company submissions in line with NICE Methods Guide (including the addendum to the methods guide to support the CDF arrangements) [5]. Since dasatinib has been considered in two separate NICE appraisals and the company has submitted two separate submissions for this reconsideration, the DSU considers each submission separately in the sections that follow. We begin with a review of TA 241, followed by an overview of the company's submission for the part review of TA 241 and the DSU critique. We then present a review of TA 251, the company's submission for the part review of TA 251 and followed with the DSU critique.

2. SUMMARY OF THE ORIGINAL SUBMISSION AND COMMITTEE'S CONSIDERATIONS FOR TA 241

In the original appraisal of TA 241, dasatinib, nilotinib and high-dose imatinib were considered for the treatment of CML resistant to prior therapy on standard-dose imatinib or failed due to intolerance [1]. To assess the cost-effectiveness of the three interventions, two of the companies submitted cost-effectiveness models (Bristol-Myers Squibb for dasatinib and Novartis for nilotinib), while a model was developed by the Assessment Group (The Peninsula Technology Assessment Group, PenTAG). The Assessment Group model was subsequently updated by another Assessment Group (The Southampton Health Technology

Appraisal Centre, SHTAC). The models considered resistance to imatinib and intolerance to imatinib as two separate populations. The range of comparators considered were standard-dose imatinib, hydroxycarbamide, allogeneic stem cell transplantation and interferon alfa. The Bristol-Myers Squibb model considered each of the CML phases of chronic, accelerated, and blast-crisis phase separately, while the Assessment Group (AG) and Novartis models only considered the chronic phase of CML due to an absence of evidence to populate the model in the accelerated and blast-crisis phases.

The clinical effectiveness data informing the models were drawn from a total of 11 studies. Only one was a comparative head-to-head randomised controlled trial (RCT) which compared dasatinib with high-dose imatinib. Two studies were dose-finding RCTs for dasatinib, while the other 8 studies were single arm studies (three of high-dose imatinib, two of nilotinib, and three of dasatinib). The AGs noted that the only comparative RCT had a number of methodological limitations and a high level of crossover; therefore the treatment arms were considered separately. Table 1 provides a summary of the clinical effectiveness data that was considered by the Appraisal Committee (as reported in the FAD). Overall survival in the AG models was estimated by extrapolating from the surrogate outcome of major cytogenetic response over a lifetime horizon. Duration of treatment was initially estimated on the basis of progression-free survival, but this was later revised to an assumption of 10 years for each of the interventions due to a lack of mature data. Health-related quality of life was estimated based on EQ-5D utility values applied to health states representing the phases of CML. Resource use and cost data in the AG models included drug acquisition costs, administration costs for interferon alfa, outpatient visits, bone marrow tests, X-rays, CT scans, blood transfusions, and inpatient terminal care. The costs of treating adverse events were not considered in the AG models since the incidence of serious adverse events was relatively low.

The Appraisal Committee reviewed the evidence available. The committee noted the poor quality of the evidence base with non-comparative studies, short treatment duration and use of surrogate outcomes to predict overall survival. The committee concluded that it was clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for people with imatinib-resistant CML. However, the committee agreed that the limited evidence base means that the magnitude of the benefit is uncertain. The committee acknowledged the clinical specialist's view that for CML that is resistant to standard-dose imatinib, high-dose

imatinib was unlikely to be as beneficial as dasatinib and nilotinib. The committee also agreed that there was no good evidence to distinguish between dasatinib and nilotinib. For imatinib intolerance, the committee noted that in the studies that reported response rates separately for this population, there was a higher response to dasatinib and nilotinib compared with the imatinib resistant CML population. The committee noted that the evidence base for blast-crisis phase CML was very limited. The committee also discussed the side effects of treatment and concluded that dasatinib and nilotinib are better tolerated than imatinib.

The Appraisal Committee examined the assumptions that had been used in the economic models provided by the companies and the Assessment Groups. The committee noted that treatment duration and estimates of overall survival were not modelled accurately across any of the models. In particular, the committee was concerned that none of the models reflected the fact that in clinical practice people will receive treatment until progression or death. The committee concluded that the treatment duration for the interventions should be at least 10 years. The committee believed that the SHTAC scenario in which the treatment durations of dasatinib, nilotinib and high-dose imatinib were set to 10 years represented the most plausible scenario. In this scenario, estimates of overall survival were 13.4 years, 12.98 years and 12.4 years for dasatinib, nilotinib and high-dose imatinib, respectively, and the monthly treatment cost of the interventions were £2,540, £2,643 and £3,253, respectively. The corresponding cost-effectiveness estimates indicated that high-dose imatinib and nilotinib were dominated by dasatinib, and the ICER for dasatinib compared with hydroxycarbamide was £43,800 per QALY gained (with all other comparators either dominated or extendedly dominated). The committee noted that if the treatment duration was continued for most of the person's lifetime, then the ICERs would be expected to increase further. The committee also concluded that there was no evidence to distinguish between dasatinib and nilotinib and that the ICERs for these treatments compared to hydroxycarbamide were uncertain and likely to be higher than £43,800 per QALY gained. The committee also discussed the cost-effectiveness of the interventions in the imatinib intolerance population and concluded that the evidence was uncertain but that dasatinib and nilotinib were likely to be as cost-effective in this population as the imatinib-resistant population given that the outcomes were generally better for imatinib intolerance.

During this appraisal, Novartis proposed a Patient Access Scheme (PAS) for nilotinib, which was agreed with the Department of Health. The company presented ICERs for the scheme reflecting the scenario that was considered the most plausible by the committee. The resulting ICER, when replicated by the SHTAC AG, was £31,300 per QALY gained for nilotinib compared with hydroxycarbamide. The company also presented an ICER with a number of further changes made to the analysis, which included setting survival benefit for nilotinib equal to that of dasatinib, but the committee did not agree with all of the adjustments made by the company. The committee concluded that the ICER for nilotinib is likely to be less than £31,300 per QALY gained. Therefore, the use of nilotinib for the treatment of chronic and accelerated phase CML that is resistant to standard-dose imatinib or imatinib intolerance could be regarded as a cost-effectiveness use of NHS resources, but only with the discount agreed as part of the PAS.

The committee noted that the ICERs for dasatinib were higher than those normally considered acceptable. Furthermore, the committee noted that given the PAS for nilotinib and the assumed equivalence of effectiveness of dasatinib and nilotinib, dasatinib is more expensive but no more effective than nilotinib. The committee also considered the use of dasatinib in the accelerated and blast-crisis phases of CML and concluded that there was insufficient evidence to suggest that dasatinib could be considered a cost-effective use of NHS resources. The committee also concluded that high-dose imatinib could not be recommended since it was dominated (more expensive and less effective than nilotinib or dasatinib) in all models.

Table 1: Clinical effectiveness outcomes for dasatinib, nilotinib and high-dose imatinib considered during the appraisal of TA 241.

	Complete cytogenetic response	Major cytogenetic response	Complete haematological response	Major molecular response
Chronic phase, imatinib resistant				
Dasatinib	37.4% (95% CI: 34.2% - 40.5%)	50.9% (95% CI: 47.6% - 54.1%)	89.2% (95% CI: 87.2% - 91.3%)	63.4% of the people who had CCyR
Nilotinib	30.3% (95% CI: 24.1% - 36.5%)	46.5% (95% CI: 35.7% - 57.6%)	78.9% (95% CI: 55.9% - 100%)	-
High-dose imatinib	Ranged from 18.4% - 36.4%	Ranged from 32.7% - 63.5%	Ranged from 55.5% - 91.8%	55.6% of the people who had CCyR
Chronic phase, imatinib intolerance				
Dasatinib	68.1% (95% CI: 62.7% - 73.5%)	75.5% (95% CI: 70.5% - 80.5%)	93.7% (95% CI: 89.5% - 97.9%)	-
Nilotinib	34.9% (95% CI: 24.9% - 45.9%)	46.5% (95% CI: 35.7% - 57.6%)	90.0% (95% CI: 78.2% - 96.7%)	-
Accelerated phase, imatinib resistant				
Dasatinib	30.9% (95% CI: 26.4% - 35.5%)	38.8% (95% CI: 34.0% - 43.6%)	48.2% (95% CI: 43.3% - 53.1%)	-
Nilotinib	14.3%	26.8%	51%	-
Accelerated phase, imatinib intolerance				
Dasatinib	36.9% (95% CI: 27.3% - 46.5%)	44.3% (95% CI: 34.4% - 54.2%)	46.3% (95% CI: 36.4% - 56.1%)	-
Nilotinib	Evidence did not allow separate calculations for imatinib intolerance			

CCyR, complete cytogenetic response; CI, confidence interval.

3. SUMMARY OF THE COMPANY'S SUBMISSION FOR REVIEW OF TA 241

3.1. CLINICAL EFFECTIVENESS EVIDENCE

The company reported on the results of a systematic literature review that was conducted to identify randomised controlled trials (RCTs) assessing treatments for adults with CML who are resistant or intolerant to prior therapy. Full details and results are provided as an appendix to the company's submission. No trials directly comparing dasatinib and nilotinib were identified.

The company used the evidence from three RCTs of dasatinib (one comparing dasatinib with high-dose imatinib [6, 7] and two dose-finding RCTs for dasatinib [8-11]) to support the efficacy of dasatinib for the treatment of chronic, accelerated and blast-crisis phase CML with resistance or intolerance to prior therapy including imatinib. Table 2 provides an overview of the studies included in the company's submission. All three RCTs had been considered previously in the appraisal of TA 241. However, additional results from two of the trials are presented in the company's submission, which had not been available previously at the time of TA 241. One of these represents a longer follow-up of the dose-finding trial CA180-034 (minimum follow-up of 24 months) [10, 11], while the other represents new results from the dose-finding trial CA180-035 in the blast-crisis phase of CML [9].

A number of additional studies for nilotinib in CML with resistance or intolerance to imatinib were also identified by the company and reported in Appendix 1. These additional studies included the trials of ENESTcmr [12-16], RE-NICE [17-20], LASOR [21], and ENESTnd Extension [22]. All of these trials were in the chronic phase of CML and compared nilotinib with high-dose imatinib. However, the level of cytogenetic response and molecular response outcomes reported in these trials was very limited. The company also presented updated results of a single arm study of nilotinib at 24 months follow-up in Appendix 3 [23].

The company indicated that a network meta-analysis comparing dasatinib, nilotinib and imatinib was not possible due to a lack of control arm studies for nilotinib and a lack of equivalent follow-up periods or endpoints reported. Therefore, the company only presented a naïve comparison of the interventions at 24 months follow-up. Table 3 provides a summary

of the company's naïve comparison in chronic CML. The company interpreted the evidence as suggesting that clinical outcomes are comparable between dasatinib and the other tyrosine kinase inhibitors in the second-line CML setting.

The company concluded that no new data had been identified to change the conclusions drawn in TA 241. In particular, the company concluded that the available data is supportive of the conclusion that there is limited evidence to distinguish between dasatinib and nilotinib for the treatment of patients resistant to prior imatinib therapy.

Table 2: Studies included in the company's submission supporting the efficacy of dasatinib for the treatment of CML with resistance or intolerance to prior therapy with imatinib.

Trial name	Treatment arms	Reported outcomes	Considered during TA 241?
Chronic phase CML			
START-R [6, 7]	Dasatinib 70 mg BID	CCyR, MCyR, PCyR, CHR, MMR, PFS, grades 3/4 adverse events	Yes
	High-dose imatinib 400 mg BID		
CA180-034 [10, 11]	Dasatinib 100 mg OD	MCyR, CCyR, CHR, PFS, OS, grades 3/4 adverse events	Yes. Additional results are presented for longer follow-up of 24 months
	Dasatinib 50 mg BID		
	Dasatinib 140 mg OD		
	Dasatinib 70 mg BID		
Accelerated phase CML			
CA180-035 [8]	Dasatinib 140 mg OD	MCyR, CCyR, CHR, MHR, PFS, OS, grades 3/4 adverse events	Yes
	Dasatinib 70 mg BID		
Blast-crisis phase CML			
CA180-035 [9]	Dasatinib 140 mg OD	MCyR, CCyR, CHR, MHR, PFS, OS, grades 3/4 adverse events	No
	Dasatinib 70 mg BID		

CCyR, Complete cytogenetic response; MCyR, Minor cytogenetic response; PCyR, Partial cytogenetic response; CHR, Complete haematologic remission; MMR, Major molecular response; PFS, Progression-free survival; CML, Chronic myeloid leukaemia; BID, twice daily; OD, once daily.

Table 3: Outcomes at 24 months follow-up in the company's naïve comparison of dasatinib, nilotinib and high-dose imatinib for the treatment of chronic phase CML.

Treatment	CCyR			PCyR			CHR			MMR			Long-term outcomes	
	Overall	Resistant	Intolerant	Overall	Resistant	Intolerant	Overall	Resistant	Intolerant	Overall	Resistant	Intolerant	OS	PFS
CA180-034 [24, 25]														
Dasatinib 100 mg OD	49.7%	43.5%	67.4%	13.8%	15.3%	9.3%	91.6%	88.7%	100%	37.0%	35.0%	43.2%	91%	80%
Dasatinib 140 mg OD	50.3%	42.3%	72.7%	12.6%	15.4%	4.5%	86.8%	86.2%	88.6%	38.2%	29.7%	66.7%	94%	75%
Dasatinib 50 mg BID	50.0%	41.9%	72.7%	11.3%	13.7%	4.5%	92.3%	91.9%	93.2%	37.8%	32.5%	53.8%	90%	76%
Dasatinib 70 mg BID	53.6%	48.0%	69.0%	7.7%	8.7%	4.8%	88.1%	88.9%	85.7%	38.4%	34.2%	51.4%	88%	76%
START-R [6, 7]														
Dasatinib 70 mg BID	-	43.5%	-	-	9.9%	-	-	93.1%	-	-	28.7%	-	NR	86%
Imatinib 400 mg BID	-	18.4%	-	-	14.3%	-	-	81.6%	-	-	12.2%	-	NR	65%
Kantarjian et al (2011) [23]														
Nilotinib 400 mg BID	44%	41%	51%	15%	15%	15%	NR	NR	NR	27.9%	NR	NR	87%	64%
Kantarjian et al (2009) [26]†														
Imatinib (median dose 604 mg daily; range 294-800mg)	-	25.0%	-	-	22.9%	-	-	12.5%	-	NR	NR	NR	96%	90%

CCyR: complete cytogenetic response; PCyR: partial cytogenetic response; CHR: complete haematological response; MMR: major molecular response; NR: not reported; OS: overall survival; PFS: progression-free survival; OD: once daily; BID: twice daily.

† Long-term outcomes reported at 1 year follow-up.

3.2. COST COMPARISON

The company presented a simple cost comparison analysis of dasatinib, nilotinib and high-dose imatinib based on the assumption of equivalent efficacy and safety across all three tyrosine kinase inhibitors. The company's analysis takes account of a new PAS consisting of a [redacted] discount to the list price of dasatinib (which is £2,504.96 for a pack of 30 tablets of 100mg or 140 mg). Table 4 shows the cost per month for each of the interventions at the recommended dose in the Summary of Product Characteristics. The manufacturer of nilotinib agreed to make nilotinib available with a PAS discount during the appraisal of TA 241 but this discount is confidential. The company has indicated that the dasatinib PAS has been designed to ensure [redacted] to that of nilotinib. The company believes that the discount of [redacted] on the list price of dasatinib is [redacted] to that of nilotinib, as inferred from publically available incremental cost-effectiveness ratios (ICERs) in health technology assessments (HTAs) reports during the appraisals of TA 241 and TA 251.

Table 4: Cost of dasatinib, high-dose imatinib and nilotinib per month [27].

Intervention	Dose per month	Cost per month
List price of dasatinib	100 mg once daily; 140 mg once daily	£2,541.49
PAS price of dasatinib	100 mg once daily; 140 mg once daily	[redacted]
List price of high-dose imatinib	600 mg once daily; 800 mg once daily	£2,794.86 £3,726.48
List price of nilotinib	400 mg twice daily	£2,644.64
PAS price of nilotinib (TA 241)	400 mg twice daily	Commercial in confidence

The company assumed that health outcomes for dasatinib, nilotinib and high-dose imatinib are equivalent, including the safety profile of the interventions. This assumption also implies that the treatment duration of the interventions is identical. Therefore, with the exception of drug acquisition costs (none of the interventions require administration costs), all other resource use, including that required for the management of adverse events, is assumed equal across the interventions.

3.3. RESULTS OF THE COMPANY'S COST COMPARISON ANALYSIS

Table 5 presents the results of the company's cost comparison analysis. The company estimated that [redacted] would be expected of between [redacted] and [redacted] per patient per month when using dasatinib compared with nilotinib or high-dose imatinib. The company concluded that there are significant advantages to the NHS in the availability of dasatinib, where evidence suggests efficacy is higher than that of imatinib and comparable to nilotinib, [redacted]

Table 5: Results of the company's cost comparison analysis.

Intervention	Cost per month	Incremental cost of dasatinib
Dasatinib (with PAS)	[redacted]	-
Imatinib 600 mg	£2,794.86	[redacted]
Imatinib 800 mg	£3,726.48	[redacted]
Nilotinib (without PAS)	£2,644.64	[redacted]

4. CRITIQUE OF THE COMPANY'S SUBMISSION

4.1. CRITIQUE OF THE CLINICAL EFFECTIVENESS EVIDENCE

No new comparative head-to-head trials comparing dasatinib with nilotinib or high-dose imatinib were identified. The additional evidence only includes dose-finding studies of dasatinib. The company presented a naïve comparison of the interventions based on outcomes reported at 24 months follow-up, but only in selected studies that reported outcomes at this time point since TA 241. For example, the single arm study of dasatinib 70 mg twice daily as reported in Hochhaus et al (2007) had response data presented at 24 months but this study was not included in the company's naïve comparison, while it was included in the original appraisal of TA 241 [28]. The DSU also notes that the previous AGs for TA 241 had identified a number of methodological limitations and a high level of asymmetric crossover in the only comparative RCT of dasatinib with high-dose imatinib (START-R trial [6, 7]).

The DSU does not consider that any additional evidence has been presented that would change the conclusions drawn during TA 241 regarding the relative efficacy of the interventions. The additional evidence presented in Table 3 does seem to support the clinical specialists' view heard during TA 241 that for CML that is resistant to standard-dose

imatinib, high-dose imatinib was unlikely to be as beneficial as dasatinib or nilotinib. For the comparison of dasatinib with nilotinib, the evidence base remains of poor quality. The clinical trials available are non-comparative and rely on the use of surrogate outcomes to predict overall survival. The presentation of results from a slightly longer follow-up of 24 months has not resolved this uncertainty. For example, the results in Table 3 suggest that response rates for the surrogate outcomes of cytogenetic and molecular response, as well as progression-free survival and overall survival, are slightly better for dasatinib compared to nilotinib. The DSU therefore concludes that the magnitude of the benefit is unclear and that there remains no good quality evidence to distinguish between dasatinib and nilotinib.

4.2. CRITIQUE OF THE COST COMPARISON ANALYSIS AND RESULTS

4.2.1. General overview

The cost comparison undertaken by the company is a cost-minimisation analysis (CMA). In CMA it is assumed that the clinical effectiveness of the interventions under comparison are equivalent and, therefore, the choice between the interventions depends only on the difference in costs, with the least costly intervention being the most cost-effective. In addition, an important assumption underpinning CMA is that there is no uncertainty, i.e. the difference in effectiveness between the interventions equals zero with no uncertainty. The company has assumed that dasatinib, nilotinib and high-dose imatinib are equivalent in terms of health outcomes but has failed to comment explicitly on the uncertainty. It is clear from TA 241 that the three interventions cannot be considered exactly equivalent given the uncertainty in the estimates of their effectiveness and the level of poor quality evidence informing the relative effectiveness of the interventions.

4.2.2. Cost-minimisation analysis

The company has assumed that all health outcomes are equivalent between the three interventions. This means that the surrogate outcomes of cytogenetic, haematological and molecular response, adverse events, progression-free survival and overall survival are the same across the interventions. It also means that the treatment duration on each intervention is assumed to be equal. Therefore, it follows that, with the exception of drug acquisition costs, all other resource use and costs are effectively the same across the interventions. This follows because resource utilisation in the model is applied to people in a particular health state, and the likelihood of being in a health state is conditioned upon health outcomes that

are assumed to be equal across the interventions. Therefore, the only difference in costs between the interventions lies in the acquisition costs of the drugs (noting that none of the drugs require administration costs).

The company has indicated that the PAS discount of [redacted] on the list price of dasatinib is [redacted] that of nilotinib, as inferred from publically available incremental cost-effectiveness ratios reported during appraisals TA 241 and TA 251. The company has indicated that the corresponding [redacted] for dasatinib compared with nilotinib are [redacted] per month. However, this estimate of [redacted] does not take into account the PAS discount on the list price of nilotinib. Under the assumption that nilotinib is available with a discount of [redacted] on its list price (as inferred by the company), then the estimated cost of nilotinib is [redacted] per month. This is [redacted] than the discounted price of dasatinib of [redacted] per month, i.e. dasatinib is estimated to [redacted] per month compared with nilotinib, assuming all other outcomes are equal.

During the appraisal of TA 241, the committee accepted that, with the PAS in place for nilotinib, the ICER of £31,300 per QALY gained for nilotinib compared with hydroxycarbamide was an acceptable upper limit to conclude that nilotinib could be regarded as a cost-effective use of NHS resources for the treatment of imatinib-resistant CML. The DSU performed an exploratory analysis to estimate the incremental cost-effectiveness ratio of dasatinib compared with hydroxycarbamide, with and without the PAS discount. Table 6 shows the results of the DSU exploratory analysis based on the outcomes of the SHTAC scenario, which was considered the most plausible scenario by the committee and using a treatment duration of 10 years. This results in an ICER of [redacted] per QALY gained for dasatinib compared with hydroxycarbamide, with the PAS in place for dasatinib. It follows that dasatinib is [redacted] as nilotinib for the treatment of imatinib-resistant CML, provided that both drugs are available with the discount agreed as part of their respective patient access schemes. During TA 241, the committee concluded that dasatinib and nilotinib were likely to be at least as cost-effective in people with imatinib intolerance as in people with imatinib-resistant CML; therefore, the cost-effectiveness in the imatinib intolerance population can be inferred from the cost-effectiveness in the imatinib-resistant population.

Table 6: DSU exploratory analysis of the cost-effectiveness of dasatinib compared with hydroxycarbamide based on the SHTAC scenario with a treatment duration of 10 years.

	Results without PAS		Results with PAS	
	Dasatinib	**HU**	**Dasatinib**	**HU**
Drug costs (£)	£232,972	£213	[redacted]	£213
Other costs (£)	£32,549[†]	£17,915	[redacted]	£17,915
Total costs (£)	£265,521	£18,128	[redacted]	£18,128
Incremental costs (£)	£247,393	-	[redacted]	-
QALYs	7.85	2.20	[redacted]	2.20
Incremental QALYs	5.65	-	[redacted]	-
ICER (£ per QALY)	£43,786		[redacted]	

[†]Assumed to be the same as nilotinib.
HU, hydroxycarbamide.

The company compared dasatinib with high-dose imatinib and estimated that the expected cost savings are up to [redacted] per month when using dasatinib. The DSU notes that even without the PAS discount, dasatinib is cheaper than high-dose imatinib. During TA 241, the appraisal committee acknowledged that high-dose imatinib was unlikely to be as beneficial as dasatinib or nilotinib in CML resistant to standard-dose imatinib. Therefore, it follows that dasatinib and nilotinib are most likely always going to dominate high-dose imatinib. This was also seen in the cost-effectiveness estimates presented during TA 241, where high-dose imatinib was more expensive and less effective than dasatinib and nilotinib.

4.2.3. Uncertainty in the evidence

An important assumption underpinning CMA is that there is no uncertainty. The analysis above implicitly assumes that the incremental effects for dasatinib compared with nilotinib (or vice versa) are known to be exactly zero. This effectively means that there is no value to the collection of additional efficacy data (or other health outcome data) to distinguish between dasatinib and nilotinib outcomes. This conclusion would appear to contradict the many uncertainties that were identified during TA 241. For example, the 95% confidence intervals on the surrogate outcomes in Table 1 for dasatinib and nilotinib overlap. This means that there is a non-zero probability that dasatinib is less (or more) effective than nilotinib. When clinical effectiveness is uncertain it is important to assess the consequences

of this uncertainty for patient outcomes. This would require a full cost-effectiveness analysis with probabilistic sensitivity analysis in order to quantify the probability that dasatinib was as effective and cost-effective as nilotinib, and to estimate the consequences of clinical uncertainty on incremental QALYs.

Uncertainty in health outcomes will also affect uncertainty in total costs. The treatment duration of the interventions was assumed to be 10 years in the absence of any other information, but if this duration differs by treatment then the length of time spent in each health state will also differ. Therefore, the corresponding resource use and costs for the interventions will be different. In the same way, uncertainty in total costs will also arise from uncertainty in survival outcomes.

The issues relating to uncertainty are illustrated in Figure 1 on the cost-effectiveness plane. Scenario A represents the company's assumption that there is no uncertainty in the difference in effects between dasatinib and nilotinib [redacted]. Scenario B represents a situation where there is no statistically significant difference in costs and effects. The 95% confidence ellipse represents the joint uncertainty in expected incremental costs and effects. The DSU considers scenario B to be a better reflection of the evidence that has been presented by the company and appraised during TA 241. A full probabilistic cost-effectiveness analysis would be required to establish exactly where the 95% confidence ellipse lies in the cost-effectiveness plane for the comparison of dasatinib with nilotinib. Without this information, it is unclear which uncertainties (e.g. link between surrogate outcomes and survival, adverse event rates, progression-free and overall survival, treatment duration) are the most significant in terms of the consequences for patient outcomes. This information could then be used to direct and focus research on those areas of uncertainty which have the most value.

Figure 1: Cost-effectiveness plane representing two scenarios. Scenario A represents a situation where the incremental difference in effect between two interventions is exactly zero and the incremental difference in cost is below zero with no uncertainty. Scenario B represents a situation where there is uncertainty in the incremental costs and effects. The ellipse represents the joint uncertainty in costs and effects with a 95% confidence region.

In summary, when the difference in effectiveness between two treatments is not statistically significant then we can only conclude that there is not sufficient evidence to distinguish between the treatments (i.e. we cannot say that they are equally effective) – a conclusion that was drawn during TA 241 for dasatinib and nilotinab.

4.2.4. Conclusions

The DSU concludes that, under the assumption of equivalence of outcomes for dasatinib, nilotinib and high-dose imatinib, the NHS would be indifferent between dasatinib and nilotinib for the treatment of imatinib-resistant or imatinib intolerance chronic phase CML. Dasatinib and nilotinib are also expected to dominate high-dose imatinab (i.e. less costly and more effective). The expected [redacted] are estimated to be [redacted] per month when using dasatinib compared to nilotinib. However, there is considerable uncertainty surrounding the assumption of equivalence and a full probabilistic cost-effectiveness analysis would be required to quantify this uncertainty and ascertain its significance for patient outcomes.

5. SUMMARY OF THE ORIGINAL SUBMISSION AND COMMITTEE'S CONSIDERATIONS FOR TA 251

In the original appraisal of TA 251, dasatinib, nilotinib and standard-dose imatinib were considered for the first-line treatment of CML [2]. To assess the cost-effectiveness of the three interventions, two of the companies submitted cost-effectiveness models (Bristol-Myers Squibb for dasatinib and Novartis for nilotinib), while a model was developed by the Assessment Group (PenTAG). The models considered different lines of therapy in the treatment pathway of CML. The Bristol-Myers Squibb model included first-line tyrosine kinase inhibitors (dasatinib, nilotinib or standard-dose imatinib), second-line tyrosine kinase inhibitors (dasatinib following first-line nilotinib, nilotinib following first-line dasatinib, and second-line treatment was split 50:50 between dasatinib and nilotinib for people who received first-line standard-dose imatinib), and third-line treatments consisted of stem cell transplantation (SCT), chemotherapy, or a combination of chemotherapy and tyrosine kinase inhibitors (dasatinib or nilotinib) for the treatment of chronic phase CML. In the advanced phases of CML (accelerated or blast-crisis phase), treatments included third-line treatment or palliative care.

The Novartis model included first-line tyrosine kinase inhibitors, second-line treatment with dasatinib, and third-line treatment with SCT or hydroxyurea (HU). In a separate scenario, the Novartis model also considered second-line treatment consisting only of SCT or HU with no third-line treatment. In the advanced phases of CML, the Novartis model included treatment with HU.

The Assessment Group (AG) noted that the relative cost-effectiveness of first-line tyrosine kinase inhibitor treatments was heavily influenced by assumptions about subsequent lines of therapy due to considerably uncertainty about cost and health outcomes of the treatments. Therefore, the AG model considered separate scenarios consisting of different lines of treatment. In one scenario, the AG model assumed that, after first-line tyrosine kinase inhibitor treatment failure, all people in the chronic phase progressed directly to a mixture of HU and SCT as second-line treatment, with no further lines of treatment before reaching the accelerated or blast-crisis phase. In a second scenario, the AG assumed that people receiving first-line dasatinib or imatinib progressed to second-line nilotinib. These people then progressed to a mixture of HU and SCT as third-line treatment, before reaching the advanced

phases of CML. For those who failed to respond to first-line nilotinib, it was assumed that a mixture of HU and SCT would follow as second-line treatment, with no further lines of treatment until the advanced phases of CML were reached. Following the first appraisal committee meeting of TA 251, the AG modelled an additional sequence of treatments. This consisted of first-line dasatinib or nilotinib being followed by second-line standard-dose imatinib, which was then followed by a combination of HU and SCT as third-line treatment. For the advanced phases, the AG model assumed that treatment only consisted of HU. This was justified mainly by a lack of evidence on the effectiveness of the tyrosine kinase inhibitors in the advanced stages of CML. All models had a lifetime time horizon.

The clinical effectiveness data informing the models were drawn largely from two RCTs: one comparing dasatinib with imatinib (DASISION trial) and one comparing nilotinib with imatinib (ENESTnd) in newly diagnosed chronic phase CML. Table 7 provides a summary of the clinical efficacy data that was considered by the Appraisal Committee as reported in the FAD. No trials directly comparing dasatinib and nilotinib were identified. Therefore, an indirect comparison of the treatments was carried out using the results of the trials. Due to the short follow-up of the trials, the AG also examined the evidence base for using cytogenetic and molecular response as surrogate measures for survival and health-related quality of life. The AG concluded that there is evidence suggesting that people who experience either a complete cytogenetic response or major molecular response following 12 months of treatment on imatinib have better long-term outcomes (up to 7 years) overall survival and progression-free survival than people who do not respond at 12-month follow-up. In the absence of evidence for dasatinib and nilotinib, the AG considered that the same relationship could be potentially applied to these treatments.

The AG used two alternative approaches to estimate survival in the model: the cumulative survival approach (base case analysis) and the surrogate survival approach (sensitivity analysis). In the cumulative survival approach, overall survival was estimated as the cumulative result of the duration of successive treatments. In the surrogate survival approach, overall survival was estimated using a surrogate relationship based on major molecular response or complete cytogenetic response at 12 months. In these approaches an important assumption was made that overall survival after second- and third-line treatment was independent of previous treatment. The mean duration of first-line treatments in the model was obtained by extrapolating treatment duration data from the trials using Weibull

survival curves. The estimated mean first-line treatment durations in the model were 7.1 years for imatinib, 7.8 years for dasatinib, and 9.0 years for nilotinib. For second-line nilotinib, a treatment duration of 2.4 years was estimated from a study of imatinib-resistant people who received second-line nilotinib, while a treatment duration of 1.9 years was estimated for second-line imatinib. Health-related quality of life was estimated based on EQ-5D utility values applied to health states representing the phases of CML, with a disutility applied to people receiving a stem cell transplant. Resource use and cost data in the AG model included drug acquisition costs, grade 3 or 4 adverse event costs, SCT and a range of medical management costs including hospitalisation and outpatient visits, which differed depending on the phase of CML. The committee noted that a PAS discount was reflected in the acquisition costs of nilotinib in both the Novartis and AG models.

The Appraisal Committee reviewed the evidence available. The committee considered that both trials were of good quality, but were of short duration and only provided surrogate outcome measures and short-term data on progression-free and overall survival. The committee concluded that the available evidence suggests that dasatinib and nilotinib provide superior clinical benefit, as measured by surrogate outcomes, to standard-dose imatinib in the first-line treatment of chronic phase CML. The committee considered the results of an indirect comparison of dasatinib and nilotinib and concluded that there was insufficient evidence to distinguish between the two interventions in terms of clinical effectiveness. The committee also discussed the adverse side effects of treatment and concluded that, although dasatinib and nilotinib were associated with different adverse events, tolerability was similar between the treatments.

The Appraisal Committee examined the assumptions that had been used in the economic models provided by the companies and the AG. The committee noted that although key differences in the treatment pathway and approaches to modelling survival differed between the models and were associated with substantial structural uncertainty, the AG model had included a comprehensive range of scenarios in an effort to address this uncertainty. The following sequence of treatments was considered the most plausible by the committee:

Sequence:

1	Dasatinib	→	nilotinib	→	SCT/HU
2	Imatinib	→	nilotinib	→	SCT/HU

3	Nilotinib	→	imatinib	→	SCT/HU
4	Dasatinib	→	imatinib	→	SCT/HU

The AG presented cost-effectiveness results for each of the sequences using a full sequencing approach and a simplified method, whereby costs and QALYs after tyrosine kinase inhibitor treatment (first- or second-line) were set to be equal across the treatment arms. The committee noted that treatment with first-line nilotinib followed by imatinib dominated first-line treatment with dasatinib followed by either imatinib or nilotinib (i.e. resulted in more QALYs and lower costs). The ICER for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib was £11,000 per QALY gained in both the full and simplified approaches. The committee concluded that nilotinib represented a cost-effective first-line treatment for chronic CML, and that dasatinib was not considered cost-effective. With regard to imatinib, the committee noted that the comparison of first-line imatinib followed by nilotinib and first-line nilotinib followed by imatinib was sensitive to a number of assumptions, including dose intensity and average time spent on second-line treatment. The committee recognised that imatinib has a proven longer-term record of safety and efficacy compared with nilotinib and dasatinib. The committee concluded that it was important to have an alternative tyrosine kinase inhibitor treatment available if it is no more expensive than the alternatives (the drug acquisition cost of imatinib treatment at 400 mg once daily was £20,980 per year compared with dasatinib 100 mg once daily at £30,477 per year and nilotinib 300 mg twice daily at £31,715 per year without the PAS). The committee therefore concluded that it would be appropriate to recommend both nilotinib and standard-dose imatinib as options for first-line chronic phase CML.

Table 7: Clinical effectiveness outcomes for dasatinib, nilotinib and imatinib considered during the appraisal of TA 251 [2].

Study	DASISION			ENESTnd		
Intervention	**Dasatinib**	**Imatinib**	**RR (95% CI)**	**Nilotinib**	**Imatinib**	**RR (95% CI)**
CCyR rates 12-months	83%	72%	1.17 (1.06-1.28)	80%	65%	1.23 (1.11-1.36)
CCyR rates 18-months	84%	78%	1.08 (0.98-1.17)	85%	74%	1.15 (1.09-1.25)
CCyR rates 24-months	86%	82%	1.05 (0.97-1.13)	87%	77%	1.13 1.04-1.22)
MMR 12-months	46%	28%	1.63 (1.29-2.09)	44%	22%	2.02 (1.56-2.65)
MMR 18-months	56%	37%	1.52 (1.25-1.85)	-	-	-
MMR 24-months	-	-	-	62%	37%	1.67 (1.40-2.00)
CMR 12-months	-	-	-	13%	4%	3.38 (1.70-6.93)
CMR 18-months	13%	7%	1.79 (1.00-3.24)	21%	6%	3.48 (2.04-6.09)
CMR 24-months	17%	8%	2.10 (1.26-3.57)	26%	10%	2.62 (1.72-4.03)
PFS 12-months	96%	97%	-	-	-	-
PFS 18-months	94.9%	93.7%	-	-	-	-
PFS 24-months	93.7%	92.1%	-	98%	95.2%	-
OS 12-months	97%	99%	-	-	-	-
OS 18-months	96%	97.9%	-	98.5%	96.9%	-
0S 24-months	95.3%	95.2%	-	97.4%	96.3%	-

CCyR, complete cytogenetic response; MMR, major molecular response; CMR, complete molecular response; PFS, progression-free survival; OS, overall survival; RR, relative risk; CI, confidence interval.

Note that a number of other outcomes were also considered by the appraisal committee but not reported here (these include confirmed CCyR rates at different time points, CCyR rates across risk categories, MMR at different time points, MMR across risk categories; CMR across risk categories, event-free survival at different time points, adverse events).

6. SUMMARY OF THE COMPANY'S SUBMISSION FOR REVIEW OF TA 251

6.1. CLINICAL EFFECTIVENESS EVIDENCE

The company reported on the results of a systematic literature review that was conducted to identify additional studies that could inform a comparison of dasatinib, nilotinib and standard-dose imatinib as first-line treatment for CML. Full details and results are provided as an appendix to the company's submission. No trials directly comparing dasatinib and nilotinib were identified.

The company used the evidence from four RCTs (DASISION [29], SWOG S0325 [30], NORD CML006 [31] and SPIRIT-2 [32]) to support the efficacy of dasatinib compared with imatinib for the treatment of chronic phase CML. Only one of these trials, DASISION, was considered in the original appraisal of TA 251, with data considered up to 24 months follow-up. In the company's resubmission, the company has presented additional results at 60 months follow-up. Table 8 provides the additional efficacy data for complete cytogenetic response, molecular response, progression-free survival and overall survival from DASISION. Efficacy data from the SWOG S0325 study was limited to major molecular response rates (47% in dasatinib arm compared with 33% in imatinib arm by 12 months follow-up) and progression-free survival (93% dasatinib vs. 90% imatinib) and overall survival (97% dasatinib vs. 97% imatinib) at 36 months follow-up (Appendix 1 of the company's submission).

The company presented details on the adverse event profile of dasatinib compared to imatinib after 12 and 60 months follow-up in the DASISION study. [redacted]

[redacted]

Table 8: Additional efficacy data from the DASISION study [4]

	Dasatinib N=259	Imatinib N=260	p-value
Primary endpoint			
cCCyR rate within 12 months	199 (77%)	172 (66%)	0.007
Secondary and tertiary endpoints			
cCCyR rate at any time*	[redacted]	[redacted]	[redacted]
MMR rate at any time*	198 (76%)	167 (64%)	0.0021
Rate of CCyR within 12 months	[redacted]	[redacted]	[redacted]
Rate of PCyR within 12 months	[redacted]	[redacted]	[redacted]
Rate of MMR within 12 months	119 (46%)	73 (28%)	< 0.0001
Time to cCCyR: Hazard ratio (95% CI)*	[redacted]		[redacted]
Time to cCCyR: Median (months)*	[redacted]	[redacted]	[redacted]
Time to MMR: Hazard ratio (95% CI)*	[redacted]		[redacted]
Time to MMR: Median (months)	[redacted]	[redacted]	[redacted]
PFS at 60 months*	[redacted]	[redacted]	[redacted]
OS at 60 months*	91%	90%	[redacted]

CI: confidence interval; cCCyR: confirmed complete cytogenetic response; CCyR: complete cytogenetic response; MMR: major molecular response; OS: overall survival; PCyR: partial cytogenetic response; PFS: progression-free survival; NR: not reported.
* 60-month follow-up data

The company presented results from a network meta-analysis (NMA) of dasatinib, nilotinib and imatinab, based on additional follow-up data from the trials. [redacted]. The company also presented an overview of published indirect treatment comparisons; however, these were not compared to the results of the company's updated NMA.

The company concluded that the available evidence indicates that treatment with dasatinib or nilotinib offers superior outcomes compared with imatinib in newly diagnosed CML. The

company also concluded that the evidence available from the indirect comparisons suggests that dasatinib and nilotinib are similarly effective for first-line CML, and that these conclusions are in line with those drawn during TA 251.

6.1. COST COMPARISON

The company presented a simple cost comparison analysis of dasatinib, nilotinib and standard-dose imatinib based on the assumption of equivalent efficacy and safety across all three tyrosine kinase inhibitors in the first-line setting. The company's analysis takes account of a new PAS consisting of a [redacted] discount to the list price of dasatinib (which is £2,504.96 for a pack of 30 tablets of 100mg or 140 mg). Nilotinib is also available with a PAS discount. The company has indicated that the dasatinib PAS has been designed to [redacted] discount to that of nilotinib. The company believes that the discount of [redacted] on the list price of dasatinib is [redacted] to that of nilotinib. Table 9 shows the cost per month for each of the interventions at the recommended dose in the Summary of Product Characteristics for first-line treatment of CML.

Table 9: Cost of dasatinib, imatinib and nilotinib per month for first-line treatment of CML [27].

Intervention	Dose per month	Cost per month
List price of dasatinib	100 mg once daily	£2,541.49
PAS price of dasatinib	100 mg once daily	[redacted]
List price of imatinib	400 mg once daily	£1,863.26
List price of nilotinib	300 mg twice daily	£2,644.64
PAS price of nilotinib (TA 251)	300 mg twice daily	Commercial in confidence

The company assumed that health outcomes for dasatinib, nilotinib and imatinib are equivalent, including the safety profile of the interventions. This assumption also implies that the treatment duration of the interventions is identical. Therefore, with the exception of drug acquisition costs, all other resource use, including that required for the management of adverse events is assumed equal across the interventions.

6.2. RESULTS OF THE COMPANY'S COST COMPARISON ANALYSIS

Table 10 presents the results of the company's cost comparison analysis. The company estimated that [redacted] would be expected of between [redacted] and [redacted] per

patient per month when using dasatinib compared with imatinib or nilotinib. The company concluded that there are significant advantages to the NHS in the availability of dasatinib, where evidence suggests that efficacy is comparable to nilotinib, [redacted]

Table 10: Results of the company's cost comparison analysis in the first-line setting.

Intervention	Cost per month	Incremental cost of dasatinib
Dasatinib (with PAS)	[redacted]	-
Imatinib	£1,863.26	[redacted]
Nilotinib (without PAS)	£2,644.64	[redacted]

7. CRITIQUE OF THE COMPANY'S SUBMISSION

7.1. CRITIQUE OF THE CLINICAL EFFECTIVENESS EVIDENCE

The company presented additional follow-up data comparing the efficacy of dasatinib with imatinib from the DASISION study [29]. The evidence in Table 8 supports the conclusion that dasatinib provides superior clinical benefit, as measured by surrogate outcomes, to standard-dose imatinib for first-line treatment of chronic phase CML. However, the rates of serious adverse events are higher for dasatinib compared to imatinib. During TA 251, the AG model included a cost of treating grade 3 or 4 adverse events that were experienced by greater than 1% of people in the trials. Table 11 shows the rates of serious adverse events in the DASISION study at 12 and 60 months follow-up.

Table 11: Rates of serious adverse events in the DASISION study [2, 4].

	12 months follow-up†		60 months follow-up*	
	Dasatinib	Imatinib	Dasatinib	Imatinib
Neutropenia (Grade 3 & 4)	20.9%	20.2%	[redacted]	[redacted]
Thrombocytopenia (Grade 3 & 4)	19.0%	10.1%	[redacted]	[redacted]
Anaemia (Grade 3 & 4)	10.1%	7.0%	[redacted]	[redacted]
Pleural effusion (All grades)	10.1%	0.0%	28.3%	0.8%

† Included in the AG model for TA 251.
* Additional follow-up data since TA 251.

No new comparative head-to-head trials comparing dasatinib with nilotinib were identified. The company presented results from an indirect comparison of the interventions for complete and partial cytogenetic response by 12 months. [redacted]. Due to the time constraints of this work, the DSU has not been able to critique the network meta-analysis undertaken by the company. Table 12 provides a comparison of the results of the company's NMA [redacted] and the mixed treatment comparison analysis that was completed by the AG during TA 251.

Table 12: Relative effectiveness of nilotinib compared to dasatinib [2, 4].

	Odds ratio for nilotinib compared to dasatinib (95% CrI)	
Indirect treatment comparison	**AG analysis for TA 251**	**Company's submission**
CCyR by 12 months	1.09 (0.61 – 1.92)	[redacted]
CCyR by 24 months	1.44 (0.76 – 2.76)	[redacted]
MMR by 12 months	1.28 (0.77 – 2.16)	[redacted]
MMR by 24 months	1.53 (0.93 – 2.51)	[redacted]

CCyR, complete cytogenetic response; MMR, major molecular response; AG, assessment group (PenTAG); CrI, credibility interval.

The DSU does not consider that any additional evidence has been presented that would change the conclusions drawn during TA 251 regarding the relative efficacy of dasatinib and nilotinib. The evidence presented in Table 12 for mean relative effectiveness seems to suggest that nilotinib is more favourable than dasatinib for the surrogate outcome measures, but the credibility interval crosses the line of no difference (odds ratio > 1) for most of the outcomes. The DSU therefore concludes that the magnitude of the benefit remains unclear and that there is insufficient evidence to distinguish between dasatinib and nilotinib for first-line treatment of chronic phase CML.

7.2. CRITIQUE OF THE COST COMPARISON ANALYSIS AND RESULTS

7.2.1. Cost-minimisation analysis

The cost comparison undertaken by the company is a cost-minimisation analysis (CMA). The company has assumed that all health outcomes (surrogate outcomes, adverse event rates, progression-free survival and overall survival) are equivalent between dasatinib, nilotinib and imatinib, with no uncertainty. Although not explicitly stated in the company's submission,

the company has also assumed that these health outcomes are not only equivalent for the first-line treatments, but also equivalent for subsequent lines of therapy, i.e. treatment duration and health outcomes for second-line tyrosine kinase inhibitors are identical. This also means that the time point at which people receive third-line treatment, consisting of stem cell transplant and hydroxyurea (SCT/HU), is identical regardless of which intervention was first-line treatment. With these assumptions in place, it follows that, with the exception of drug acquisition costs, all other resource use and costs are identical across the interventions.

The company has provided a PAS discount of [redacted] on the list price of dasatinib, which is believed to be [redacted] that of nilotinib. The company has indicated that [redacted] for dasatinib compared with nilotinib for newly diagnosed chronic phase CML are [redacted] per month. However, this estimate [redacted] does not take into account the PAS discount on the list price of nilotinib. Under the assumption that nilotinib is available with a discount of [redacted] on its list price, then the estimated [redacted] for dasatinib compared with nilotinib are [redacted] per month, assuming all other health outcomes are equal across the interventions at first-, second- and third-line treatment. The [redacted] for dasatinib compared with imatinib are [redacted] per month under these same assumptions.

7.2.2. Sequence of treatments

A simple CMA for the assessment of cost-effectiveness of the tyrosine kinase inhibitors in the first-line setting is unlikely to be valid due to the need to model subsequent lines of treatment in the pathway. If dasatinib becomes available as a second-line treatment, following the part review of TA 241, then two new sequence of treatments may become clinically relevant:

Sequence:

5	Nilotinib	→	dasatinib	→	SCT/HU	
6	Imatinib	→	dasatinib	→	SCT/HU	

It may also be relevant to consider an additional line of therapy. This would increase the number of potential treatment sequences further:

Sequence:

7	Nilotinib	→	dasatinib	→	imatinib	→	SCT/HU

8	Dasatinib	→	nilotinib	→	imatinib	→ SCT/HU
9	Imatinib	→	nilotinib	→	dasatinib	→ SCT/HU
10	Imatinib	→	dasatinib	→	nilotinib	→ SCT/HU
11	Nilotinib	→	imatinib	→	dasatinib	→ SCT/HU
12	Dasatinib	→	imatinib	→	nilotinib	→ SCT/HU

With these three treatment options, there are now a total of 15 potential treatment strategies. However, during TA 251, three of these strategies were ruled out: first-line dasatinib, nilotinib or imatinib followed by SCT/HU (the committee accepted that SCT/HU would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor). Each of the remaining 12 sequences should be considered as a separate comparator when assessing the cost-effectiveness of the interventions in the first-line setting.

The CMA only holds when strategies with the same number of lines of therapy are compared against each other. For strategies with three lines of therapy, i.e. sequences 1 – 4 (considered during TA 251) and sequences 5 – 6, the most cost-effective option will be the strategy which has the lowest total costs for first- and second-line treatment (assuming health outcomes are identical for the interventions at each line of therapy with no uncertainty). These total costs will depend on the treatment duration at each line of therapy. For example, a strategy with dasatinib starting at second-line (and nilotinib at first-line) might turn out to be more cost-effective than a strategy with dasatinib at first-line, due to differences in treatment duration at first- and second-line. Without knowing the treatment duration at each line of therapy, we can only conclude that [redacted], sequences 2 (imatinib → nilotinib → SCT/HU) and 3 (nilotinib → imatinib → SCT/HU) [redacted] of the other sequences that include dasatinib as a replacement for nilotinib or imatinib. During TA 251, the committee recommended the use of nilotinib and imatinib on the basis that sequences 2 and 3 were considered a cost-effective use of NHS resources. Therefore, it follows that, under the assumption of equivalence in health outcomes, dasatinib may also be considered a cost-effective use of resources but it is not known whether this should be at first- or second-line.

The CMA breaks down when strategies with a different number of lines of therapy are compared against each other. This is because the mean age starting SCT/HU increases when an additional line of therapy is introduced, and the probability of having a life-extending SCT

decreases with age. Survival following SCT is also affected by age and remission status at the time of transplantation. People who receive SCT after tyrosine kinase inhibitor treatment are expected to have a higher SCT risk score by virtue of being both older and more years post-diagnosis. The additional line of therapy means that total costs will increase substantially, but these costs may be offset in part by fewer people predicted to have an expensive SCT. Similarly, health outcomes might be expected to increase with an additional line of therapy but survival following SCT will not be the same with more years post-diagnosis.

7.2.3. Uncertainty in the evidence

An important assumption underpinning the company's cost comparison analysis is that there is no uncertainty in the relative effectiveness of the interventions when introduced at first-, second- or third-line. This is a particularly strong assumption given the evidence presented in the company's submission and during TA 251. Firstly, it is clear from Table 12 that there is a difference in the relative efficacy of dasatinib and nilotinib. This difference may not be statistically significant but it still exists, and there is a non-zero probability that dasatinib is less (or more) effective than nilotinib. Secondly, the relationship between overall survival and surrogate outcomes of complete cytogenetic and major molecular response is uncertain. Thirdly, the mean treatment duration of first-line tyrosine kinase inhibitors in the AG model was estimated to be 7.1 years for imatinib, 7.8 years for dasatinib and 9.0 years for nilotinib, i.e. not the same across the interventions. Fourthly, Table 11 shows that the adverse event profile of the interventions is not identical, with a higher rate of serious adverse events associated with dasatinib compared to imatinib. These uncertainties mean that the time spent on first-line treatment will differ between the interventions and, therefore, the corresponding health outcomes and costs will also differ.

The relative cost-effectiveness of first-line tyrosine kinase inhibitor treatments is influenced by health outcomes and costs associated with subsequent lines of treatment. The evidence base to inform second- and third-line treatment is also subject to substantial uncertainty. During TA 251, the AG extrapolated data from a study of imatinib-resistant people who received second-line nilotinib treatment to estimate the duration of treatment on second-line nilotinib (2.4 years) but such a study does not exist for second-line dasatinib. In addition, due to a lack of any other information, the AG made the assumption that overall survival after second- and third-line treatment was independent of previous treatment.

The DSU has not been able to quantify the cost-effectiveness of the interventions in the first-line setting. A full cost-effectiveness analysis with probabilistic sensitivity analysis and a comparison of all the potential treatment strategies would be required. The DSU did not have access to the AG model in order to make the required modifications. An approximate estimate could have been derived from a breakdown of total costs by the different lines of treatment; however, this information was not reported in TA 251 for the scenario considered most plausible by the committee.

7.2.4. Conclusions

The DSU concludes that, under the assumption of equivalence of outcomes for dasatinib, nilotinib and imatinib, and with dasatinib offered with a PAS discount to its list price, a sequence of three lines of therapy with dasatinib included could be considered a cost-effective use of NHS resources. However, when dasatinib becomes a relevant treatment option, there is the possibility of sequences with four lines of therapy. Without a full incremental analysis of all the potential treatment strategies, it is unclear which strategy would be expected to represent the best use of NHS resources.

There is also considerable uncertainty surrounding the assumption of equivalence of outcomes for dasatinib, nilotinib and imatinib for first-line treatment of chronic phase CML. A full probabilistic cost-effectiveness analysis would be required to quantify this uncertainty and to assess the relative cost-effectiveness of the interventions when dasatinib is offered with a PAS discount to its list price. Without access to a model it is impossible to assess how the [redacted] per month on the acquisition cost of dasatinib translates into total costs for dasatinib treatment compared to nilotinib in the first-line setting.

8. DISCUSSION

In their submission for the reconsideration of dasatinib for the treatment of CML with resistance or intolerance to prior imatinib treatment (part review of NICE Guidance TA 241) and dasatinib for the first-line treatment of CML (part review of NICE Guidance TA 251), the company proposed a PAS discount on the list price of dasatinib.

The company's submission also presented results of a review to identify additional evidence since the previous appraisals on the clinical efficacy and safety of dasatinib. No new comparative head-to-head trials comparing dasatinib with nilotinib in either the first- or second-line setting were identified. The additional evidence included studies with longer follow-up but a lack of equivalent follow-up periods or endpoints reported across studies limited the comparison between dasatinib and nilotinib. The DSU does not consider that any new data has been identified that would change the conclusions drawn in TA 241 and TA 251 that there is insufficient evidence to distinguish between dasatinib and nilotinib treatment in the first- and second-line settings.

The company's submission presented a cost-minimisation analysis comparing dasatinib, nilotinib and imatinib, based on an assumption of equivalent efficacy and safety across the interventions. With the PAS discount, and the assumption of equivalence of health outcomes, the DSU believes that the NHS would be indifferent between dasatinib and nilotinib for the treatment of imatinib-resistant or imatinib intolerance chronic phase CML, and that high-dose imatinab is dominated by dasatinib and nilotinib. The DSU also believes that, under the assumption of equivalence of outcomes, a sequence of three lines of treatment with dasatinib included at first-line could be considered a cost-effective use of NHS resources. However, when dasatinib becomes a relevant treatment option, there is the possibility of sequences with four lines of therapy and a fully incremental analysis of all potential treatment strategies would be required to establish the relative cost-effectiveness of the interventions in newly diagnosed CML.

No new information has been presented in the company's submission to support NICE end of life considerations or to make recommendations for use of dasatinib through the CDF.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Dasatinib for treating imatinib-resistant chronic myeloid leukaemia and for people for whom treatment with imatinib has failed because of intolerance (part review TA241) [ID1006]

&

Dasatinib for the first-line treatment of chronic myeloid leukaemia (part review of TA251) [ID1014]

You are asked to check the ERG report from the Decision Support Unit to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 09 September 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Dear members of the Decision Support Unit,

Thank you for providing Bristol-Myers Squibb Pharmaceuticals Ltd (BMS) the opportunity to respond to the DSU report for dasatinib for the treatment of chronic myeloid leukaemia (CML).

As noted within the report, previous NICE appraisals have reviewed the clinical effectiveness evidence for dasatinib versus nilotinib and imatinib. During the undertaking of TA251, the Appraisal Committee concluded that the available evidence suggests that dasatinib and nilotinib provided superior clinical benefit, as measured by surrogate outcome measures, to standard-dose imatinib in the first-line treatment of people with chronic phase CML.[1] The Appraisal Committee also concluded from indirect comparisons that dasatinib and nilotinib could be considered **equally as effective** in treating newly diagnosed CML.[2] In the comparison of dasatinib and nilotinib in the second line setting, the TA241 Appraisal Committee agreed with clinical specialists that there was limited evidence to distinguish between the two products for the treatment of patients resistant to prior imatinib therapy.[3] However in both of these appraisals, nilotinib was made available to the NHS at a discounted price, and this enabled the Committee to approve nilotinib for use in both settings. Thus, under the assumption of comparable efficacy and a discounted dasatinib price, it should follow that dasatinib would be cost-effective versus nilotinib in the same analyses and scenarios undertaken to evaluate the cost-effectiveness of nilotinib during TA241 and TA251.

Under the assumption of comparable efficacy, a cost-minimisation analysis versus nilotinib can be considered appropriate. The clinical conclusions drawn by the Appraisal Committee during TA241 and TA251 remain unchanged based on identified evidence, with additional indirect comparisons and real-world data provided to support this conclusion within the submissions. Additionally, it should be noted that available data in the first-line CML setting is supportive of comparable efficacy in the second-line CML setting, and vice versa. The available evidence from indirect comparisons and real-world data support comparable outcomes between treatments. The very small differences the comparative effectiveness of dasatinib and nilotinib underscore the similarities in long-term predicted outcomes, and when applied as part of a cost-utility analysis can result in very small QALY differences, that can impact ICERs disproportionately, exaggerating the cost-effectiveness of dasatinib. Further, based on the assumption of comparable efficacy and due to the similarities in mechanism of action, monitoring requirements and resource use are also likely to be comparable. Although there is some uncertainty around the assumption of comparable efficacy, this would be the case with any well-designed non-inferiority study, as even these studies are unlikely to identify zero probability that two therapy have different effectiveness.

We are in agreement with the DSU conclusions that the NHS would be indifferent between dasatinib and nilotinib for the treatment of imatinib-resistant or imatinib intolerance chronic phase CML, but would note that this would actually have potential to prove cost-saving to the NHS. Further, we agree with the conclusion that dasatinib included at first-line could be considered a cost-effective use of NHS resources, under the assumption of comparable outcomes, and applying a sequence of three lines of treatment with dasatinib. However, we disagree with the assertion that this would be impacted by addition of a fourth line of therapy, as under the assumption of comparable outcomes, the cost-effectiveness of dasatinib and nilotinib would be impacted by the same factors in a similar manner.

BMS acknowledges that this appraisal has been conducted on a shortened timescale, with a significant amount of information and without the opportunity for clarifications. With this in mind, clarifications and amendments have been provided in tables below.

In conclusion, we would like to reiterate that **there are significant advantages to the NHS in the availability of dasatinib, where evidence suggests efficacy comparable to nilotinib, with a lower acquisition cost in the first- and second-line CML setting.**

Please do not hesitate to contact me if any further information is required.

Kind regards,

James Harrison

Issue 1 Cost-minimisation

Description of problem	Description of proposed amendment	Justification for amendment	DSU response
Throughout the DSU report, there are statements referring to cost-minimisation as inappropriate within this context, and that it relies on the assumption that the uncertainty is zero.	Reference is made throughout the DSU document and we would suggest that these are updated accordingly.	Under the assumption of comparable efficacy, a cost-minimisation analysis versus nilotinib can be considered appropriate. The clinical conclusions drawn by the Appraisal Committee during TA241 and TA251 remain unchanged based on identified evidence, with additional indirect comparisons and real-world data provided to support this conclusion within the submissions. Additionally, it should be noted that available data in the first-line CML setting is supportive of comparable efficacy in the second-line CML setting, and vice versa. Further, based on the assumption of comparable efficacy and due to the similarities in mechanism of action, monitoring requirements and resource use are also likely to be comparable. Although there is some uncertainty around the assumption of comparable efficacy, this would be the case with any well-designed non-inferiority study, as even these studies are unlikely to identify zero probability that two therapy have different effectiveness. The available evidence from indirect comparisons and real-world data support comparable outcomes between treatments. The very small differences	This is not a factual inaccuracy. The DSU report does not say that a cost-minimisation analysis is inappropriate. The DSU report simply highlights an important assumption underpinning the cost-minimisation analysis, which is that there is no uncertainty, i.e. the company have assumed that the incremental effects for dasatinib compared with nilotinib or imatinib are known to be exactly zero. The cost comparison analysis within the company's submission does not include uncertainty.

		the comparative effectiveness of dasatinib and nilotinib underscore the similarities in long-term predicted outcomes, and when applied as part of a cost-utility analysis can result in very small QALY differences, that can impact ICERs disproportionately, exaggerating the cost-effectiveness of dasatinib. Further it should be noted that there is still a considerable amount of non-efficacy data required for cost-utility analysis, and this data will also be subject to assumptions and uncertainty, as is indeed the representation of the disease in the model structure	
Section 4.2.2 Page 22-23 The DSU has conducted exploratory analyses for dasatinib versus hydroxycarbamide using the previous AG model. This analysis is based on outdated clinical practice and applies a historical comparator. This needs to be clearly labelled in order to provide context and clarity.	DSU performed an exploratory analysis to estimate the incremental cost-effectiveness ratio of dasatinib compared with a historical comparator (hydroxycarbamide), with and without the PAS discount, applying assumptions based on the previous AG preferred scenario, which may not reflect current clinical practice.	Although supportive to the use of dasatinib, and in agreement with the assertion that availability of dasatinib is beneficial to the NHS, it should be noted that assumptions applied within this analysis may be outdated, as clinical practice has evolved during the interim period between these appraisals.	This is not a factual inaccuracy. The DSU report states in the sentence which follows the one highlighted that the DSU exploratory analysis is based on the outcomes of the AG scenario considered the most plausible scenario by the committee.

Issue 2 Licensed indication

Description of problem	Description of proposed amendment	Justification for amendment	
Throughout the DSU report, it is stated that dasatinib is available for the first-	Amendments should reflect the licensed indication, which is	This should be amended to reflect	This is not a factual inaccuracy.

line treatment of CML, but this should reflect the licensed indication, which is the treatment of newly diagnosed Ph+ chronic phase CML.	the treatment of newly diagnosed Ph+ chronic phase CML.	accurately the licensed indication.	It is clear from the DSU report that first-line treatment of CML refers to the licensed indication, which is the treatment of newly diagnosed Ph+ chronic phase CML. The NICE Guidance for TA 251 also refers to this indication as first-line treatment for chronic myeloid leukaemia.

Issue 3 Identification of studies for naïve indirect comparison

Description of problem	Description of proposed amendment	Justification for amendment	
Section 3.1 Page 16 Studies evaluating the efficacy of nilotinib does not refer to the limited relevance to the population of interest.	These additional studies included the trials of ENESTcmr [4-8], RE-NICE [9-12], LASOR [13], and ENESTnd Extension [14]. All of these trials were in the chronic phase of CML and compared nilotinib with high-dose imatinib. However, enrolled patients had limited relevance to population of interest, and the level of cytogenetic response and molecular response outcomes reported in these trials was very limited.	Four studies were identified evaluating the use of nilotinib as a second-line therapy. Three of these studies (ENESTcmr, RE-NICE and LASOR) enrolled patients who had demonstrated a CCyR while receiving imatinib but had not achieved MMR or CMR, which is not within the licensed indication for nilotinib.[15-17] For a third study (ENESTnd), patients had previously received either imatinib or nilotinib 300 mg twice daily before receiving nilotinib 400 mg twice daily, and only six months of follow-up were available. Study NCT00109707 includes patients resistant or intolerant to imatinib therapy, utilises the SPC-recommended dose, and provides 24-month	This is not a factual inaccuracy.

		follow-up data,[18] and so this study was used as the primary source of comparative evidence.	
Section 4.1 Page 20 The selection of study for naïve indirect comparison was undertaken based on applicability to the patient population of interest, application of the licensed dose, and availability of 24-month follow-up data. This is not reflected in the critique of evidence.	For example, the single arm study of dasatinib 70 mg twice daily as reported in Hochhaus et al (2007) had response data presented at 24 months but this study was not included in the company's naïve comparison due to use of a dosing regimen not applied within SPC and not possible in clinical practice, while it was included in the original appraisal of TA 241 [19]	It is acknowledged that only selected studies were presented within the naïve indirect comparison table. However, this was based on applicability to the patient population of interest, application of the licensed dose, and availability of 24-month follow-up data. This facilitated comparison of studies and patients that were as similar as possible.	This is not a factual inaccuracy.

Issue 4 Clinical data inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	
Section 3.1 Page 18 Table 3 The table title should reflect that this is CP CML studies only.	Outcomes at 24 months follow-up in the company's naïve comparison of dasatinib, nilotinib and high-dose imatinib for the treatment of CP CML.	The current table title does not reflect accurately the data provided	This is not a factual inaccuracy. However, for additional clarity the DSU has amended the caption of Table 3.

<table>
<tr>
<td>Section 3.1

Page 18

Table 3

As per the footnote provided within Appendix 3 describing the comparison, dasatinib PFS/OS data from CA180-034 are based on six-year outcomes, not 24 months, in order to reflect the longer follow-up available for dasatinib. However, no footnote has been provided for context, and this comparison has been used to inform the conclusion that nilotinib survival is improved versus dasatinib, which is inaccurate.</td>
<td>We propose that the data is amended to reflect the 24 month data available from Shah et al 2010 (full reference in justification), listed below.

Further, where comparison is made between nilotinib and dasatinib survival outcomes, this should reflect outcomes measured at the same time point.
<table>
<tr><th></th><th>OS</th><th>PFS</th></tr>
<tr><td>100 mg QD</td><td>91%</td><td>80%</td></tr>
<tr><td>140 mg QD</td><td>94%</td><td>75%</td></tr>
<tr><td>50 mg BID</td><td>90%</td><td>76%</td></tr>
<tr><td>70 mf BID</td><td>88%</td><td>76%</td></tr>
</table>
</td>
<td>Currently the table compares six-year survival for dasatinib with two-year survival for comparators, which is not an informative comparison. While a footnote could be added to the table (as per the Appendix 3 table), this would inform the comparison that the DSU is intending to make, and so inclusion of the two-year data can be considered more appropriate.

The full reference for the data in the amendment is: Shah NP, Kim DW, Kantarjian H, Rousselot P, Llacer PE, Enrico A, et al. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica. 2010;95(2):232-40.</td>
<td>The DSU has amended the OS and PFS outcomes reported in Table 3 for 24 month follow-up for CA180-034.</td>
</tr>
<tr>
<td>Section 3.1

Page 18

Table 3

As per the footnote provided within Appendix 3 describing the comparison, imatinib PFS/OS data from Kantarjian 2008 is based on 12-month follow-up</td>
<td>A footnote should be added to the table to reflect the shorter follow-up for this study.</td>
<td>Although 36-month follow-up data is available from this study, it would bias against imatinib in this comparison of outcomes and so was not used within Appendix 3. A footnote would provide accuracy but would not bias the comparison.</td>
<td>A footnote has been added to Table 3 of the DSU report to indicate that the results reported for Kantarjian et al (2009) are for 1 year follow-up.</td>
</tr>
</table>

data.			
Section 3.1 Page 18 Table 3 Data sources for some studies are incorrect.	The correct references should be used. For the table in its current form, this would be: 10. Shah NP, Kim DW, Kantarjian H, Rousselot P, Llacer PE, Enrico A, et al. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica. 2010;95(2):232-40. 11. Shah NP, Guilhot F, Cortes JE, Schiffer CA, le Coutre P, Brummendorf TH, et al. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. Blood. 2014;123(15):2317-24 8. Kantarjian, H., et al., Efficacy of imatinib dose escalation in patients with chronic myeloid leukemia in chronic phase. Cancer, 2009. 115(3): p. 551-60. Where the table is amended (as per the comment above), the cited references should be correct.	The cited references do not contain the required information and so are inaccurate.	The DSU has amended the references in Table 3.

Issue 5 Calculation of monthly costs

Description of problem	Description of proposed amendment	Justification for amendment	
Section 3.2 Page 19 Table 4 The methods for calculation of monthly costs is not presented.	Monthly costs for therapies are based on a month length of 30.4375 days. Currently there is a discrepancy between pack costs	Currently there is a discrepancy between pack costs for a 30-day supply and monthly costs. The different pack sizes necessitated calculation of a monthly cost for each, and an average month length was applied.	This is not a factual inaccuracy. The monthly costs reported in Table 4 of the DSU report are identical to those presented in the company's submission.

Issue 6 Clinical efficacy conclusions

Description of problem	Description of proposed amendment	Justification for amendment	
Section 4.1 Page 21 The conclusions on the relative efficacy of nilotinib and dasatinib for PFS and OS are based on different follow-up periods, and as such are innacurate.	The sentence should be amended to reflect DSU conclusions on the relative impact of the therapies on survival outcomes. Our conclusions are: For example, the results in Table 3 suggest that response rates for the surrogate outcomes of cytogenetic and molecular response, as well as PFS and OS, are slightly better for dasatinib compared to nilotinib.	These conclusions are derived from a table comparing six-year survival for dasatinib with two-year survival for comparators, which is not an informative comparison. When 24-month follow-up was compared between the two therapies, dasatinib can be considered to have a marginally larger effect.	The DSU has amended the sentence as follows: For example, the results in Table 3 suggest that response rates for the surrogate outcomes of cytogenetic and molecular response, as well as PFS and OS, are slightly better for dasatinib compared to nilotinib.

Issue 7 Clinical effectiveness data from TA251

Description of problem	Description of proposed amendment	Justification for amendment	
Section 5 Page 30 Table 7 The RR for CMR at 18 months is incorrectly reported from TA251	The RR is 1.90, based on p51 of the TA251 AG report.	This represents an inaccuracy that should be amendment.	The RR reported in Table 7 of the DSU report for CMR at 18 months was taken from Table 14, page 85 of the AG report. The value of 1.79 (95% CI, 1.00 – 3.24) agrees with the AG report. Page 51 of the AG report does not contain any information on CMR. The DSU cannot locate this potential factual inaccuracy.

Issue 8 Clinical efficacy data from updated submission

Description of problem	Description of proposed amendment	Justification for amendment	
Section 6.1 Page 31 The DSU report specified that no cytogenetic or molecular response outcomes were available in the NORD CML006 and SPIRIT-2 studies. However, this is not the case.	This statement should be removed.	NORD CML006[20] and SPIRIT-2[21] both report outcomes relevant to evaluating the efficacy of dasatinib, including CCyR, MMR, OS and PFS.	The DSU has removed this statement. However, the company should consider correcting their submission: Tables 2, 3 and 4 of Appendix 1 where it states that cytogenetic and molecular response outcomes were not reported for these studies. The company did not present the outcomes in their submission.
Real world data provided has not been reflected within the DSU report.	Additional information describing this data should be noted as supportive.	Although not explicitly called out in the submission, real world retrospective data was provided as part of the submission that can be considered supportive of the conclusion that dasatinib and nilotinib have comparable efficacy. The data is derived from a retrospective analysis of 483 consecutive patients with newly diagnosed chronic phase CML treated with dasatinib, imatinib or nilotinib at the MD Anderson Cancer Center.[22] Rates of response (both cytogenetic and molecular) were similar between dasatinib and nilotinib at all time points,[22] supporting the conclusion that there	This is not a factual inaccuracy.

		are no clinically relevant differences in outcomes between the two therapies.	

Issue 9 Clarification of source of NMA data

Description of problem	Description of proposed amendment	Justification for amendment	
Section 7.1 P35 The DSU notes that results from the NMA do not match those reported in Appendix 3. A clarification for this is provided.	It is proposed that the clarification provided within this document is added to the DSU report.	Subsequent to the conducting the SLR, additional data from the ENESTChina study, conducted entirely in the Chinese population, was made available. In order to provide results incorporating all available evidence, an update to the NMA was conducted examining comparative effectiveness in terms of CCyR and PCyR by 12 months, including the ENESTChina study. As such, Appendix 3 data can be considered the more appropriate data, with additional context provided by addition of the ENESTChina study.	This is not a factual inaccuracy. Table 12 of the DSU report uses data from Appendix 3, which the company states is the most appropriate source.

Issue 10 Treatment sequencing

Description of problem	Description of proposed amendment	Justification for amendment	
Section 7.2.2 P36 The DSU discusses in detail the	It is proposed that the DSU report comment on the likelihood that the cost-effectiveness of dasatinib and nilotinib would be impacted by the same factors in a similar manner, under	We agree with the conclusion that dasatinib included at first-line could be considered a cost-effective use of NHS resources, under the	This is not a factual inaccuracy.

potential for different treatment sequences. The clinical plausibility of each can be queried, but under assumption of comparable clinical outcomes, the cost-effectiveness of dasatinib and nilotinib would be impacted by the same factors in a similar manner.	assumption of comparable clinical outcomes.	assumption of comparable outcomes, and applying a sequence of three lines of treatment with dasatinib. However, we disagree with the assertion that this would be impacted by addition of a fourth line of therapy, as under the assumption of comparable outcomes, the cost-effectiveness of dasatinib and nilotinib would be impacted by the same factors in a similar manner.	

Issue 11 The use of surrogate outcomes in CML

Description of problem	Description of proposed amendment	Justification for amendment	
Section 7.2.3 P38 The DSU reports that the relationship between overall survival and surrogate outcomes of complete cytogenetic and major molecular response is uncertain. This may have been the case during the previous appraisal, but is less likely to reflect the nature of the evidence currently.	It is proposed that the DSU update the report to reflect the wealth of evidence supporting a correlation between surrogate outcomes and survival in CML.	Cytogenetic and molecular response are used in clinical practice to define treatment response or failure within European LeukemiaNet guidelines. The use of early responses in CML as a marker for longer term outcomes is well established.[23] Long-term follow-up of patients receiving TKIs in clinical studies have demonstrated that early achievement of CCyR is associated with significant long term survival,[24-27] while outcomes are poorer in patients not in CCyR after 12 months of TKI therapy.[24,28] In one study, TKI-treated patients classed as failures according to ELN-	This is not a factual inaccuracy.

		defined response criteria had a significantly lower OS and PFS, and there was a benefit for those achieving CCyR, but not MMR, at 12 and 18 months.[24] Similarly, a recent systematic review of TKI use in CML patients confirmed the use of CCyR at 12 months as a gold standard for a good response.[29] Further, it should be noted that the case for comparable outcomes between nilotinib and dasatinib is not reliant on surrogate outcomes, as survival outcomes are also considered.	

Issue 12 Conclusions from TA241 and TA251

Description of problem	Description of proposed amendment	Justification for amendment	
Section 8 P40 The DSU does not consider that any new data has been identified that would change the conclusions drawn in TA 241 and TA 251 that there is insufficient evidence to distinguish between dasatinib and nilotinib treatment in the first- and second-line settings. However, as part of TA 251, the Appraisal Committee concluded from indirect comparisons that	The DSU does not consider that any new data has been identified that would change the conclusions drawn in TA 241 and TA 251 that there is insufficient evidence to distinguish between dasatinib and nilotinib treatment <u>in the second-line settings, and that dasatinib and nilotinib could be considered equally as effective in treating newly diagnosed CML.</u>	As part of TA 251, the Appraisal Committee concluded from indirect comparisons that dasatinib and nilotinib could be considered equally as effective in treating newly diagnosed CML.[2] This should be reflected in the DSU report.	This is not a factual inaccuracy.

dasatinib and nilotinib could be considered equally as effective in treating newly diagnosed CML.[2]			

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