NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70)

1 Guidance

1.1 Standard-dose imatinib[1] is recommended as an option for the first-line treatment of adults with chronic phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML).

1.2 Nilotinib is recommended as an option for the first-line treatment of adults with chronic phase Philadelphia-chromosome-positive CML if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme.

1.3 Dasatinib is not recommended for the first-line treatment of chronic phase Philadelphia-chromosome-positive CML.

1.4 People currently receiving dasatinib that is not recommended according to 1.3 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 Clinical need and practice

2.1 CML is a cancer of myeloid blood cells characterised by a proliferation of granulocytes in blood and bone marrow. More than 90% of people with CML have an acquired chromosomal abnormality, the Philadelphia chromosome, which is caused by reciprocal translocations between chromosomes 9 and 22. These

[1] The summary of product characteristics (SPC) for imatinib states that the recommended dosage of imatinib is 400 mg per day for patients in chronic phase CML.

translocations result in a *BCR-ABL* fusion gene that encodes a constitutionally active tyrosine kinase protein. This protein leads to uncontrolled cell proliferation. People with Philadelphia-chromosome-negative CML have different translocations that result in similar *BCR-ABL* fusion genes and its tyrosine kinase protein.

2.2 CML has three phases. The initial chronic phase lasts for several years. In this phase the symptoms are usually mild and non-specific and can include 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 people with CML are diagnosed during the chronic phase. In approximately 40% of these people CML is asymptomatic and is diagnosed as a result of a routine blood test. The disease may then progress through an accelerated phase. During this phase disease progression is more rapid, and immature blast cells in blood and bone marrow proliferate. Symptoms include bruising, bleeding and infections. The final phase is called the blast crisis phase because a blast cell crisis occurs. There is a rapid increase in immature forms of cells, which replace normal cells in bone marrow and affect other organs. Symptoms include fever, sweating, pain and enlargement of organs. When this phase is reached CML is often fatal within 3–6 months.

2.3 CML is diagnosed by finding characteristic cells in blood and bone marrow. The Philadelphia chromosome is identified using cytogenetic techniques to detect abnormal chromosomes. Various criteria, including the percentage of blast cells in blood or bone marrow, have been proposed to define the accelerated and blast crisis phases.

2.4 An estimated 560 people are diagnosed with CML in the UK each year. Slightly more men than women are diagnosed (annual age-

standardised rate 1.2 per 100,000 for men and 0.7 per 100,000 for women). The median age at diagnosis is 60 years.

2.5 A potential cure for CML is an allogeneic stem cell transplant, also known as bone marrow transplantation, but individual characteristics and the lack of availability of a matched donor mean this is not possible for many people with CML.

2.6 However, the progression of CML can be slowed by imatinib. Imatinib produces high rates of remission in the chronic phase but is less effective when the disease has progressed. Standard-dose imatinib is associated with improved survival, with the latest results of the follow-up of the IRIS (International Randomised Study of Interferon versus STI571) trial (8-year follow-up) showing overall survival of 85%. After the introduction of imatinib into routine clinical practice, 5-year relative survival increased from 27.1% in 1990–92 to 48.7% in 2002–04, for all age groups combined ($p < 0.0001$ for the trend).

2.7 Guidance on the use of imatinib for chronic myeloid leukaemia (NICE technology appraisal guidance 70) recommends the standard dosage of imatinib (400 mg once daily) as first-line treatment for people with Philadelphia-chromosome-positive CML in the chronic phase. It also recommends imatinib for CML that initially presents in the accelerated phase or blast crisis phase, and for CML that presents in the chronic phase and then progresses to the accelerated or blast crisis phase, if imatinib has not been used previously. Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance (NICE technology appraisal guidance 241) recommends nilotinib, but not dasatinib or high-dose imatinib, for the treatment of imatinib-resistant CML and

for people with CML for whom treatment with imatinib has failed because of intolerance.

2.8 Response to treatment is assessed haematologically by white cell count and cytogenetically by searching for the Philadelphia chromosome in bone marrow aspirates. A molecular response can be assessed using polymerase chain reaction techniques.

2.9 A complete haematological response has been defined as all of the following, maintained for at least 4 weeks:

- white blood cell count no higher than the upper limit of normal
- absolute neutrophil count at least 1 x 10^9 per litre
- platelet count below 450 x 10^9 per litre and no higher than the upper limit of normal
- no blast cells or promyelocytes in peripheral blood
- less than 2% basophils in peripheral blood
- no extramedullary involvement.

2.10 A complete cytogenetic response is defined as no Philadelphia-positive chromosomes in at least 20 cells in metaphase in a bone marrow aspirate. A partial cytogenetic response is defined as 35% or fewer Philadelphia-positive chromosomes in metaphase in a bone marrow aspirate. A major cytogenetic response is defined as either a complete cytogenetic response or a partial cytogenetic response.

2.11 A major molecular response is defined as either a *BCR-ABL/ABL* ratio of less than 0.10% or a 3-log (base 10) reduction in *BCR-ABL* transcripts. A complete molecular response is defined as undetectable levels of *BCR-ABL*.

3 The technologies

Dasatinib

3.1 Dasatinib (Sprycel, Bristol-Myers Squibb), a tyrosine kinase inhibitor, is an orally active inhibitor of Src and the Src family of tyrosine kinases. These are involved in cell growth, differentiation, migration and survival, and many are involved in oncogenesis, tumour metastasis and angiogenesis.

3.2 Dasatinib has a 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'.

3.3 The most common reported side effects with dasatinib are headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections, haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombocytopenia and anaemia. The SPC states: 'Dasatinib should be administered with caution to patients who have or may develop prolongation of the QT interval.' For full details of side effects and contraindications, see the SPC.

3.4 Dasatinib is available at a cost of £2504.96 for a pack of 30 100 mg tablets (excluding VAT; 'British national formulary' [BNF] edition 62). The cost of dasatinib treatment is £30,477 per year, assuming a treatment regimen of 100 mg once daily. Costs may vary in different settings because of negotiated procurement discounts.

Imatinib

3.5 Imatinib (Glivec, Novartis Pharmaceuticals) is an orally active tyrosine kinase inhibitor, designed to competitively inhibit *BCR-ABL*

tyrosine kinase activity. By blocking specific signals in cells expressing *BCR-ABL,* imatinib reduces the uncontrolled proliferation of white blood cells that is a characteristic feature of CML.

3.6 Imatinib has a marketing authorisation for the treatment of adult and paediatric patients with newly diagnosed Philadelphia-chromosome (*BCR-ABL*) positive CML for whom bone marrow transplantation is not considered as the first line of treatment, and for adult and paediatric patients with Philadelphia-chromosome-positive CML in chronic phase after failure of interferon alfa therapy (recommended dose 400 mg once daily) or in accelerated phase or blast crisis (recommended dose 600 mg once daily).

3.7 The most common side effects with imatinib include nausea, vomiting, oedema (fluid retention), muscle cramps, skin rash, diarrhoea, abdominal pain, headache and fatigue. For full details of side effects and contraindications, see the SPC.

3.8 Imatinib is available at a cost of £1724.39 for a 400 mg 30-tablet pack (excluding VAT; BNF edition 62) resulting in an annual cost of imatinib treatment of £20,980 per year, assuming a treatment regimen of 400 mg per day. Costs may vary in different settings because of negotiated procurement discounts.

Nilotinib

3.9 Nilotinib (Tasigna, Novartis Pharmaceuticals), a tyrosine kinase inhibitor, is an orally active phenylaminopyrimidine derivative of imatinib. Nilotinib has a marketing authorisation for the treatment of 'adult patients with newly diagnosed Philadelphia-chromosome-positive chronic myelogenous leukaemia (CML) in the chronic phase' (300 mg twice a day) and adult patients with 'chronic phase and accelerated phase Philadelphia-chromosome-positive CML with resistance or intolerance to prior therapy including imatinib'

(400 mg twice a day). The SPC states that 'efficacy data in patients with CML in blast crisis are not available'.

3.10 The most common side effects with nilotinib include thrombocytopenia, neutropenia, anaemia, headache, nausea, constipation, diarrhoea, rash, pruritus, fatigue and increased blood levels of lipase and bilirubin. Nilotinib prolongs the QT interval and should be used with caution in people who have or may develop prolongation of the QT interval. For full details of side effects and contraindications, see the SPC.

3.11 Nilotinib is available at a cost of £2432.85 for a 150 mg 112-tablet pack (excluding VAT; BNF edition 62). The cost of nilotinib treatment is £31,715 per year, assuming a treatment regimen of 300 mg twice a day. The manufacturer of nilotinib (Novartis) has agreed a patient access scheme with the Department of Health which makes nilotinib available with a discount applied to all invoices. The size of the discount is commercial in confidence (see section 5.2). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Group conducted a systematic review of evidence on the clinical efficacy of dasatinib, nilotinib and standard-dose imatinib compared with each other and with other treatment options in treatment-naive people with newly diagnosed Philadelphia-chromosome-positive CML in the chronic phase. Two randomised controlled trials were identified that met the inclusion criteria of the

Assessment Group systematic review: one comparing dasatinib and imatinib (DASISION ['Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia'] trial; Kantarjian et al. 2010) and one comparing nilotinib and imatinib (ENESTnd ['Evaluating nilotinib efficacy and safety in clinical trials of newly diagnosed patients'] trial; Saglio et al. 2010). The DASISION study provided an additional seven conference abstracts and the ENESTnd study provided an additional six conference abstracts. One conference abstract of a systematic review assessing first-line treatments for CML and one journal article were identified and provided indirect comparisons of dasatinib and nilotinib. Additional data were also retrieved from the manufacturers' submissions for dasatinib and nilotinib.

4.1.2 The DASISION trial was a multinational open-label randomised controlled trial to assess the efficacy and safety of dasatinib (100 mg once daily, n = 259) compared with imatinib (400 mg once daily, n = 260) in newly diagnosed (3 months or less) people with chronic phase CML. The primary outcome was complete cytogenetic response within 12 months. Secondary outcomes included major molecular response at any time, time to confirmed complete cytogenetic response and major molecular response (defined as a complete cytogenetic or major molecular response on two consecutive assessments at least 28 days apart), rates of complete cytogenetic response and major molecular response by 12 months, progression-free survival and overall survival. Adverse events were assessed continuously for all study participants. All study participants had a minimum follow-up of 12 months, with a median duration of 14 months of treatment for dasatinib and 14.3 months for imatinib.

4.1.3 The ENESTnd trial was a multicentre open-label randomised controlled trial to assess the efficacy and safety of nilotinib (300 mg

twice a day, n = 282, or 400 mg twice a day, n = 281) compared with imatinib (400 mg once daily, n = 283) in newly diagnosed (6 months or less) people with chronic phase CML. Only nilotinib 300 mg twice a day has a marketing authorisation for the first-line treatment of CML in the chronic phase. The primary outcome was major molecular response at 12 months. Secondary outcomes included complete cytogenetic response by 12 months, time to and duration of major molecular response, progression to advanced phase or blast crisis phase CML, and event-free and progression-free survival. Adverse events of all study participants who received at least one dose of a study drug were monitored. All study participants had a minimum follow-up of 24 months, with a median duration of 14 months of treatment.

4.1.4 Participants in both trials were of a similar age (46–49 years) and gender distribution (56–63% male). However the median age was younger than that of the general CML population, in which the median age at diagnosis is 58 years (including people diagnosed in the accelerated phase or blast crisis phase). Study participants were stratified to prognostic risk groups (low, intermediate or high risk) by the Hasford risk score for the DASISION trial and the Sokal risk score for the ENESTnd trial. Risk distribution was fairly similar between both trials with ENESTnd reporting a slightly lower percentage of people with intermediate risk and a slightly higher percentage with high risk, compared with DASISION. Both trials included people who had an Eastern Cooperative Oncology Group (ECOG) performance status score of between 0 and 2. The exclusion criteria were slightly different for the two trials and were based on the known adverse events of the drugs (for example, pleural effusion for dasatinib and QT interval prolongation for nilotinib). The two trials used different measures of response as primary outcomes (complete cytogenetic response for DASISION

and major molecular response for ENESTnd), although both trials reported the other measure of response as a secondary outcome.

4.1.5 The Assessment Group considered that both trials were good quality, international, multicentre, open-label phase III randomised controlled trials. However, there was no discussion of how people were randomised in either trial. The trials were reported as open-label so treatment allocation concealment, and outcome assessors or carer blinding, were not possible. The Assessment Group commented that these factors have been shown to potentially bias results of randomised controlled trials, although they are unlikely to have an impact because the outcomes of the trials were objective. Baseline patient characteristics were similar across treatment groups and were well reported in both trials. According to the Assessment Group's quality assessment of both trials, the statistical analysis and handling of data were well reported. However, it also noted the large contribution from both manufacturers as sponsors of the study and to manuscript development. Finally, the study populations were not completely representative of a UK CML population, as a result of the lower median age in both trials, the high proportion of Asian people in the ENESTnd trial and the unknown ethnicity of participants in the DASISION trial.

4.1.6 The DASISION trial reported that, at 12-month follow-up, 85% and 81% of people continued to receive treatment with dasatinib and imatinib respectively. At 24-month follow-up, 77% and 75% of people continued to receive treatment with dasatinib and imatinib respectively. The ENESTnd trial reported that at 12-month follow-up 84% and 79% of people continued to receive treatment with nilotinib and imatinib respectively. At 24-month follow-up, 75% and 68% of people continued to receive treatment with nilotinib and imatinib respectively. The primary causes of discontinuation, which

were similar across treatment groups in both trials, were drug-related adverse events, disease progression and suboptimal response or treatment failure.

4.1.7 The DASISION trial reported that statistically significantly more people receiving dasatinib had a complete cytogenetic response compared with people taking imatinib at 12-month follow-up (83% versus 72%, relative risk [RR] = 1.17 [95% confidence interval {CI} 1.06 to 1.28]) but not at 18 months (84% versus 78%, RR 1.08 [95% CI 0.98 to 1.17]) or 24 months (86% versus 82%, RR = 1.05 [95% CI 0.97 to 1.13]). A statistically significantly higher proportion of people receiving dasatinib had a confirmed complete cytogenetic response (confirmed complete cytogenetic response is based on two consecutive assessments 28 days apart) compared with people receiving imatinib at 12-month follow-up (77% versus 66%, RR = 1.16 [95% CI 1.04 to 1.30]) and 18 months (78% versus 70%, RR = 1.11 [95% CI 1.00 to 1.24]), but not at 24 months (80% versus 74%, RR = 1.08 [95% CI 0.98 to 1.19]). At 12 and 18-month follow-up, complete cytogenetic response rates were higher for people taking dasatinib across all risk categories compared with people taking imatinib.

4.1.8 The ENESTnd trial reported that statistically significantly more people receiving nilotinib had a complete cytogenetic response compared with people taking imatinib at 12-month follow-up (80% versus 65%, RR = 1.20 [95% CI 1.08 to 1.34]). Nilotinib continued to be statistically significantly superior compared with imatinib at 18-month follow-up (85% versus 74%, RR = 1.11 [95% CI 1.01 to 1.21) and 24-month follow-up (87% versus 77%, RR = 1.10 [95% CI 1.01 to 1.19]). Complete cytogenetic response rates from the trial at 12 months across risk categories for people taking nilotinib compared with people taking imatinib are commercial in confidence and therefore not included here.

4.1.9 The DASISION trial reported that statistically significantly more people receiving dasatinib had a major molecular response compared with people taking imatinib at 12-month follow-up (46% versus 28%, RR = 1.63 [95% CI 1.29 to 2.09]) and at 18-month follow-up (56% versus 37%, RR = 1.52 [95% CI 1.25 to 1.85]). A statistically significantly higher proportion of people taking dasatinib also had a major molecular response at any time (cumulative major molecular response rates, which included people who may have relapsed or been lost to follow-up) compared with people taking imatinib at 12-month follow-up (52% versus 34%, RR = 1.54 [95% CI 1.25 to 1.91]), 18-month follow-up (57% versus 41%, RR = 1.39 [95% CI 1.15 to 1.67]) and 24-month follow-up (64% versus 46%, RR = 1.39 [95% CI 1.18 to 1.64]). At 12, 18 and 24-month follow-up, major molecular response rates were higher for people taking dasatinib across all risk categories compared with people taking imatinib.

4.1.10 The ENESTnd trial reported that statistically significantly more people receiving nilotinib had a major molecular response compared with people taking imatinib at 12-month follow-up (44% versus 22%, RR = 2.02 [95% CI 1.56 to 2.65]) and 24-month follow-up (62% versus 37%, RR = 2.02 [95% CI 1.56 to 2.65]). A statistically significantly higher proportion of people taking nilotinib also had a major molecular response at any time compared with people taking imatinib at 12-month follow-up (submitted to NICE in confidence), at 18 months (66% versus 40%, RR = 1.65 [95% CI 1.40 to 1.95]) and at 24 months (71% versus 44%, RR = 1.67 [95% CI 1.40 to 1.89]). At 12, 18 and 24-month follow-up, major molecular response rates were higher for people taking nilotinib across all risk categories compared with people taking imatinib.

4.1.11 The DASISION trial reported that at 18-month follow-up, complete molecular response rates were statistically significantly higher for

people receiving dasatinib compared with people taking imatinib (13% versus 7%, RR = 1.79 [95% CI 1.00 to 3.24]) and this difference was maintained at 24-month follow-up (17% versus 8%, RR = 2.10 [95% CI 1.26 to 3.57]). The ENESTnd trial reported that at 12-month follow-up, complete molecular response rates were statistically significantly higher for people receiving nilotinib compared with people taking imatinib (13% versus 4%, RR = 3.38 [95% CI 1.70 to 6.93]) and this difference was maintained at 24-month follow-up (26% versus 10%, RR = 2.62 [95% CI 1.72 to 4.03]).

4.1.12 The DASISION trial reported that at 12, 18 and 24-month follow-up, time to a complete cytogenetic response and a confirmed complete cytogenetic response was statistically significantly shorter for people receiving dasatinib compared with people taking imatinib (both hazard ratios 1.5, $p < 0.0001$). The median time to a confirmed complete cytogenetic response was 3.1 and 5.6 months for dasatinib and imatinib respectively. The time to a major molecular response was also statistically significantly shorter for people receiving dasatinib (hazard ratio 2.0, $p < 0.0001$) compared with people taking imatinib at 12-month follow-up. The median time to major molecular response was 6.3 and 9.2 months for dasatinib and imatinib respectively. These statistically significant differences were maintained at 18 and 24-month follow-up. The ENESTnd trial reported that the median time to major molecular response was statistically significantly shorter for people receiving nilotinib (8.3 months, 95 % CI 5.8 to 8.3) compared with people receiving imatinib (11.1 months, 95% CI 8.5 to 13.6). It was also reported that, of people who had a major molecular response at 12-month follow-up, 93% of people taking nilotinib and 92% of people taking imatinib maintained this response at 24 months.

4.1.13 The DASISION trial reported that at 12-month follow-up, five people taking dasatinib and nine people taking imatinib had progressed to advanced phase or blast crisis. At 24-month follow-up, nine people taking dasatinib and 15 people taking imatinib had progressed to advanced phase or blast crisis (95% CIs not reported). The ENESTnd trial reported that the rate of progression to advanced phase or blast crisis was statistically significantly lower for people taking nilotinib compared with people taking imatinib at 12-month follow-up (two versus 11 people, p = 0.01) and 24-month follow-up (two versus 17 people, p = 0.0003).

4.1.14 The DASISION trial reported that rates of progression-free survival and overall survival were similar for dasatinib and imatinib at 12 months (progression-free survival 96% versus 97%; overall survival 97% versus 99%), 18 months (progression-free survival 95% versus 94%; overall survival 96% versus 98%) and at 24 months (progression-free survival 94% versus 92%; overall survival 95% versus 95%). The ENESTnd trial reported no statistically significant differences in progression-free survival between nilotinib and imatinib at 24-month follow-up (98% versus 95%, p = 0.07). No statistically significant differences in overall survival were reported between nilotinib and imatinib at 18 months (99% versus 97%, p = 0.28) or 24 months (97% versus 96%, p = 0.64) respectively.

4.1.15 The DASISION trial reported that discontinuation rates as a result of adverse events at 12-month follow-up were 5% and 4% for people taking dasatinib and imatinib respectively. Haematological event rates were similar between the two treatment arms at 12, 18 and 24-month follow-up except for grade 3 or 4 thrombocytopenia, for which nearly twice as many events were experienced by people taking dasatinib (19–20%) compared with people taking imatinib (10–11%). People taking imatinib experienced an increased

frequency of fluid retention and superficial oedema across all grades at 12, 18 and 24-month follow-up. People taking dasatinib experienced higher rates of pleural effusion (10–14%) compared with people taking imatinib (0%) at 12, 18 and 24-month follow-up. Other non-haematological events, including rash, vomiting, nausea and myalgia, were lower at each follow-up timepoint for people taking dasatinib compared with imatinib.

4.1.16 The ENESTnd trial reported that discontinuation rates as a result of adverse events were 5% and 7% at 12-month follow-up and 6% and 9% at 24-month follow-up for nilotinib and imatinib respectively. Haematological event rates across all grades were lower for people taking nilotinib compared with people taking imatinib at 12-month follow-up. Grade 3 or 4 neutropenia events were approximately double for people taking imatinib (20%) compared with nilotinib (12%). Non-haematological events, including nausea, diarrhoea, vomiting and muscle spasm events, were approximately three times higher for people taking imatinib compared with people taking nilotinib across all grades. Oedema events across all grades, including eyelid and periorbital oedema, were also higher for imatinib compared with nilotinib. Conversely, rash, headache, pruritus and alopecia events were up to three times higher for nilotinib compared with imatinib across all grades. Nilotinib carries a US Food and Drug Administration (FDA) 'black box' warning for possible heart problems caused by QT interval prolongation, in which prolonged cardiac ventricular repolarisation can result in ventricular tachycardia and death. No-one in the ENESTnd trial experienced an increased QT interval of more than 500 milliseconds (at which complexities may arise) at 12, 18 or 24-month follow-up. Finally, the number of hospitalisations, hospital days and length of stay were lower for nilotinib compared with imatinib at 12-month follow-up.

4.1.17 No trials were identified by the Assessment Group that directly compared dasatinib and nilotinib. Therefore, an indirect comparison of nilotinib with dasatinib was carried out using results from the DASISION and ENESTnd trials. The primary outcomes reported by the Assessment Group were major molecular response and complete cytogenetic response at 12-month follow-up. As part of its submission, Bristol-Myers Squibb commissioned a mixed treatment comparison to indirectly compare nilotinib with dasatinib for major molecular response and complete cytogenetic response at 12-month follow-up. These mixed treatment comparisons also included randomised controlled trials of historical interventions such as hydroxyurea and interferon-based treatments. No statistically significant differences were identified in any of the analyses between dasatinib and nilotinib for major molecular response, complete cytogenetic response or complete molecular response at 12 and 24-month follow-up.

4.1.18 Another study identified by the Assessment Group conducted a matching-adjusted indirect comparison of nilotinib and dasatinib from the DASISION and ENESTnd trials (Signorovitch et al. 2011). In this study, which was sponsored by Novartis, individual patient data for people receiving nilotinib 300 mg were weighted to match the baseline characteristics for people taking dasatinib including age, gender, ECOG performance status score and haematology lab values. After matching, people taking nilotinib had statistically significantly higher major molecular response rates (56.8% versus 45.9%, $p = 0.001$) and overall survival (99.5% versus 97.3%, $p = 0.046$) compared with people taking dasatinib.

4.1.19 Because of short-term follow-up in the DASISION and ENESTnd trials, the Assessment Group conducted a systematic review to assess the evidence base for using cytogenetic response and molecular response as surrogate measures for survival and health-

related quality of life in people receiving tyrosine kinase inhibitor treatment. The systematic review identified 11 publications, all related to imatinib, which reported both potential surrogate outcomes (complete cytogenetic response and major molecular response) and final patient-relevant outcomes (progression-free survival and overall survival). Of these, five were reports of two cohort studies, one was a report of a single randomised controlled trial and five were reports of a randomised controlled trial comparing imatinib with interferon-alpha plus cytarabine.

4.1.20 The Assessment Group reported that the results of its systematic review suggested that people who experienced a complete cytogenetic response or major molecular response after 12 months of imatinib treatment experienced better long-term (up to 7 years) overall survival and progression-free survival than people whose disease did not respond at 12-month follow-up. Overall survival decreased from 100% (95% CI 99.3 to 100) at 12 months to 97.4% (95% CI 94.9 to 98.6) at 60 months for people who had a complete cytogenetic response and from 100% (95% CI 98.1 to 100) at 12 months to 74.1% (95% CI 62.4 to 82.4) at 60 months for people who did not have a complete cytogenetic response. Similarly, progression-free survival decreased from 100% (95% CI 99.3 to 100) at 12 months to 95.5% (95% CI 93.1 to 97.0) at 72 months for people who had a complete cytogenetic response and from 98.9% (95% CI 94.0 to 99.8) at 12 months to 80.0% (95% CI 56.7 to 91.5) at 72 months for people who did not have a complete cytogenetic response. The results also showed that overall survival decreased from 100% (95% CI 99.1 to 100) at 12 months to 96.0% (95% CI 93.2 to 97.5) at 84 months for people who had a major molecular response and from 100% (95% CI 99.4 to 100) at 12 months to 89.2% (95% CI 83.5 to 93.4) at 84 months for people who did not have a major molecular response. Similarly, progression-free survival decreased from 100% (95% CI 98.5 to 100) at 12 months

to 99.0% (95% CI 95.3 to 99.6) at 84 months for people who had a major molecular response and from 99.6% (95% CI 97.8 to 99.9) at 12 months to 89.9% (95% CI 84.2 to 93.9) at 84 months for people who did not have a major molecular response. The Assessment Group highlighted a number of limitations with its review, which were a consequence of the lack and quality of data available (that is, aggregate data instead of individual patient data). The Assessment Group concluded that, without evidence that the surrogate outcomes of cytogenetic and molecular response show the efficacy of dasatinib and nilotinib as first-line treatments for chronic phase CML, and assuming a tyrosine kinase inhibitor's class-specific relationship between the surrogate outcomes and the patient-relevant outcomes, these results can be potentially applied to other drugs in the same class.

4.1.21 The Assessment Group provided an erratum to the assessment report following the identification of errors in the original report around the calculation of some of the relative risks and their 95% confidence intervals for the response rates taken from the DASISION and ENESTnd trials. These errors are presented in sections 4.1.10 and 4.1.11 respectively. The first error that was corrected for (from section 4.1.10) was major molecular response for nilotinib compared with imatinib at 24-month follow-up from the ENESTnd trial (62% versus 37%, RR = 1.67 [95% CI 1.40 to 2.00]). The second error that was corrected for (from section 4.1.10) was major molecular response at any time for nilotinib compared with imatinib at 24-month follow-up from the ENESTnd trial (71% versus 44%, RR = 1.63 [95% CI 1.37 to 1.84]). The third error that was corrected for (from section 4.1.11) was complete molecular response rate for dasatinib compared with imatinib at 18-month follow-up from the DASISION trial (13% versus 7%, RR = 1.90, 95% CI 1.00 to 3.24). The Assessment Group noted that these

errors did not have any further impact on the results of the cost-effectiveness analyses presented in the assessment report.

4.2 Cost effectiveness

4.2.1 The two manufacturers submitted cost-effectiveness models. The Assessment Group critically appraised these submitted models and developed its own economic model to assess the relative cost effectiveness of dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of people with CML.

Manufacturers' submissions

Bristol-Myers Squibb: dasatinib

4.2.2 Bristol-Myers Squibb developed a 'time in state' (area under the curve) model to assess the cost effectiveness of dasatinib (100 mg daily), nilotinib (600 mg daily) and standard-dose imatinib (400 mg daily) as first-line treatments for people with CML. The analysis was conducted from a UK NHS perspective using a 40-year time horizon. It was based on a starting age of 46 years (the average age of people in the DASISION trial) until 86 years. Costs and benefits were discounted at an annual rate of 3.5%. The health states modelled as monthly cycles represented the chronic phase, advanced phases (accelerated or blast phase) and death. In the chronic phase, treatments modelled included: first-line tyrosine kinase inhibitors, second-line tyrosine kinase inhibitors, and third-line treatments consisting of stem cell transplantation, chemotherapy, or a combination of chemotherapy and tyrosine kinase inhibitor treatment (dasatinib or imatinib). In the advanced phase treatments included third-line treatment or in-hospital palliative care. For people receiving first-line dasatinib, second-line treatment was nilotinib (800 mg daily). For people receiving first-line nilotinib (600 mg daily), second-line treatment was dasatinib. For people receiving first-line standard-dose imatinib, second-line

treatment was split 50:50 between dasatinib (100 mg daily) and nilotinib (800 mg daily).

4.2.3 The impact of tyrosine kinase inhibitor treatments on CML progression and survival was estimated using a combination of data on the effect of tyrosine kinase inhibitors on cytogenetic response and data on the impact of cytogenetic response on progression-free survival and overall survival. Treatment effect was defined as the probability that each tyrosine kinase inhibitor achieves a complete cytogenetic response, partial cytogenetic response and less than partial response (calculated as the residual of complete and partial cytogenetic response) at 12 months. Clinical-effectiveness data for cytogenetic response to first-line tyrosine kinase inhibitor treatment were taken directly from the DASISION and ENESTnd randomised controlled trials and an unpublished systematic review and mixed treatment comparison commissioned by Bristol-Myers Squibb. It was assumed that the effectiveness of second-line tyrosine kinase inhibitor treatment was the same as second-line treatment after imatinib because data for second-line treatment after dasatinib and nilotinib were not available. Clinical-effectiveness data for second-line treatment were based on the Peninsula Technology Assessment Group (PenTAG) report for the ongoing appraisal on dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant or intolerant CML.

4.2.4 Progression-free survival and overall survival were estimated from cytogenetic response after first-line tyrosine kinase inhibitor treatment. Clinical-effectiveness data for second-line treatments were not used to estimate either progression-free survival or overall survival. Data for overall survival and progression-free survival according to different levels of cytogenetic response were taken from two published sources: the imatinib treatment arm from the

IRIS study was used to estimate overall survival for complete and partial cytogenetic response for all three tyrosine kinase inhibitor treatments; data for overall survival for a less than partial response for dasatinib and nilotinib were taken from a UK Medical Research Council-funded randomised controlled trial comparing interferon with cytotoxic chemotherapy for the treatment of CML in the chronic phase; and progression-free survival for all levels of cytogenetic response were also taken from the IRIS study. The IRIS study covered a period of 6 years during which the majority of people receiving first-line imatinib remained alive and were on first-line treatment at the end of the trial. To extrapolate beyond the trial data, a Weibull parametric survival function was used to predict overall survival and progression-free survival.

4.2.5 Discontinuation and switch rates for first-line dasatinib and nilotinib were based on 12-month treatment failure rates (defined as 'less than partial cytogenetic response') from the DASISION and ENESTnd trials respectively. For first-line imatinib, 12-month discontinuation and switch rates were estimated for people with partial and less than partial cytogenetic response from an observational study of 224 people taking imatinib with chronic phase CML recruited from a single UK centre.

4.2.6 Health state utility values were obtained from a cross-sectional study based in the UK, US, Australia and Canada using the time trade-off method. The utility values were based on survey responses from a sample of the general population (n = 353, of whom 97 were from the UK). The model assumed that only people with complete cytogenetic response had disease that responded and that those with either partial or less than partial response had disease that didn't respond. Utility values were: 0.85 for the chronic phase with response; 0.68 for the chronic phase with no response; 0.79 for the accelerated phase with response; 0.50 for the

accelerated phase with no response; 0.50 for the blast crisis phase with response and 0.31 for the blast crisis phase with no response. For people who received a stem cell transplant, a baseline utility value of 0.71 was applied, which was taken from the Southampton Health Technology Assessments Centre assessment report published in 2011 on dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML. Utility decrement weights, which accounted for any treatment-related haematological adverse events, were also included. These were derived from the chemotherapy literature and a Liverpool Reviews and Implementation Group assessment report published in 2006 on erlotinib for the treatment of relapsed non-small cell lung cancer. If utility estimates for adverse events were not available, a 5% (−0.05) decrement was assumed. Annual haematological event rates for first and second-line tyrosine kinase inhibitor treatments were taken from the DASISION, ENESTnd and IRIS trials and an earlier Bristol-Myers Squibb submission for second-line CML.

4.2.7 Drug acquisition costs were taken from the BNF 61. Bristol-Myers Squibb assumed the same BNF-derived cost for first and second-line nilotinib, which did not reflect the price discount available under the approved patient access scheme. Dose intensities for the three first-line tyrosine kinase inhibitors were 100% in the first 2 years of treatment. From the third year of treatment onwards, the dose intensity for each tyrosine kinase inhibitor was estimated as dasatinib 90.1%, nilotinib 88.8% and standard-dose imatinib 94.0%. Costs associated with outpatient visits, tests and hospitalisations were also included in the model. The expected level of resource use according to disease phase and level of response was estimated from a survey of six UK haematologists. Adverse event costs were also included for serious haematological events. For people receiving third-line treatment, it was assumed that 30.6% received stem cell transplantation, 50.0% received a combination of

chemotherapy and tyrosine kinase inhibitor treatment and 18.2% received palliative care.

4.2.8 The cost-effectiveness results indicated that: dasatinib was associated with 20.46 years of overall survival (10.64 quality adjusted life years [QALYs]) at a total cost of £498,217; imatinib was associated with 18.83 years of overall survival (9.89 QALYs) at a total cost of £478,293; and nilotinib was associated with 20.59 years of overall survival (10.70 QALYs) at a total cost of £506,613. The base-case incremental cost-effectiveness ratios (ICERs) were £26,305 per QALY gained for dasatinib compared with imatinib and £144,778 per QALY gained for nilotinib compared with dasatinib.

4.2.9 In one-way sensitivity analyses, the input parameters that had the greatest effect on the ICERs were the monthly first-line drug acquisition costs, dose intensities for dasatinib and nilotinib and 12-month response rates. The results of the probabilistic sensitivity analyses showed that, at a threshold of £30,000, the probabilities of dasatinib being cost effective compared with standard-dose imatinib and nilotinib were 63% and 100% respectively.

4.2.10 In its critique of the cost-effectiveness evidence submitted by Bristol-Myers Squibb, the Assessment Group identified a number of specific concerns with the economic model. It was noted that the model assumed an ongoing cost of £2400 per month after stem cell transplantation, which was significantly higher than the Assessment Group's estimate of £113 per month. The Assessment Group also noted that the Committee for the technology appraisal of dasatinib, high-dose imatinib and nilotinib when imatinib has failed because of resistance or intolerance considered the ongoing cost of £2400 per month to be an unreasonably high estimate, given that only a minority of people who survive transplantation develop complications that incur high ongoing costs. The Assessment Group also identified a number of formulae errors in the model,

which, when corrected for, changed the ICERs to £36,000 per QALY gained for dasatinib compared with imatinib and to £103,000 per QALY gained for dasatinib compared with nilotinib (dasatinib now providing more benefit at greater cost than nilotinib). At the time of submission to NICE, Bristol-Myers Squibb was unable to incorporate in its model the reduced price of first and second-line nilotinib under the approved patient access scheme discount. This was because the manufacturer did not have knowledge of the patient access scheme discount, which was approved during the course of this appraisal. When this discounted price was applied in the model by the Assessment Group (along with correction of formulae errors), the ICER for dasatinib compared with imatinib increased to £45,600 per QALY gained and nilotinib dominated dasatinib (that is, nilotinib was more effective and less costly). The Assessment Group also noted that the model assumed that dasatinib was taken in combination with other chemotherapy drugs as a third-line treatment during the advanced phase in all treatment arms, and that all people in the nilotinib treatment arm and half of all people in the imatinib treatment arm who were eligible for second-line treatment received dasatinib, which is not recommended in the guidance on dasatinib, high-dose imatinib and nilotinib when imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241). When the model was adjusted by the Assessment Group so that dasatinib was not included as third-line treatment, the ICER for dasatinib compared with imatinib increased further, from £45,600 to £64,000 per QALY gained. Nilotinib also continued to dominate dasatinib. When the model was further adjusted by the Assessment Group so that dasatinib was not included as a second-line treatment, and instead it was assumed that all people eligible for second-line treatment in the imatinib arm received nilotinib, the ICER for

dasatinib compared with imatinib increased further, from £64,000 to £96,000 per QALY gained.

Novartis: nilotinib

4.2.11 Novartis developed a Markov model to assess the cost effectiveness of nilotinib 600 mg daily compared with standard-dose imatinib as first-line treatments in people with chronic phase CML. The analysis was conducted from a UK NHS and Personal Social Services perspective using a lifetime horizon with costs and benefits discounted at 3.5%. People entered the model in the chronic phase. The model estimated when one tyrosine kinase inhibitor treatment would fail and therefore when the person would be switched to an alternative treatment. At each cycle, people had a probability of remaining on current treatment, progressing to an alternative treatment or dying. People were able to remain in chronic phase, accelerated phase or blast phase for more than one cycle and could die from non-CML causes at any time. People who received a stem cell transplant could die from transplant-related mortality or remain well. People who were not eligible to receive a stem cell transplant in the chronic phase instead received hydroxyurea treatment. People for whom hydroxyurea therapy failed then progressed to accelerated phase. On progression to accelerated or blast phase, all people were assumed to receive hydroxyurea treatment. People in advanced disease phase had a probability of progressing to blast phase, and finally from blast phase to CML-related death. In the blast phase, people could only die as a result of CML. The model used monthly cycles for the first 6 months followed by quarterly cycles thereafter.

4.2.12 Two different scenarios were modelled to reflect the availability of second-generation tyrosine kinase inhibitors as second-line treatment. In the first scenario, which was the base-case analysis used by the manufacturer, second-line treatment consisted of

dasatinib (100 mg daily) followed by stem cell transplant or hydroxyurea as third-line treatment. In the second scenario, second-line treatment consisted only of stem cell transplant or hydroxyurea with no third-line treatment available. The impact of first-line tyrosine kinase inhibitor treatment on CML progression and survival was estimated using a combination of data on the effect of tyrosine kinase inhibitors on time to discontinuation and the relationship between time to discontinuation and progression-free and overall survival. In order to model lifetime costs and QALYs, the available evidence was extrapolated in the economic model.

4.2.13 Utility values were based on EQ-5D responses from people receiving standard-dose imatinib in the IRIS study. The modelled baseline utilities were 0.854 for the chronic phase and 0.595 for the accelerated or blast crisis phase health states. Disutilities corresponding to grade 3 and 4 adverse events relating to tyrosine kinase inhibitor treatments were estimated from utility values taken from the published literature. These were then weighted by the duration and probability of experiencing the adverse event, to calculate the overall disutility. These disutilities were applied only in the first 18 months for first- and second-line tyrosine kinase inhibitors. Disutilities associated with adverse events for each tyrosine kinase inhibitor were nilotinib 0.010, standard-dose imatinib 0.016 and dasatinib 0.019. Novartis did not identify any published evidence of utility values after stem cell transplant for CML. Therefore, an assumed baseline utility value of 0.813 was used, with a further decrement of 0.079, which was taken from a study of chronic graft-versus-host disease following bone marrow transplant. This utility decrement was applied to the long-term utility for 52% of people after transplant to reflect common adverse events associated with stem cell transplant.

4.2.14 Drug acquisition costs were taken from the BNF 61. For nilotinib, Novartis applied an approved patient access scheme discount, the details of which are commercial in confidence and therefore not provided here. Costs associated with grade 3 or 4 adverse events, stem cell transplantation, routine hospital appointments for administration and monitoring and inpatient stay for end-of-life care were also included in the model. When published data were not available, resource use was estimated from clinical specialist opinion.

4.2.15 The base-case cost-effectiveness results with dasatinib as second-line treatment indicated that nilotinib was associated with an overall survival of 13.54 years (10.40 QALYs) and a total cost of £217,373 and that imatinib was associated with an overall survival of 12.83 years (9.85 QALYs) and a total cost of £227,744. Therefore, imatinib was dominated by nilotinib. The cost-effectiveness results with stem cell transplant or hydroxyurea as second-line treatment indicated that nilotinib was associated with an overall survival of 11.38 years (8.71 QALYs) and a total cost of £170,643 and that imatinib was associated with an overall survival of 9.97 years (7.62 QALYs) and a total cost of £166,015. The resulting ICER for nilotinib compared with imatinib was £5908 per QALY gained.

4.2.16 In one-way sensitivity analyses, the input parameters that had the greatest impact on the ICERs were the first-line drug acquisition costs for nilotinib without the patient access scheme discount and the time to discontinuation of first-line tyrosine kinase inhibitor treatments. The results of the probabilistic sensitivity analysis for the base-case scenario indicated that nilotinib had a 100% probability of being cost effective compared with imatinib at a threshold of £30,000 per QALY.

4.2.17 The Assessment Group identified several areas of uncertainty. The model did not incorporate major molecular response and complete

cytogenetic response rates from the ENESTnd trial, both of which are important measures of clinical effectiveness. There was also uncertainty around the chosen sequence of second-line tyrosine kinase inhibitor treatments and the cost and utility of people who had a stem cell transplant.

Assessment Group model

4.2.18 For the cost-effectiveness analysis of first-line tyrosine kinase inhibitor treatments for CML the Assessment Group identified two major sources of uncertainty. First, the short-term clinical-effectiveness evidence from the DASISION and ENESTnd trials, which had current follow-up of only 2 years. Given that CML is a chronic disease, with survival from diagnosis of approximately 15–20 years, it was necessary to extrapolate clinical-effectiveness data over many years, introducing substantial uncertainty. Second, the relative cost effectiveness of first-line tyrosine kinase inhibitor treatments was heavily influenced by the Assessment Group's assumptions about subsequent lines of treatment and there was much uncertainty around the nature and cost of these treatments. As a result of this extensive structural uncertainty, the Assessment Group presented a range of deterministic scenario analyses, which varied according to key structural assumptions. These scenarios involved alternative treatment sequences following the failure of first-line tyrosine kinase inhibitors, alternative approaches to estimating survival (cumulative and surrogate survival methods) and assumptions about whether costs and outcomes occurring after first-line tyrosine kinase inhibitor treatment were equal between treatment arms. Furthermore, because it was not possible for the Assessment Group to assert that any one scenario was correct, a single base-case analysis was not designated.

4.2.19 The model was a state-transition model with states for the main disease phases and for the different possible treatments in each

phase. People entered the model in the chronic phase. At the end of each cycle, people had a probability of remaining in their current health state, progressing to an alternative state or dying. In two of the base-case scenarios (1 and 2), the Assessment Group model assumed that, after first-line tyrosine kinase inhibitor treatment failure, all people in the chronic phase progressed directly to a mixture of hydroxyurea or stem cell transplant as second-line treatment, with no further lines of treatment before reaching the accelerated or blast crisis phase. In the other two base-case scenarios (3 and 4), the Assessment Group assumed that people receiving first-line imatinib or dasatinib progressed to second-line nilotinib. These people then progressed to a mixture of stem cell transplant and hydroxyurea as third-line treatment, before reaching the accelerated or blast crisis phase. For people whose disease failed to respond to first-line nilotinib, it was assumed that they would progress directly to hydroxyurea or stem cell transplant as second-line treatment, with no further lines of treatment before reaching the accelerated or blast crisis phase. For simplicity, the Assessment Group assumed that people in all three treatment arms who progressed to the accelerated or blast crisis phase would only receive hydroxyurea treatment. This was justified mainly because of a lack of evidence on the effectiveness of tyrosine kinase inhibitor treatments in the advanced stages of CML. For each scenario the model cycle length was 3 months with a half-cycle correction. A lifetime (50 years) horizon was used, based on a mean age at diagnosis of chronic phase CML of 57 years. The analyses were conducted from a UK NHS and Personal Social Services perspective, with costs and benefits discounted at a rate of 3.5%.

4.2.20 The Assessment Group used two alternative approaches to estimate survival: the cumulative survival approach and the surrogate survival approach. In the base-case analyses (scenarios

1, 2, 3 and 4), the cumulative survival approach was used, whereby overall survival was estimated as the cumulative result of the duration of successive treatments. This method did not take into account the complete cytogenetic response and major molecular response rates from the DASISION and ENESTnd trials. An important assumption behind this approach was that overall survival after second-line nilotinib and after second or third-line hydroxyurea or stem cell transplant was independent of previous treatment.

4.2.21 To estimate the mean duration of first-line tyrosine kinase inhibitor treatments in its economic model, the Assessment Group extrapolated treatment duration data using Weibull survival curves from the DASISION, ENESTnd and IRIS trials respectively. The estimated mean first-line treatment durations used in the economic model were imatinib 7.1 years, dasatinib 7.8 years and nilotinib 9.0 years. To estimate survival on hydroxyurea after first-line tyrosine kinase inhibitor failure, the Assessment Group used survival data from a subgroup of 61 people who received a range of treatments following resistance or intolerance to imatinib from a single cohort study. This resulted in an estimated mean overall survival on hydroxyurea following tyrosine kinase inhibitor failure of 7.0 years and a 5-year survival of 50%. Because of a lack of relevant data, it was also assumed that overall survival on hydroxyurea was independent of previous treatment. The estimated mean time on hydroxyurea in accelerated phase and blast crisis phase was 9.6 months and 6 months respectively. These estimates were then used to calculate transition probabilities from accelerated phase to blast crisis phase, and from chronic phase to accelerated phase, while on hydroxyurea treatment.

4.2.22 The proportion of people having a stem cell transplant after first-line tyrosine kinase inhibitor failure was based on clinician opinion,

which indicated a sharp decline in the estimated proportion of people who would receive a stem cell transplant in the chronic phase after the age of 65 years and that no people aged older than 75 years would be likely to receive a stem cell transplant. To estimate overall survival following a stem cell transplant, the Assessment Group used data from a study of people with chronic phase CML receiving stem cell transplants in a London hospital between 2000 and 2010. Of these, 74% survived to 3 years and 72% to 6 years. Finally, the model required the estimated duration of second-line nilotinib treatment in people for whom first-line dasatinib or imatinib failed (scenarios 3 and 4). The Assessment Group extrapolated data from a phase II study of imatinib-resistant people who received second-line nilotinib treatment. This resulted in an estimated mean time on second-line nilotinib treatment of 2.4 years.

4.2.23 The Assessment Group also presented scenario analyses using a simplified method (scenarios 2 and 4). In this approach, per patient costs and QALYs after tyrosine kinase inhibitor treatment (first- or second-line) were set to be equal across the treatment arms. The costs and QALYs while patients were on tyrosine kinase inhibitors were modelled specific to each treatment arm. However, because slightly different proportions of people were predicted to have died during the time when they were taking first- or second-line tyrosine kinase inhibitors, there were small differences between treatment arms in the total costs and QALYs accrued after this timepoint. The Assessment Group included this approach to allow for the 'pure' cost effectiveness of first-line tyrosine kinase inhibitor treatments and second-line nilotinib, given the high uncertainty around the nature and costs of subsequent lines of treatment and the likelihood that people would be treated with first-line tyrosine kinase inhibitors for many years.

4.2.24 In the surrogate survival approach, which was explored in sensitivity analyses, overall survival for the three first-line tyrosine kinase inhibitor treatments was estimated using a surrogate relationship based on major molecular response at 12 months or complete cytogenetic response at 12 months. The methods of estimating overall survival based on the surrogate relationships with major molecular response and complete cytogenetic response were taken from the results of the Assessment Group's clinical-effectiveness systematic review and network meta-analysis of surrogate outcomes at 12 months. The Assessment Group found that the modelled data appeared to closely predict the overall survival observed in the DASISION and ENESTnd trials and the longer-term survival data from the imatinib treatment arm in the IRIS randomised controlled trial.

4.2.25 The Assessment Group undertook a systematic review to identify relevant CML health state utility values for its economic model. Two studies based on a large sample of people receiving imatinib treatment in the IRIS trial were identified that estimated EQ-5D utility values for CML health states. After adjusting for the mean age at diagnosis (57 years), a utility value of 0.83 was estimated for the chronic phase health state for all three first-line tyrosine kinase inhibitor treatments and for people receiving hydroxyurea as second- or third-line treatment. For people in the accelerated phase and blast phase, utility values of 0.73 and 0.52 were used respectively. For people receiving a stem cell transplant as second- or third-line treatment in the chronic phase, it was assumed that people at low risk of mortality (75%) would incur a disutility of 0.041 and people at high risk of mortality (25%) would incur a disutility of 0.079. Both disutilities were subtracted from general England and Wales population age-related utility values.

4.2.26 Cost estimates in the Assessment Group economic model included drug acquisition costs, grade 3 or 4 adverse event costs, stem cell transplantation and a range of medical management costs such as consultant outpatient visits and hospitalisation, which differed according to whether the person was in the chronic or advanced (accelerated and blast crisis) phase. All costs were inflated to 2011–12 values if appropriate. Drug acquisition costs for the three tyrosine kinase inhibitor treatments and hydroxyurea were taken from BNF 61 and MIMS. The cost of first- and second-line nilotinib used in the Assessment Group model also reflected the approved patient access scheme discount provided by Novartis. Dose intensities for the three tyrosine kinase inhibitor treatments were applied to the costs, to accurately reflect the dosage of the drugs administered in the relevant clinical trials. The average dose intensities used in the base-case analyses were 99% for first-line dasatinib, submitted to NICE in confidence for nilotinib and 100% for imatinib. These were based on information from the manufacturers' submissions. For second-line nilotinib, an average dose intensity of 99% was taken from a phase II trial of nilotinib for people resistant to or intolerant of imatinib. For second- and third-line hydroxyurea, an assumed average dose intensity of 100% was used.

4.2.27 The Assessment Group economic model included treatment of grade 3 or 4 adverse events related to first or second-line tyrosine kinase inhibitors. Rates of grade 3 or 4 adverse events were taken from the DASISION and ENESTnd trials for the first 12 months of treatment. Only the cost of treating neutropenia, thrombocytopenia and anaemia were included because other grade 3 or 4 events were experienced by no more than 1% of people in both trials. Because the number of additional adverse events from 13 to 24 months was so small, only events in the first year of tyrosine kinase inhibitor treatment were included in the model.

4.2.28 The costs of medical management and monitoring were the same as those used in the Bristol-Myers Squibb model, which were estimated from a survey of six UK haematologists. These costs, which differed for the chronic and advanced (accelerated and blast crisis) phase, included nurse and consultant outpatient visits, tests and hospital inpatient stay. For people receiving a stem cell transplant as second- or third-line treatment, a one-off mean per patient cost of £81,600 was applied, which was followed by monthly drug and monitoring costs of longer-term post-stem cell transplant care. It was also assumed that people in the blast crisis phase would incur the extra costs of palliative care.

4.2.29 For all four scenarios, the predicted mean duration of first-line treatment for nilotinib, imatinib and dasatinib was 8.9, 7.0 and 7.7 years respectively. In scenario 1 (without second-line nilotinib), predicted mean survival after stem cell transplantation for nilotinib, imatinib and dasatinib was 4.9, 5.8 and 5.5 years while predicted mean time on hydroxyurea in the chronic and advanced phase was similar for the three treatments. The predicted mean overall survival for nilotinib, imatinib and dasatinib was 17.4, 16.5 and 16.8 years respectively. Similar results were obtained for scenario 2. In scenario 3 (with second-line nilotinib), predicted time on second-line nilotinib was 2.2 years for people taking first-line imatinib or dasatinib. The predicted mean survival after stem cell transplantation for nilotinib, imatinib and dasatinib was 4.9, 4.2 and 3.9 years while predicted mean time on hydroxyurea in the chronic and advanced phase was again similar for the three treatments. The predicted mean overall survival for nilotinib, imatinib and dasatinib was 17.4, 17.3 and 17.6 years respectively.

4.2.30 The Assessment Group noted the wide variation in the cost-effectiveness results across the four scenarios in the base-case analysis. In scenario 1 of the Assessment Group's base-case

analysis (assuming no second-line nilotinib), nilotinib, imatinib and dasatinib were associated with a total discounted cost of £201,808, £186,827 and £253,172 respectively. Nilotinib was associated with more discounted QALYs than imatinib and dasatinib: 9.4 compared with 9.0 for imatinib and 9.2 for dasatinib, resulting in a cost per QALY gained of £36,000 for nilotinib compared with imatinib, while dasatinib was dominated by nilotinib.

4.2.31 In scenario 2 of the Assessment Group's base-case analysis (simplified method, still assuming no second-line nilotinib), nilotinib, imatinib and dasatinib were associated with a total discounted cost of £204,222, £186,627 and £254,166 respectively. Nilotinib was associated with more discounted QALYs than imatinib and dasatinib: 9.7 compared with 9.0 for imatinib and 9.3 for dasatinib, resulting in a cost per QALY gained of £26,000 for nilotinib compared with imatinib, while dasatinib was dominated by nilotinib.

4.2.32 In scenario 3 of the Assessment Group's base-case analysis (assuming the use of second-line nilotinib after first-line imatinib or dasatinib), nilotinib, imatinib followed by nilotinib and dasatinib followed by nilotinib were associated with total discounted costs of £201,808, £222,398 and £287,487 respectively. Nilotinib was associated with fewer discounted QALYs than imatinib or dasatinib followed by nilotinib: 9.4 compared with 9.5 for imatinib followed by nilotinib and 9.7 for dasatinib followed by nilotinib, resulting in costs per QALY gained of £213,000 for imatinib followed by nilotinib compared with nilotinib, and £460,000 for dasatinib followed by nilotinib compared with nilotinib.

4.2.33 In scenario 4 of the Assessment Group's base-case analysis (simplified method, still assuming the use of second-line nilotinib after first-line imatinib or dasatinib), nilotinib, imatinib followed by nilotinib, and dasatinib followed by nilotinib were associated with total discounted costs of £198,517, £222,398 and £288,241

respectively. Nilotinib was associated with fewer discounted QALYs than imatinib or dasatinib followed by nilotinib: 9.1 compared with 9.5 for imatinib followed by nilotinib and 9.7 for dasatinib followed by nilotinib, resulting in costs per QALY gained of £50,000 for imatinib followed by nilotinib compared with nilotinib, and £307,000 for dasatinib followed by nilotinib compared with nilotinib.

4.2.34 In the Assessment Group's deterministic sensitivity analyses, the input parameters that had the greatest impact on the ICERs for nilotinib compared with imatinib included changes to the dose intensities of first-line nilotinib or imatinib. When the dose intensity of first-line nilotinib was increased to 100%, the ICERs for nilotinib compared with imatinib increased to £63,000 per QALY gained in scenario 1, and to £44,000 per QALY gained in scenario 2. In scenarios 3 and 4, the ICERs for imatinib followed by second-line nilotinib compared with nilotinib decreased to £93,000 and £26,000 per QALY gained respectively. When the dose intensity of imatinib was increased from 100% to 106% (the value used in the Novartis model), the ICER for nilotinib compared with imatinib decreased to £19,000 per QALY gained in scenario 1, and to £15,000 per QALY gained in scenario 2. In scenarios 3 and 4, the ICERs for imatinib followed by second-line nilotinib compared with nilotinib increased to £286,000 and £65,000 per QALY gained respectively. The ICERs were also very sensitive to assumptions made about the duration of first-line tyrosine kinase inhibitor treatment. When first-line nilotinib was assumed to have the same mean duration as imatinib (7.0 years), this resulted in imatinib being dominated by nilotinib in scenarios 1 and 2. Other influential parameters on the ICERs for nilotinib compared with imatinib included assumptions about stem cell transplantation (cost, proportion of people receiving stem cell transplant and post transplant survival), time on hydroxyurea in the chronic phase, and medical management costs in the chronic phase. The lowest ICERs for dasatinib compared

with imatinib were £110,000 and £82,000 per QALY gained in scenarios 1 and 2 and £298,000 per QALY and £259,000 per QALY gained in scenarios 3 and 4.

4.2.35 The Assessment Group also presented one-way deterministic sensitivity analyses based on the surrogate survival method in which overall survival was estimated from response according to major molecular response or complete cytogenetic response at 12 months (scenarios 1a, 1b, 2a and 2b). When overall survival was estimated from the major molecular response surrogate relationship, the ICERs for nilotinib compared with imatinib increased to £53,000 per QALY gained in scenario 1a and to £36,000 per QALY gained in scenario 2a. This was because the gain in overall survival for nilotinib was 0.6 years using this method, compared with 0.9 years when based on the cumulative survival method. Conversely, when overall survival was estimated from the complete cytogenetic response surrogate relationship, the ICERs for nilotinib compared with imatinib decreased to £29,000 per QALY gained in scenario 1b and to £22,000 per QALY gained in scenario 2b. This was because the estimated gain in overall survival for nilotinib compared with imatinib increased to 1.3 years when using this method. The Assessment Group also noted that in both scenarios, the ICERs for dasatinib compared with imatinib remained very high when the surrogate survival method was used.

4.2.36 The Assessment Group did not conduct and present probabilistic sensitivity analyses because of the large amount of structural uncertainty, which was related to the estimate of long-term survival and subsequent treatment sequences following first-line tyrosine kinase inhibitor failure in its model. As a result, it commented that structural uncertainty would dominate total (structural and parameter) uncertainty and that, if a probabilistic sensitivity analysis

based on parametric uncertainty was presented, this would be potentially misleading.

Assessment Group model – revised analyses following consultation on the assessment report and the Assessment Group's economic model

4.2.37 In response to comments received from the manufacturers on the assessment report and the Assessment Group's economic model, the Assessment Group produced an addendum to the assessment report, which outlined changes to its base-case cost-effectiveness assumption in relation to the cost of ongoing medical management in chronic phase CML. Following clarification from its UK clinical adviser, the Assessment Group accepted comments made by Novartis that it had overestimated the frequency of outpatient visits and bone marrow aspirations, and it calculated revised base-case cost-effectiveness estimates assuming lower medical management costs during the chronic phase. The Assessment Group revised its estimates for haematologist or oncologist visits from 0.9 to 0.33 visits per month for people receiving tyrosine kinase inhibitor treatments and to 0.72 visits per month for people receiving hydroxyurea. It was also assumed that there would be no outpatient nurse visits and that no monthly bone marrow aspirations would be given to patients, as opposed to 0.3 per month used in the original Assessment Group model.

4.2.38 Incorporating the revised assumptions for medical management costs in the Assessment Group's base-case scenario 1 analysis (no second-line nilotinib), resulted in a total discounted cost of £170,000 for nilotinib, £159,000 for imatinib and £224,000 for dasatinib. Nilotinib was associated with more discounted QALYs than imatinib and dasatinib: 9.4 compared with 9.0 for imatinib and 9.2 for dasatinib, resulting in a cost per QALY gained of £25,000 for nilotinib compared with imatinib, while dasatinib was dominated by nilotinib.

4.2.39 The Assessment Group's revised base-case scenario 2 analysis (simplified method, still assuming no second-line nilotinib), resulted in a total discounted cost of £172,000 for nilotinib, £159,000 for imatinib and £225,000 for dasatinib. Nilotinib was associated with more discounted QALYs than imatinib and dasatinib: 9.7 compared with 9.0 for imatinib and 9.3 for dasatinib, resulting in a cost per QALY gained of £20,000 for nilotinib compared with imatinib, while dasatinib was dominated by nilotinib.

4.2.40 In scenario 3 of the Assessment Group's revised base-case analysis (assuming the use of second-line nilotinib after first-line imatinib or dasatinib), nilotinib, imatinib followed by nilotinib and dasatinib followed by nilotinib were associated with total discounted costs of £170,000, £188,000 and £252,000 respectively. Nilotinib was associated with fewer discounted QALYs than imatinib or dasatinib followed by nilotinib: 9.4 compared with 9.5 for imatinib and 9.7 for dasatinib, resulting in costs per QALY gained of £192,000 for imatinib followed by nilotinib compared with nilotinib, and £450,000 for dasatinib followed by nilotinib compared with nilotinib.

4.2.41 In scenario 4 of the Assessment Group's revised base-case analysis (simplified method, still assuming the use of second-line nilotinib after first-line imatinib or dasatinib), nilotinib, imatinib followed by nilotinib, and dasatinib followed by nilotinib were associated with total discounted costs of £166,000, £188,000 and £253,000 respectively. Nilotinib was associated with fewer discounted QALYs than imatinib or dasatinib followed by nilotinib: 9.1 compared with 9.5 for imatinib followed by nilotinib and 9.7 for dasatinib followed by nilotinib, resulting in costs per QALY gained of £46,000 for imatinib followed by nilotinib compared with nilotinib, and £301,000 for dasatinib followed by nilotinib compared with nilotinib.

4.2.42 In its addendum to the assessment report the Assessment Group also explored the impact on the estimated ICERs of altered assumptions about dose intensity while on first-line imatinib and survival after stem cell transplantation. The Assessment Group noted the comments from Novartis that the mean dose intensity of first-line imatinib at 24-month follow-up in the ENESTnd trial was 106% and that this value could inform the modelling, but that it was not clear whether it was preferable to using the value of 100% from the IRIS trial, which was used in the Assessment Group's base-case analyses. Novartis also commented that the Assessment Group model assumptions relating to survival after stem cell transplantation might be over-optimistic (mean survival of approximately 17 years) and that a lower mean survival estimate of 10 years might be more plausible. Novartis claimed that the most relevant estimate of the 6-year survival probability after stem cell transplantation used by the Assessment Group was between 30% and 60%. When the Assessment Group estimated this probability as the midpoint of this range (45%), and assumed that survival after stem cell transplantation followed an exponential distribution, the resulting mean survival was 7.5 years. The Assessment Group explored this value in a sensitivity analysis, acknowledging the uncertainty around its estimate of 17 years.

4.2.43 Assuming that survival after stem cell transplantation was 7.5 years reduced the ICERs for nilotinib compared with imatinib to £17,000 per QALY gained in scenario 1, and to £18,000 per QALY gained in scenario 2. In scenarios 3 and 4, the ICERs for imatinib followed by nilotinib compared with nilotinib were £61,000 per QALY gained (scenario 3) and £49,000 per QALY gained (scenario 4). Assuming a dose intensity for first-line imatinib of 106% and survival after stem cell transplantation of 7.5 years further reduced the ICERs for nilotinib compared with imatinib to £6,000 per QALY gained in scenario 1, and to £8,000 per QALY gained in scenario 2. In

scenarios 3 and 4, the ICERs for imatinib followed by nilotinib compared with nilotinib were £84,000 per QALY gained (scenario 3) and £65,000 per QALY gained (scenario 4). In all four scenarios, the ICERs for dasatinib compared with imatinib remained above £200,000 per QALY gained.

Additional analyses presented by Bristol-Myers Squibb and the Assessment Group following the first appraisal committee meeting and consultation on the appraisal consultation document (ACD)

4.2.44 Bristol-Myers Squibb provided additional economic analyses as part of its response to the ACD. These incorporated the changes made by the Assessment Group to its model in response to comments received from Novartis. These changes to the Bristol-Myers Squibb model included the revised medical management costs during the chronic phase and a mean dose intensity of first-line imatinib of 106%. The revised model also included an estimate of the reduced price of first- and second-line nilotinib under the approved patient access scheme discount and corrections to seven of the eight formulae errors that were originally identified by the Assessment Group. As a result of corrections to the formulae errors alone, the ICER for dasatinib compared with imatinib was £33,200 per QALY gained. When the revised medical management costs and price reduction of nilotinib were also applied, the ICER for dasatinib compared with imatinib was £34,400 per QALY gained. When a mean dose intensity of imatinib of 106% was also applied the ICER for dasatinib compared with imatinib was £26,500 per QALY gained. Bristol-Myers Squibb did not present ICERs for the comparison of dasatinib with nilotinib following these changes to its model.

4.2.45 In its response to the additional modelling results presented by Bristol-Myers Squibb, the Assessment Group commented that dasatinib remained in the model as a second- and third-line

treatment option despite not being recommended in the guidance on dasatinib, high-dose imatinib and nilotinib when imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241). The Assessment Group therefore adjusted the model so that dasatinib was not included as a second or third-line treatment. As a result of this change, the ICERs for dasatinib compared with imatinib were £81,000 per QALY gained when the revised medical management costs and price reduction of nilotinib were applied and £75,000 per QALY gained when a mean dose intensity of imatinib of 106% was also applied. When the Assessment Group adjusted the model so that dasatinib was not included as a second or third-line treatment and also corrected all of the eight formulae errors that were originally identified, the ICERs for dasatinib compared with imatinib were £87,000 per QALY gained when the revised medical management costs and price reduction of nilotinib were applied and £80,000 per QALY gained when a mean dose intensity of imatinib of 106% was also applied.

4.2.46 Following the first appraisal committee meeting, the Assessment Group provided new analyses, which modelled two additional treatment sequences in scenarios 3 and 4. In these new treatment sequences, people receiving first-line dasatinib or nilotinib progressed to second-line standard-dose imatinib followed by a combination of stem cell transplant and hydroxyurea as third-line treatment. These new analyses enabled comparison with the treatment sequences that were originally modelled by the Assessment Group; that is, people receiving first-line imatinib or dasatinib who progressed to second-line nilotinib followed by a combination of stem cell transplant and hydroxyurea as third-line treatment and people receiving first-line nilotinib who progressed to a combination of stem cell transplant and hydroxyurea as second-line treatment.

4.2.47 The Assessment Group did not identify any clinical data for the time on second-line standard-dose imatinib for people whose disease failed to respond to first-line dasatinib or nilotinib. The Assessment Group therefore assumed that the time on second-line imatinib of 1.9 years, which was calculated as the mean time on second-line nilotinib weighted by the ratio of the mean time on first-line imatinib to the mean time on first-line nilotinib, was the same following first-line dasatinib or nilotinib. It was also assumed that second-line imatinib, similar to second-line nilotinib, had a constant rate of failure over time. In the absence of any available clinical evidence, the Assessment Group assumed that the mean dose intensity of second-line imatinib of 100% and the cost of adverse events of £166 per patient were equal to first-line imatinib. The additional analyses presented by the Assessment Group also incorporated the revised assumptions for ongoing medical management costs in chronic phase CML (see sections 4.2.37 to 4.2.41).

4.2.48 In scenario 3 of the Assessment Group's additional analyses, imatinib followed by nilotinib, nilotinib followed by imatinib and dasatinib followed by imatinib were associated with total discounted costs of £188,000, £192,000 and £247,000 respectively. Imatinib followed by nilotinib was associated with fewer discounted QALYs than dasatinib or nilotinib followed by imatinib: 9.5 compared with 9.6 for dasatinib and 9.8 for nilotinib, resulting in an ICER of £11,000 per QALY gained for nilotinib followed by imatinib compared with imatinib followed by nilotinib, while dasatinib followed by imatinib was dominated by nilotinib followed by imatinib. Very similar results were reported in scenario 4 (simplified method), with an ICER of £11,000 per QALY gained for nilotinib followed by imatinib compared with imatinib followed by nilotinib, while dasatinib followed by imatinib was again dominated by nilotinib followed by imatinib. When compared with the results presented for scenarios 3 and 4 of the Assessment Group's revised

base-case analysis, a treatment pathway of dasatinib followed by nilotinib was also dominated by nilotinib followed by imatinib in both scenarios. Furthermore, a comparison of nilotinib followed by imatinib with nilotinib (followed by a combination of stem cell transplant and hydroxyurea as second-line treatment) resulted in ICERs of £57,000 per QALY gained in the non-simplified method (scenarios 1 and 3) and £31,000 per QALY gained in the simplified method (scenarios 2 and 4).

4.2.49 In the Assessment Group's deterministic sensitivity analyses, the input parameters that had the greatest impact on the ICERs for nilotinib followed by imatinib compared with imatinib followed by nilotinib included changes to the dose intensities of nilotinib or imatinib. When the dose intensity of first-line nilotinib was increased to 100% (the dose intensity of first-line nilotinib in the base-case analysis is commercial in confidence and therefore not included here), the ICERs for nilotinib followed by imatinib compared with imatinib followed by nilotinib increased to £52,000 per QALY gained in scenario 3, and to £42,000 per QALY gained in scenario 4. When the dose intensity of first and second-line imatinib was increased from 100% to 106%, this resulted in imatinib followed by nilotinib being dominated by nilotinib followed by imatinib in both scenarios. The ICERs were also very sensitive to assumptions made about the duration of first and second-line tyrosine kinase inhibitor treatment. When first-line nilotinib was assumed to have the same mean duration as first-line imatinib (7.0 years), this resulted in imatinib followed by nilotinib being dominated by nilotinib followed by imatinib in both scenarios. When second-line nilotinib was assumed to have the same mean duration as first-line nilotinib (8.9 years), the ICERs in scenarios 3 and 4 for nilotinib followed by imatinib compared with imatinib followed by nilotinib increased to £63,000 and £41,000 per QALY gained respectively. When second-line imatinib was assumed to have the same mean

duration as first-line imatinib, the ICERs in scenarios 3 and 4 for nilotinib followed by imatinib compared with imatinib followed by nilotinib increased to £42,000 and £31,000 per QALY gained respectively. The lowest ICERs for dasatinib followed by imatinib compared with imatinib followed by nilotinib in scenarios 3 and 4 were £110,000 and £75,000 per QALY gained.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of dasatinib, nilotinib and standard-dose imatinib, having considered evidence on the nature of CML and the value placed on the benefits of the interventions by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.3.2 The Committee discussed current clinical practice for the treatment of CML. The Committee heard from the clinical specialists that standard-dose imatinib is the usual first-line treatment for people presenting with chronic phase CML, in line with the guidance on first-line imatinib for CML (NICE technology appraisal guidance 70), and that clinical experience of dasatinib and nilotinib for chronic phase CML is largely restricted to the context of clinical trials.

4.3.3 To understand the full CML treatment pathway, the Committee discussed the possible treatment pathway for people with chronic phase CML that has failed to respond to first-line tyrosine kinase inhibitor treatment. It was noted by the Committee that nilotinib, but not dasatinib or high-dose imatinib, was recommended in the guidance on dasatinib, high-dose imatinib and nilotinib when standard-dose imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241). However, the clinical specialists stated that, for a very small proportion of

people whose CML is resistant to standard-dose imatinib or who are intolerant of imatinib, there may be clinical reasons for the use of dasatinib, including comorbidities and disease resistance to nilotinib. The Committee also heard from the clinical specialists that standard-dose imatinib could be a potential second-line treatment if dasatinib or nilotinib were to replace it as the standard first-line treatment. The Committee noted the views of the clinical specialists that the use of standard-dose imatinib in the second-line setting would preferably be limited to people who were intolerant to first-line dasatinib or nilotinib, and that standard-dose imatinib would be less likely to be offered to people with resistance to first-line dasatinib or nilotinib because the clinical specialists believed it is a less effective agent. The clinical specialists also commented that hydroxyurea would not be used as a second-line treatment for CML in place of a tyrosine kinase inhibitor because it does not affect the progression of the disease and is used for palliative purposes or as a short-term measure between lines of treatment.

4.3.4 The Committee discussed the clinical-effectiveness evidence for dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of CML. It was aware of two comparative trials, one that compared dasatinib with imatinib and one that compared nilotinib with imatinib. It noted that no trials directly comparing dasatinib and nilotinib were available.

4.3.5 The Committee considered that both trials were good quality international randomised controlled trials and that the demographic characteristics of the participants and the overall trial designs were sufficiently similar to enable indirect comparison of dasatinib and nilotinib. However, it was also noted that both the clinical trials were of short duration and provided only short-term data on progression-free and overall survival and that surrogate outcome measures were used. The Committee also noted that the trial populations

may not be completely representative of a UK CML population, because of the lower age at diagnosis compared with the general population. However, the Committee was reassured by the views of the clinical specialists that the age difference was not a major factor, and it concluded that the populations included in the trials were broadly relevant to UK clinical practice.

4.3.6 The Committee considered the results of the clinical trials, which showed that statistically significantly more people receiving dasatinib and nilotinib had a complete cytogenetic response and a major molecular response than people receiving standard-dose imatinib at 12-month follow-up. The Committee also noted the views of the clinical specialists and patient experts that nilotinib and dasatinib are more effective drugs with a theoretically superior mechanism of action to standard-dose imatinib, although imatinib remains very effective for the majority of patients. The 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.

4.3.7 The Committee considered the results of the indirect comparison of dasatinib and nilotinib conducted by the Assessment Group, which showed no statistically significant differences in rates of complete cytogenetic response and major molecular response by 12 months between the two treatments. The Committee was also aware of another published study, which conducted a matching-adjusted indirect comparison of dasatinib and nilotinib, and showed statistically significantly higher major molecular response rates and overall survival by 12 months for people taking nilotinib compared with dasatinib. The Committee noted the comment from the clinical specialist that this study had been sponsored by Novartis. Overall, the Committee concluded that there was insufficient evidence to

distinguish between dasatinib and nilotinib in terms of clinical effectiveness.

4.3.8 The Committee considered the Assessment Group's analysis of short-term surrogate response markers as predictors of longer-term patient-relevant outcomes. The Committee noted that the clinical evidence was taken from a mixture of longer-term randomised and observational studies of imatinib only. However, the Committee accepted that the results of the analysis, which showed that people with either a complete cytogenetic response or major molecular response after 12 months experienced better long-term survival, could be potentially applied to people receiving dasatinib or nilotinib.

4.3.9 The Committee discussed the adverse side effects of tyrosine kinase inhibitors for people with CML. It noted from the clinical trials that all three drugs were well tolerated and that discontinuation rates due to adverse events for people taking dasatinib and nilotinib compared with standard-dose imatinib were similar. However, the Committee noted that health-related quality of life was not reported in either trial. The Committee also heard from the patient experts that, in their experience, side effects associated with tyrosine kinase inhibitors were considered to be easily manageable over time, were not a major concern for people with CML, and that, although dasatinib and nilotinib were associated with different adverse effects, tolerability was similar between both drugs. The Committee also noted that QT interval prolongation was listed in the special warnings and precautions for use in the SPC for both dasatinib and nilotinib. However, the Committee was reassured by the views of the clinical specialists that there was no increased cardiovascular risk at the licensed doses. The Committee concluded that all three drugs appeared to be well tolerated and represented important treatments for people with CML.

4.3.10 The Committee discussed the cost effectiveness of dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of CML. The Committee noted that the acquisition costs of dasatinib and nilotinib were in excess of £30,000 per person per year, and that the cost of standard-dose imatinib had recently increased to approximately £20,000 per person per year. It also noted that the Department of Health had approved a patient access scheme for nilotinib, the details of which are commercial in confidence. The patient access scheme discount was reflected in the acquisition cost of nilotinib used in both the Assessment Group's and Novartis' cost-effectiveness analyses.

4.3.11 The Committee considered the economic models provided by the manufacturers, Bristol-Myers Squibb and Novartis, and also by the Assessment Group. It noted key differences in the treatment pathways and approaches to modelling overall survival in the three economic models (see sections 4.2.2 to 4.2.4, 4.2.11 to 4.2.12 and 4.2.18 to 4.2.24). The Committee also considered the comments received from both manufacturers on the Assessment Group's economic model and the responses provided by the Assessment Group to these comments.

4.3.12 The Committee noted that the Assessment Group's economic model included a range of scenarios because of uncertainty about the impact of dasatinib and nilotinib on long-term survival and about subsequent lines of treatment at the time of modelling. It noted that four base-case scenarios were modelled, which varied according to the methodology used to estimate overall survival, subsequent second- and third-line treatment options and whether costs and QALYs per person progressing beyond the first- and second-line tyrosine kinase inhibitor should be considered equal across treatment arms. The Committee was aware that nilotinib was the only tyrosine kinase inhibitor considered as a possible second-line

treatment in the Assessment Group's original economic analyses (in two of the four base-case scenarios), and that this reflected the guidance on dasatinib, high-dose imatinib and nilotinib when standard-dose imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241). The Committee further noted that the Assessment Group had conducted extensive deterministic sensitivity analyses to explore uncertainty around key structural assumptions in its model. The Committee concluded that, although assumptions in the modelling around survival and subsequent lines of treatment were associated with substantial uncertainty, the Assessment Group, by considering the impact of alternative assumptions, had made considerable effort to address this.

4.3.13 The Committee considered the original outputs of the economic model developed by the Assessment Group as part of its assessment report sent for consultation (before revisions were made following the comments received on the assessment report). The Committee acknowledged the wide variation in the cost-effectiveness results across the scenarios presented by the Assessment Group, which reflected the considerable structural uncertainty in the modelling of first-line tyrosine kinase inhibitors for CML. However, it also noted that in the base-case analysis for all scenarios, dasatinib was either dominated by nilotinib or generated ICERs of more than £300,000 per QALY gained compared with imatinib. The Committee noted that in the two scenarios that did not consider the use of second-line nilotinib following first-line treatment with dasatinib or standard-dose imatinib, the ICERs for nilotinib compared with standard-dose imatinib were £36,000 per QALY gained (scenario 1) and £26,000 per QALY gained (scenario 2). The Committee also noted that in the scenarios that did consider second-line nilotinib following first-line treatment with dasatinib or standard-dose imatinib (that is, scenarios 3 and 4),

nilotinib generated fewer QALYs but generated substantial cost savings compared with imatinib followed by second-line nilotinib. The Committee concluded that the Assessment Group's original base-case cost-effectiveness results indicated that dasatinib was not cost effective and that nilotinib was on the border of cost effectiveness (the range usually considered a cost-effective use of NHS resources is between £20,000 and £30,000 per QALY gained) in many of the analyses presented when the patient access scheme was applied.

4.3.14 The Committee carefully considered the comments received from consultees on the Assessment Group's economic model and the Assessment Group's response to these comments. The Committee noted the key criticisms from Bristol-Myers Squibb about the different modelling approaches used to estimate survival on first- and second-line treatment, which Bristol-Myers Squibb argued were inconsistent with the underlying disease and resulted in incorrect or unreliable treatment durations being modelled. However, the Committee agreed that only short-term data were available for survival on first-line dasatinib and nilotinib and that the Assessment Group had adequately acknowledged and addressed the advantages and disadvantages of different survival modelling approaches by presenting a range of scenarios rather than a single base-case cost-effectiveness analysis. It noted that, by using a cumulative survival approach in its base-case scenario analyses, the Assessment Group had used a similar approach to modelling survival as Novartis in its economic model and that the surrogate survival approach used in its sensitivity analyses was similar to the approach used by Bristol-Myers Squibb in its model. The Committee also noted that many of the weaknesses associated with these alternative approaches to modelling survival that were highlighted by Bristol-Myers Squibb were clearly acknowledged by the Assessment Group and were also reflected in both

manufacturers' models. It agreed with the Assessment Group that, although probabilistic sensitivity analysis has an important role in exploring parameter uncertainty in NICE appraisals, its usefulness is limited in situations in which there is substantial structural uncertainty: in this case there is extensive uncertainty around the possible treatment sequences following first-line tyrosine kinase inhibitor treatment failure and modelling of short-term survival data. The Committee therefore concluded that the Assessment Group had adequately addressed this structural uncertainty by presenting a range of deterministic scenario analyses.

4.3.15 The Committee also considered the comments received from Novartis about the Assessment Group's economic model. The Committee noted that the Assessment Group had accepted Novartis' comments in relation to the costs of medical management in the chronic phase and had subsequently reduced the cost in its model. The Committee noted that when these changes were made, the revised base-case ICERs for the scenarios that compared nilotinib with imatinib followed by no second-line nilotinib were £25,000 (scenario 1) and £20,000 per QALY gained (scenario 2). The Committee also noted that, in response to additional comments received from Novartis, the Assessment Group had also explored the effect of adjustments to the mean dose intensity of imatinib (increased from 100% to 106%) and mean survival after stem cell transplantation (reduced from 17 years to 7.5 years). The Committee agreed that the adjustment to mean survival after stem cell transplantation, which resulted in ICERs of £17,000 and £18,000 per QALY gained in scenarios 1 and 2, was plausible, but that an increased dose of imatinib taken from a single time point in one trial could not be assumed to reflect the evidence as a whole or clinical practice. For all scenarios, dasatinib continued to be dominated by nilotinib or to generate ICERs of over £200,000 per QALY gained compared with imatinib. The Committee was satisfied

that the Assessment Group had appropriately addressed comments received from the manufacturers on its economic model and that the ICERs generated from the Assessment Group's revised analysis provided a suitable basis for recommendation.

4.3.16 The Committee considered which of the scenarios modelled by the Assessment Group gave the most realistic estimates of cost effectiveness for dasatinib, nilotinib and standard-dose imatinib. At the time of the first appraisal committee meeting, the Committee was aware that there was considerable uncertainty about which treatments would be given to people with chronic phase CML following first-line treatment – this was driven by uncertainty about the final guidance that would be issued by NICE on the second-line treatment of chronic and accelerated phase CML; that is, in adults whose CML is resistant to standard-dose imatinib or who are intolerant of imatinib (published as NICE technology appraisal guidance 241 by the time of the second appraisal committee meeting). The Committee was also aware at the first appraisal committee meeting that a scenario of second-line imatinib following first-line treatment with nilotinib or dasatinib had not been modelled by the Assessment Group despite clinical specialist opinion that this would be a plausible treatment pathway for people with CML that is intolerant to a first-line second-generation tyrosine kinase inhibitor. The Committee also considered the comments received from consultees following consultation on the ACD that scenarios 1 and 2 of the Assessment Group's model did not reflect clinical practice and should not be used to inform the recommendations. The Committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor. The Committee therefore considered that scenarios 3 and 4 were initially incomplete (at the time of the first appraisal committee meeting) but that scenarios 1 and 2 of the Assessment Group's model provided

only relatively approximate estimates of the cost effectiveness of first-line treatment with tyrosine kinase inhibitors.

4.3.17 The Committee therefore considered the further additional analyses carried out by the Assessment Group after consultation on the ACD. It noted that the Assessment Group had modelled two additional scenarios – one comprising first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. The Committee agreed that these analyses were an important addition to the Assessment Group's model because they enabled a comparison in scenarios 3 and 4 of all the relevant first- and second-line treatment sequences.

4.3.18 The Committee thus considered the ICERs from scenarios 3 and 4 of the Assessment Group's model, including the results from the further additional analyses presented by the Assessment Group following the first appraisal committee meeting. The Committee noted that the ICER for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib was £11,000 per QALY gained for both scenarios and that this was in the range normally considered a cost-effective use of NHS resources. It also noted that treatment with first-line nilotinib followed by imatinib resulted in more QALYs and lower costs than first-line treatment with dasatinib followed either by imatinib or nilotinib (that is, nilotinib dominated dasatinib). The implications of these results were consistent with those from scenarios 1 and 2. The Committee concluded that the results of the Assessment Group's analyses indicated that nilotinib represented a cost-effective first-line treatment for people with chronic phase CML, and that dasatinib did not.

4.3.19 With regard to imatinib, the Committee was aware that the ICERs for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib were sensitive to a number of parameters, including assumptions about the dose intensity of nilotinib and the average time spent on second-line nilotinib or imatinib treatment. The Committee noted that changes to these input parameters, notably adjusting the modelled dose intensity of first-line nilotinib to SPC-recommended levels, reversed the relative cost effectiveness of nilotinib and imatinib. In addition, the Committee recognised that, although more of the sensitivity analyses produced favourable ICERs for nilotinib when compared with standard-dose imatinib, imatinib has a proven longer-term record of safety and efficacy: there were 7 years of survival data for first-line imatinib from the IRIS trial, with positive results for complete cytogenetic response and disease progression, while there were still only short-term survival data for dasatinib and nilotinib. Finally, the Committee considered that it was important to have an alternative tyrosine kinase inhibitor treatment available if it is no more expensive than alternatives. The Committee therefore concluded that it would be appropriate to recommend both nilotinib and standard-dose imatinib as options for the first-line treatment of people with chronic phase CML. In addition it recognised that, given that imatinib and nilotinib have comparable cost effectiveness, should one of the drugs become significantly cheaper, it should be preferred (taking into consideration administration costs, required dose and product price per dose).

4.3.20 The Committee further concluded that the recommendations for first-line tyrosine kinase inhibitors should be considered for review in 2 years' time when the price of standard-dose imatinib may be affected by the entry of new manufacturers.

4.3.21 The Committee was aware that the additional analyses produced by the Assessment Group following the first appraisal committee meeting indicated that the ICERs for first-line nilotinib followed by imatinib compared with first-line nilotinib and no subsequent tyrosine kinase inhibitor were £57,000 and £31,000 per QALY gained using the Assessment Group's non-simplified method and simplified method, respectively. The Committee also noted that the original analyses produced by the Assessment Group indicated that the ICERs for first-line imatinib followed by nilotinib compared with first-line nilotinib and no subsequent tyrosine kinase inhibitor were £213,000 and £50,000 per QALY gained using the non-simplified method and simplified method, respectively. The Committee acknowledged that the analyses produced apparently inconsistent results (with NICE technology appraisal guidance 241) about the cost effectiveness of second-line treatment with a tyrosine kinase inhibitor but accepted that consideration of second-line treatments was outside the remit of this appraisal. It also accepted that the evidence on which to reach a definite conclusion was insufficient and conflicting, that there was considerable uncertainty around these ICERs, and that more data were needed to fully assess the cost effectiveness of first and second-line tyrosine kinase inhibitor treatments. Meanwhile it considered the implication of this appraisal, that both imatinib and nilotinib (with the agreed discount under the patient access scheme) should be available first and second line, to be reasonable.

4.3.22 The Committee gave further consideration to its conclusion on the cost effectiveness of dasatinib compared with imatinib and nilotinib from the Assessment Group's model in the light of consultation points raised by Bristol-Myers Squibb. The Committee noted that the ICERs for first-line treatment with dasatinib followed either by nilotinib or imatinib compared with first-line treatment with standard-dose imatinib followed by nilotinib exceeded £300,000 per QALY

gained. The Committee further noted that this result was broadly unaltered by changes to all input parameters in the deterministic sensitivity analyses. As described in section 4.3.19, it was also aware that first-line treatment with dasatinib followed either by imatinib or nilotinib was dominated by first-line nilotinib followed by imatinib. The Committee also noted that the conclusions from these estimates were corroborated by the results generated by the Bristol-Myers Squibb model, when corrected by the Assessment Group (see section 4.2.10). These corrections (which concerned formulae errors and included the patient access scheme discount for nilotinib) resulted in an ICER of £46,000 per QALY gained for dasatinib compared with imatinib, with nilotinib dominating dasatinib. When the model was further adjusted by the Assessment Group so that dasatinib was not taken as a second- or third-line treatment after imatinib or nilotinib, the Committee noted that the ICER for dasatinib compared with imatinib increased to £96,000 per QALY gained, which it agreed could not be considered cost effective.

4.3.23 The Committee was aware that, as part of its response to the consultation on the ACD, Bristol-Myers Squibb had made some adjustments to its model by incorporating changes that the Assessment Group had made to its own model following feedback from Novartis (see section 4.3.15). The Committee noted from the information submitted from Bristol-Myers Squibb incorporating identical medical management costs to those used in the Assessment Group's model, correcting formulae errors, and incorporating an estimate of the discount for nilotinib agreed under the patient access scheme, led to an ICER for dasatinib compared with standard-dose imatinib of £34,400 per QALY gained. The Committee heard from the Assessment Group, however, that the adjustments made by Bristol-Myers Squibb did not include the removal of dasatinib as a second- and third-line treatment option in

line with the guidance on dasatinib, high-dose imatinib and nilotinib when imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241). It was also noted that the removal of second and third-line dasatinib would increase the ICER for dasatinib compared with standard-dose imatinib considerably.

4.3.24 Following the second appraisal committee meeting, the Committee was made aware of errors in the assessment report in the calculation of some of the relative risks and 95% confidence intervals. So the Assessment Group sent the Committee an erratum to the assessment report, which outlined the incorrect and corrected values (see section 4.1.21). This showed that correcting the errors did not affect the statistical significance of any of the results from the trials. The Committee also heard that none of the incorrect values had any impact on the results of the Assessment Group's cost-effectiveness analyses so the ICERs remained unchanged. Therefore the Committee did not alter its view that imatinib and nilotinib, but not dasatinib, could be recommended as cost-effective first-line treatments for adults with chronic phase CML.

4.3.25 The Committee considered the comments received from some consultees after consultation on the ACD that it was inappropriate to exclude dasatinib as a second or third-line treatment from the modelling. However, the Committee agreed that, with the publication of the guidance on dasatinib, high-dose imatinib and nilotinib when imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241), it would not be appropriate to include dasatinib as a second or third-line treatment in the modelling for this appraisal. The Committee was aware that NICE technology appraisal guidance 241 considered the use of the tyrosine kinase inhibitors in cases of imatinib resistance

or intolerance only but had not considered their use following first-line treatment with nilotinib or dasatinib. The Committee considered that this was because standard-dose imatinib was the only recommended first-line tyrosine kinase inhibitor for the treatment of chronic phase CML at the time of appraisal, and it agreed that the same rationale that underpinned the recommendations in the guidance on dasatinib, high-dose imatinib and nilotinib when imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241) should also apply to the use of dasatinib after first-line treatment with an alternative first-line tyrosine kinase inhibitor. The Committee noted that further adjustments to Bristol-Myers Squibb's model by the Assessment Group, to remove dasatinib as a second- and third-line treatment option in line with NICE technology appraisal guidance 241, resulted in an ICER for first-line dasatinib compared with standard-dose imatinib of at least £75,000 per QALY gained. The Committee concluded that Bristol-Myers Squibb's modelling results, when adjusted by the Assessment Group to reflect second-line treatments approved by NICE, supported the results generated by the Assessment Group's model.

4.3.26 The Committee heard from the clinical specialists and some consultees that, for a small group of people with specific kinase domain mutations that would make their CML resistant to nilotinib, dasatinib would be offered as second-line treatment. However, the Committee considered that, because these mutations would be determined after first-line treatment failure, this would not be relevant to the first-line treatment decision for people presenting with chronic phase CML. Furthermore, this subgroup of people with specific kinase domain mutations was not distinguished in the evidence base for dasatinib. The Committee also heard from consultees after consultation on the ACD that there are other important subgroups for whom dasatinib would be used rather than

nilotinib, including people with long QT syndrome or diabetes. However, the Committee noted that it had not been presented with any evidence to support this and therefore could not make any recommendations for dasatinib in these subgroups. The Committee concluded that the ICERs for dasatinib were substantially outside the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained), and that dasatinib could not be recommended as a cost-effective use of NHS resources for the first-line treatment of adults with chronic phase CML.

4.3.27 The Committee recognised the innovative nature and substantial change in the treatment of CML that imatinib has provided since it has been introduced and recommended for use by NICE in the guidance on imatinib in CML (NICE technology appraisal guidance 70), and discussed whether dasatinib and nilotinib should be considered innovative treatments. The Committee considered that while the introduction of dasatinib and nilotinib was also an important development in terms of pharmacological progress beyond imatinib, the critical innovation was the first-generation tyrosine kinase inhibitor. Furthermore, the Committee had not been made aware of any benefits from this progress that were not captured in the QALYs modelled.

4.3.28 The Committee discussed whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way. The Committee considered that there were no issues directly relating to the equalities legislation. However, the Committee noted that in both manufacturers' submissions, stem cell transplantation would be considered for people for whom first- and second-line tyrosine kinase inhibitor treatment fails and, because only a small number of people would be eligible for stem cell transplantation, this could raise potential

equity issues in relation to race, age (the elderly), and people with comorbidities. However, the Committee concluded that the recommendations do not differentiate between any groups of people, and therefore there was not considered to be an equalities issue.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal 70)	Section
Key conclusion		
Standard-dose imatinib is recommended as an option for the first-line treatment of adults with chronic phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML).		1.1, 1.2, 1.3
Nilotinib is recommended as an option for the first-line treatment of chronic phase Philadelphia-chromosome-positive CML in adults if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme.		
Dasatinib is not recommended for the first-line treatment of chronic phase Philadelphia-chromosome-positive CML.		
The 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.		4.3.6
Overall, the Committee concluded that there was insufficient evidence to distinguish between dasatinib and nilotinib in terms of clinical effectiveness.		4.3.7
The Committee noted that the incremental cost-effectiveness ratio (ICER) for first-line nilotinib was £11,000 per quality-adjusted life year (QALY) gained and concluded that the results of the Assessment Group's analyses indicated that nilotinib represented a cost-effective first-line treatment for people with chronic phase CML.		4.3.18
The Committee noted that changes to some input parameters, notably adjusting the modelled dose intensity of first-line nilotinib to summary of product characteristics (SPC)-recommended levels reversed the relative cost effectiveness of nilotinib and imatinib. In addition, the Committee noted that imatinib has a proven longer-term record of safety and efficacy: there were 7-year survival data for first-line standard-dose imatinib from the IRIS (International Randomised Study of Interferon versus STI571) trial, with favourable results for complete cytogenetic response and disease progression, while there were still only short-term survival data for dasatinib and nilotinib. The Committee considered that it would be important to have an alternative tyrosine kinase inhibitor treatment available if it is no more expensive than alternatives. The Committee therefore concluded that it would be appropriate to recommend both nilotinib and standard-dose imatinib as options for the first-line treatment of people with chronic phase CML. In addition it recognised that, given that imatinib and nilotinib have comparable cost effectiveness, should one of the drugs become significantly cheaper, it should be preferred (taking into consideration administration costs, required dose and product price per dose).		4.3.19
The Committee noted that the ICERs for first-line treatment with dasatinib followed either by nilotinib or imatinib compared with first-line treatment with standard-dose imatinib followed by nilotinib exceeded £300,000 per QALY gained. The Committee concluded that the ICERs for dasatinib were substantially outside the range normally considered a cost-effective use of NHS resources and that dasatinib could not be recommended as a cost-effective use of NHS resources for the first-line treatment of adults with		4.3.22, 4.3.26

chronic phase CML.	

Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical specialists that standard-dose imatinib is the usual first-line treatment for people presenting with chronic phase CML, and that clinical experience of dasatinib and nilotinib for chronic phase CML is largely restricted to the context of clinical trials.	4.3.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee considered that while the introduction of dasatinib and nilotinib was also an important development in terms of pharmacological progress beyond imatinib, the critical innovation was the first-generation tyrosine kinase inhibitor. Furthermore, the Committee had not been made aware of any benefits from this progress that was not captured in the QALYs modelled.	4.3.27
What is the position of the treatment in the pathway of care for the condition?	Dasatinib and nilotinib have marketing authorisations for the treatment of adult patients with newly diagnosed Philadelphia-chromosome-positive CML in the chronic phase. Imatinib has a marketing authorisation for the treatment of adult and paediatric patients with newly diagnosed Philadelphia-chromosome (*BCR-ABL*) positive CML for whom bone marrow transplantation is not considered as the first line of treatment.	3.2, 3.9 3.6
Adverse effects	The Committee noted from the clinical trials that dasatinib, nilotinib and standard-dose imatinib were well-tolerated and that discontinuation rates due to adverse events for people taking dasatinib and nilotinib compared with standard-dose imatinib were similar. The Committee heard from patient experts that, in their experience, side effects associated with tyrosine kinase inhibitors were considered to be easily manageable over time. The Committee was also aware that QT interval prolongation was listed in the special warnings and precautions for use in the SPC for both dasatinib and nilotinib. However, the Committee was reassured by the views of the clinical specialists that there was no increased cardiovascular risk at the licensed doses. The Committee concluded that all three drugs appeared to be well tolerated and represented important treatments for people with CML.	4.3.9

Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee was aware of two comparative clinical trials, one that compared dasatinib with imatinib and one that compared nilotinib with imatinib. It also noted that no trials directly comparing dasatinib and nilotinib were available. The Committee considered that both trials were good quality international randomised controlled trials and that the demographic characteristics of the participants and the overall trial designs were sufficiently similar to enable indirect comparison of dasatinib and nilotinib.	4.3.4, 4.3.5
Relevance to general clinical practice in the NHS	The Committee noted that the populations in the two clinical trials may not be completely representative of a UK CML population, because of the lower age at diagnosis compared with the general population. However, the Committee was reassured by the views of the clinical specialists that the age difference was not a major factor, and it concluded that the populations included in the trials were broadly relevant to UK clinical practice.	4.3.5
Uncertainties generated by the evidence	The Committee noted that the clinical trials were of short duration and provided only short-term data on progression-free and overall survival and that surrogate outcome measures were used. The Committee noted that the clinical evidence used in the Assessment Group's analysis of short-term surrogate response markers as predictors of longer-term patient-relevant outcomes was taken from a mixture of longer-term randomised and observational studies of imatinib only. However, the Committee agreed that the results of the analysis could be potentially applied to people receiving dasatinib or nilotinib.	4.3.5, 4.3.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No clinically relevant subgroups for which there is evidence of differential effectiveness were identified by the Committee.	N/A
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee considered the results of the clinical trials, which showed that statistically significantly more people receiving dasatinib and nilotinib had a complete cytogenetic response and a major molecular response than people receiving imatinib at 12-month follow-up. The Committee also noted the views of the clinical specialists and patient experts that nilotinib and dasatinib are more effective drugs with a theoretically superior mechanism of action to standard-dose imatinib, although imatinib remains very effective for the	4.3.6, 4.3.7

	majority of patients. The Committee concluded that the available evidence suggests that dasatinib and nilotinib provided superior clinical benefit as measured by surrogate outcome measures than standard-line imatinib in the first-line treatment of people with chronic phase CML. The Committee considered the results of the indirect comparison of dasatinib and nilotinib conducted by the Assessment Group, which showed no statistically significant differences in rates of complete cytogenetic response and major molecular response by 12 months between the two treatments. The Committee was also aware of another published study, which conducted a matching-adjusted indirect comparison of dasatinib and nilotinib, and showed statistically significantly higher major molecular response rates and overall survival by 12 months for people taking nilotinib compared with dasatinib. The Committee noted the comment from the clinical specialist that this study had been sponsored by Novartis. Overall, the Committee concluded that there was insufficient evidence to distinguish between dasatinib and nilotinib in terms of clinical effectiveness.	
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the economic models provided by the manufacturers, Bristol-Myers Squibb and Novartis and also by the Assessment Group. It noted key differences in the treatment pathways and approaches to modelling overall survival in the three models.	4.3.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that the Assessment Group's modelling included a range of scenarios because of uncertainty about the impact of dasatinib and nilotinib on long-term survival and about subsequent lines of treatment. It noted that four base-case scenarios were modelled, which varied according to the methodology used to estimate overall survival, subsequent second- and third-line treatment options and whether costs and QALYs per person progressing beyond the first- and second-line tyrosine kinase inhibitor should be considered equal across treatment arms. The Committee was aware that nilotinib was the only tyrosine kinase inhibitor considered as a possible second-line treatment in the Assessment Group's model (in two of the four base-case scenarios), and that this reflected the guidance on dasatinib, high-dose imatinib and nilotinib when standard-dose imatinib has failed because of	4.3.12

	resistance or intolerance (NICE technology appraisal guidance 241). The Committee further noted that the Assessment Group had conducted extensive deterministic sensitivity analyses to explore uncertainty around key structural assumptions in its model. The Committee concluded that, although assumptions in the modelling around survival and subsequent lines of treatment were associated with substantial uncertainty, the Assessment Group, by considering the impact of alternative assumptions, had made considerable effort to address this.	
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	No potential significant and substantial health-related benefits that had not been included in the economic models were identified.	N/A
Are there specific groups of people for whom the technology is particularly cost effective?	No specific groups of people for whom the technologies are particularly cost effective were identified.	N/A
What are the key drivers of cost effectiveness?	The Committee noted that the acquisition costs of dasatinib and nilotinib were in excess of £30,000 per person per year, and that the cost of standard-dose imatinib had recently increased to approximately £20,000 per person per year. The Committee was aware that the ICERs for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib were sensitive to a number of parameters, including assumptions about the dose intensity of nilotinib and the average time spent on second-line nilotinib or imatinib treatment. The Committee noted that the cost effectiveness of dasatinib was unaltered by changes to all input parameters in the deterministic sensitivity analyses.	4.3.10 4.3.19 4.3.22
Most likely cost-effectiveness estimate (given as an ICER)	The Committee acknowledged the wide variation in the cost-effectiveness results across the scenarios presented by the Assessment Group, which reflected the considerable structural uncertainty in the modelling of first-line tyrosine	4.3.13

	kinase inhibitors for CML.	
	The Committee concluded that the Assessment Group's original base-case cost-effectiveness results indicated that dasatinib was not cost effective and that nilotinib was on the border of cost effectiveness in many of the analyses presented when the patient access scheme was applied.	
	The Committee was satisfied that the Assessment Group had appropriately addressed comments received from the manufacturers on its economic model and that the ICERs generated from the Assessment Group's revised analysis provided a suitable basis for recommendation.	4.3.15
	The Committee accepted that hydroxyurea and stem cell transplantation would not be used routinely in the second-line setting in place of a tyrosine kinase inhibitor and that therefore scenarios 1 and 2 of the Assessment Group's model provided only relatively approximate estimates of the cost effectiveness of first line treatment with tyrosine kinase inhibitors.	4.3.16
	The Committee noted that the Assessment Group had modelled two additional scenarios – one comprising first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising first-line treatment with dasatinib followed by second-line standard-dose imatinib. The Committee agreed that these analyses were an important addition to the Assessment Group's model because they enabled a comparison in scenarios 3 and 4 of all the relevant first- and second-line treatment sequences.	4.3.17
	The Committee noted that the ICER for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib was £11,000 per QALY gained in scenarios 3 and 4 of the Assessment Group's model and that this was within the range normally considered a cost-effective use of NHS resources.	4.3.18
	The Committee noted that dasatinib was associated with fewer QALYs and was more costly than nilotinib in all scenarios and that the ICERs for dasatinib compared with standard-dose imatinib exceeded £200,000 per QALY gained.	4.3.15, 4.3.18, 4.3.22
	The Committee recognised that, although more of the sensitivity analyses in the Assessment Group's model produced favourable ICERs for nilotinib compared with standard-dose imatinib, imatinib	4.3.19

	has a proven longer-term record of safety and efficacy: there were 7 years of survival data for first-line imatinib from the IRIS trial, with positive results for complete cytogenetic response and disease progression, while there were still only short-term survival data for dasatinib and nilotinib. The Committee acknowledged that the additional analyses by the Assessment Group produced apparently inconsistent results (with NICE technology appraisal 241) about the cost effectiveness of second-line treatment with a tyrosine kinase inhibitor but accepted that consideration of second-line treatments was outside the remit of this appraisal.	4.3.21
Additional factors taken into account		
Patient access schemes (PPRS)	The Committee noted that the Department of Health had approved a patient access scheme for nilotinib, which makes it available with a discount applied to all invoices. The size of the discount is commercial in confidence.	4.3.10
End-of-life considerations	N/A	N/A
Equalities considerations and social value judgements	The Committee concluded that the recommendations do not differentiate between any groups of people, and therefore there was not considered to be an equalities issue.	4.3.28

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on

a drug, treatment or other technology, decisions on funding should be made locally.

5.2 The Department of Health and the manufacturer have agreed that nilotinib will be available to the NHS with a patient access scheme in which a discount is applied to all invoices. The level of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate the level of discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme can be directed to the manufacturer at: NICE to include at time of publication

5.3 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Published

- Improving outcomes in haematological cancers – the manual. NICE cancer service guidance (2003).
- Guidance on the use of imatinib for chronic myeloid leukaemia. NICE technology appraisal guidance 70 (2003).

- Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. NICE technology appraisal guidance 241 (2012).

7 Review of guidance

7.1 The guidance on this technology will be considered for review by the Guidance Executive in May 2014. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens
Chair, Appraisal Committee
March 2012

Appendix A: Appraisal Committee members, and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr David Black
Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden
Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett
Director for Health Improvement and Medical Director, NHS Barnet, London

David Chandler
Lay member

Dr Mary Cooke
Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

Dr Chris Cooper
General Practitioner, St John's Way Medical Centre, London

Professor Peter Crome
Consultant Geriatrician and Professor of Geriatric Medicine, Keele University

Dr Christine Davey
Research Adviser, North and East Yorkshire Alliance Research and Development Unit, York

Richard Devereaux-Phillips
Director, Public Policy and Advocacy NW Europe, BD, Oxford

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell
Consultant in Public Health, Bradford and Airedale Primary Care Trust

Dr Wasim Hanif
Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler
Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Henry Marsh
Consultant Neurosurgeon, St George's Hospital, London

Professor Gary McVeigh
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Professor Katherine Payne
Professor of Health Economics, University of Manchester

Dr Danielle Preedy
Lay member

Dr Martin Price
Head of Outcomes Research, Janssen-Cilag, Buckinghamshire

Alan Rigby
Senior Lecturer and Chartered Statistician, University of Hull

Dr Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi
Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Dr John Stevens
Lecturer in Bayesian Statistics in Health Economics, School of Health and Related Research, Sheffield

Dr Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Dr Judith Wardle
Lay member

C NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Matthew Dyer
Technical Lead

Zoe Charles
Technical Adviser

Lori Farrar
Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG):

- Hoyle M, Pavey T, Ciani O, Crathorne L, Jones-Hughes T, Cooper C, Osipenko L, Venkatachalam M, Rudin C, Ukoumunne O, Garside R, Anderson R. Dasatinib, nilotinib and standard dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. (2011) University of Exeter (Report for NICE).

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Bristol-Myers Squibb
- Novartis Pharmaceuticals

II Professional/specialist and patient/carer groups:

- African Caribbean Leukaemia Trust
- Chronic Myeloid Leukaemia Support Group
- Leukaemia CARE
- Macmillan Cancer Support
- The Hepatitis B Foundation UK
- British Society for Haematology
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health
- NHS North Yorkshire and York

- Welsh Government

IV Commentator organisations (without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency
- NHS Quality Improvement Scotland
- Leukaemia & Lymphoma Research
- Peninsula Technology Assessment Group, University of Exeter (PenTAG)
- National Coordinating Centre for Health Technology Assessment
- National Collaborating Centre for Cancer

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70) by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Jane Apperley, Professor of Haematology, nominated by NCRI/RCP/RCR/ACP/JCCO and Bristol-Myers Squibb – clinical specialist
- Professor Richard Clark, Professor of Haematology and Consultant Haematologist, nominated by the Royal College of Pathologists – clinical specialist
- Richard Willoughby, nominated by the CML Support Group – patient expert
- Sandy Craine, nominated by the CML Support Group – patient expert

D The following individuals were nominated as NHS Commissioning experts by the selected NHS Trust allocated to this appraisal. They gave their expert/NHS commissioning personal view on Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid

leukaemia (incl part-review of TA 70) by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Diane Tomlinson, Senior Pharmacist selected by NHS North Yorkshire and York – NHS Commissioning expert

E Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Bristol-Myers Squibb
- Novartis Pharmaceuticals