Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende asciminib til behandling af kronisk myeloid leukæmi

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. asciminib
2. Forhandlingsnotat fra Amgros vedr. asciminib
3. Ansøgers endelige ansøgning vedr. asciminib

Den 24. maj 2023

Notat vedrørende Udkast til Medicinrådets anbefaling vedr. asciminib til behandling af kronisk myeloid leukæmi

Vi takker for modtagelsen af udkastet til Medicinrådets anbefaling vedr. asciminib til behandling af kronisk myeloid leukæmi, modtaget fredag den 12. maj 2023. Det skønnes, at 6 patienter årligt vil være egnede til behandling med asciminib.

I udkastet fremgår det, at man har fravalgt at vurdere den sundhedsøkonomiske analyse. Det anføres, at det ikke er muligt at vurdere, om der er forskel i effekt mellem asciminib og bosutinib pga. det ublindede design i ASCEMBL studiet, samt at der er en ubalance i centrale baselinekarakteristika mellem de to behandlingsarme.

Nedenfor følger vore kommentarer til de punkter, hvor en tilretning af teksten vil give et mere retvisende billede af evidensen for asciminib.

1. Studiedesign

I udkastet anføres det ublindede design af ASCEMBL studiet som en årsag til, at det ikke er muligt at vurdere, om der er forskel i effekt mellem asciminib og bosutinib. I EPAR fremgår det, at det ublindede design iflg. CHMP var acceptabelt, da administrationsforholdene for asciminib og bosutinib var markant forskellige. For såvel det primære endepunkt, MMR rate ved 24 uger, og det sekundære endepunkt, MMR rate ved 96 uger, vurderede CHMP, at asciminib var både statistisk og klinisk signifikant bedre end bosutinib.

Jvf. EPAR viste resultater af prædefinerede sensitivitetsanalyser konsistens med de primære resultater og bekræftede dermed deres robusthed [1].

2. Sammenligning af baseline karakteristika

I udkastet anføres, at patienterne i bosutinib-armen muligvis er tungere behandlet inden indgang i studiet ift. patienter i asciminib-armen, samt at dette kan medføre, at resultaterne i højere grad bliver til fordel for asciminib.

I publikationen af fase 3 studiet samt i EPAR præsenteres resultater fra en multivariat analyse, som viser, at odds for at opnå MMR rate ved uge 24 var større med asciminib vs. bosutinib, uafhængigt af, hvilken linje behandling patienten var på, og uafhængigt af, om patienterne havde ophørt deres sidste TKI behandling pga, manglende effekt (figur 2 i supplement) [2]. Denne subgruppe-analyse var yderligere beskrevet i detaljer i ansøgningen under appendiks B.

På baggrund af disse yderligere analyser konkluderes det i EPAR, at der ikke er evidens for bias på baggrund af ubalancen i populationerne.

3. Overkrydsning fra bosutinib til asciminib i ASCEMBL studiet

I udkastet til vurderingsrapporten er anført, at muligheden for at krydse over fra bosutinib kunne medføre, *"at flere stoppede med bosutinib, da der ikke ville ikke være så stort et tab ved at stoppe behandling"*.

Dette er ikke korrekt. De 76 patienter i behandling med bosutinib kunne således kun krydse over til asciminib ved påvist mangel på effekt (defineret ved objektivt målbare parametre), ikke pga.

bivirkninger[1].Det anføres ligeledes i vurderingen, at muligheden for overkrydsning potentielt kan have introduceret en bias i ophør af behandling grundet uønskede hændelser, således at de patienter, der ikke modtog behandling med det nye lægemiddel, i højere grad rapporterede bivirkninger som medførte behandlingsophør.

Dette er ikke en korrekt antagelse, idet skift pga. bivirkninger ikke var muligt.

4. Bivirkninger

I vurderingen af sikkerhed anføres, at patienter behandlet med asciminib oplevede lidt færre uønskede hændelser end patienter i bosutinib-armen på trods af længere behandlingsvarighed (91,0% vs. 97,4%).

Derefter anføres, at det samme var tilfældet for nedenstående hændelser:

- Grad ≥ 3 uønskede hændelser (56,4% vs. 68,4%)
- Alvorlige uønskede hændelser (17,9% vs. 26,3%)
- Uønskede hændelser, der førte til dosisjustering eller pausering (42,3% vs. 64,5%)
- Uønskede hændelser, der førte til behandlingsophør (7,7% vs. 26,3%).

Overnævnte markante forskelle mellem behandlingerne for de fire sidstnævnte kategorier af uønskede hændelser bør ikke beskrives som "lidt færre uønskede hændelser" i vurderingsrapporten.

Det fremhæves i udkastet til vurderingsrapporten, at der kan være bias imod bosutinib pga. af muligheden for overkrydsning, men som tidligere nævnt gav intolerabilitet ikke mulighed for at skifte til asciminib. De observerede forskelle skyldes således ikke bias, men formentlig snarere, at der er tale om to forskellige lægemidler med forskellig virkningsmekanisme.

5. Sundhedsøkonomisk analyse

Der er præsenteret en solid cost-utility analyse, som viser, at asciminib er omkostningseffektivt sammenlignet med bosutinib, som Medicinrådet i udkastet til vurderingsrapporten vælger at se bort fra.

Ud fra ovennævnte argumentation vedrørende specielt muligheden for overkrydsning i ASCEMBL studiet udelukkende pga. manglende effekt på bosutinib (pkt. 2) samt de nævnte sub-gruppedata (pkt. 1) mener vi, at resultaterne af analysen står til troende og bør inddrages formelt i Medicinrådets vurdering.

Med venlig hilsen,
Novartis Healthcare A/S

Pia Krogsgaard Villadsen
Value & Access Director

Anders Holmen Møller
Nordic Head of HEOR

Referencer

1. EMA. Assessment report. Scemblix. EMEA/CHMP/634238/2022 .
2. Réa D, Mauro MJ, Boquimpani C et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood 2021; 138(21):2031–2041.

[1] I forbindelse med valideringen af ansøgningen nævnte vi fra Novartis' side fejlagtigt, at overkrydsning fra bosutinib til asciminib kunne finde sted både pga. manglende effekt og tolerabilitet. Det beklager vi. I resten af ansøgningen fremgår det, at overkrydsning kun var tilladt ved manglende effekt, (objektivt dokumenteret), hvilket også fremgår af både publikation og EPAR.

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30.05.2023

BMC/MGK

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.06.2023
Leverandør	Novartis
Lægemiddel	Scemblix (asciminib)
Ansøgt indikation	Voksne patienter med Philadelphia-kromosom positiv kronisk myeloid leukæmi i kronisk fase (Ph+ CML-CP), som tidligere er blevet behandlet med to eller flere tyrosinkinasehæmmere.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Scemblix (asciminib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Scemblix	20 mg	60 stk.	34.218,10	[redacted]	[redacted]
Scemblix	40 mg	60 stk.	34.218,10	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Scemblix, indkøbes lægemidlet til AIP.

Aftaleforhold

[redacted]

Informationer fra forhandlingen

Leverandøren ser Scemblix som en 3. linje behandling. Bosulif (bosutinib) er anvendt som komparator i vurderingsrapporten fra Medicinrådet og leverandøren har prisfastsat Scemblix, så de årlige lægemiddelomkostninger er på niveau med Bosutinib.

Konkurrencesituationen

På nuværende tidspunkt indgår fem lægemidler i lægemiddelrekommandationen for CML, som er baseret på RADS baggrundsnotatet fra 2016. Her er 2 ud af 3 lægemidler til førstelinje førstevalg er gået af patent (Glivec(imatinib) og Sprycel (dasatinib)).

[redacted]

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler, som indgår i Medicinrådets vurderingsrapport.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Scemblix	40 mg	60 stk.	40 mg, 2 gange dagligt	[redacted]	[redacted]
Tasigna	200 mg	112 stk.	300 mg 2 gange dagligt	[redacted]	[redacted]
Bosulif	500 mg	28 stk.	500 mg, 1 gang dagligt	[redacted]	[redacted]
Sprycel	140 mg	60 stk.	2 gange 70 mg, 1 gang dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
Sverige	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Application for the assessment of Scemblix for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors

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1. Basic information

Contact information	
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Overview of asciminib	
Proprietary name:	Scemblix
Generic name:	Asciminib
Marketing authorization holder in Denmark:	Novartis Healthcare
ATC code:	L01EA06
Pharmacotherapeutic group	
Active substance(s)	Asciminib
Pharmaceutical form(s):	Tablet
Mechanism of action:	Asciminib is the first and only CML treatment that works by binding to the ABL myristoyl pocket. This novel mechanism of action, also known in scientific literature as a STAMP inhibitor (=Specifically Targeting the ABL Myristoyl Pocket), can help address non-sufficient efficacy or tolerability issues in CML patients already in TKI therapy by inhibiting the activity of the fusion oncoprotein BCR-ABL1, which is associated with the over-production of leukemic cells.
Dosage regimen:	40 mg BID
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Treatment of patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP), previously treated with two or more tyrosine kinase inhibitors (TKIs)

Overview of asciminib	
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	20 mg, 60 tabs and 40 mg 60 tabs
Orphan drug designation	Yes, EMA has granted an orphan drug designation

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2. Abbreviations

Abbreviation / term	Definition
AIC	Akaike information criterion
AE	Adverse event
Allo-SCT	Allogeneic stem cell transplantation
AP	Advanced phase
BD	Twice-daily
BIC	Bayesian information criterion
BP	Blast phase
CCyR	Complete cytogenetic response
CML	Chronic myeloid leukemia
CP	Chronic phase
DCO	Data cut-off
EFS	Event-free survival
ELN	European LeukemiaNet
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
KM	Kaplan-Meier
ITC	Indirect treatment comparison
MAIC	Matched-adjusted indirect comparison
MCyR	Major cytogenetic response
MMR	Major molecular response
MMRM	Mixed effect model repeated measure
MR	Molecular response
NICE	National Institute for Health and Care Excellence
NR	No response
OS	Overall survival
PD	Progressed disease
PCyR	Partial cytogenetic response
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
QoL	Quality of life
RCT	Randomized controlled trial
RDI	Relative dose intensity
RFS	Relapse free survival
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
STAMP	Specifically targeting the ABL myristoyl pocket
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation

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3. Tables and Figures

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4. Summary

The objective of this submission is to assess the cost-effectiveness of asciminib (brand name: Scemblix) for the treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP) for patients previously treated with two or more tyrosine kinase inhibitors (TKIs).

CML, a myeloproliferative neoplasm characterized by uncontrolled growth of myeloid cells in the bone marrow and accumulation of these cells in the blood, accounts for approximately 15–20% of all cases of leukemia in adults [1, 2]. Despite the significant advances in the CML treatment landscape, many patients treated with two or more TKIs experience intolerance and/or resistance. Failure rates increase with increasing therapy line [3] and worsening the prognosis and impact likelihood of surviving. 8-year OS decrease from 83% for 1st line patients, to 22% for 3rd line patients [4].

CML occurs in approximately 60-70 people a year in Denmark [5]. The relevant patient population in 3rd line CML-CP treatment in Denmark is estimated to be approximately 6 patients per year. The estimate is based on data from the Swedish CML register, adjusted to the Danish population and validated by local clinical experts [6, 7] (name of expert included in the reference).

There is currently no established standard of care (SoC) in ≥3rd line CML-CP. According to local clinical expert, bosutinib is a highly relevant comparator in 3rd line and is the only TKI that has been specifically studied in patients with CML-CP who are resistant and/or intolerant to ≥2 TKIs [8, 9].

According to clinical experts, the efficacy between 2nd generation TKIs (if adverse events are handled properly) is seen as similar. In order to address the issues raised during the dialog meeting with the Medicinrådet, nilotinib and dasatinib as possible comparators, a sensitivity analysis was included based on bosutinib efficacy from ASCEMBL using dasatinib and nilotinib prices.

PICO summary (patient, intervention, comparator and outcomes)	Population	Adult patients with CML-CP (excluding T315I or V299L mutation) having previously been treated with a minimum of two prior ATP-binding site TKIs
	Intervention	Asciminib is a first-in-class oral, potent, allosteric inhibitor of ABL/BCR-ABL1 tyrosine kinase. Asciminib inhibits the ABL1 kinase activity of the BCR-ABL1 fusion protein by specifically targeting the ABL myristoyl pocket (STAMP)
	Comparator(s)	Bosutinib
	Outcomes	Treatment duration Overall survival* Progression-free survival* Safety Health-related quality of life (EQ-5D-5L)
Health Economic summary	Type of economic analysis that is submitted (cost-utility analysis, cost-minimising analysis, etc.)	A cost-utility analysis was developed using a non-homogenous, partitioned survival model
	Relative efficacy documentation is based mainly on:	Head-to-head trial
	Selected comparators	Bosulif (bosutinib)
	Results of the health economic analysis	ICER (DKK per QALY): [redacted]

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	Sensitivity analysis (bosutinib efficacy from ASCEMBL using dasatinib and nilotinib prices)	ICER (vs nilotinib) (DKK per QALY): [redacted] ICER (vs dasatinib) (DKK per QALY): [redacted]

* Overall and progression free survival data from ASCEMBL are highly immature. In this analysis, survival outcomes are estimated based on surrogate endpoints.

Asciminib is the first and only CML treatment that works by binding to the ABL myristoyl pocket. This novel mechanism of action, also known in scientific literature as a STAMP inhibitor (=Specifically Targeting the ABL Myristoyl Pocket), can help address non-sufficient efficacy or tolerability issues in CML patients already in TKI therapy by inhibiting the activity of the fusion oncoprotein BCR-ABL1, which is associated with the over-production of leukemic cells.

A cost-utility analysis (CUA) has been carried out, evaluating asciminib compared to bosutinib in a Danish clinical setting. Costs were considered from a Danish health care perspective.
The population for the analysis was based on the trial population in ASCEMBL study and is assumed to be representative for the eligible population in Denmark [6].

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

Chronic myeloid leukemia (CML), a myeloproliferative neoplasm characterized by uncontrolled growth of myeloid cells in the bone marrow and accumulation of these cells in the blood, accounts for approximately 15–20% of all cases of leukemia in adults[1, 2, 10].

The disease is defined by the invariable presence of the Philadelphia chromosome (Ph) in a patient with myeloproliferative neoplasm, which results from a reciprocal translocation between the long arms of chromosomes 9 and 22 [t(9;22)]. With disease progression, additional cytogenetic abnormalities can develop, as well as mutations of the BCR-ABL kinase domain, which are associated with treatment resistance [11]. A qualitative PCR is useful for diagnosing CML, while a quantitative PCR is ideal for monitoring residual disease [12].

Despite the significant advances in the CML treatment landscape, many patients treated with two or more TKIs experience intolerance and/or resistance. Failure rates increase with increasing therapy lines [3] and OS decreases as treatment line increases [4]. 8-year OS decrease from 83%, for 1st line patients, to 22% for 3rd line patients [4].

Mutations within the ATP binding site of the BCR-ABL1, are a common cause of TKI resistance and patients harboring the T315I mutation have worse outcomes in terms of overall survival (OS) and progression-free survival (PFS) [13, 14]. The T315I mutation, which is the most challenging mutation, indicates a poor prognosis and patients with the T315I mutation are usually resistant to all available TKIs (imatinib, bosutinib, nilotinib and dasatinib) but may benefit from ponatinib [15, 16].
V299L mutants have been found in the Imatinib, Dasatinib and Bosutinib treated patients and have exhibited both the primary and secondary resistance to those drugs. Although the frequency of the ABL-V299L mutant is considered rare, the median survival rate of it is poor. [17, 18]

In line with the approved label, this application will *focus on third line CML-CP patients.*

5.1.1 Signs and Symptoms

Common signs and symptoms of CML are similar for 1st to 3rd line CML-CP patients. These result from anemia and splenomegaly, which include fatigue, weight loss, malaise, easy satiety, and left upper quadrant fullness or pain. Rare manifestations include bleeding (associated with a low platelet count and/or platelet dysfunction), thrombosis (associated with thrombocytosis and/or marked leukocytosis), gouty arthritis (from elevated uric acid levels), priapism (usually with marked leukocytosis or thrombocytosis), retinal hemorrhages, and upper gastrointestinal ulceration and bleeding (from elevated histamine levels due to basophilia) [19].

Progression of CML is associated with increasing treatment resistance and symptoms, and is generally manifested by headaches, significant weight loss, bone and joint pain, pain from splenic infarction, unexplained fever, thrombosis, infections, persistent splenomegaly and leukocytosis despite treatment, and extra-medullary disease [19, 20].

5.1.2 Staging/Classification of Disease

Upon the confirmation of CML diagnosis, the next step is to determine the phase of the disease for selection of appropriate treatment. CML is a triphasic myeloproliferative disorder that begins from a latent phase called the chronic phase (CP), and most patients are at first diagnosed as being in this phase (patients with CML-CP). Untreated CML-CP progresses spontaneously to a more advanced accelerated phase (AP) and subsequently to its very aggressive blast crisis phase (BP) in 3–5 years after disease onset. [2, 21, 22]

5.1.3 Therapeutic Response Monitoring and Assessment of Treatment Response

European LeukemiaNet (ELN) guidelines recommend monitoring using quantitative PCR every 3 months until MMR is achieved, then every 3 to 6 months [23]. According to the ELN guidelines, patients are classified into three groups depending on the degree of remission at specific time points so that more careful monitoring or treatment change can be undertaken, as appropriate, depending on MR levels. These groups are “optimal” (no change of therapy is indicated), “warning” (more frequent monitoring is recommended to permit timely change in case of subsequent treatment failure), and “failure” (the patient should receive a different treatment) [24].
Molecular response (MR) refers to a decrease in the amount of BCR-ABL1 chimeric mRNA transcripts using reverse transcriptase polymerase chain reaction (RT-PCR) and has the greatest sensitivity [25, 26]. Once CCyR is achieved, only molecular methods make it possible to follow the dynamics of minimal residual disease (MRD) over time. A major advantage of quantitative PCR is the strong correlation between the results obtained from the peripheral blood and the bone marrow, allowing molecular monitoring without bone marrow aspirations [10, 25, 26].
An international scale (IS) for reporting MR, which enables the alignment of BCR-ABL1 values generated by diverse analytical systems, was introduced to standardize BCR-ABL1 measurements, thereby improving the accuracy of MR measurements and facilitating inter-laboratory studies and patient portability. On the IS, the standardized baseline is set to 100%, which is defined as the average expression of BCR-ABL1 transcripts in 30 patients with untreated CML enrolled in the International Randomized Study of Interferon and STI571 (IRIS) trial.

5.1.4 Prognostic significance of cytogenetic and molecular response

Following initiation of first-line therapy, achievement of CCyR (≤1% BCR-ABL1 IS) within 12 months is an established prognostic indicator of long-term survival. In the IRIS study, estimated 6-year PFS rate was 97% vs. 80% for patients achieving a CCyR at 6 months compared with those with no cytogenetic response, respectively [27]. Similarly, among patients with newly diagnosed CML-CP treated with imatinib or 2nd generation TKIs, the 3-year event-free survival (EFS; 98% vs. 67%) and OS (99% vs. 94%) were higher for patients who achieved CCyR at 12 months compared with those who did not[26, 28].

MMR (≤0,1% BCR-ABL1 IS) as a predictor of PFS and OS has also been evaluated in several studies, the achievement of which is associated with durable long-term cytogenetic remission and lower rate of disease progression. However, for patients who already are in stable CCyR, the added prognostic value of MMR for OS is not yet clearly established [26].

The CML IV study showed that MR4.5 (≤0,0032% BCR-ABL1 IS) at 4 years was associated with a significantly higher OS (independent of therapy) vs. MR2.0 (which corresponds to CCyR). [29]

It is also important to note that MRs at MMR level are considered a predictor for survival. After achievement of MMR, there is very low probability of subsequent loss of response and a high likelihood of achieving a subsequent DMR (MR4.0 or ≤0,01% BCR-ABL1 IS), which may facilitate discontinuation of TKI therapy. [26, 29]

ELN guidelines describes the following procedures for monitoring therapeutic response [30]:

- Response of TKI treatment should be evaluated on a regular basis and should be modified in accordance with the international guidelines. Evaluation procedures includes clinical response, the development of blood status, cytogenetics of the bone marrow and RT-qPCR of the *BCR-ABL1* in peripheral blood.
- The efficacy of the TKI at given times (milestones) is prognostically important.
- RT-qPCR is measured in peripheral blood every 3 months to confirm (stable) MR3, then every 3- 6 month. If the patient has not achieved 10% BCR-ABL (EMR) at the 3-month check-up, the test should be repeated as soon as possible.
- The kinetics of the response after 3, 6, 12 months and thereafter, form the basis for categorizing the patient's treatment response as «optimal», «warning» or «failure» (defined above). The requirements for the response kinetics apply regardless of which TKI is used in the first line.

Table 1 Definition of the hematological response

Abbreviation / term	Definition	Meaning
CCyR	Complete cytogenetic response	No (or less than 1% of) cells in the bone marrow have the Philadelphia chromosome.
CMR	Complete Molecular Response	The PCR test does not find the BCR-ABL gene.
DMR	Deep molecular response	A deep molecular response is commonly defined as BCR-ABL1 values of ≤0.01% IS, (international scale) which is representing a 4 log reduction in BCR-ABL1 (MR4) . Various BCR-ABL1 cut off values exists, where molecular response 4 (MR4) is ≤0.01% IS, MR4.5 ≤0.0032% IS, and MR5 <0.001% IS
MCyR	Major cytogenetic response	No more than 35% of the cells in the bone marrow have the Philadelphia chromosome.
MMR	Major molecular response	A major molecular response is commonly defined as BCR-ABL1 values of ≤0.1% IS, (international scale) which is representing a 3-log reduction in BCR-ABL1 (MR3)

MR	Molecular response	It is based on how much of the BCR-ABL gene (which is found in CML cells) can be detected by the PCR test. This test can be done on either the blood or bone marrow.
PCyR	Partial cytogenetic response	Between 1% and 35% of the cells in the bone marrow still have the Philadelphia chromosome.
TFR	Treatment-free remission	Is achieved when a patient who has discontinued TKI therapy maintains a major molecular response (MMR) and does not need to restart therapy.

5.1.5 Treatment strategy and guideline

Following the introduction of TKIs, the goals of CML-CP treatment irrespective of the line of therapy have become multifold and include preventing disease progression to more advanced stages (AP and BP), reducing the risk of death, extending the patient's life to the length typical of the general population, and improving the quality of life. These goals are achieved by reducing the number of Ph+ cells as much as possible, *i.e.* reach major molecular response (MMR; BCR-ABL1 IS <0,1%) or deeper response (deep molecular response; DMR/MR4; BCR-ABL1 IS <0,01% or MR4.5; BCR-ABL1 IS <0,0032%). The ELN 2020 recommendations for treating CML were recently updated to include deep molecular response (DMR) and treatment-free remission (TFR) as treatment goals. For a selected category of patients receiving 1st line and 2nd line therapy, TFR has emerged as a potential goal of therapy once an appropriate and sustained DMR response has been achieved. The treatment algorithm depends on the phase of the disease at the point of diagnosis[2, 31]. Definitions and meaning for the abbreviations are described in Table 1

Danish Clinical practice

Danish clinical practice is described in the guideline by Dansk Studiegruppe for Kroniske Myeloide Sygdomme (DSKMS). The latest clinical guideline is from 2020. [5]

1st line

Once the diagnosis of "CML in chronic phase" is confirmed, treatment with tyrosine kinase inhibitors (TKI) must be initiated. According to current recommendations from the Danish Medicines Council, the first choice is: imatinib, tablets, 400 mg, once daily. The patient must be informed about the diagnosis, treatment rationale and side effects of imatinib treatment. The goal for the treatment (disease control or treatment free remission) should be determined at the start of treatment, among other things based on the patient's age, comorbidity and any fertility wish. At the start of treatment, the patient should be checked every 2 weeks for the first 6 weeks with standard toxicity assessment: general condition and side effects, hematological quantities, leukocyte fractions, weight, and blood pressure (fluid retention), extra attention should be paid to symptoms of heart failure, P-ALT, P-basic phosphatase, P-bilirubin, P-creatinine. The treatment with imatinib or other TKIs must be given continuously. Treatment breaks at the start of treatment (the first few years) increase the risk of developing resistance.
Treatment response should be assessed according to ELN's recommendations for CML treatment from 2020 (ELN-European LeukemiaNet) [24].

Table 4 Milestones for treating CML expressed as BCR-ABL1 on the International Scale (IS).

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤ 0.01% (MR[4]).

A change of treatment may be considered if MMR is not reached by 36–48 months.

NA not applicable, *ACA* additional chromosome abnormalities in Ph+ cells, *ELTS* EUTOS long term survival score.

[a]Loss of MMR (BCR-ABL1 > 0.1%) indicates failure after TFR

2nd line

In case of imatinib resistance (inadequate response to treatment according to current ELN recommendations), tyrosine kinase domain mutations must be investigated before imatinib treatment is replaced with dasatinib, nilotinib or bosutinib (2nd generation TKIs). In case of imatinib intolerance (significant side effects), imatinib treatment can be replaced with dasatinib, nilotinib or bosutinib (2nd generation TKIs).
Second-generation TKIs (2G-TKI) induce durable responses in less than half of patients with imatinib resistance, and allogeneic CMT should be considered if second-line therapy is suboptimal.
The treatment goals for 1st and 2nd line treatment are the same, and the responses to 2nd line treatment must also be assessed according to the same criteria as the 1st line treatment (ELN-European LeukemiaNet).
Ponatinib (3G-TKI) should be considered for certain point mutations in BCR/ABL1 and for resistance to 2G-TKI, where further treatment with imatinib is not relevant.

3rd line

As a 3rd line, in case of intolerance or treatment failure to 2G-TKIs, any of the untested TKIs is used; alloSCT is recommended in suitable patients.

The table 4 above present the European LeukemiaNet 2020 recommendations which is the guidance for monitoring treatment effectiveness reflected in Danish clinical practice. Those recommendations are the same as in 1st line

Perspectives from Danish clinical experts - 2022

Based on input from local clinical experts [6], , the main challenges for patients in need of 3rd line treatment are intolerance and/or resistance. Resistance and lack of efficacy are managed by addressing lack of adherence (as described above compliance issues can lead to lack of optimal response), analyse the ABL mutation status (*i.e*. to identify any resistance mutations), and take comorbidity and off target effects of the TKIs into account. For intolerance, side effects may be addressed by dose modifications or treating the side effect. According to input from local clinical experts, resistance represents around 25% of the cases and intolerance 75% [6].

Unmet medical need and positioning of asciminib in the medical algorithm

Several TKIs are available for the treatment of patients with CML that have resulted in improved life expectancy of patients with CML. However, patients with CML still have several unmet medical needs, particularly those who have failed prior TKIs.
Intolerance: A challenge for the treatment of patients with CML is poor specificity of currently available TKIs, which is a key driver of off-target adverse events and intolerability. For 20%–65% of the patients in the 3rd line setting, a previous history of treatment intolerance results in a limited number of available treatment options. Moreover, there

are a few unique toxicities specific to each agent that further limit the availability of treatment options with a favourable risk-benefit profile in later lines, particularly among those with comorbidities [32, 33].

Resistance: Sequential treatment with TKIs is frequently accompanied by the emergence of mutations, resulting in limited sensitivity to the remaining TKIs. [33, 34]

Resistance and intolerance: For the treatment of patients with resistance and/or intolerance to prior TKIs, limited treatment options exist in later lines and there is insufficient guidance for clinical decision-making regarding selection of a particular TKI following failure of a 2nd generation TKI [24-26]. This results in a lack of tolerable and efficacious treatment options in later lines, and therefore TKI cycling (sequential use of available TKIs) remains the only option for some patients which is associated with a decreased probability of response and poor survival. Evidence suggest that the treatment failure rates are as high as 75%–80% in 3rd line setting and patients with failure have higher rates of progression and death [3, 14, 35]. The long-term overall survival (OS) rates are significantly lower for patients who receive three or more lines of treatment compared with those who are able to maintain imatinib as their 1st first-line therapy (8-year OS rate: 22% vs. 83%, respectively; P<0,01) [4]. Additional factors, including nonadherence to oral TKIs, also contribute to lower clinical and quality of life outcomes, and in turn, higher associated healthcare costs [36-41].

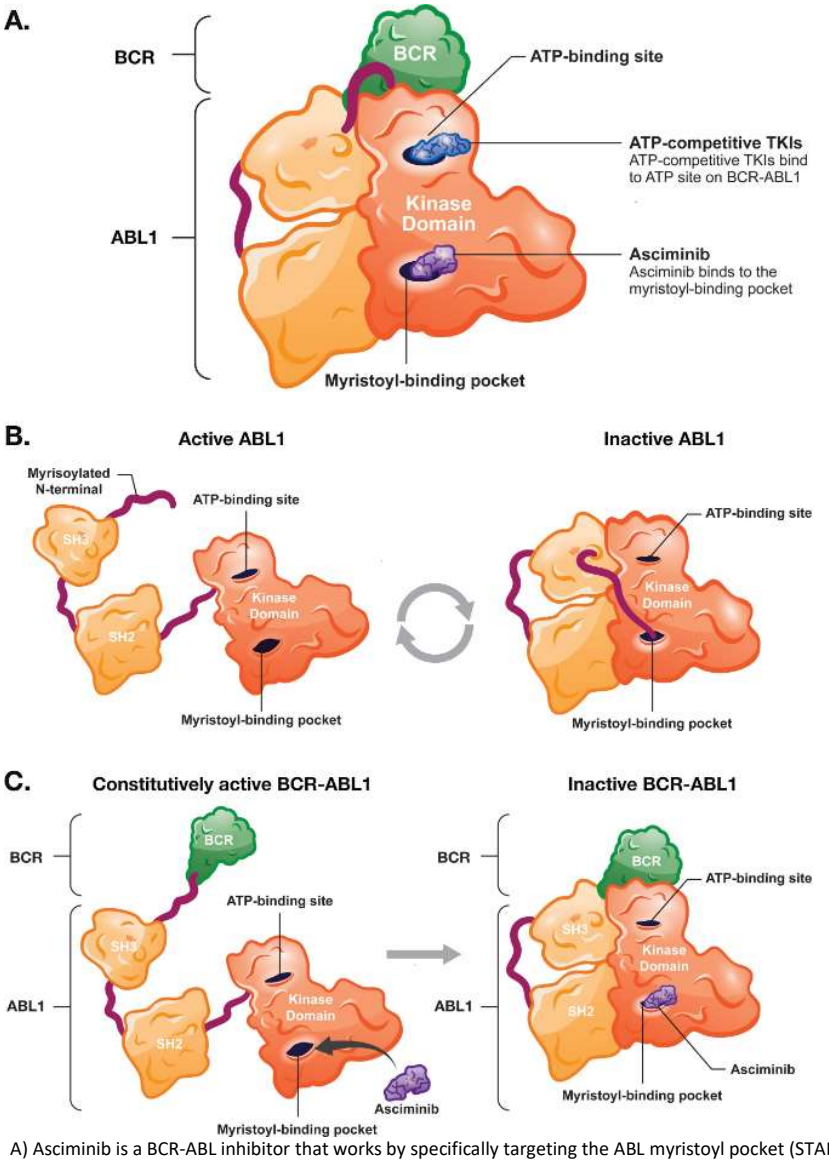
Asciminib is a potent, first-in-class, specific, orally bioavailable BCR-ABL1 inhibitor that is distinct from approved ABL1 kinase inhibitors in that it does not bind to the Adenosine triphosphate- (ATP) binding site of the kinase. By binding the myristoyl site, asciminib mimics myristate and restores inhibition of kinase activity (Figure 1).

Asciminib is indicated for the treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more TKIs and will be a treatment alternative after failure in 2nd line. Asciminib was developed to address the key medical unmet needs in later line CML-CP:

1. Safety profile related to specificity and affinity to the target, resulting in a poor quality of life
2. Lack of efficacy due to emergence of mutations in BCR-ABL1 and due to poor treatment adherence related to toxicity

According to input from local clinical experts, there is a need for an effective and tolerable drug with a new mechanism of action for patients that is in need of third line treatment [6].

Figure 1 Asciminib's unique mechanism of action is distinct from ATP-competitive TKIs. [42]



A) Asciminib is a BCR-ABL inhibitor that works by specifically targeting the ABL myristoyl pocket (STAMP), in contrast to ATP-competitive TKIs. (B) Under normal conditions, ABL1 kinase is autoregulated by the binding of its myristoylated N-terminal to the myristoyl-binding pocket, rendering the kinase inactive. (C) In CML, autoregulation is lost with the formation of the BCR-ABL1 fusion oncoprotein, which is constitutively active. Asciminib binds to the myristoyl-binding pocket, restores the inactive conformation, and inhibits ABL1 kinase.ATP, adenosine triphosphate; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

5.1.6 Incidence and prevalence of CML in Denmark

Approximately 60-70 new cases of CML are diagnosed in Denmark per year. The incidence is appr. 1: 100,000 and with an age of debut around 63 –65 years of age. The prevalence is expected to increase to 2000-2500 in 2050 [5].

Table 2 CML Incidence and prevalence in the past 5 years

Year	2023	2024	2025	2026	2027
Incidence in Denmark	60-70	60-70	60-70	60-70	60-70
Prevalence in Denmark	900	900	900	900	900

Table 3 Estimated number of patients eligible for treatment (3rd line CP-CML)

Year	2023	2024	2025	2026	2027
Number of patients in Denmark who are expected to start to use the pharmaceutical in the coming years	5	5	5	5	5

Based on data from the Swedish CML register, adjusted to the Danish population and validated by local clinical experts [6, 43], we estimate that appr. 6 new patients a year will transition to 3rd line CML-CP treatment in Denmark. 5 of those patients will be eligible for treatment with asciminib due to tolerability and safety reasons (exclude the T315i mutated patients).

5.1.7 Patient populations relevant for this application

It is expected that asciminib will be used according to label, and this analysis do not include patients in accelerated phase or blast crisis, or patients with T315I or V299L mutations as these patients were excluded from the ASCEMBL trial and not included in the approved indication. Based on clinical expert input [6], patients that are most relevant for asciminib are patients with intolerance to two or more ATP-binding site TKIs, as asciminib has a different and more tolerable safety profile [44]. It is estimated that approximately 6 patients will enter 3rd line treatment yearly [6], in which the majority of these patients will be eligible for asciminib.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Danish clinical practice regarding treatment in 3th line states that, in case of intolerance or treatment failure to 2G-TKIs, any of the untested TKIs is used; alloSCT is recommended in suitable patients. [5]

Choice of comparator(s)

In our analysis, bosutinib will be considered as the comparator versus asciminib for the following reasons:

- **ASCEMBL is a head-to-head clinical trial between asciminib and bosutinib** (the first head-to-head including a 2nd generation TKI) for CML-CP patients relapsed/intolerant to ≥2 prior TKIs, which support the use of bosutinib as comparator. This is in accordance with the methods guide for evaluating new pharmaceutical, stating *"If the intervention has been directly compared with one or more relevant comparators in one or more randomized trials, the company should base its application on these studies."*
- **There are no established SoC in ≥3rdline CML-CP** in the national treatment guidelines. According to clinical experts consulted [6], choice of treatment is based on a patient-by-patient decision and the reason to switch to a later line of treatment (resistance or intolerance to 2nd line treatment).
- **The feedback from Danish medical expert** is that:
    - 75% of the switch to third line CP-CML treatment is due to intolerance to the 2nd generation TKI used in 2nd line. The drug of choice for intolerant patients will be an other 2nd generation TKI

- 2nd generation TKIs (bosutinib, dasatinib and nilotinib) is seen as SoC in 3rd line for patients without T315I mutation [6]. Of these substances, bosutinib is the only one that has been specifically studied in patients with CML-CP who are resistant and/or intolerant to ≥2 TKIs (3rd line or later).

- According to clinical experts, **the efficacy between 2nd generation TKIs** (if adverse events are handled properly) is seen **as similar**, but most patients are treated with nilotinib or dasatinib in 2nd line, and hence bosutinib is more relevant in 3rd and later lines [6].
- Ponatinib is excluded as a relevant comparator in this analysis as ponatinib is mostly prescribed for T315I mutated patients [6] and asciminib is indicated for non T315I mutated CML-CP patients.

As express by the Danish medical expert [6], Bosutinib is part of the standard practice in 3rd line in Denmark and the most commonly used treatment in 3rd line. Thus, we believe there is no need for an analysis that shows/describes that bosutinib is cost-effective in the 3rd line.

5.2.2 Description of the comparator(s)

Based on the sections above, bosutinib is considered the most relevant comparator in Denmark.

Generic name(s) (ATC-code): Bosutinib L01XE14

Pharmaceutical form: Film-coated tablet

Posology & dosing:

- *Newly diagnosed CP Ph+ CML*: The recommended dose is 400 mg bosutinib once daily.

  *CP, AP, or BP Ph+ CML with **resistance or intolerance** to prior therapy*: The recommended dose is 500 mg bosutinib once daily.

Method of administration: orally

Should the pharmaceutical be administered with other medicines? No

- Treatment duration/criteria for end of treatment: Treatment with bosutinib should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs. The lack of efficacy criteria in the study protocol were based on the 2013 European LeukemiaNet (ELN) [30]
- Necessary monitoring, both during administration and during the treatment period: The monitoring requirements for patients who use bosutinib in the proposed indication is needed, full details of which are reported in the SPC [45].

Need for diagnostics or other tests (i.e. companion diagnostics): No

Packaging:

- Bosulif 100 mg film-coated tablets are yellow, oval biconvex, debossed with “Pfizer” on one side and “100” on the other side.
  - Bosulif 100 mg is available in blisters containing either 14 or 15 film-coated tablets in cartons of 28 or 30 film-coated tablets or 112 film-coated tablets.
- Bosulif 400 mg film-coated tablets are orange, oval biconvex, debossed with “Pfizer” on one side and “400” on the other side.

  - Bosulif 400 mg is available in blisters containing either 14 or 15 film-coated tablets in cartons of 28 or 30 film-coated tablets.

- Bosulif 500 mg film-coated tablets are red, oval biconvex, debossed with “Pfizer” on one side and “500” on the other side.
  - Bosulif 500 mg is available in blisters containing either 14 or 15 film-coated tablets in cartons of 28 or 30 film-coated tablets.

5.3 The intervention

Pharmaceutical form: Film-coated tablet

Dosing: The recommended total daily dose of asciminib is 80 mg, to be administered as 40 mg twice daily at approximately 12 hour intervals.

Any change in the dose regimen is at the prescriber’s discretion, as necessary for the management of the patient.

Method of administration: asciminib is for oral use. The film coated tablets should be swallowed whole with a glass of water and should not be broken, crushed or chewed.

The tablets should be taken orally without food. Food consumption should be avoided for at least 2 hours before and 1 hour after taking asciminib.

Treatment duration/criteria for treatment discontinuation: Treatment with asciminib should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

Should the pharmaceutical be administered with other medicines? No

Necessary monitoring, during administration, during the treatment period, and after the end of treatment: The monitoring requirements for patients who start treatment with asciminib in the proposed indication is needed, full details of which are reported in the SPC [45].

Need for diagnostics or other tests (i.e. companion diagnostics): No

For the treatment of patients with resistance and/or intolerance to prior TKIs, limited treatment options exist in later lines and there is insufficient guidance for clinical decision-making regarding selection of a particular TKI following failure of a second-generation TKI [24-26]. This results in a lack of tolerable and efficacious treatment options in later lines, and therefore TKI cycling (sequential use of available TKIs) remains the only option for some patients which is associated with a decreased probability of response and poor survival. Evidence suggest that the treatment failure rates are as high as 75%–80% in third line setting and patients with failure have higher rates of progression and death [3, 14, 46]. The long-term overall survival (OS) rates are significantly lower for patients who receive three or more lines of treatment compared with those who are able to maintain imatinib as their first-line therapy (8-year OS rate: 22% vs. 83%, respectively; P<0.01) [47].

Another challenge for the treatment of patients with CML is poor specificity of currently available TKIs, which is a key driver of off-target adverse events and intolerability. For 20%–65% of the patients in the third-line setting, a previous history of treatment intolerance results in a limited number of available treatment options. Moreover, there are few unique toxicities specific to each agent that further limit the availability of treatment options with a favorable risk-benefit profile in later lines, particularly among those with comorbidities [32, 33].

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Asciminib is the first and only CML treatment that works by binding to the ABL myristoyl pocket. This novel mechanism of action, also known in scientific literature as a STAMP inhibitor (=Specifically Targeting the ABL Myristoyl Pocket), can help address non-sufficient efficacy or tolerability issues in CML patients already in TKI therapy by inhibiting the activity of the fusion oncoprotein BCR-ABL1, which is associated with the over-production of leukemic cells.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

The possibility to carry out an ITC was investigated since nilotinib and dasatinib were identified as possible candidates for a scenario analysis in 3rd line treatment. Based on the poor result of the SLR (Appendix A) it was not feasible to do an indirect comparison. Based on the insight developed in chapter 5.2.1 (the efficacy between 2nd generation TKIs is seen as similar), we included, in appendix J, the results of the sensitivity analysis in the health economic analysis based on bosutinib efficacy from ASCEMBL using dasatinib and nilotinib prices.

6.2 List of relevant studies

NA

7. Efficacy and safety

Clinical results for asciminib are currently available from two studies:

- ASCEMBL: pivotal phase III randomized controlled trial (RCT) of asciminib vs. bosutinib among CML-CP patients previously treated with ≥2 ATP-binding site TKIs
- CABL001X2101: phase-I, open-label dose finding study to define the maximum tolerated dose/ recommended dose for expansion (MTD/RDE), safety, tolerability, pharmacokinetics (PK), and to provide preliminary evidence of efficacy of asciminib given as single agent or in combination with either nilotinib or imatinib or dasatinib.

The head-to-head study ASCEMBL is the only relevant study for this STA and is reported below.

7.1 ASCEMBL

The clinical efficacy and safety of asciminib in the treatment of patients with Philadelphia chromosome positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) with treatment failure or intolerance to two or more tyrosine kinase inhibitors were evaluated in the multicentre, randomised, active controlled and open label phase III study ASCEMBL. Resistance to last TKI was defined as any of the following: failure to achieve either haematological or cytogenetic response at 3 months; BCR ABL1 (on the International Scale, IS) >10% at 6 months or thereafter; >65% Ph+ metaphases at 6 months or >35% at 12 months or thereafter; loss of complete haematological response (CHR), partial cytogenetic response (PCyR), complete cytogenetic response (CCyR) or major molecular response (MMR) at any time; new BCR ABL1 mutations which potentially cause resistance to study medicinal product or clonal evolution in Ph+ metaphases at any time. Intolerance to last TKI was defined as non haematological toxicities unresponsive to optimal management, or as haematological toxicities recurring after dose reduction to the lowest recommended dose.
In this study, a total of 233 patients were randomised in a 2:1 ratio and stratified according to major cytogenetic response (MCyR) status at baseline to receive either asciminib 40 mg twice daily (N=157) or bosutinib 500 mg once

daily (N=76). Patients with known presence of T315I and/or V299L mutations at any time prior to study entry were not included in ASCEMBL. Patients continued treatment until unacceptable toxicity or treatment failure occurred.
The study is summarized in the table below.

Table 4 Market authorisation study[48]

ASCEMBL	A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs Réa, D., M. J. Mauro, C. Boquimpani, Y. Minami, E. Lomaia, S. Voloshin, A. Turkina, D.-W. Kim, J. F. Apperley, A. Abdo, L. M. Fogliatto, D. D. H. Kim, P. l. Coutre, S. Saussele, M. Annunziata, T. P. Hughes, N. Chaudhri, K. Sasaki, L. Chee, V. García-Gutiérrez, J. E. Cortes, P. Aimone, A. Allepuz, S. Quenet, V. Bédoucha and A. Hochhaus (2021). "A Phase 3, Open-Label, Randomized Study of Asciminib, a STAMP Inhibitor, vs Bosutinib in CML After ≥2 Prior TKIs." Blood.
Sample size (n)	233 patients randomized in a 2:1 ratio (based on a computer-generated randomization list via a Web-based system) to receive either asciminib (ABL001) 40 mg orally twice a day (BID) (Number of patients: 157) or bosutinib 500 mg orally once daily (QD) (Number of patients: 76). Randomization was stratified by MCyR status at baseline.
Study design	Randomized, open-label, active-controlled, multicenter, phase 3 trial. Patients were randomized in a 2:1 ratio to asciminib 40 mg BID or bosutinib 500 mg QD. Randomization was stratified by major cytogenetic response (MCyR) at screening. Patients with documented treatment failure (specifically meeting lack of efficacy criteria adapted from the 2013 ELN recommendations) while on bosutinib treatment were offered the option to switch to asciminib treatment within 96 weeks after the last patient was randomized to the study.
Patient population	Eligible patients were ≥18 years of age, with CML-CP previously treated with ≥2 TKIs. Patients must have experienced treatment failure (lack of efficacy) as defined in the 2013 European LeukemiaNet (ELN) recommendations for patients receiving a second-line (2L) TKI or intolerance of the most recent TKI therapy at the time of screening. At screening, BCR-ABL1 transcript levels on the international scale (BCR-ABL1IS) must have been ≥1%. After a protocol amendment, for patients with intolerance, BCR-ABL1IS >0,1% was required at screening. Patients with known bosutinib-resistant BCR-ABL1 mutations of T315I or V299L detected at any time before study entry were ineligible.
Intervention(s)	Asciminib (ABL001) 40 mg orally twice a day (BID).
Comparator(s)	Bosutinib 500 mg orally once daily (QD)
Follow-up period	The study is ongoing. The median duration of follow-up was 2,3 years from randomization to last contact date.
Primary endpoints reported include results	The primary endpoint of the study was MMR rate at 24 weeks. MMR is defined as BCR ABL1 IS ratio ≤0,1%.
Other outcomes reported include results	The key secondary endpoint is MMR at week 96 while on study treatment, without meeting any treatment-failure criteria before week 96 to compare additional parameters of the efficacy asciminib versus bosutinib. Other secondary endpoints include complete cytogenetic response rates to compare additional parameters of the efficacy of asciminib versus bosutinib. Cytogenic response will include Complete, Partial, Major, Minor, Minimal and no response. Also, time to MMR and duration of MMR, time to CCyR and duration of CCyR, time to treatment failure, progression-free survival, OS, safety and tolerability, and pharmacologic parameters are secondary endpoints in this study. Response rates by a given time point were

	calculated based on the cumulative rate of patients who achieved a response at any time up to this time point. Response rates at a given time point were calculated based on the number of patients with a response at this time point, regardless of whether they had previously achieved a response. The CCyR endpoint was analysed only in patients who were not in CCyR at baseline. After randomization, bone marrow assessments were required only if a patient was not in MMR and at the end of treatment. If a patient was in MMR at the same time when a bone marrow assessment was scheduled, as per protocol, CCyR was imputed from MMR on a specific date if there was no valid cytogenetic assessment.

Patients with Ph+ CML-CP were 51,5% female and 48,5% male, with median age 52 years (range: 19 to 83 years). Of the 233 patients, 18,9% were 65 years or older, while 2,6% were 75 years or older. Patients were Caucasian (74,7%), Asian (14,2%) and Black (4,3%). Of the 233 patients, 80,7% and 18% had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, respectively. Patients who had previously received 2, 3, 4, 5 or more prior lines of TKIs were 48,1%, 31,3%, 14,6% and 6%, respectively.

Patient baseline characteristics are presented in the appendix C

Results

The primary endpoint of the study was MMR rate at 24 weeks. MMR is defined as BCR ABL1 IS ratio ≤0,1%. A secondary endpoint was complete CCyR rate at 24 weeks. CCyR is defined as no metaphases in bone marrow with a minimum of 20 metaphases examined. The main efficacy outcomes from the ASCEMBL study are summarised in Appendix D.

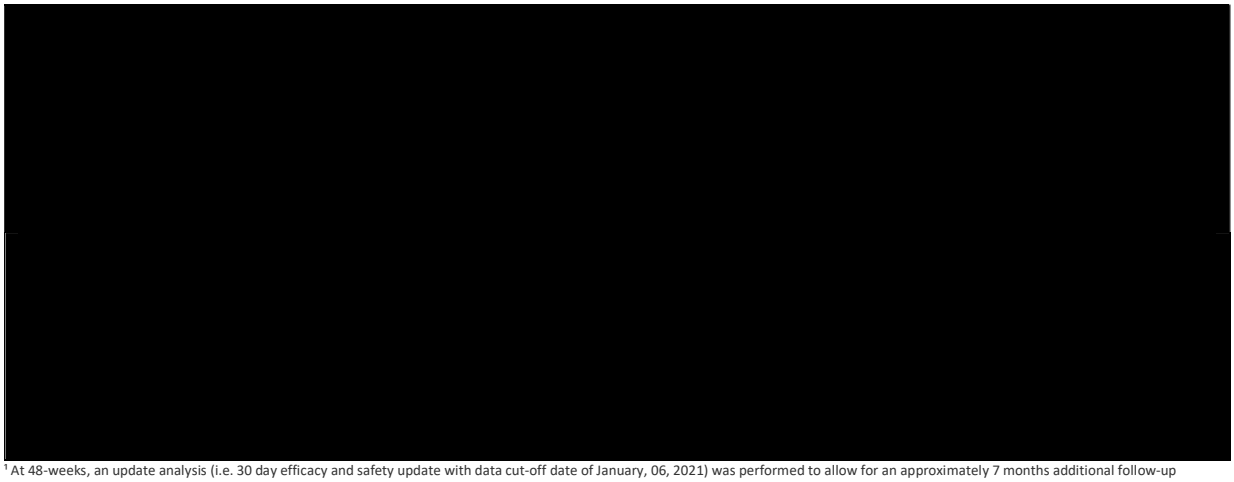
In ASCEMBL, 12,7% of patients treated with asciminib and 13,2% of patients receiving bosutinib had one or more BCR ABL1 mutation detected at baseline. MMR at 24 weeks was observed in 35,3% and 24,8% of patients receiving asciminib with or without any BCR ABL1 mutation at baseline, respectively. MMR at 24 weeks was observed in 25% and 11,1% of patients receiving bosutinib with or without any mutation at baseline, respectively. The MMR rate at 24 weeks in patients in whom the randomised treatment represented the 3rd, 4thor 5th or more line of TKI was 29,3%, 25%, and 16,1% in patients treated with asciminib and 20%, 13,8%, and 0% in patients receiving bosutinib, respectively.

The MMR rate at 48 weeks was 29,3% (95% CI: 22,32; 37,08) in patients receiving asciminib and 13,2% (95% CI: 6,49; 22,87) in patients receiving bosutinib. The Kaplan Meier estimated proportion of patients receiving asciminib and maintaining MMR for at least 48 weeks was 96,1% (95% CI: 85,4; 99,0).

The key secondary endpoint was the MMR rate at Week 96 while on study treatment without meeting any lack of efficacy criteria (based on 2013 European LeukemiaNet (ELN) recommendations) prior to 96 weeks. Patients with documented treatment failure as per 2013 ELN recommendations while on bosutinib treatment had the option to switch to asciminib treatment within 96 weeks after the last patient has been randomized on study. At this new cut-off, clinical superiority of asciminib versus bosutinib increased compared to the primary analysis, as reflected by a more than 2-fold improvement in MMR rate compared to bosutinib at Week 96: 37,58% (95% CI: 29,99; 45,65) in the asciminib arm compared to 15,79 % (95% CI: 8,43; 25,96) in the bosutinib arm, corresponding to a common treatment difference (after adjusting for baseline MCyR status) of 21,74% (95% CI: 10,53; 32,95) which was clinically and

statistically significant; p=0,001. These results are presented in Figure 2 and Figure 3 and support the long-term benefit of asciminib over bosutinib.
At Week 96 cut-off, 99 of the 233 patients (42,5%) were continuing the study treatment with 84 patients (53,5%) and 15 patients (19,7%) still ongoing in the asciminib and bosutinib arms, respectively.

Figure 2 MMR rate (%) (a) at and (b) by scheduled time points (FAS), from the 24-week, 30-day update[1] and 96-week analysis[2] [44]



[1] At 48-weeks, an update analysis (i.e. 30 day efficacy and safety update with data cut-off date of January, 06, 2021) was performed to allow for an approximately 7 months additional follow-up period
[2] At each weeks the % is referring to the same N which is 157 for asciminib and 76 for bosutinib
a) At time point: Value occurred at the exact time
b) By time point: Value occurred any time before the time you are talking about and up to X time

Figure 3 Cumulative incidence curve of MMR (FAS); 96-week analysis (October 06, 2021) [44]

Discontinuation from treatment for any reason without prior achievement of MMR is considered a competing event. (Non responders were censored at their last molecular assessment date.)

Patients are planned to receive treatment up to the end of study treatment (EOsT) period defined as up to 96 weeks after the last patient received the first dose or up to 48 weeks after the last patient had switched to asciminib treatment (whichever was longer unless patients had discontinued study treatment earlier). After the EOsT, the assigned study treatment would be made available to patients if the investigator believed they might benefit from

therapy. This would be outside of this study through alternative options including, but not limited to, an expanded access/compassionate use/managed access program or access to commercial supplies in applicable countries.
In addition to primary analysis, the following analyses are planned:

- A 96-week analysis
- EOsT analysis with a cut-off date 30 days after the EOsT period. Of note, this analysis could be conducted at the same time as 96-week analysis.
- Progression-free survival (PFS) and overall survival (OS) update analysis at the end of the 5 years follow-up period.

Median duration of exposure with asciminib was 103,1 weeks (min-max: 0,1-201,1) vs 30,5 weeks (min-max: 1,0-188,3) for bosutinib; 17 months of additional data compared to the Week 24 cut-off.
Updated safety results continue to demonstrate that asciminib safety profile remains favourable in the intended target population. No new safety findings emerged with the longer follow-up data.

Twenty-four patients randomized to bosutinib switched to asciminib treatment after meeting lack of efficacy criteria as per protocol. The duration of exposure for those patients is describe in Table 5.

Table 5 Duration of exposure to study drug (bosutinib patients switch to asciminib)

Subgroup analyses demonstrated a homogeneous and consistent treatment effect in favour of asciminib across most major demographic and prognostic subgroups, see Appendix B.

7.2 Other relevant studies[42]

Study 3	"Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure." Hughes, T. P., M. J. Mauro, J. E. Cortes, H. Minami, D. Rea, D. J. DeAngelo, M. Breccia, Y.-T. Goh, M. Talpaz, A. Hochhaus, P. le Coutre, O. Ottmann, M. C. Heinrich, J. L. Steegmann, M. W. N. Deininger, J. J. W. M. Janssen, F.-X. Mahon, Y. Minami, D. Yeung, D. M. Ross, M. S. Tallman, J. H. Park, B. J. Druker, D. Hynds, Y. Duan, C. Meille, F. Hourcade-Potelleret, K. G. Vanasse, F. Lang and D.-W. Kim (2019). New England Journal of Medicine **381**(24): 2315-2326.
Sample size (n)	326 participants
Study design	CABL001X2101 was a multi-center, open-label dose finding study to define the maximum tolerated dose/ recommended dose for expansion (MTD/RDE), safety, tolerability,

	pharmacokinetics (PK) and to provide preliminary evidence of efficacy of asciminib given as single agent or in combination with either nilotinib or imatinib or dasatinib. The study was designed to include 5 arms: Arm 1: asciminib as single agent in patients with CML-CP/-AP; arm 2: asciminib in combination with nilotinib in patients with CML-CP/-AP; arm 3: asciminib in combination with imatinib in patients with CML-CP/-AP; arm 4: asciminib in combination with dasatinib in patients with CML-CP/-AP; and arm 5: asciminib as single agent in patients with CML-BP and Ph+ ALL. Arms 2, 3, and 4 were introduced during protocol amendments. Each arm began with a dose escalation part to determine the MTD, or the RDE(s) of study treatment followed by an expansion part to further evaluate the safety and tolerability, if deemed appropriate. Protocol amendment 9 incorporated an additional Arm 1 expansion to further assess asciminib as single agent in patients with CML-CP/-AP harboring the T315I mutation. This study utilized a Bayesian logistic regression model (BLRM) to guide dose escalation and estimate the MTD for asciminib as a single agent in patients with CML-CP/-AP, asciminib in combination with either nilotinib or imatinib or dasatinib in patients with CML-CP/-AP patients, and asciminib as single agent in patients with CML-BP and Ph+ ALL. The MTD was defined as the highest drug dosage that was unlikely (<25% posterior probability) to cause dose-limiting toxicities (DLTs) in 33% or more of the treated patients in the first cycle (cycle defined as 28 days) of study treatment under that schedule.
Patient population	Patients were eligible if they were 18 years of age or older, had Ph+ CML-CP or CML-AP, and had hematologic, cytogenetic, or molecular disease that was relapsed or refractory to at least two different TKIs before study entry or had unacceptable side effects from the TKIs, as determined by investigators according to standard criteria. Patients with a BCR-ABL1 T315I mutation were eligible after they had received at least one TKI if no other effective therapy was available. Additional cohorts of patients were subsequently enrolled through a protocol amendment
Intervention(s)	Asciminib was administered once or twice daily (at doses of 10 to 200 mg)
Comparator(s)	NA
Follow-up period	The median follow-up was 14 months
Primary endpoints reported include results	The primary objective was to determine the maximum tolerated dose or the recommended dose (or both) of asciminib administered twice daily in patients with CML-CP or CML-AP. The maximum tolerated dose of asciminib was not reached.
Other outcomes reported include results	Secondary objectives included assessments of safety, pharmacokinetics, and efficacy. Asciminib demonstrated clinically meaningful efficacy in patients with CML-CP exhibiting relapsed disease associated with the presence of the T315I mutation, provided there was no acceptable alternative (N=45), resulting in a 42,2% MMR rate by 24 weeks. MMR rates by 48, 72, and 96 weeks were 44,4%, 46,7%, and 48,9% respectively. MMR rate by the cut-off date (January 06, 2021) was higher among patients who were ponatinib naive vs. ponatinib pre-treated (68,4% vs. 34,6%, respectively). Among those who achieved MMR (T315I mutation analysis cohort), median (min-max) time to first MMR was 12,2 (4-84) weeks. The KM estimated proportion of patients maintaining their first MMR at 96 weeks was 84,0% (95% CI:

	68,1; 100,0%). The proportion of patients maintaining their first MMR beyond 96 weeks was 84,0% up to 168 weeks

7.3 Ongoing studies for the intervention

Title of the study and RCT (clinical-trials.gov)	Objective of the study (patient pop., etc.)	Intervention	Comparator	Outcome	Starting date	Expected end date
A Phase 3b, Multi-center, Open-label, Treatment Optimization Study of Oral Asciminib in Patients with Chronic Myelogenous Leukemia in Chronic Phase (CML-CP) Previously Treated With 2 or More Tyrosine Kinase Inhibitors (NCT04948333)	This study is an international, multi-center, non-comparative, phase IIIb, treatment optimization study of daily 80 mg asciminib (as either as 40 mg BID of asciminib or as 80 mg QD) in adult patients previously treated with 2 or more TKIs. Up to 30 patients who are intolerant to ongoing TKI treatment but in major molecular response (MMR) will also be allowed to enter the trial. Enrolment will be used to have a balance in the allocation of treatment into either asciminib 40 mg b.i.d. or 80 mg q.d. Although this trial will not be powered to compare both treatments, descriptive data from both treatment groups is expected to provide additional insight into the optimal patient management. In patients not achieving MMR at 48 weeks or losing the response after the week 48 up to week 108, asciminib dose may be escalated to 200 mg q.d. if in the investigator's opinion the patient may benefit from the escalation. In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management.	Asciminib	N/A		October 13, 2021	June 11, 2026

8. Relative efficacy

The relative efficacy is based on direct comparisons from the phase 3, open-label, randomized study where asciminib was compared to bosutinib.
A systematic literature search was carried out and is presented in Appendix A. The literature search did not identify any other direct comparisons than the ASCEMBL trial.

8.1 Results from head-to-head studies

Results from the ASCEMBL trial is presented in chapter 7.1 and further details on results relating to the health economic analysis are presented in subsequent chapters. Only data at cut-off 96 weeks will be use in the analysis. Others data cut-off are given for information

8.2 Safety – intervention and comparator

Asciminib demonstrated a favourable safety and tolerability profile in a population resistant and/or intolerant to two or more prior TKIs.
At the Week 96 cut-off, the median duration of exposure to study drug was approximately three times longer in the asciminib treatment group (103,14 weeks; range: 0,1 to 201,1) compared to the bosutinib treatment group (30,50 weeks; range: 1,0 to 188,3).

AEs of any cause, that occurred in at least 5% of patients in either treatment group are presented in table in the appendix C, with the most frequently reported AEs in the asciminib arm reported as thrombocytopenia (23,1%), headache (19,9%), neutropenia (19,2%) and fatigue (14.7%), hypertension (13.5%), arthralgia (12.8%), diarrhea (12.8%), nausea (11.5%), nasopharyngitis (10.9%), anemia (10.3%). In the bosutinib arm the most commonly reported AEs were diarrhea (72.4%), nausea (46.1%), increased ALT (30.3%), vomiting (26.3%), rash (23.7%), increased AST (21.1%), neutropenia (17.1%), thrombocytopenia (14.5%), headache (15.8%), abdominal pain (15.8%). Events were primarily grade 1 or 2 in severity and grade 3/4 AEs were reported in 56,4% patients in the asciminib treatment arm compared to 68,4% in bosutinib arm. In asciminib group, nasopharyngitis and anemia increased above 10% since the 24 weeks cut-off, due to two additional patients and one additional patient, respectively. All three of whom had AEs of grade 1-2. The proportion of patients with grade ≥3 events was lower in the asciminib treatment group (56.4%) compared to the bosutinib treatment group (68.4%) [44].
In the asciminib group, nasopharyngitis and anemia increased above 10% since the 24 weeks cut-off, due to two additional patients and one additional patient, respectively. All three of whom had AEs of grade 1-2. The proportion of patients with grade ≥3 events was lower in the asciminib treatment group (56.4%) compared to the bosutinib treatment group (68.4%) [44].

Regardless of the longer duration of exposure in asciminib group, overall, patients in the asciminib treatment group vs those in the bosutinib treatment group experienced less AEs (91,0% vs 97,4%), less severe AEs (grade ≥3; 56,4% vs 68,4%), less SAEs (17,9% vs 26,3%), less AEs leading to dose adjustment/interruptions (42,3% vs 64,5%) and less AEs leading to treatment discontinuation (7,7% vs 26,3%) [48, 49]. No new on-treatment AE with a fatal outcome occurred since the 24 weeks cut-off and the frequency of on-treatment AEs with fatal outcome frequency continued to be 1.3% in both treatment groups [44]. Asciminib continued to be safe and tolerable even after the longer duration of exposure since the Week 24 cut-off.

8.3 Utility value from ASCEMBL

EQ-5D utilities with Danish tariffs were generated from EQ-5D-5L responses collected in the ASCEMBL trial according to local methodology [50] . EQ-5D-5L was administered at screening/baseline (Day -21 to -1). Data were collected at screening, and at each of the on-treatment visits (Week 4, 8, 12, 16, 24, 36, 48, and 96) while patients remained in the study (with the exception of the switch phase).
The EQ-5D-5L is composed of a descriptive system of five dimensions and a visual analogue scale (VAS). EQ-5D-5L analyses reported herein are focused on the VAS, a measure of self-rated health, rated on a scale from 0 (worst imaginable health state) to 100 (best imaginable health sate). A clinically meaningful difference of 7 points was used for interpretation of changes in VAS score, as commonly reported in the literature

The EQ-5D-5L analysis of change from baseline and difference between treatments was conducted using a mixed-effects model for repeated measures (MMRM), which adjusts for repeated assessments over time as well as baseline PRO score. The MMRM analysis population included patients with change from baseline scores (i.e., patients with baseline and at least one post-baseline assessment), and the analysis included all data up to week 96. Baseline PRO score, stratification factor (cytogenic response), treatment arm, study visit, and interaction of treatment arm and study visit were included in the models as fixed effects; subject was included as a repeated effect. An unstructured covariance matrix was used as recommended for repeated measures models.

Utility data is from the time of the latest available cut-off of (week 96 data).

The health states of interest included in the analysis are:

- Overall and by randomized treatment arm.
- On/off treatment.
- Pre-/post-progression.

Utility values by health state were estimated from a mixed-effect model for repeated measures (MMRM), accounting for multiple assessments per patients, and including baseline EQ-5D value as a covariate, in the EQ-5D analysis population (patients with baseline and post-baseline EQ-5D data).
Among all randomized patients (N=233), 219 had EQ-5D utility values (94% of all randomized), 150/154 (97%) in asciminib arm and 69/74 (93%) in bosutinib arm. Across the 219 patients, in total there are 1 411 EQ-5D utility assessments are available with 219 assessments at baseline and 1 192 assessments post-baseline. There were 204 patients with both baseline and post-baseline assessments (142 in asciminib arm; 64 in bosutinib arm; the EQ-5D analysis population), and a total of 1 105 post-baseline assessments were included in the modelling estimation.

Considering on/off treatment, in the EQ-5D analysis population only a total of 14 patients had EQ-5D assessments in the off-treatment phase. There were a total of 17 EQ-5D assessments in the off-treatment phase (1,5% of the post-baseline assessments). There were no EQ-5D assessments post-progression (12 patients with progression). There were five patients who died, among these patients there were three EQ-5D assessments within 84 days of death (none within 28 days of death).
Multiple models can be run and different scenarios generated for health state utility values. Within the model the user may select:

- “utility by arm”, the model does not differentiate whether the patient is on-treatment with a third line TKI or off-treatment and having moved on to later lines. The model only considers if the patients are treated with asciminib or bosutinib in the third line.
- “utility by treatment”, the model does not differentiate if the patient is treated with asciminib or bosutinib. It only considers whether the patients are on third line treatment or have moved to later lines after discontinuing third line treatment.
- “utility by arm and treatment”, the model considers both variables i.e. third line treatment as well as whether the patient is on-treatment/off-third line treatment.

The EQ-5D utility was modeled with baseline and treatment arm as fixed effects and a random intercept was used to account for repeated measurements within each subject. Missing data is handled through missing at random assumption.
In the context of randomized trials which repeatedly measure patients over time, MMRM models are a popular approach of analysis, because they handle missing data in the outcome ‘automatically’, under the missing at random assumption.

The completion rate of the questionnaire during the scheduled visits is reported in Table 6.

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Table 6 Mean utility value by time period (Danish tariffs)[51]

Week	Asciminib (N=154)		Bosutinib (N=74)	
	N	Mean (SD) – (CI)	N	Mean (SD) – (CI)
Baseline	150	[redacted]	69	[redacted]
4	138	[redacted]	66	[redacted]
8	129	[redacted]	60	[redacted]
12	125	[redacted]	54	[redacted]
16	118	[redacted]	51	[redacted]
24	108	[redacted]	41	[redacted]
36	86	[redacted]	24	[redacted]
48	89	[redacted]	21	[redacted]
96	69	[redacted]	13	[redacted]

N: number of responses at the different weeks

Table 7 Overview of the HSUV measured during clinical trials with danish tariffs [52]

By arm and treatment	**On-treatment: Asciminib**	[redacted]
	On-treatment: Bosutinib	[redacted]
	Off-treatment: Asciminib	[redacted]
	Off-treatment: Bosutinib	[redacted]
By treatment	**On-treatment**	[redacted]
	Off-treatment	[redacted]
By arm	**Asciminib arm**	[redacted]
	Bosutinib arm	[redacted]

Table 7 summarizes the mean utility available in the model. Generally the utility values were similar between treatment arms and appeared slightly lower when off-treatment. This should be interpreted with caution due to the low numbers of observations for patients off treatment within the ASCEMBL trial at the latest data cut-off available (96 weeks).

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9. Health economic analysis

A cost-utility analysis was developed using a non-homogenous, partitioned survival model to estimate total life years (LYs), quality-adjusted life years (QALYs), and lifetime costs of treatment of CML-CP patients (excluding T315i or V299L patients) who were previously treated with two or more TKIs and who are eligible to receive treatment with either asciminib or bosutinib.

Model structure

The model captures progression of CML through three main phases: the CP (chronic phase), AP (acute phase) and BP (blast phase). The CP is represented by two health states that capture time on third line treatment and time in CP after discontinuation of third line therapy. AP and BP are represented by a single state each. The health state structure also contains two sub-models for patients who receive an allogeneic stem cell transplantation (Allo-SCT), which is possible for a proportion of patients either at discontinuation of third line treatment (in the CP), or at progression to AP or progression to BP (in progressed disease). The Allo-SCT sub-models include two states that capture relapse free and post relapse survival. The model structure is laid out in Figure 4.

The model is implemented as a set of partitioned survival models. The model uses a one-month cycle length. This was determined to be the optimal length to allow for accurate modelling of disease progression. Since cycle length is just one month, therefore, half-cycle correction was not carried out. The model captures the trajectory of the cohort who have not undergone an Allo-SCT. Health state occupancy is determined by a series of partitions derived ultimately from the time-to-treatment discontinuation (TTD) curve. Treatment discontinuation will occur due to a treatment failure or a treatment intolerance. Those two parameters are defined as as follow:

- Treatment failure definition is on the ELN criteria [23] defining failure of a second line treatment adapted to include discontinuation of randomized treatment as an event:
    I. No CHR or >95% Ph+ metaphases at three months after initiation of therapy or thereafter
    II. BCR::ABL1 ratio >10% IS and/or >65% Ph+ metaphases at six months after initiation of therapy or thereafter
    III. BCR::ABL1 ratio >10% IS and/or >35% Ph+ metaphases at 12 months after initiation of therapy or thereafter
    IV. Loss of CHR, CCyR or PCyR at any time after initiation of therapy
    V. Detection of new BCR::ABL1 mutations which potentially cause resistance to study treatment at any time after initiation of therapy
    VI. Confirmed loss of MMR in 2 consecutive tests
    VII. New clonal chromosome abnormalities in Ph+ cells: CCA/Ph+: at any time after initiation of therapy
    VIII. Discontinuation from randomized treatment for any reason

- The following events constituted a “treatment intolerance”
    I. Intolerance was defined as nonhematologic grade 3 or 4 toxicity while on therapy, persistent grade 2 toxicity, that is unresponsive to optimal management, including dose adjustments; or hematologic grade 3 or 4 toxicity while on therapy, that recurs after dose reduction to the lowest recommended dose.
    II. December 14, 2018, allowed the inclusion of patients intolerant to their most recent tyrosine kinase inhibitor (TKI) and BCR-ABL1 transcript levels on the international scale (BCR-ABL1IS) >0.1%

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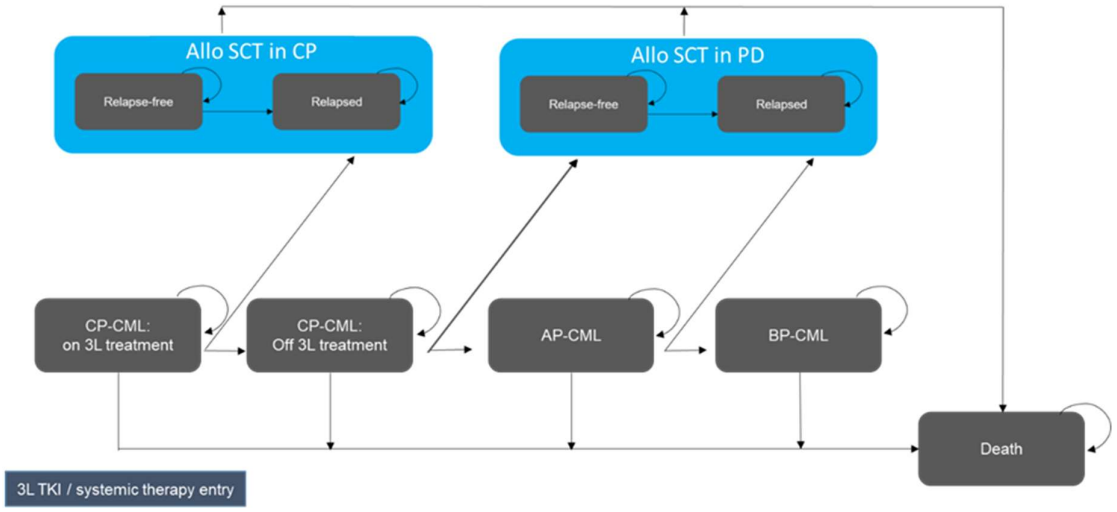
State occupancy in the main model is implemented using a series of survival curves capturing the discontinuation of third line treatment, progression to AP, BP and to death. Discontinuation of third line treatment is derived by fitting a survival model to trial data on treatment discontinuation for asciminib and bosutinib. The model assumes a fixed duration of OS following discontinuation of third line treatment, independent of which third line treatment was given. The model further assumes that, prior to death, patients spend a period of time in AP and then a further period of time in BP. Figure 5 illustrates the partitioning of the cohort across the five states constituting the main model.

With an asciminib median duration of exposure on 103,1 weeks (96 weeks cut-off), very few deaths or progression events were observed in ASCEMBL trial. Consequently, extrapolation of OS from the ASCEMBL trial data was unlikely to provide meaningful conclusions. Instead, mean OS of 3,5 years post discontinuation of third-line treatment is assumed. The approach aligns with the NICE resubmission of bosutinib, which estimated a mean OS of 3,5 years based on data from Kantarjian 2007 [53]. Based on local medical expert feedback [6] the OS was reflecting Danish clinical practice . Mean time in the AP and BP states was assumed to be 10 months and 6 months, respectively. This assumption is in line with the bosutinib resubmission to NICE and was validated by local medical experts [6].

Patients undergoing an allo-SCT (at either the chronic or progressed stages) leave the main model and join one of the two allo-SCT sub-models (also partitioned survival models). One model captures disease trajectory following allo-SCT at discontinuation of third line treatment; the other model captures disease trajectory following allo-SCT at transition to either AP or BP. The allo-SCT sub-models follow the traditional three state partitioned survival structure.

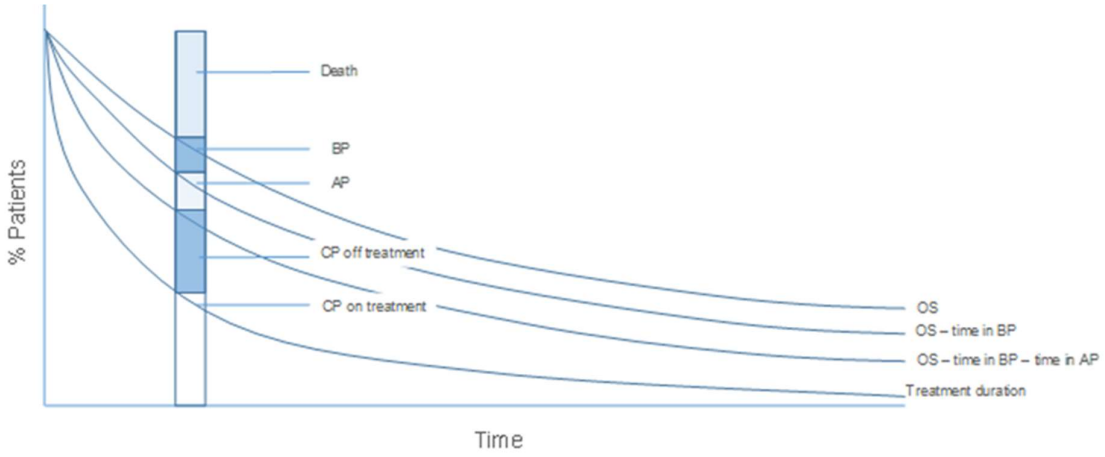
Allogeneic stem cell transplantation (Allo-SCT) is included in the analysis as it is a part of the treatment pathway of CML patients, but Allo-SCT was not an alternative treatment choice in the ASCEMBL trial. Modelling of Allo-SCT is based on data sourced from published literature and Danish clinical expert input (see chapter 9.2.4 and Table 40 for the economic impact of those assumptions)

Figure 4 Model structure



Abbreviations: 3L, third-line treatment; Allo-SCT, allogeneic stem cell transplantation; AP, accelerated phase; BP, blast crisis phase; CP, chronic phase; CML, chronic myeloid leukaemia; PD, progressed disease; TKI: tyrosine kinase inhibitor.

Figure 5 Illustration of partitioned survival model structure



Time horizon

All outcomes were evaluated over a 40-year time horizon. Patients entering the model were assumed to be 52 years of age consistent with the median age of patients randomized to receive Asciminib or Bosutinib in ASCEMBL trial [44] (mean age was 51 years).
Accordingly, outcomes are modelled until patients reach 91 years of age to ensure all long-term benefits and costs associated with treatment are captured, or until substantially all patients are projected to be dead. The 40-year time horizon therefore corresponds to a lifetime projection, consistent with the local guidance [54]

Discount rate

The model assumed a discount rate for costs, LYs and QALYs of 3,5% the first 35 years and 2,5% the following years, consistent with local guidance [54].

9.1 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

9.1.1 Presentation of input data used in the model and how they were obtained

The parameters used to populate the model in this analysis were derived from the ASCEMBL trial. For the estimation of long-term survival after the observed period of the trial, the trial data was supplemented with evidence from external data sources as follows:

Table 8 Input data used in the model

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated
Patient characteristics	ASCEMBL: Median age 52; 47,8% female	Starting age 52 (median); 47,8% female	Direct trial data
Treatment duration, TTD	Mean TTD at 96 weeks Asciminib: 89,93 weeks Bosutinib: 50,04 weeks	Long term mean TTD Asciminib: 126 months Bosutinib: 21,7 months	Parameterization in CML-CP on third line TTD using a Log-Logistic distribution

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated
Adverse events (measured in DKK)		- Alanine aminotransferase increased = 671 - Aspartate aminotransferase increased = 672 -Diarrhoes = 2 041 -Hypertension = 2 041 -Lipase increased = 3 225 -Neutropenia = 3 176 -Thrombocytopenia = 5 831	From ASCEMBL, grade 3-4 with frequency ≥ 5% for at least one of the drug By assumptions on resource use, costs based on: - Rigshospitalets Labportal - Interaktiv DRG code - DRG takter 2022
Adverse events (measured as occurrence)	ASCEMBL: Alanine aminotransferase increased -Asciminib: 0,6% -Bosutinib: 14,5% Aspartate aminotransferase increased: -Asciminib: 1,9% -Bosutinib: 6,6% Diarrhoes: -Asciminib: 0% -Bosutinib: 10,5% Hypertension: -Asciminib: 6,4% -Bosutinib: 3,9% Lipase increased: -Asciminib: 3,8% -Bosutinib: 5,3% Neutropenia: -Asciminib: 15,4% -Bosutinib:11,8% Thrombocytopenia: -Asciminib: 17,9% -Bosutinib: 6,6%	Alanine aminotransferase increased -Asciminib: 0,6% -Bosutinib: 14,5% Aspartate aminotransferase increased: -Asciminib: 1,9% -Bosutinib: 6,6% Diarrhoes: -Asciminib: 0% -Bosutinib: 10,5% Hypertension: -Asciminib: 6,4% -Bosutinib: 3,9% Lipase increased: -Asciminib: 3,8% -Bosutinib: 5,3% Neutropenia: -Asciminib: 15,4% -Bosutinib:11,8% Thrombocytopenia: -Asciminib: 17,9% -Bosutinib: 6,6%	Grade 3 and 4 AE of more than 5% in any arm
Adverse reaction 3 (measured as utility loss)	NA	-0,05 for all AE except Lipase increased = -0,07	TA426: NICE appraisal Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of CML [55] Nafees 2008 [56]
Health state A (measured as utility)	CML-CP (on 3L treatment) -Asciminib: [redacted] -Bosutinib: [redacted] CML-CP (off 3L treatment) -Asciminib: [redacted] -Bosutinib: [redacted]	CML-CP (on 3L treatment) -Asciminib: [redacted] -Bosutinib: [redacted] CML-CP (off 3L treatment) -Asciminib: [redacted] -Bosutinib: [redacted]	Trial-based utility analysis of asciminib and bosutinib (using Danish tariff)
Health state B (measured as utility)	NA	CP: Allo-SCT (relapse free): [redacted] CP: Allo-SCT (relapsed): [redacted] PD-AP: [redacted] PD-BP: [redacted] PD: Allo-SCT (relapse free): [redacted] PD: Allo-SCT (Relapsed): [redacted]	AlloSCT; NICE TA 451: Ponatinib for previously treated CML [57] AP and BP: [58]
Mean OS from discontinuation of 3rd line treatment	NA	3,5 years	TA401: NICE submission for bosutinib [59]
Average time spent in AP phase	NA	8 months	TA401: NICE submission for bosutinib [59]
Average time spent in BP phase	NA	7,5 months	TA401: NICE submission for bosutinib [59]

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated
Overall survival	NA	Mean OS Asciminib: [redacted] months Bosutinib: [redacted] months	Parameterization curves of expected survival time on AP, BP and off third line treatment added to the TTD curve
Patients receiving Allo-SCT	NA	On discontinuation of 3rd line treatment: [redacted] % On progression to accelerated phase: [redacted] % On progression to blast crisis phase: [redacted] % Cost of Allo-SCT: [redacted] DKK	Medical expert [6] Cost of Allo-SCT include a one time procedure [57]

9.1.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

9.1.2.1 Patient population

The Danish patient population: Asciminib is indicated for treatment of adult patients with Ph+ CML-CP previously treated with two or more TKIs. It is assumed that the Danish patient population eligible for asciminib will be according to indication. The majority of the patient population will have received imatinib in 1st line and subsequently nilotinib or dasatinib in 2nd line. Local clinical experts' advice that asciminib may be a good 3rd line treatment option for patients in chronic phase, not harbouring T315I mutation and intolerant or failure to ATP-binding site TKIs. Local clinical experts have estimated the average patient age in the range of 55 to 60 [6]

Patient population in the clinical documentation submitted: The clinical documentation submitted are the following; the head-to-head randomized clinical trial ASCEMBL (comparator arm: bosutinib) and input on local clinical practice from key medical experts [6]. Based on the selection criteria for ASCEMBL (incl. CMP-CP, Ph+, absence of T315I or V299L, patients treated with at least 2 prior TKIs)we assume that the patient population recruited for ASCEMBL is generally similar to the Danish practice. Hence, all clinical data input taken directly from ASCEMBL is assumed to be relevant.

Patient population in the health economic analysis submitted: the model population is in line with the clinical documentation and practice. As discussed in 5.1.7. patient population relevant for the assessment, it is difficult to ascertain the average age for this patient population, due to the lack of a national register. We have chosen the ASCEMBL study as our main data source, in line with the relative efficacy input used in the model. Average age from ASCEMBL was 52 years, and this falls around the age range estimated by local clinical experts. This uncertainty will be explored in sensitivity analysis.

Table 9 Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
Age	52	52	55 to 60 [6]
BCR-ABL1	Positive	Positive	Positive
Disease phase	CP	CP	CP
T315I mutation	Not detected	Not detected	Not detected
V299L mutation	Not detected	Not detected	Not detected
Prior TKIs	2 or more	2 or more	2 or more

9.1.2.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 2.2): Asciminib is a first-in-class oral, potent, allosteric inhibitor of ABL/BCR-ABL1 tyrosine kinase. Asciminib inhibits the ABL1 kinase activity of the BCR-ABL1 fusion protein by specifically targeting the ABL myristoyl pocket (STAMP). Asciminib is expected to be used according to the indication; treatment of adult patients with Ph+ CML-CP previously treated with two or more TKIs.

Intervention in the clinical documentation submitted: The clinical documentation submitted are the following; the head-to-head randomized clinical trial ASCEMBL (comparator arm: Bosutinib) and input on local clinical practice from key medical experts [6]

Intervention as in the health economic analysis submitted: the model intervention is in line with the clinical documentation and practice.

Table 10 Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	80 mg/day (ASCEMBL)	80 mg/day (ASCEMBL)	80 mg/day (assumed used in line with SmPC)
Length of treatment	Until failure, progression to AP or BP or undesired toxicity	Until failure, progression to AP or BP or undesired toxicity	Until failure, progression to AP or BP or undesired toxicity
Criteria for discontinuation	- General discontinuation criteria* - Detection of T315I or V299L mutations at any time - Pregnancy during study - Treatment failure. Patients randomized to bosutinib treatment who experienced treatment failure were offered to switch to asciminib treatment. - Disease progression (CML-related death, AP, and BC).	- General discontinuation criteria* - Detection of T315I or V299L mutations at any time - Pregnancy during study - Treatment failure. Patients randomized to bosutinib treatment who experienced treatment failure were offered to switch to asciminib treatment. - Disease progression (CML-related death, AP, and BC).	-Missing achieving MMR (major molecular respons, BCR/ABL1 ≤0.1% IS) after 12 month of treatment -Loosing achieved MMR indicating treatment failure -Progression to AP or BP -Undesired toxicity -Pregnancy -T315I or V299L case by case evaluation
The pharmaceutical's position in Danish clinical practice	Adult patients with Ph+ CML-CP (excl. T315I or V299L) previously treated with two or more TKIs	Adult patients with Ph+ CML-CP (excl. T315I or V299L) previously treated with two or more TKIs	Adult patients with Ph+ CML-CP (excl. T315I or V299L) previously treated with two or more TKIs. Expected to be used in 3L in line with indication in Danish clinical practice

* Discovery of patient ineligibility, errors in treatment compliance (study treatment, other prescribed or non-prescribed medications), missed/unscheduled/off schedule/incomplete/incorrect assessments, major protocol deviation, use of prohibited treatment, any other protocol deviation that resulted in a significant risk to the patient's safety

Patients suffering from CML and being treated in third line has, due to several co-morbidities, and a long history of medical treatment been establishing, as part of their normal life, a strong focus and practice regarding management of different medications. It was why, for those patients, the fact that asciminib should be taken twice a day with approx. 12 hours apart, and the patient must not eat two hours before and 1 hour after will not be an issue

9.1.2.3 Comparators

The current Danish clinical practice: Bosutinib can, according to input from local clinical experts, be used in all treatment lines. However, the majority of the patients will receive imatinib in 1st line and subsequently nilotinib or dasatinib in 2nd line [60]. Bosutinib is therefore more relevant for 3rd line treatment; hence, bosutinib is a highly relevant comparator based on local clinical practice. In patients resistant or intolerant to previous TKIs, recommended dose of bosutinib according to label (SmPC) is 500 mg daily dose [61, 62]. In Danish clinical practice; however, 400 mg seems to more often be used according to input from local clinical experts [6]. Due to experience from Nordic clinical trials with bosutinib, this is a strategy local clinicians have gained more experience with.

Comparator(s) in the clinical documentation submitted: The ASCEMBL trial investigates efficacy and tolerability of asciminib vs bosutinib in a head-to-head comparison.
Comparator(s) in the health economic analysis submitted: the model input is sourced from ASCEMBL. In ASCEMBL, bosutinib 500 mg/day was used, in accordance to SmPC and clinical practice at the time of the trial conception. Due to recent experience from Nordic clinical trials with bosutinib, most Danish patients get the 400 mg dosage. It is not possible to adjust for the bosutinib efficacy from ASCEMBL. In order to maintain internal consistency with regards to cost and effect, the model use bosutinib 500 mg from ASCEMBL. We will show in a sensitivity analysis how a change from bosutinib 500 to 400 mg affects the model results (chapter 9.6.3). Note that this change only takes into account the costs and do not adjust efficacy accordingly.

Table 11 Comparator

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	500 mg/day (ASCEMBL)	500 mg/day (ASCEMBL)	400 mg/day (according to SPC, 500 mg is recommended dose; however, 400 mg daily dose is used in local clinical practice.)
Length of treatment	Until resistance, progression to AP or BP or undesired toxicity	Until resistance, progression to AP or BP or undesired toxicity	Until resistance, progression to AP or BP or undesired toxicity
The comparator's position in the Danish clinical practice	ASCEMBL; 3rd line and later according to SmPC	ASCEMBL; 3rd line and later according to SmPC	Can be used in all lines (SmPC); however, according to RADS and input from medical experts is mainly used in 3rd line and later (sometimes in 2nd line, rarely in 1st line) [6, 60]

In the bosutinib summary of product characteristics under the section 4.2 it's stated that for newly diagnosed CP Ph+ CML the recommended dose is 400 mg bosutinib once daily. For CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy the recommended dose is 500 mg bosutinib once daily.
The Nordic CML group has been conducted a study called Bosupeg. In this study, it was demonstrated how gastrointestinal side effects can be mitigated and managed, if patients are started at a lower dose and then increase, if the patient tolerate the drug.
In the ASCEMBL study patients who were unable to tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated in order to allow the patient to continue the study treatment. For asciminib, only 1-step dose reduction to total daily dose of 40 mg was allowed, and for bosutinib 2-step sequential dose reduction up to total daily dose of 300 mg was allowed [44].

Table 9-2 Dose reduction steps for asciminib and bosutinib

Dose levels	Asciminib	Bosutinib
Starting dose level	40 mg tablet BID (total daily dose 80 mg)	500 mg (1 x 500 mg tablet QD)
Dose level – 1	20 mg tablet BID (total daily dose 40 mg)	400 mg (4 x 100 mg tablets QD)
Dose level – 2	Not allowed	300 mg (3 x 100 mg tablets QD)
Dose reduction was based on the worst toxicity demonstrated at the last dose.		
Asciminib 20 mg tablets were dispensed to patients in the instance of dose reduction.		
Bosutinib 100 mg tablets were dispensed to patients in the instance of dose reduction.		

[redacted]

In ASCEMBL, the bosutinib patients managed an average mean daily dosage of [redacted] [44] which is higher than in clinical practice. It is at the advantage of bosutinib versus asciminib and resulting in a better efficacy of bosutinib in ASCEMBL versus real practice.

9.1.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: Relevant outcomes include MMR at 24 weeks (primary endpoint) and MMR at 96 weeks (key secondary endpoint). These are established as relevant endpoints. TTD was also captured from ASCEMBL.

Relevance of the documentation for Danish clinical practice: MMR is an established marker for efficacy in 1st and 2nd line CML-CP patients. Asciminib is a novel treatment for 3rd or later lines CML-CP patients, and thus data on the correlation between MMR and OS are lacking. Still, local clinical experts are convinced that asciminib represents a better treatment option for these patients [6]. Patients who switch or stop treatment due to lack of efficacy or tolerability, have a worse prognosis than well controlled patients on treatment. Thus, TTD indicates better efficacy and prognosis.

Correlation between MMR and OS in 3rd line

To show the correlation between MMR and OS a real-world disease management analysis was done [63]. The analysis has included all adult (18+ years) patients newly diagnosed with CML in chronic phase (ICD-O-3: 9875/3) by HMDS (Hematological Malignancy Diagnostic Service) between 1st September 2004 to 31st August 2019 whilst resident in the HMRN (Hematological Malignancy Research Network) region and treated within the Network. The HMRN region covers the former two adjacent UK Cancer Networks with a total population of 3,8 million (Yorkshire and the Humber & Yorkshire Coast Cancer Networks) and collects detailed information about all hematological malignancies diagnosed in the region. Subjects were described in terms of their baseline demographic and prognostic characteristics and each patient's treatment pathway characterized from date of diagnosis to date of death or, for patients still alive, end of follow up. The Swedish CML register didn't allow us to do that analysis since it was not possible to exclude the T315i patients.

The result look as follow:

[redacted]

At 3rd line, 5-year OS was [redacted] for patients reaching MMR versus [redacted] for patients not reaching MMR. Based on that result and the insides collected from the Nordic medical expert we could assume that MMR and OS are correlated.

The relative efficacy outcomes in the submitted health economic analysis: TTD is assumed to correlate with efficacy and used in the model to estimate OS, see chapter 9.2. TTD is assumed to be representative of the time patient responds to the treatment (CCyr or MMR being strongly associated with progression rate and survival by physicians)

Table 12 Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study MMR rate, % (95% CI) at 24 weeks	MMR is not directly applied in the model. TTD correlated to efficacy is used. Mean treatment duration: Asciminib: [redacted] months Bosutinib: [redacted] months	Asciminib: [redacted] (95%CI: 18,87; 33,04) Bosutinib: [redacted] (95% CI: 6,49; 22,87)
Secondary endpoint MMR at 96 weeks	MMR is not directly applied in the model. TTD correlated to efficacy is used. Mean treatment duration: Asciminib: [redacted] months Bosutinib: [redacted] months	Asciminib: [redacted] (95% CI: [redacted]) Bosutinib: [redacted] (95% CI: [redacted])

Table 13 Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study MMR rate, % (95% CI) at 24 weeks **Secondary endpoint MMR at 96 weeks**	-Molecular response (MR) was assessed based on levels of BCR-ABL1 transcripts that were determined by real-time quantitative PCR (RQ-PCR) testing of peripheral blood -Testing for MMR was every 12 wk.	MMR rate is in line with ELN guideline (2020) and with Danish guideline [5, 24]	MMR rate at 3, 6, 12 months are in line with ELN guideline (2020) and with Danish guideline [5, 24]

Danish clinical practice/guideline refers to ELN: Hochhaus et al 2020 regarding evaluation of response [24].

Table 4 Milestones for treating CML expressed as BCR-ABL1 on the International Scale (IS).

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤ 0.01% (MR[4]).

A change of treatment may be considered if MMR is not reached by 36–48 months.

NA not applicable, *ACA* additional chromosome abnormalities in Ph+ cells, *ELTS* EUTOS long term survival score.

[a]Loss of MMR (BCR-ABL1 > 0.1%) indicates failure after TFR

9.1.2.5 Adverse reaction outcomes

Incidence of AE were extracted directly from ASCEMBL, as described in the clinical dossier. AEs considered in the model were all-cause grade 3/4 AEs with an incidence ≥5% in either the intervention or comparator arm. Grade 1-2 events were not considered because they are generally self limited and therefore not likely to be associated with substantial treatment costs or impaired HRQoL. Data from ASCEMBL was used to estimate incidence of all-cause grade 3/4 AEs for asciminib and bosutinib.

Table 14 Adverse reaction outcomes

Adverse reaction outcome	Clinical documentation		Used in the model (numerical value)	
	Asciminib	Bosutinib	Asciminib	Bosutinib
Alanine aminotransferase increased	0,64%	14,47%	0,64%	14,47%
Aspartate aminotransferase increased	1,92%	6,57%	1,92%	6,57%
Diarrhoea	0%	10,52%	0%	10,52%
Hypertension	6,41%	3,94%	6,41%	3,94%
Lipase increased	3,84%	5,26%	3,84%	5,26%
Neutropenia	15,38%	11,84%	15,38%	11,84%
Thrombocytopenia	17,94%	6,57%	17,94%	6,57%

The AE profile of bosutinib in ASCEMBL does not differ from the one observed in clinical practice.

9.2 Extrapolation of relative efficacy

As the overall survival (OS) and progression-free survival (PFS) for asciminib and bosutinib were not matured from ASCEMBL trial, long term survival needed to be assessed using a proxy/surrogacy approach. Novartis has used time to treatment discontinuation (TTD) as a surrogacy endpoint to extrapolate OS. The same assumption was used and accepted by NICE [64].

In summary, OS data was extrapolated based on the following approach:
TTD is assumed to be representative of the time the patient responds to the treatment. An extrapolated curve is fitted to TTD data taken from 3rd line patients from the ASCEMBL trial. The extrapolated TTD curve was used as a proxy to estimate OS.

- For the post 3rd line health states used in the model, a constant mean overall survival post treatment discontinuation, based on literature and local medical expert feedback, was used for:

  - Mean survival post 3rd line treatment discontinuation until death (CP-CML: off 3L treatment until death).
  - Average time spent in the AP phase until death (AP-CML until death).
  - Average time spent in the BP phase until death (BP-CML until death).
- OS curve was created by adding expected mean survival post 3rd line treatment discontinuation to the TTD curve.
- "PFS AP" and "PFS BP" was found by subtracting average time spent in the accelerated and blast phase before death from the OS curve.

The following sections detail the methodology applied and fit to the clinical trial data.

9.2.1 Treatment duration

Time to treatment discontinuation (TTD) data from ASCEMBL was used for the comparison of asciminib with bosutinib. The median TTD was [redacted] and [redacted] months for asciminib and bosutinib respectively at the 96-week cut-off. Figure 6 shows the Kaplan-Meier (KM) curves for time to treatment discontinuation for asciminib and bosutinib.

Figure 6 Time to treatment discontinuation curves from ASCEMBL trial

Parametric distributions were fitted to the observed TTD KM data in order to inform the transition probabilities over a lifetime horizon. A number of different models were fitted separately for the asciminib and bosutinib arms, including: Weibull, log-logistic, Gompertz, exponential, generalized gamma, log-normal, gamma and splines – RCS Weibull, RCS lognormal and RCS log-logistic. AIC and BIC were assessed. A description of the requirements and methods for parametrisation and extrapolation used is included in appendix G.

Table 15 AIC and BIC for the TTD curves of asciminib and bosutinib from the ASCEMBL trial

	Asciminb		Rank		Bosutinib		Rank	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	693,55	696,61	11	11	469,92	472,25	10	5
Weibull	677,33	683,44	9	8	469,34	474,00	9	6
Gompertz	663,22	669,33	1	1	464,71	469,37	3	3
Lognormal	670,65	676,76	4	2	465,49	470,15	4	4

Log-Logistic	672,42	678,53	5	3	463,69	468,35	1	1
Gamma	679,92	686,03	10	10	470,55	475,21	11	9
Gen. Gamma	672,48	681,65	8	5	467,04	474,03	8	7
RCS Weibull	669,66	681,88	2	6	466,83	476,15	7	11
RCS Log-Logistic	669,73	681,96	3	7	465,62	474,94	5	8
RCS Lognormal	672,45	684,68	7	9	466,61	475,93	6	10

As presented in Table 15 Gompertz ranked highest for asciminib and third for bosutinib, while Log-logistic ranks highest for bosutinib and third for asciminib (on BIC, which is the most penalizing of the two measurements). Another possible extrapolation method, which fits the data well was Log-Normal, which ranks second and fourth respectively. Upon inspection of Figure 28 (appendix G), it is clear that the Gompertz distribution does not produce a clinically plausible extrapolation. Of the remaining two, Log-logistic produced the most conservative estimate for the asciminib curve and since the Log-logistic curve for bosutinib ranks first and looks clinically plausible (see Figure 29 (appendix G)) Log-logistic was chosen for both extrapolations.
The log-logistic model is considered to provide the most accurate prediction of long-term TTD based on what was observed in the ASCEMBL trial (based on the AIC and BIC for the TTD curves presented on Table 15). Figure 7 presents the long-term extrapolation of TTD curves based on log-logistic model. According to good practice, the TTD curve was capped to the general age-related mortality, which occurs around month 275.

Figure 7 Final long-term extrapolated TTD curve used in the health economic model with KM data from the ASCEMBL trial

USED IN THE HEALTH ECONOMIC MODEL WITH KM DATA FROM THE ASCEMBL TRIAL

9.2.2 Constant mean overall survival post treatment discontinuation

As the long-term progression-free survival (PFS) curve (progression to accelerated or blast phase CML) and OS curve for asciminib and bosutinib was not mature in the ASCEMBL trial, the TTD curve was used as a proxy to determine OS.

In order to determine the patient distribution over time for the four health states, “CP-CML off 3L treatment”, “AP-CML”, “BP-CML” and “Death”, the average time spent in each health state was used as a surrogate for survival time.

After adjustment made by local clinical expert [6] to a prior NICE appraisal (assessment of bosutinib) [59], the average survival in the advanced phase (AP-CML) was estimated to 8 months, and the average survival in blast crisis phase (BP-CML) was estimated at 7,5 months. We appreciate this is based on an assumption from an assessment conducted by NICE. However, there is no additional evidence that provides further validity of the average time of these health states in a Danish setting. Danish practice follows to a great extent the European Leukemia Net organization[24], regarding

guideline, diagnosis, treatment, and monitoring. Thus, we believe it is considered relevant for the Danish clinical setting as the overall guiding principles are similar for all European countries.
Average OS from treatment discontinuation was estimated at 3,5 years (42 months) [59].

The OS curve was derived by adding 3,5 years to the area under the extrapolated TTD curve for asciminib and bosutinib. The parametric function of the exponential curve only has one parameter, which is the inverse of the area under the curve. Thus, the overall survival curve may be estimated from this. As no other parametric functions would allow for a direct estimation of the parametric curve through area under the curve, the exponential function was chosen. From this OS curve, the PFS - AP and PFS - BP can be determined by subtracting expected time spent in these health states before death (8 and 7,5 month, respectively) from the area under the OS curve. Hereafter, the same methodology as with the OS curve was employed (exponential curve from the inverse of the area under the curve). The calculation of the area under the curves, for the remaining health state, are detailed further below (asciminib as an example):

- OS = area under the TTD curve + average survival from treatment discontinuation [redacted] months) = [redacted] months (Figure 8)
- PFS - AP curve = OS – mean time in acute phase – mean time in blast phase = [redacted] months – [redacted] months – [redacted] months = [redacted] months (Figure 9)
- PFS - BP curve = OS – mean time in blast phase = [redacted] months – [redacted] months = [redacted] months (Figure 9)

The resulting three mean survival times were used to compute the three survival curves.
The general mortality was added to these curves, which results in the three curves presented in Figure 9. The time spent in each phase is the difference between the curves. The time spent in the "CML-CP off 3L treatment phase" was calculated as the remaining patients who were not in either of the before-mentioned phases.

Figure 8 Overall survival for Asciminib and Bosutinib with mean overall survival post discontinuation

To reiterate, the time spent in the PFS - AP and PFS - BP is the difference between the PFS - AP and PFS - BP curve and the difference between the OS curve and the PFS - BP curve respectively. This is [redacted] and [redacted] months respectively.
As patients in clinical practice would typically discontinue their TKI treatment in case of progression, it was assumed that the TTD curve will not cross PFS - AP curve, the PFS - AP curve will not cross the PFS - BP and the PFS - BP curve will not cross the OS curve. Consequently, the TTD curve was capped to the PFS - AP. The final parametric curves are presented in Figure 9.

Comment:
The discrepancy between the time spends on AP ([redacted] months) and BP ([redacted] months) observed in the Danish clinical practice (included in the input cell of the model) and the number estimated by the model is due to:

- the nature of estimating a survival curve and the fact that is done on an interval bases and not smooth bases
- the discount rates

Exponential function was used to estimate OS derived from the area under the curve of the extrapolated TTD curve. The exponential function is dropping quite fast. Giving a larger area under the curve the difference between observed data and the estimated curve will be bigger. Based on the larger area under the curve for the asciminib arm versus the bosutinib arm, the difference between the observed data and the estimated data will be more important for asciminib than bosutinib. As a result, the time on AP and BP, before introducing the discount rate, is as follow:

- Asciminib:
  - AP: [redacted] months instead of [redacted] (diff: [redacted])
  - BP: [redacted] months instead of [redacted] (diff: [redacted])
- Bosutinib:
  - AP: [redacted] months
  - BP: [redacted] months

Including the discount rate, the difference between the two arms will increase since the time spent on 3rd line for asciminib is higher than for bosutinib. As a result, the asciminib arm patients will reach AP and BP much later than the bosutinib arm and will have a higher discount rate impact. After introducing the discount rate, the time spend on AP and BP is as follow:

- Asciminib:
  - AP: [redacted] months instead of [redacted] (diff: [redacted])
  - BP: [redacted] months instead of [redacted] (diff: [redacted])
- Bosutinib:
  - AP: 7 months instead of 8 (diff:1)
  - BP: 6,45 months instead of 7,5 (diff: 1,05)

Thus, to conclude from the explanation above, the discrepancy is manly driven by the discount rate.

Figure 9 Survival curves used for OS and time spent in heath states in the health economic model (months)

[redacted]

9.2.3 Validation of ASCEMBL extrapolation

9.2.3.1 Short term OS

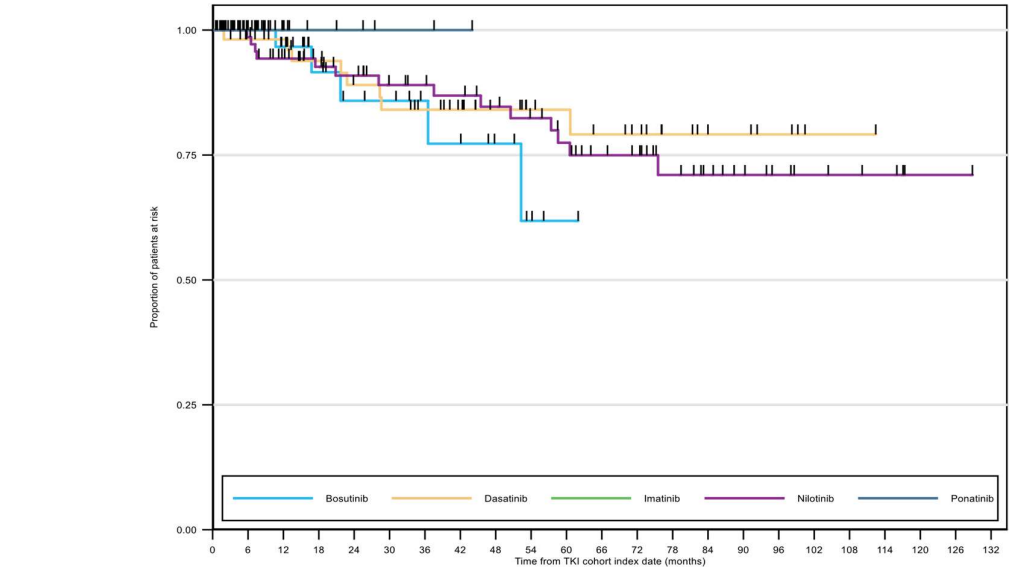
The ASCEMBL trial design allowed crossover meaning that in case patients experienced lack of response, switching to a different treatment was an option. This meant patients in the bosutinib arm could switch e.g. to asciminib. As patients with their disease under control are assumed to continue on treatment, TTD can be considered a surrogate endpoint for efficacy. As presented in Figure 10 below, the immature OS curve from ASCEMBL does not show a rapid decline in overall survival with time. A possible reason for this is the crossover ability to switch to other treatments. This is in contrast to the OS curve in Figure 11 [43], which is based on real world overall survival observed from a Swedish CML registry (CML-CP patients treated with two prior TKIs). It is noteworthy that patients participating in

clinical trials are often in better health than patients observed in real world clinical practice, where patients may have more co-morbidities.

Figure 10 ASCEMBL, OS at 96 weeks cut off

[redacted]

Figure 11 Swedish CML register, OS for CML-CP patients treated with two or more prio TKI [43]



Number at risk

Bosutinib	48	38	27	18	14	13	10	9	6	2	1	0	0	0	0	0	0	0	0	0	0	0
Dasatinib	56	49	46	40	36	34	31	27	22	18	17	15	13	9	6	6	4	1	1	0	0	0
Imatinib	8	7	4	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Nilotinib	78	70	60	56	52	45	42	41	38	35	31	26	24	18	14	10	8	6	5	4	1	0
Ponatinib	19	10	4	3	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 48 in Appendix A, illustrates the difficulty in capturing OS/PFS in the target population of this analysis as OS/PFS outcomes are not reached in a majority of published studies on third line CML-CP patients. Included are studies identified within our systematic literature review which included bosutinib.

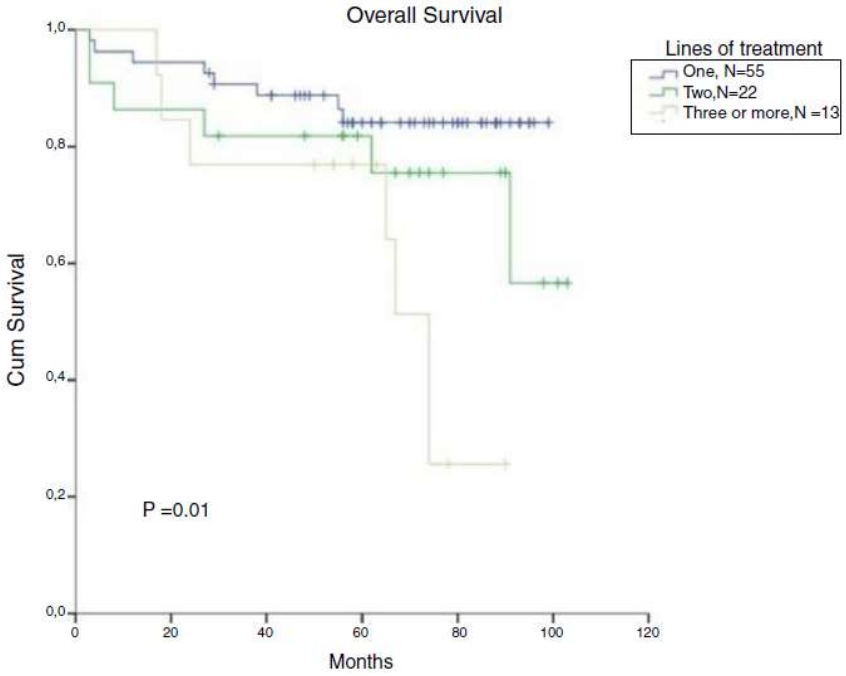
The OS curve estimated in the model is validated through the Swedish CML register. However, it is to be acknowledge that OS data from ASCEMBL does not exactly match the model estimate or the Swedish CML register data. With the immature ASCEMBL OS data, this discrepancy, or its significance, cannot yet be fully determined. Some plausible explanations have been explored above, but more data is needed to confirm this. Based on previous trials on CML, and the disease course when well treated, it may take decades to obtain mature OS data.

In light of the limitations of capturing OS in this setting, we believe that using TTD data as a surrogate mechanism is an appropriate and sound approach.

9.2.3.2 Long term OS

In order to assess validity of the model extrapolation of long term OS, a retrospective study with a cohort of 90 CML patients of which 13 had undergone three or more lines of treatment was identified [47]. The objective of the study was to assess the clinical outcomes of intolerant, relapsed or refractory patients who could not be treated with new TKIs or experimental therapies. The study reported a 22% overall survival at 8 years (96 months) for third line CML-CP patients who were intolerant, relapsed or refractory to TKI, as presented in Figure 12.

Figure 12 Cumulative survival in CML patients, stratified according to the number of treatment lines



As shown in Figure 13, the OS curve extrapolated in this analysis estimates an OS at 8 years for bosutinib that is comparable to the OS findings presented in Figure 12. This suggests that extrapolated curve shape of bosutinib is a good fit to express long term OS in third line CML-CP.

Figure 13 Long term extrapolation of ASCEMBL vs 8 years OS from publication

[redacted]

9.2.3.3 Conclusion

At the time of this analysis, it is not possible to utilise the immature OS data from the ASCEMBL trial in this analysis. As such, the OS curves have been based on ASCEMBL TTD data, show a good fit of the bosutinib curve shape for 3rd line CML-CP:

- In the short term: validated by the Swedish CML registry [43]
- In the long term: validated by the Bosi publication from 2019 [47]

The Swedish CML register is acknowledged globally. To our knowledge, this register is the best available source of OS data in CML-CP patients treated with two or more TKIs. In lack of long-term data from this register, we had to use a different source of validation for the long-term OS.

9.2.4 Parametric fit to Allo-SCT treatment

Allogeneic stem cell transplantation (Allo-SCT) is included in the analysis as it is a part of the treatment pathway of CML patients. Allo-SCT was not an alternative treatment choice in the ASCEMBL trial, and as such there are limitations to the inclusion of transplantations within the model. Modelling of Allo-SCT is based on data sourced from published literature and clinical expert input. Several sensitivity analyses were performed to assess the impact of including (varied proportion of patients receiving an Allo-SCT) or excluding (no patients receiving an Allo-SCT) Allo-SCT from the model.
The model allows patients to receive an Allo-SCT either during treatment or following the end of treatment. As presented in Figure 4, the model structure incorporates two tunnel structures which emulate the survival patterns of patients that receive an Allo-SCT after discontinuing treatment in the chronic phase or when progressing from "off 3L treatment CP-CML" to "AP-CML" or from "CP-CML" to "BP-CML". The proportion of patients receiving an Allo-SCT was estimated by a local clinical expert [6]:

- 10 % after discontinuation of third line treatment.
- 25% upon progression to accelerated phase.
- 15 % upon progression to blast crisis phase.

Survival of patients in the "AP-CML" and "BP-CML" is assumed to be equal as no differentiating factors were not identified in literature.
After receiving a stem cell transplant, patients are assumed to transfer to a relapse free survival state until relapse or death. The relapse free survival curves and OS curves for Allo-SCT patients in the chronic phase and progressed disease phase were sourced from Jabbour et al. 2011 [28]. In the lack of evidence from Denmark, we decided to base SCT survival on Jabbour 2011 data to align with a previous appraisal in CML [59].

9.3 Documentation of health-related quality of life (HRQoL)

In the model, health state utility values were assigned to every health state in order to determine the total QALYs for each treatment arm. The model allows for utility data from different sources to be used including values taken from the literature and derived from the EQ-5D data collected in the ASCEMBL trial.

9.3.1 Overview of health state utility values (HSUV)

9.3.1.1 Utilities from Literature

Systematic literature reviews (SLR) of economic evaluations and HRQoL studies for CML were conducted by Novartis. For utility values applied in the AP and BP health states the company drew on values reported in Szabo et al. [58] This study was identified in the company review of HRQoL evidence, which searched for utility values in a general CML population including patients in receipt of 1st, 2nd and 3rd line therapy (see Appendix H). The Szabo study recruited

from the general population and implemented a TTO analysis for several health states. Specifically, we selected values for patients unresponsive to treatment in the AP and BP.
For patients receiving SCT, we drew on values reported in from the NICE submission for ponatinib [57] which used published values from the literature. Separate values were applied for patients who were relapse-free and those that had relapsed. The model, however, did not account for when SCT was received (pre-progression vs post-progression). Relevant health state utility values identified are shown in Table 16

Table 16 Overview of HSUV derived from the literature search (presented in Appendix H)

Health state	Value [C.I.]	Tariff (value set) used	Source
CP-CML (on treatment)	0,85 (0,61- 0,94)	UK	Szabo et al. [58]
CP-CML (off treatment)	0,68 (0,48- 0,81)	UK	
AP CML	0,65 (0,84- 0,45)	UK	Szabo et al. [58]
BP CML	0,41 (0,62- 0,19)	UK	
SCT in CP – relapse free	0,71 (0,57-0,85)	UK	NICE TA 451 [57]
SCT in CP – relapsed	0,59 (0,47-0,70)	UK	
SCT in PD – relapse free	0,71 (0,57-0,85)	UK	
SCT in PD – relapsed	0,59 (0,47-0,70)	UK	

9.3.1.2 Utility Values from ASCEMBL

EQ-5D utilities with Danish tariffs were generated from EQ-5D-5L responses collected in the ASCEMBL trial according to local methodology [50] . EQ-5D-5L was administered at screening/baseline (Day -21 to -1). Data were collected at screening, and at each of the on-treatment visits (Week 4, 8, 12, 16, 24, 36, 48, and 96) while patients remained in the study (with the exception of the switch phase).
The EQ-5D-5L is composed of a descriptive system of five dimensions and a visual analogue scale (VAS) Table 18. EQ-5D-5L analyses reported herein are focused on the VAS, a measure of self-rated health, rated on a scale from 0 (worst imaginable health state) to 100 (best imaginable health sate). A clinically meaningful difference of 7 points was used for interpretation of changes in VAS score, as commonly reported in the literature
The EQ-5D-5L analysis of change from baseline and difference between treatments was conducted using a mixed-effects model for repeated measures (MMRM), which adjusts for repeated assessments over time as well as baseline PRO score. The MMRM analysis population included patients with change from baseline scores (i.e., patients with baseline and at least one post-baseline assessment), and the analysis included all data up to week 96. Baseline PRO score, stratification factor (cytogenic response), treatment arm, study visit, and interaction of treatment arm and study visit were included in the models as fixed effects; subject was included as a repeated effect. An unstructured covariance matrix was used as recommended for repeated measures models.

Utility data is from the time of the latest available cut-off of (week 96 data).

The health states of interest included in the analysis are:

- Overall and by randomized treatment arm.
- On/off treatment.
- Pre-/post-progression.

Utility values by health state were estimated from a mixed-effect model for repeated measures (MMRM), accounting for multiple assessments per patients, and including baseline EQ-5D value as a covariate, in the EQ-5D analysis population (patients with baseline and post-baseline EQ-5D data).

Among all randomized patients (N=233), 219 had EQ-5D utility values (94% of all randomized), 150/154 (97%) in asciminib arm and 69/74 (93%) in bosutinib arm. Across the 219 patients, in total there are 1 411 EQ-5D utility assessments are available with 219 assessments at baseline and 1 192 assessments post-baseline. There were 204 patients with both baseline and post-baseline assessments (142 in asciminib arm; 64 in bosutinib arm; the EQ-5D analysis population), and a total of 1 105 post-baseline assessments were included in the modelling estimation.

Considering on/off treatment, in the EQ-5D analysis population only a total of 14 patients had EQ-5D assessments in the off-treatment phase. There were a total of 17 EQ-5D assessments in the off-treatment phase (1,5% of the post-baseline assessments). There were no EQ-5D assessments post-progression (12 patients with progression). There were five patients who died, among these patients there were three EQ-5D assessments within 84 days of death (none within 28 days of death).
Multiple models can be run and different scenarios generated for health state utility values. Within the model the user may select:

- "utility by arm", the model does not differentiate whether the patient is on-treatment with a third line TKI or off-treatment and having moved on to later lines. The model only considers if the patients are treated with asciminib or bosutinib in the third line.
- "utility by treatment", the model does not differentiate if the patient is treated with asciminib or bosutinib. It only considers whether the patients are on third line treatment or have moved to later lines after discontinuing third line treatment.
- "utility by arm and treatment", the model considers both variables i.e. third line treatment as well as whether the patient is on-treatment/off-third line treatment.

The EQ-5D utility was modeled with baseline and treatment arm as fixed effects and a random intercept was used to account for repeated measurements within each subject. Missing data is handled through missing at random assumption.
In the context of randomized trials which repeatedly measure patients over time, Mixed Models for Repeated Measures models are a popular approach of analysis, because they handle missing data in the outcome 'automatically', under the missing at random assumption.
The completion rate of the questionnaire during the scheduled visits is reported in Table 17.

Table 17 Mean utility value by time period (Danish tariffs)[51]

Week	Asciminib (N=154)		Bosutinib (N=74)	
	N	**Mean (SD) – (CI)**	**N**	**Mean (SD) – (CI)**
Baseline	150	[redacted]	69	[redacted]
4	138	[redacted]	66	[redacted]
8	129	[redacted]	60	[redacted]
12	125	[redacted]	54	[redacted]
16	118	[redacted]	51	[redacted]
24	108	[redacted]	41	[redacted]
36	86	[redacted]	24	[redacted]
48	89	[redacted]	21	[redacted]
96	69	[redacted]	13	[redacted]

N: number of responses at the different weeks

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Table 18 Summary of EQ-5D-5L EQ VAS by time window (Full analysis set)

n in Change from baseline column is the number of subjects with assessments at baseline and at the respective post-baseline time window

Table 19 Overview of the HSUV measured during clinical trials with danish tariffs [52]

		LS mean (SE) - [C.I.]
By arm and treatment	**On-treatment: Asciminib**	
	On-treatment: Bosutinib	
	Off-treatment: Asciminib	
	Off-treatment: Bosutinib	
By treatment	**On-treatment**	
	Off-treatment	
By arm	**Asciminib arm**	
	Bosutinib arm	

Table 19 summarizes the mean utility available in the model. Generally the utility values were similar between treatment arms and appeared slightly lower when off-treatment. This should be interpreted with caution due to the low numbers of observations for patients off treatment within the ASCEMBL trial at the latest data cut-off available (96 weeks).

As recommended by the Medicinrådet, the HSUV by treatment is used for the model base case.

9.3.1.3 Adjustment for age and sex

Age-matched general population utilities were used to adjust utility values for age-related declines in HRQoL. The utilities used are the expected remaining QALYs in the general population included in the Medicinrådet guidelines. [65]

The baseline starting age of 52 and the proportion of women (51,5%) in the model is based on the mean values of the patients (51 years) in the ASCEMBL trial.

9.3.1.4 Adverse events

All adverse events identified in ASCEMBL and those considered in the model are reversable. Due to the intervals between visits, the disutility from AEs is not adequately captured in ASCEMBL. At time of visits, when reporting EQ5D for the last week, due to the reversable adverse event the full disutility, someone might get, might not be capture. Disutilities were sourced from the literature representing the overall impact of the AE in QALYs. AE disutilities were taken directly from other TAs, or published literature. In the absence of available data, the QALY loss for an AE was assumed to be 0.05 in line with assumptions applied in TA426 [55]. TA451 [57], and TA401 [59](bosutinib) did not directly model individual adverse event disutilities, as the former assumed the same decrement for all disutilities, and the latter assumed that adverse events were already captured through the treatment utilities. Hence we used input from the TA426.[55] (NICE multiple Technology appraisal for Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia).

The impact of AEs on HRQoL is captured as a one-off QALY loss in the first cycle of the model (The disutility was taken from the literature and thus don't have data on the duration of the disutility due to AEs).The AE disutilities used in the model are presented in Table 20. Confidence intervals for those utility values are not available since those values are coming from literature.

Table 20 Utility decrements for adverse events

Event	Decrement	Tariff (value set) used	Source
Alanine aminotransferase increased	-0,05	UK	Assumption, consistent with TA426 [55]
Aspartate aminotransferase increased	-0,05	UK	Assumption, consistent with TA426 [55]
Diarrhoea	-0,05	UK	Assumption, consistent with TA426 [55]
Hypertension	-0,05	UK	Assumption, consistent with TA426 [55]
Lipase increased	-0,07	UK	Nafees 2008 [56]
Neutropenia	-0,05	UK	Assumption, consistent with TA426[55]
Thrombocytopenia	-0,05	UK	Assumption, consistent with TA426 [55]

9.3.2 Health state utility values used in the health economic model

Utility values for the CP-CML on and off third line treatment health states were taken directly from the ASCEMBL trial using the EQ-5D-5L values. Utility values associated with the others health states were derived from the literature review as these were not captured in the ASCEMBL trial. Table 21 and Table 22 summarizes the mean utility used in the model.

Table 21 Summary of the HSUV used in the model

	Mean [C.I.]	Tariff (value set) used	Comments
CP-CML (on treatment)			
Asciminib	[redacted]	DK	ASCEMBL [52]
Bosutinib	[redacted]	DK	ASCEMBL [52]
CP-CML (off treatment)			
Asciminib	[redacted]	DK	ASCEMBL [52]
Bosutinib	[redacted]	DK	ASCEMBL [52]
CP-AlloSCT (relapse free)			
Asciminib	0,71 (0,57-0,85)	UK	TA451 [57]

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Bosutinib			
CP-AlloSCT (relapsed)			
Asciminib	0,59 (0,47-0,70)	UK	TA451 [57]
Bosutinib			
PD-AP			
Asciminib	0,65 (0,84- 0,45)	UK	Szabo et al.[58]
Bosutinib			
PD-BP			
Asciminib	0,41 (0,62- 0,19)	UK	Szabo et al.[58]
Bosutinib			
PD-AlloSCT (relapse free)			
Asciminib	0,71 (0,57-0,85)	UK	TA451 [57]
Bosutinib			
PD-AlloSCT (relapsed)			
Asciminib	0,59 (0,47-0,70)	UK	TA451[57]
Bosutinib			

Table 22 Utility decrements for adverse events

Event	Decrement	Tariff (value set) used	Source
Alanine aminotransferase increased	-0,05	UK	Assumption, consistent with TA426 [55]
Aspartate aminotransferase increased	-0,05	UK	Assumption, consistent with TA426 [55]
Diarrhoea	-0,05	UK	Assumption, consistent with TA426 [55]
Hypertension	-0,05	UK	Assumption, consistent with TA426 [55]
Lipase increased	-0,07	UK	Nafees 2008 [56]
Neutropenia	-0,05	UK	Assumption, consistent with TA426[55]
Thrombocytopenia	-0,05	UK	Assumption, consistent with TA426 [55]

For the utility values derived from the ASCEMBL trial data, values “By treatment” are used in the CEM as recommended by Medicinrådet [54].

Since only utility values for the CP-CML, on and off third line treatment health states, were capture in the ASCEMBL trial, Danish utility value was only applicable for the CP-CML health states.

9.4 Resource use and costs

For each treatment, the following measures of costs are calculated:

Table 23 Costs used in the model

Costs	DKK (per unit of measurement used in the model)
Medication acquisition	DKK (per day)
Adverse events	DKK (per frequency)
Disease monitoring	DKK (per time period /patient)
Allo-SCT	DKK (per procedure)
Subsequent treatment (all health state after third line)	DKK (per time period /patient)
Disease management	DKK (per time period /patient)
Terminal care	DKK (one time)

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Medication acquisition costs

Drug costs (Apotekets indkøbspris) for all the drugs except asciminib are sourced from Danish medicine agency [66]. Drug dosage and administration are based on the respective labels for each drug. Administration cost for oral drugs is assumed to be zero. Mean relative dose intensity (RDI) for asciminib and bosutinib is based on data from the ASCEMBL trial. As no identifiable source of information was available to estimate the RDI of other treatments, an average RDI of asciminib and bosutinib from the ASCEMBL trial was used ([redacted]). Drug acquisition costs per intervention are outlined in Table 24.

Table 24 Drug acquisition costs

Drug	Apotekets indkøbspris (DKK)	Strength	Number of tab/cap per pack	Daily dose – CP*	Daily dose - Progressed Disease	Mean RDI	Daily cost - CP incl RDI (DKK)	Daily cost - PD incl RDI (DKK)
Asciminib	34 218,10	40	60	80,00	80,00	[redacted]	1 014,00	1 014,00
Bosutinib	23 916,68	500	28	500,00	500,00	[redacted]	726,04	726,04
Ponatinib	53 565,00	45	30	45,00	45,00	[redacted]	1 535,53	1 535,53
Dasatinib	24 574,48	100	30	100,00	140,00	[redacted]	704,47	986,26
Nilotinib	22 940,00	200	112	800,00	800,00	[redacted]	704,59	704,59
Imatinib	14 042,56	400	30	400,00	600,00	[redacted]	402,55	603,83

*Resistant or intolerant to earlier TKI

Adverse events costs

The costs associated with treatment of AEs are presented in Table 25. Grade 3 and 4 AEs that occurred in at least 5 % of the study population are included in the model.

The AE costs were combined with the AE rates to calculate the total costs of AEs for each treatment arm. The costs of AEs in the model are calculated using local Danish rates.

Table 25 Adverse events costs (grade 3-4 that occurred in at least 5 %)

	Unit cost DKK	Definition	Details
Alanine aminotransferase increased	6 365	Two physician visits + blood tests[2]	(3176 x 2)+ 13 DRG navn : MDC16[4] Blood test, Alanintransaminase : Klinisk biokemisk afdeling - Metodeliste (rh.dk)
Aspartate aminotransferase increased	6 365	Two physician visits + blood tests[2]	(3176 x 2)+ 13 DRG navn : MDC16[4] Blood test, Aspartattransaminase : Klinisk biokemisk afdeling - Metodeliste (rh.dk)
Diarrhea	2 041	DRG 09MA98	DRG navn: MDC09[4]
Hypertension	2 041	DRG 09MA98	DRG navn: MDC09[4]
Lipase increased	3 225	Abnorm serumlipase	Diagnos: DR748D, duration < 12hours [3]
Neutropenia	3 176	Neutropeni UNS	Diagnos: DD709, duration < 12hours [3]
Thrombocytopenia	5 831	Transfusion af plasma og/eller behandlet blod	DRG: 16PR01 [4]

1-Værdisætning af enhedsomkostninger, Medicinrådet- Værdisætning af enhedsomkostninger-vers. 1.2 (medicinraadet.dk) [67]
2-Rigshospitalets Labportal [68]
3-Interaktiv DRG code - https://interaktivdrg.sundhedsdata.dk/#/ [69]
4-DRG takster 2022[70]

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Table 26 Summarized adverse events costs by treatment

Treatment	AE cost (DKK)
Asciminib	[redacted]
Bosutinib	[redacted]

Disease monitoring costs

Resource use associated with treatment of CML was not collected as part of the ASCEMBL trial. Typical resource use associated with monitoring patients were specified estimated following discussions with local clinician expert [6]. The unit costs associated with monitoring and administration are presented in Table 27 and Table 28.

Table 27 Disease monitoring cost

Item	Resource per month	Unit cost DKK	Definition	Details
Blood count	1	261	Blood tests refer to total cost for several test[1]	Leukocytter;Csv,- Erythrocytter;Csv- Hæmoglobin;B-Trombocytter; B- Laktatdehydrogenase- Reticulocytter; B-Erytrocytter, vol.fr.;B- C-reaktivt protein [CRP];P- Kreatinin; P -Calcium;P -Albumin; P- Urat; P-Aspartattransaminase [ASAT];P, KBA- Alanintransaminase (ALAT);P, KBA
Electrolytes	1	261		
Liver function	1	28	Aspartattransaminase [ASAT];P, KBA[1] + Alanintransaminase (ALAT);P, KBA[1]	
Serum Amylase	1	261	Blood tests refer to total cost for several test[1]	Leukocytter;Csv,- Erythrocytter;Csv- Hæmoglobin;B-Trombocytter; B- Laktatdehydrogenase- Reticulocytter; B-Erytrocytter, vol.fr.;B- C-reaktivt protein [CRP];P- Kreatinin; P -Calcium;P -Albumin; P- Urat; P-Aspartattransaminase [ASAT];P, KBA- Alanintransaminase (ALAT);P, KBA
Renal Function	1	79	CREACLEA[2]	

1- LMV priser [71]
2- Rigshospitalets Labportal Klinisk biokemisk afdeling - Metodeliste (rh.dk) [68]

Table 28 Total monitoring costs

	All treatments (DKK)
Total monitoring cost	890

Stem Cell Transplant Costs

The cost of stem cell transplantation is presented in Table 29.

Table 29 Cost of stem cell transplantation

	Unit cost DKK	Details
Stam cell transplantation, cost per patient	747 851	DRG: 26MP22[1], DRG-navn: Allogen stamcelletransplantation

1- DRG takster 2022 [70]

Subsequent treatment Costs

Local clinical experts indicate that the failure of a TKI treatment usually leads to treatment with a different TKI, with patients potentially cycling through TKIs being reintroduced back to an earlier failed therapy if at least a partial response was achieved. Hence patients are expected to be treated with a TKI throughout their disease, and potentially with a number of different therapies. Within the model patients are assumed to commence therapy with a fourth line TKI. Either imatinib, bosutinib, ponatinib, nilotinib or dasatinib may be used after discontinuation of the third line treatment and treatment is expected to continue throughout the CP state. The proportion of patients on each TKI was informed by local clinical expert opinion [6] . Drug acquisition costs per day are assumed to be the same regardless of whether the TKI is used in the third or fourth line of treatment.

Since no data was available to inform estimates for the RDI of treatments after the third line, the average RDI of asciminib and bosutinib from the ASCEMBL trial was used [redacted] for other therapies. Patients are treated until progression to the AP phase (meaning the patients will receive subsequent treatment during the time the patients are in CP off treatment). The aim is to keep the patient on an optimal treatment to avoid progression from CP to AP.

The proportion of patients on fourth line TKI treatments is presented in Table 30. For third line patients treated with bosutinib, the medical experts estimated that 70 % of patients would receive asciminib as a subsequent treatment. As asciminib is not available to patients at the time of this analysis, and to reflect the actual clinical treatment setting in the bosutinib arm, the 70 % of asciminib patients estimated by the expert is allocated to ponatinib (reflecting medical expert input on Asciminib arm).

Patients progressing to AP and BP are also treated with TKIs. The inputs for subsequent treatment in progressed disease is shown in Table 31.

The model allows for patients in the Allo-SCT sub models to receive systemic treatment in the relapse-free survival health state. The proportional estimates for subsequent treatment in the Allo-SCT sub models are shown in Table 32.

Table 30 Subsequent systemic treatment in chronic phase

Treatment in 3L	Asciminib	Nilotinib	Dasatinib	Ponatinib	Imatinib	Bosutinib	Weighted cost per day (DKK)
Asciminib	0%	0%	0%	100%	0%	0%	1 535,53
Bosutinib	0%	0%	0%	100%	0%	0%	1 535,53

Table 31 Subsequent systemic treatment in progressed disease

Treatment in 3L	Nilotinib	Dasatinib	Ponatinib	Imatinib	Bosutinib	Weighted cost per day (DKK)
Asciminib	0%	0%	100%	0%	0%	1 535,53
Bosutinib	0%	0%	100%	0%	0%	1 535,53

Table 32 Subsequent systemic treatment following Allo-SCT

	Nilotinib	Dasatinib	Ponatinib	Imatinib	Bosutinib	Weighted cost per day (DKK)
Following a SCT prior to relapse						
SCT in CP	0%	0%	0%	0%	0%	0,00
SCT in PD	0%	0%	0%	0%	0%	0,00
Following relapse						
SCT in CP	0%	0%	100%	0%	0%	1 535,53

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SCT in PD	0%	0%	0%	0%	0%	0,00

Disease management Costs

Resource use for disease management was adapted from data utilised in NICE TA451 (ponatinib)[57].
Resource use for patients on third-line treatment was based on data from TA451 for patients in CML with a complete cytogenic response (table 5-23 in TA451). Resource use in the CP off treatment state was based on data from TA451 for patients in CP without a complete cytogenic response (table 5-23 in TA451). Data in TA451 did not distinguish AP and BP except for days in hospital. The relevant data wase assumed to apply to patients in both AP and BP states.

Detailed data on resource use following allo-SCT was unavailable. Resource use was limited to an annual check-up with a haematologist following successful Allo-SCT (relapse-free). This assumption on resource use reflects the management of patients over the longer term following successful Allo-SCT. In the initial period following Allo-SCT, clinical contact is expected to be more frequent. For patients relapsing after Allo-SCT, resource use was assumed to be the same as for patients in AP.

Available data was presented to local medical expert and changes applied following advice to better reflect local clinical practice [6]. Health state resource use per 3 months is available in Table 33.
Costs associated to health care resource use are presented in Table 34 and total costs by health state are available in Table 35. All costs used in the model are calculated using local Danish rates.

Table 33 Health state resource use

	Resource use per 3 months							
	CP - CML						Progressed disease	
	On 3L treatment	Off 3L treatment	Post allo-SCT - Relapse-free	Post allo-SCT - Relapsed	AP	BP	Post allo-SCT - Relapse-free	Post allo-SCT - Relapsed
Outpatient visits	[redacted]							
Full blood count	[redacted]							
Hospital days	[redacted]							
Blood transfusion	[redacted]							
Cytogenetic analysis	[redacted]							
Bone marrow aspiration	[redacted]							
FISH	[redacted]							
PCR	[redacted]							
Cytochemistry analysis	[redacted]							
Blood film exam	[redacted]							
Blood chemistry	[redacted]							
Kinase domain mutation	[redacted]							
Platelet transfusion	[redacted]							

Table 34 Resource use cost

	Unit cost (DKK)	Definition	Details
Outpatient visits	3 176	DRG: 16MA98	MDC16 1-dagsgruppe, pat. mindst 7 år[1]
Full blood count	261	Blood tests refer to total cost for several test[4]	Leukocytter;Csv,- Erythrocytter;Csv- Hæmoglobin;B- Trombocytter; B- Laktatdehydrogenase-Reticulocytter; B- Erytrocytter, vol.fr.;B- C-reaktivt protein [CRP];P- Kreatinin; P -Calcium;P -Albumin; P- Urat; P-Aspartattransaminase [ASAT];P, KBA- Alanintransaminase (ALAT);P, KBA
Hospital days	4 094	Indlæggelsestakst på hæmatologisk på Rigshospitalet	3 958 x 1,0344 = 4 094 (price index from 2019 to 2022) Daily cost included in Baggrund for Medicinrådets anbefaling vedrørende tisagenlecleucel som mulig standardbehandling til diffust storcellet B-celle lymfom [72].
Blood transfusion	4 223	DRG: 16PR02	Transfusion af blod, øvrig[1]
Cytogenetic analysis	4 907	KROMOHÆM	Laboratorieundersøgelse: Kromosomanalyse, HÆM-ONK[2]
Bone marrow aspiration	1 700	MARVMRK	Laboratorieundersøgelse: Hæm. Markørundersøgelse, VOKSNE over 16 år; Knoglemarv[2,5]
3 176DKK)FISH	4 589,50	FISH	Laboratorieundersøgelse: FISH, ikke CLL Afhængig af analyse mellem 2305kr-6874kr[2]
PCR	3 150	DRG: 31PR03	Genetisk risikovurdering og rådgivning[1]
Cytochemistry analysis	1 700	MARVMRK	Laboratorieundersøgelse: Hæm. Markørundersøgelse, VOKSNE over 16 år; Knoglemarv[2,5]
Blood film exam	54	Blood tests refer to total cost for several test[4]	Leukocytter;Csv, Erythrocytter;Csv, Trombocytter; B
Blood chemistry	62	Blood tests refer to total cost for several test[4]	Kreatinin;Asc, Glukose;Asc, Kalium;Asc, Natrium;Asc
Kinase domain mutation	3 250	ABLMUT	Laboratorieundersøgelse: Mutationsscreening i ABL-kinase domænet[2]
Platelet transfusion	5 831	DRG: 19PR01	Transfusion af plasma og/eller behandlet blod[1]

1-DRG takster 2022 [70]
2-Klinisk biokemisk afdeling, Rigshospitalet København
3-Interaktiv DRG code - https://interaktivdrg.sundhedsdata.dk/#/ [69]
4-LMV priser [71]
5-Rigshospitalets Labportal Klinisk biokemisk afdeling - Metodeliste (rh.dk) [68]

Table 35 Total health state costs per cycle

	Health state	Unit cost per 3 months (DKK)
CML-CP	On 3L treatment	[redacted]
	Off 3L treatment	[redacted]
	Post allo-SCT - Relapse-free	[redacted]
	Post allo-SCT - Relapsed	[redacted]
Progressed disease	AP	[redacted]
	BP	[redacted]
	Post allo-SCT - Relapse-free	[redacted]
	Post allo-SCT - Relapsed	[redacted]

The high costs in the accelerated phase, blast phase and post allo-SCT - Relapsed are driven by the higher number of hospital days and necessary blood transfusions.

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Terminal care cost

As no data are available on end-of-life care costs for CML-CP patients, we used an already submitted end-of-life cost estimation done in 2020 for mMCC and approved by Medicinrådet. [73]

An average cost of end-of-life care for terminal cancer patients was obtained from literature [74]. As this publication reports end of life care costs across four cancer types (breast, colorectal, lung, and prostate), the average was taken across the reported costs.

The costs included in the "Baggrund for Medicinrådets anbefaling vedrørende avelumab til behandling af metastatisk Merkelcellekarcinom (mMCC)" is inflated to 2022 prices (2,2% inflated from 2020).

Costs for terminal care applied in the model is 73 557,04 DKK

9.5 Results

9.5.1 Base case overview

Table 36 Base case overview

Comparator	Bosutinib
Type of model	Partitioned survival model
Time horizon	40 years (lifetime)
Treatment line	3rd line. Previously treated with two or more TKIs.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in ASCEMBL for 3rd line patients only [44]. Danish population weights were used to estimate health-state utility values for 3rd line patients. For patients in later line treatment literature was used to evaluate quality of life.
Included costs	Medication acquisition costs Adverse events costs Disease monitoring costs Allo-SCT costs Subsequent treatment (all health state after third line) costs Disease management costs Terminal care costs
Dosage of pharmaceutical	Based on: 80mg daily for asciminib 500mg daily for bosutinib
Mean treatment duration: Parameterization in CML-CP on 3rd line TTD using a Log-Logistic distribution	Asciminib: [redacted] months Bosutinib: [redacted] months
Mean OS from discontinuation of 3rd line treatment	Asciminib: 3,5 years Bosutinib: 3,5 years
Average time spent in AP phase	Asciminib: 7,2 months Bosutinib: 8 months
Average time spent in BP phase	Asciminib: 6,6 months Bosutinib: 7,5 months
Parametric function for OS: Parameterization curves of expected survival time on AP, BP and off 3rd line treatment added to the TTD curve	Asciminib: [redacted] months Bosutinib: [redacted] months

9.5.2 Base case results

Table 37 Base case results

Per patient	Intervention	Comparator	Difference
Life years gained			
Total life years gained	[redacted]	[redacted]	[redacted]
CP On Treatment	[redacted]	[redacted]	[redacted]
CP Off Treatment	[redacted]	[redacted]	[redacted]
AlloSCT RF	[redacted]	[redacted]	[redacted]
AlloSCTRel	[redacted]	[redacted]	[redacted]
AP	[redacted]	[redacted]	[redacted]
BP	[redacted]	[redacted]	[redacted]
AlloSCT RF	[redacted]	[redacted]	[redacted]
AlloSCTRel	[redacted]	[redacted]	[redacted]
QALYs			
Total QALYs	[redacted]	[redacted]	[redacted]
CP On Treatment	[redacted]	[redacted]	[redacted]
CP Off Treatment	[redacted]	[redacted]	[redacted]
AlloSCT RF	[redacted]	[redacted]	[redacted]
AlloSCTRel	[redacted]	[redacted]	[redacted]
AP	[redacted]	[redacted]	[redacted]
BP	[redacted]	[redacted]	[redacted]
AlloSCT RF	[redacted]	[redacted]	[redacted]
AlloSCTRel	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Costs			
Total costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug monitoring costs	[redacted]	[redacted]	[redacted]
SCT costs	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Incremental results		Intervention vs. Comparator	
ICER (per QALY)		[redacted]	

9.6 Sensitivity analyses

9.6.1 Deterministic sensitivity analyses

A one-way sensitivity analysis was performed to evaluate the sensitivity of the ICER to model parameters. Each parameter was varied using lower and upper bounds based on either:

- ±10 % of the mean value
- or 95 % CI
- or user defined inputs

Table 38 presents the lower and upper bounds used in the univariate sensitivity analysis along with the base values for the comparison of asciminib and bosutinib. Impacts on the ICER are also presented. The sensitivity analysis is also summarized as a tornado diagram (Figure 14) to highlight the variables that had the most impact on the ICER. As expected with a novel therapy, the ICER is quite sensitive to the drug cost of asciminib.

Table 38 One-way sensitivity analyses results

	Base	Low	High	Low			High		
				Inc. Costs	Inc. QALYs	ICER	Inc. Costs	Inc. QALYs	ICER
Base case						[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean time in AP health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean time in BP health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% who move to SCT - On discontinuation of 3L treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% who move to SCT - On progression to accelerated phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% who move to SCT - On progression to blast crisis phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib - Post Discontinuation Survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib - Post Discontinuation Survival	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost - Asciminib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost - Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asciminib - Monitoring cost per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosutinib - Monitoring cost per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs - CP on 3L treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs - CP off 3L treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs - CP AlloSCT Relapse Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs - CP AlloSCT Relapsed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs - AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs - BP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs - PD AlloSCT Relapse free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Base	Low	High	Low			High		
				Inc. Costs	Inc. QALYs	ICER	Inc. Costs	Inc. QALYs	ICER
Disease management costs - PD AlloSCT Relapsed	[redacted]								
Terminal care cost	[redacted]								
Asciminib - adverse event costs	[redacted]								
Bosutinib - adverse event costs	[redacted]								
Asciminib - Subsequent treatment costs - CP	[redacted]								
Bosutinib - Subsequent treatment costs - CP	[redacted]								
Asciminib - Subsequent treatment costs - PD	[redacted]								
Bosutinib - Subsequent treatment costs - PD	[redacted]								
Asciminib - Subsequent treatment costs - SCT in CP - Relapsed	[redacted]								
Asciminib - CP on 3L treatment Utility	[redacted]								
Asciminib - CP off 3L treatment Utility	[redacted]								
CP AlloSCT Relapse Free Utility	[redacted]								
CP AlloSCT Relapsed Utility	[redacted]								
AP Utility	[redacted]								
BP Utility	[redacted]								
PD AlloSCT Relapse free Utility	[redacted]								
PD AlloSCT Relapsed Utility	[redacted]								
Bosutinib - CP on 3L treatment Utility	[redacted]								
Bosutinib - CP off 3L treatment Utility	[redacted]								

Figure 14 Tornado diagram, incremental ICER

[redacted]

9.6.2 Probabilistic sensitivity analyses

For the base-case scenario, a probabilistic sensitivity analysis (PSA) was performed to evaluate the impact of uncertainty associated with model parameters. New parameter values were sampled from the distributions for efficacy, safety, utility, and costs with 1,000 iterations run to allow for uncertainty in model parameters to be accounted for. Mean incremental costs along with cost components, incremental QALYs along with health state QALYs and ICERs were calculated.

The resulting cost-effectiveness plane is presented in Figure 15. The results of the PSA cluster relatively well together. The PSA results were also used to calculate cost-effectiveness acceptability curves presented in Figure 16. The various distributions used for the PSA are presented in appendix J (Table 58).

The mean ICER result from the PSA is DKK [redacted] closely mimicking the ICER of DKK [redacted] resulting from the deterministic analysis.

Figure 15 Cost effectiveness plane with 1 000 iterations

Figure 16 Cost-effectiveness acceptability curve

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9.6.3 Scenario Analysis

11 scenarios were run with deterministic methodology. The default parameters and revised parameter values are shown in Table 39. Total cost and QALYs for both the arms and the ICER for various scenarios are presented in Table 40.

Table 39 Input parameters for scenario analysis

Parameter	Default	1	2	3	4	5	6	7	8	9	10	11
Discount rate 1 - Costs	4%				0%	4%						
Discount rate 2 - Costs	3%				0%	4%						
Discount rate 1 - QALYs	4%				0%	4%						
Discount rate 2 -QALYs	3%				0%	4%						
Discount rate 1 - LYs	4%				0%	4%						
Discount rate 2 - LYs	3%				0%	4%						
Asciminib distribution for treatment duration	Log-logistic	Weibull	Gompertz	Lognormal								
Bosutinib distribution for treatment duration	Log-logistic	Weibull	Gompertz	Lognormal								
Mean time in AP health state	8,00							15,00				
Mean time in BP health state	7,50								9,00			
% who move to SCT - On discontinuation of 3L treatment	10,0%									0,0%	25,0%	
% who move to SCT - On progression to accelerated phase	25,0%									0,0%	30,0%	
% who move to SCT - On progression to blast crisis phase	15,0%									0,0%	45,0%	
Asciminib - Post Discontinuation Survival	3,50						7					
Bosutinib - Post Discontinuation Survival	3,50						7					
Bosutinib daily dosage CP	500											400

Table 40 Scenario results - asciminib vs bosutinib in DKK

Scenario	Asciminib		Bosutinib		Incremental		ICER
	Total costs	Total QALYs	Total costs	Total QALYs	Costs	QALYs	
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10. Budget impact analysis

Number of patients

The number of patients is based on the estimates as discussed in chapter 5.1.6.

Table 41 Number of patients expected to be treated over the next five-year period - if Scemblix is introduced

	Year 1 cumulative	Year 2 cumulative	Year 3 cumulative	Year 4 cumulative	Year 5 cumulative
Scemblix	5	10	15	20	25
Bosulif	1	2	3	4	5
Total number of patients	6	12	18	24	30

Table 42 Number of patients expected to be treated over the next five-year period - if Scemblix is NOT introduced

	Year 1 cumulative	Year 2 cumulative	Year 3 cumulative	Year 4 cumulative	Year 5 cumulative
Scemblix	0	0	0	0	0
Bosulif	6	12	18	24	30
Total number of patients	6	12	18	24	30

Expenditure per patient

The average drug expenditure per patient is based on the results from the health economic model. Prices used are in Apotekets indkøbspris and undiscounted (DKK). Year 1 cost consists of the cumulative drug costs for the first 12 months in the model. Year 2 cost consists of the cumulative drug costs for the next 12 months, and so on for years 3-5.

Table 43 Costs per patient per year (DKK) - if Scemblix is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Scemblix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosulif	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 44 Costs per patient per year (DKK) - if Semblix is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Scemblix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bosulif	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 45 Expected budget impact of recommending the pharmaceutical for the current indication (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Other related costs in the specialist health services	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minus:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Other related costs in the specialist health services	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As can be seen from Table 45, the budget impact of this recommendation is minor. To further reduce uncertainty, we have assumed that 83% (5 of 6 eligible patients) of all eligible patients are treated with asciminib, while in a real-world clinical setting, some patients will not receive asciminib like the T315i mutated patients.

In conclusion, asciminib have demonstrated a superior efficacy vs. bosutinib in a head-to-head clinical trial, and the health economic model shows that asciminib is cost-effective, given the severity of the disease. The budget impact of this recommendation is estimated to be low.

11. Discussion on the submitted documentation

Danish clinical expert has stated that there is an unmet need for a novel efficacious therapy amongst patients intolerant or resistant to existing TKIs on the market [6]. These patients have a drastically shorter expected lifespan than the average CML patient. The 8-year probability of survival decreases from 83 % for first line patients to just 22 % for third line patients [47]. Asciminib was developed to adress the shortcomings of existing TKIs.

In the ASCEMBL trial the proportions of patients that achieved a major molecular response at 96 weeks was 37,58 % and 15,79 % for asciminib and bosutinib, respectively. MMR is an established endpoint in CML and it has been shown

that MMR correlates with survival [29]. Additionally, asciminib demonstrated a better safety profile than bosutinib, which is likely to impact both quality of life and overall survival due to better tolerability and adherence. However these clinically meaningful benefits are challenging to encapsulate in to QALYs and OS through the health economic model, due to the nature of the disease. Well-treated CML patients have low mortality rates and have a survival rate comparable to the general population. Both study cross-over (patients in the bosutinib-arm could get subsequent treatment, e.g. asciminib) and the fact that clinical trial patients tend to experience less co-morbidities and better overall health than in the real world setting, may have contributed to challenges in demonstrating meaningful OS benefits. Consequently, it remains challenging to demonstrate significant benefits in OS through clinical trials in CML. Based on ASCEMBL trial data (96 week DCO), it was not feasable to establish a causal relationship between MMR and mortality rates in third line CML-CP patients.

However, the ASCEMBL trial demonstrated a substantial improvement in time on treatment with asciminib compared to bosutinib (median treatment duration of 81 weeks and 50 weeks at 96 weeks DCO, respectively). This improvement led to a more than twice as large proportion of patients reaching MMR. Due to the aforementioned challenges in demonstrating OS outcomes, TTD was used as a surrogate endpoint to extrapolate OS showing substantial improvements in both QALYs and LYs gained. Novartis is aware of the limitations in using TTD as a surrogate endpoint to model OS. To validate model results, a review of available literature and registries was conducted. Available natural history data on third line CML-CP patients (Swedish CML registry[43]) and Danish clinical expert opinion [6] support the use of the methodology employed for OS extrapolation in this analysis.

According to methodology guideline from MC; Bosutinib is the most relevant comparator to be used in the base case, as this is included in ASCEMBL. This is further supported by local clinical experts, stating that most often other TKIs (Dasatinib and Nilotinib) have been used in 1st and 2nd line. However, to address the issues raised during the dialog meeting with the Medicinrådet, a sensitivity analysis was done based on bosutinib efficacy from ASCEMBL using dasatinib and nilotinib prices. The impact on the result was minimum.

The differences in drug costs between asciminib and bosutinib is to be likely offset by notable gains in efficacy demothroughtrated in the ASCEMBL trial at 96 weeks DCO. Based on clinical trial results from ASCEMBL trial, clinical expert opinion on the unmet need amongst the patient group, the low budget impact and the robust results of the cost-effectiveness analysis indicate that asciminib is a cost effective novel alternative to bosutinib in the Danish clinical setting. Having considered the same uncertainties, asciminib was recommended by NICE in August 2022 [64].

In summary, asciminib appears to demonstrate a cost-effective alternative to bosutinib offering the potential for significant QALY gains in patients for whom bosutinib is still a viable treatment option. Asciminib is an important addition to the available treatments for CML in patients who have already progressed to third or later lines of treatment, offering improved outcomes compared with existing treatment options.

12. List of experts

[redacted] hematologists at Department of Hematology, Rigshospitalet, Denmark

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Appendix A Literature search for efficacy and safety of intervention and comparator(s)

A.1 Search strategy

Relevant studies were identified by searching the following databases through the Ovid platform:
Excerpta Medica dataBASE (Embase),
Medical Literature Analysis and Retrieval System Online (MEDLINE), and
Cochrane Central Register of Controlled Trials (CENTRAL)

Databases were searched using predefined search strategies. Original searches for the SLR were executed on November 9, 2020. The SLR was updated in 2021 (May 13) and in 2022 (January 04). Study design filters recommended by the Scottish Intercollegiate Guidelines Network (SIGN) for Embase and MEDLINE to identify RCTs were slightly modified to also capture single-arm trials and non-randomized studies; furthermore, SIGN filters to capture observational studies were also incorporated into the search strategies for the above mentioned databases. The population terms were adapted from previous systematic reviews/meta-analyses with a focus on patients with CML. The intervention terms included terms related to the generic and brand name of the interventions of interest as well as their Chemical Abstracts Service Registry Number.
Note: For the current SLR update all published records from 2021 till January 4, 2022 were retrieved to overcome the technical limitations of "Date-filter" on OVID platform. The records from 2021 were excluded as duplicates if already captured in previous searches, remaining citations were screened as per the SLR process.

Table 46 Study eligibility criteria for the systematic literature review

Criteria	Description	
Population	*Inclusion criteria:* Adult populations (≥18 years) with CML-CP where ≥75% of patients have prior experience with ≥2 TKIs *Subgroups of interest:* Resistant to prior TKIs Intolerant of prior TKIs Subgroups of patients based on response to prior TKIs *Exclusion criteria:* Patients with CML in advanced phases Studies with mixed population where <75% of patients matched the target population	
Interventions	Any of the following treatments as monotherapy or in combination with other agents:	
	Asciminib Nilotinib Imatinib Dasatinib Bosutinib Radotinib [a]	Ponatinib HQP1351 (olverembatinib) Allo-SCT Homoharringtonine (omacetaxine) Hydoxycarbamide PF-114 [a]
Comparators	Placebo or best supportive care Any intervention of interest	
Outcomes	*Response outcomes* Deep molecular response (MR^4, $MR^{4.5}$, and MR^5) Major molecular response (MMR) Cytogenetic response (e.g. CCyR) Hematological response (e.g. CHR) Time to response Duration of response *Survival outcomes* Overall survival (OS) Progression-free survival (PFS) Event-free survival (EFS)	*Safety outcomes* All-cause AEs (any grade or grade 3/4) Treatment-related AEs (any grade or grade 3/4) Treatment discontinuation due to Aes *Other outcomes* Health Related quality of life measures Time to treatment discontinuation (TTD)

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Criteria	Description
Study design	*Inclusion criteria:* Randomized and non-randomized controlled trials Single-arm trials Phase I trials Dose-ranging, dose-finding, and dose-escalating trials Observational studies *Exclusion criteria:* Editorials Comments Letters Surveys Case studies Reviews Conference abstracts [b]
Language	Only studies published in English will be included
Time	No time restriction

A.2 Systematic selection of studies (e.g. PRISMA chart)

Searches were executed on November 9, 2020, and May 15, 2021 for original SLR and previous update respectively . A total of 12 384 citations were identified through searches of Embase, MEDLINE and CENTRAL, while searches of conference proceedings, hand search of references in published reviews, and provision of the first interpretable results (FIR) report of ASCEMBL, resulted in an additional 461 citations. Of these, 2 791 were removed as duplicates, and the remaining 10 054 citations were screened leading to the exclusion of a further 9 812 citations (including 1 630 with study designs that were not of interest [e.g. meta-analyses, case reports, in vivo/in vitro studies, and cost-effectiveness analysis] and 2 317 that were excluded for "Other" reasons [e.g. conference proceedings, summaries and narrative reviews]).

Of the 236 abstracts that were included for full-text screening, 160 were excluded: 14 as a duplicate publication, another for study design, 76 for population, ten for outcomes, five for interventions and 54 for other reasons (e.g. conference abstracts captured via main searches, letters to the editor). This resulted in 76 citations being included in the evidence base, corresponding to 38 studies. Of the 38 included studies, 13 were only described in conference proceedings, without associated full-text publications.

Searches for the current SLR update were executed on January 4, 2022. A total of 700 citations were identified from Embase, MEDLINE and CENTRAL databases while 10 citations were retrieved from conference proceedings. After removal of 297 records, that were already captured in the SLR, as duplicates, 413 citations were screened. Of these, 351 were excluded and 62 were included for full-text screening. Primary reasons for exclusion included, 125 for population and 203 for study design not of interest (review, case-study, letter and cost-effectiveness studies). At the full-text screening stage, 46 citations were excluded; two as duplicates, 26 for population, 16 for outcomes not of interest and the remaining two citations were excluded for other reasons (workshop, book chapter, letter and conference proceedings). After the current update, the SLR includes a total of 92 citations representing 44 studies. The flow of the study is presented in Figure 17.

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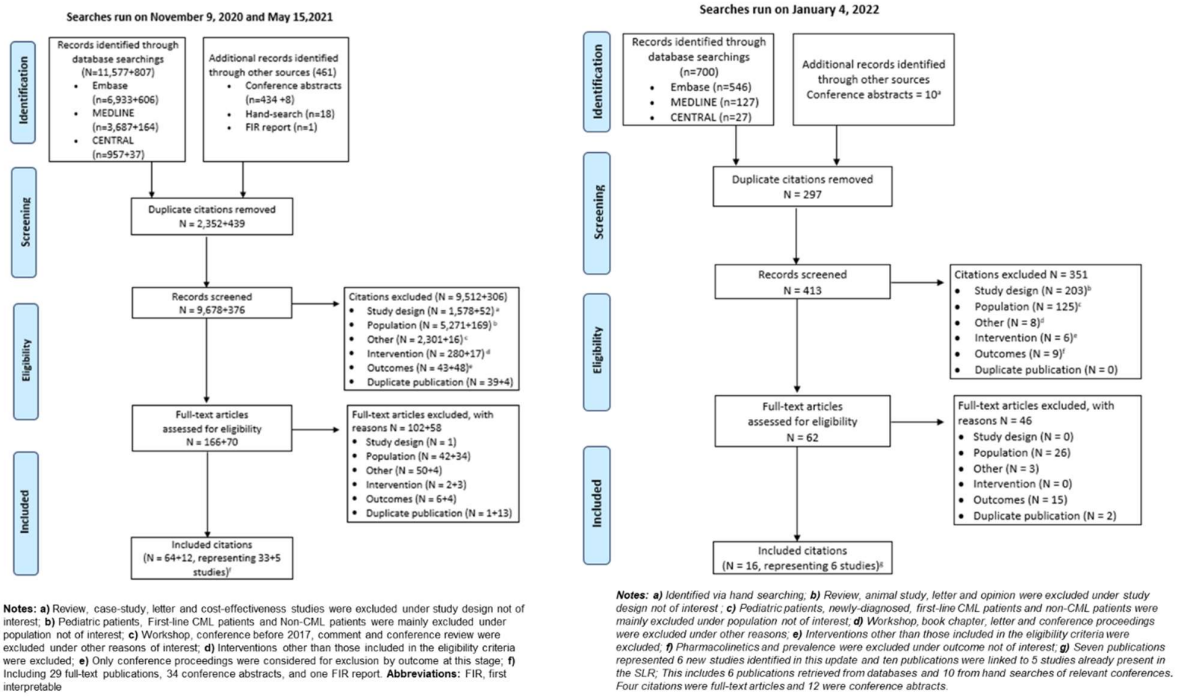
Figure 17 PRISMA diagram



The identified studies reports including Dasatinib and/or Nilotinib as an intervention are presented in Table 47.

Table 47 study characteristic of study report including dasatinib or nilotinib as an intervention

Study	Intervention	Study design	Primary completion date	Study site locations	Exposure to prior regimens
Khan 2017	Ponatinib Bosutinib Dasatinib Nilotinib Imatinib	Observational retrospective study	--	--	Failure to first- or second-line TKIs
Sasaki 2020	Ponatinib Bosutinib Dasatinib Nilotinib Imatinib	Observational retrospective study	--	--	≥2 prior lines of TKI
Giles 2010	Nilotinib	Phase II single-arm trial	--	International	Resistance to or intolerance of imatinib Failure to respond to dasatinib
Tan 2019	Dasatinib	Single-center retrospective chart review	March 2016	China	Failure of imatinib, AND Failure of nilotinib
Rossi 2013	Nilotinib Dasatinib	Multicenter prospective observational study	--	Italy	Failed imatinib, AND Failed dasatinib or nilotinib
Ibrahim 2010	Nilotinib Dasatinib	Single-center prospective observational study	January 2008	United Kingdom	Failed imatinib, AND Failed dasatinib or nilotinib
Ongoren 2017	Nilotinib Dasatinib	Observational retrospective study	--	Turkey	2 prior lines of TKI
Garg 2009	Nilotinib Dasatinib	Observational retrospective study	--	United States	2 prior lines of TKI

Study	Intervention	Study design	Primary completion date	Study site locations	Exposure to prior regimens
Ribeiro 2015	Nilotinib Dasatinib	Observational retrospective study	--	--	2 prior lines of TKI
Garcia-Gutierrez 2012	Nilotinib Dasatinib	Observational retrospective study	--	Spain	2 prior lines of TKI
Gugliotta 2020	Ponatinib, Dasatinib, Nilotinib, Imatinib	Observational retrospective study	--	Italy	0-3 prior TKI
Chitanava 2020	Dasatinib, Nilotinib, Bosutinib, Ponatinib	Observational retrospective study	--	Russia	2 prior TKIs

Table 48 Reported OS/PFS in the included Bosutinib studies

Study	Intervention	Study design	Primary completion date	N	PFS	OS
ASCEMBL	Asciminib	Open-label phase III RCT	October 2021 (estimated)	157	Not reached	Not reached
	Bosutinib			76	Not reached	Not reached
Khoury 2012	Bosutinib	Phase II single-arm trial	March 2010	119	Not reached	Not reached
BYOND	Bosutinib	Phase IV single-arm trial	September 2021 (estimated)	110	--	Not reached
Garcia-Gutierrez 2019	Bosutinib	Multicenter retrospective chart review	January 2016	62	Not reached	--
Takahashi 2017	Bosutinib	Open-label phase I/II single-arm trial	June 2015	10	Not reached	--

A.3 Quality assessment

No phase III RCT, which is the gold standard when doing ITC, was identified. Only retrospective observational study was identified.

Appendix B Main characteristics of included studies

ASCEMBL:	**NCT number: NCT03106779**
A Phase 3, Multi-center, Open-label, Randomized Study of Oral ABL001 Versus Bosutinib in Patients With Chronic Myelogenous Leukemia in Chronic Phase (CML-CP), Previously Treated With 2 or More Tyrosine Kinase Inhibitors	
Objective	The purpose of this pivotal study was to compare the efficacy of asciminib (ABL001) and bosutinib in CML-CP previously treated with a minimum of two prior ATP-binding site TKIs.
Publications – title, author, journal, year	"A Phase 3, Open-Label, Randomized Study of Asciminib, a STAMP Inhibitor, vs Bosutinib in CML After ≥2 Prior TKIs." Réa, D., M. J. Mauro, C. Boquimpani, Y. Minami, E. Lomaia, S. Voloshin, A. Turkina, D.-W. Kim, J. F. Apperley, A. Abdo, L. M. Fogliatto, D. D. H. Kim, P. l. Coutre, S. Saussele, M. Annunziata, T. P. Hughes, N. Chaudhri, K. Sasaki, L. Chee, V. García-Gutiérrez, J. E. Cortes, P. Aimone, A. Allepuz, S. Quenet, V. Bédoucha and A. Hochhaus (2021). [48]
Study type and design	Randomized, open-label, active-controlled, multicenter, phase 3 trial. Patients were randomized in a 2:1 ratio to asciminib 40 mg BID or bosutinib 500 mg QD. Randomization was stratified by major cytogenetic response (MCyR) at screening. Patients with documented treatment failure (specifically meeting lack of efficacy criteria adapted from the 2013 ELN recommendations) while on bosutinib treatment were offered the option to switch to asciminib treatment within 96 weeks after the last patient was randomized to the study. Eligible patients were ≥18 years of age, with CML-CP previously treated with ≥2 TKIs.
Sample size (n)	233 patients randomized in a 2:1 ratio (based on a computer-generated randomization list via a Web-based system) to receive either asciminib (ABL001) 40 mg orally twice a day (BID) (Number of patients: 157) or bosutinib 500 mg orally once daily (QD) (Number of patients: 76). Randomization was stratified by MCyR status at baseline

Main inclusion and exclusion criteria	Inclusion criteria: 1. Male or female patients with a diagnosis of CML-CP ≥ 18 years of age 2. Patients must meet all of the following laboratory values at the screening visit: • < 15% blasts in peripheral blood and bone marrow • < 30% blasts plus promyelocytes in peripheral blood and bone marrow • < 20% basophils in the peripheral blood • ≥ 50 x 109/L (≥ 50,000/mm3) platelets • Transient prior therapy related thrombocytopenia (< 50,000/mm3 for ≤ 30 days prior to screening) is acceptable • No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly 3. BCR-ABL1 ratio > 0.1% IS according to central laboratory at the screening examination for patients intolerant to the most recent TKI therapy 4. Prior treatment with a minimum of 2 prior ATP-binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib) 5. Failure (adapted from the 2013 ELN Guidelines Bacarrani 2013) or intolerance to the most recent TKI therapy at the time of screening • Failure is defined for CML-CP patients (CP at the time of initiation of last therapy) as follows. Patients must meet at least 1 of the following criteria. • Three months after the initiation of therapy: No CHR or > 95% Ph+ metaphases • Six months after the initiation of therapy: BCR-ABL1 ratio > 10% IS and/or > 65% Ph+ metaphases • Twelve months after initiation of therapy: BCR-ABL1 ratio > 10% IS and/or > 35% Ph+ metaphases • At any time after the initiation of therapy, loss of CHR, CCyR or PCyR • At any time after the initiation of therapy, the development of new BCR-ABL1 mutations which potentially cause resistance to study treatment • At any time after the initiation of therapy, confirmed loss of MMR in 2 consecutive tests, of which one must have a BCR-ABL1 ratio ≥ 1% IS • At any time after the initiation of therapy, new clonal chromosome abnormalities in Ph+ cells: CCA/Ph+ • Intolerance is defined as: • Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal) • Hematologic intolerance: Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer Exclusion Criteria: 1. Known presence of the T315I or V299L mutation at any time prior to study entry Known second chronic phase of CML after previous progression to AP/BC Previous treatment with a hematopoietic stem-cell transplantation Patient planning to undergo allogeneic hematopoietic stem cell transplantation 2. Cardiac or cardiac repolarization abnormality, including any of the following: • History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG) • Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block) • QTcF at screening ≥450 msec (male patients), ≥460 msec (female patients) • Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:

	• Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia • Concomitant medication(s) with a known risk of Torsades de Pointes per www.crediblemeds.org that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication. • Inability to determine the QTcF interval • Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g. uncontrolled diabetes, active or uncontrolled infection, pulmonary hypertension) • History of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis • History of acute or chronic liver disease • Treatment with medications that meet one of the following criteria and that cannot be discontinued at least one week prior to the start of treatment with study treatment • Moderate or strong inducers of CYP3A • Moderate or strong inhibitors of CYP3A • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of ABL001 and one month after last dose of bosutinib. Highly effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception • Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) total hysterectomy or bilateral tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment • Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject. • Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. • In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. • Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking study medication. In the case of oophorectomy alone, women are considered post-menopausal and not of child bearing potential only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
Intervention	asciminib (ABL001) 40 mg orally twice a day (BID) Number of patients: 157

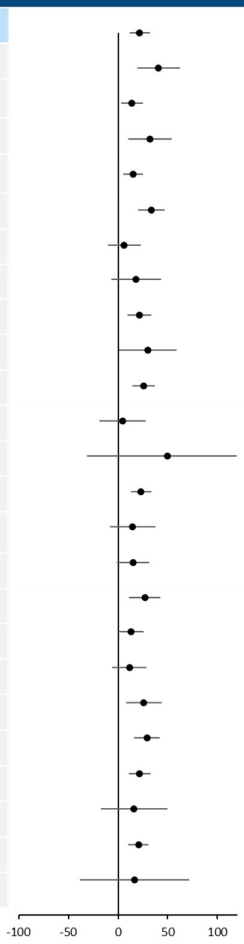
ASCEMBL: A Phase 3, Multi-center, Open-label, Randomized Study of Oral ABL001 Versus Bosutinib in Patients With Chronic Myelogenous Leukemia in Chronic Phase (CML-CP), Previously Treated With 2 or More Tyrosine Kinase Inhibitors	NCT number: NCT03106779
Comparator(s)	bosutinib 500 mg orally once daily (QD) (Number of patients: 76
Follow-up time	The study is ongoing. The median duration of follow-up was 2,3 years from randomization to last contact date.
Is the study used in the health economic model?	*Yes*
Primary, secondary and exploratory endpoints	The primary endpoint of the study was MMR rate at 24 weeks. MMR is defined as BCR ABL1 IS ratio ≤0.1%. The key secondary endpoint is MMR at week 96 while on study treatment, without meeting any treatment-failure criteria before week 96 to compare additional parameters of the efficacy asciminib versus bosutinib. Other secondary endpoints include complete cytogenetic response rates to compare additional parameters of the efficacy of asciminib versus bosutinib. Cytogenic response will include Complete, Partial, Major, Minor, Minimal and no response. Also, time to MMR and duration of MMR, time to CCyR and duration of CCyR, time to treatment failure, progression-free survival, OS, safety and tolerability, and pharmacologic parameters are secondary endpoints in this study. Response rates by a given time point were calculated based on the cumulative rate of patients who achieved a response at any time up to this time point. Response rates at a given time point were calculated based on the number of patients with a response at this time point, regardless of whether they had previously achieved a response. The CCyR endpoint was analyzed only in patients who were not in CCyR at baseline. After randomization, bone marrow assessments were required only if a patient was not in MMR and at the end of treatment. If a patient was in MMR at the same time when a bone marrow assessment was scheduled, as per protocol, CCyR was imputed from MMR on a specific date if there was no valid cytogenetic assessment.
Method of analysis	The Cochrane-Mantel-Haenszel χ^2 test, stratified by the cytogenetic response status (MCyR vs no MCyR) at baseline, was used to compare MMR rates between the treatment groups, at the 5% level of significance (2-sided test). The Mantel-Haenszel estimates of the common risk difference and the corresponding 95% confidence intervals (CIs) are presented, as well as the MMR rates and 95% CIs based on the Pearson-Clopper method, for each treatment arm. The cumulative incidence of MMR was calculated considering discontinuation from study treatment of any reason and without prior achievement of MMR as a competing risk.

ASCEMBL:	NCT number: NCT03106779
A Phase 3, Multi-center, Open-label, Randomized Study of Oral ABL001 Versus Bosutinib in Patients With Chronic Myelogenous Leukemia in Chronic Phase (CML-CP), Previously Treated With 2 or More Tyrosine Kinase Inhibitors	

Subgroup analyses	At Week 96, subgroup analyses continue to demonstrate a consistent treatment effect in favorvof asciminib across major prognostic factors including BCR::ABL1 mutation status at baseline,vreasons for discontinuation of last prior TKI, and number of prior lines of TKI therapy (Figure). The MMR rate at Week 96 was higher in patients on asciminib regardless of baseline cytogenetic response (MCyR or no MCyR) or the detection of BCR::ABL1 mutations. The subgroup analysis by line of therapy of randomized treatment confirmed the benefit of asciminib in heavily pretreated patients. A consistent treatment benefit (MMR rate at Week 96) was observed with asciminib compared to bosutinib whether given as 3rd-line therapy (41.5% vs. 30.0%), 4th-line therapy (36.4% vs. 10.3%), or ≥ 5th-line therapy (29.0% vs. 0%). These results demonstrate the efficacy of asciminib irrespective of the number of previous lines of TKI treatment. The MMR rate at Week 96 was also higher in patients on asciminib regardless of the detection of BCR::ABL1 mutations at baseline. This further supports the superior clinical benefit of asciminib over bosutinib considering that mutations are a common cause of TKI resistance in patients sequentially treated with different TKIs targeting the ATP-binding site [13, 75]. At Week 96, a clinically relevant treatment effect in favor of asciminib is observed in both patients intolerant to last prior TKI (50.9% versus 36.4%, treatment difference of 14.5%) and patients resistant to last prior TKI (30.5% versus 7.4%, treatment difference of 23.1%). Variability in the treatment effect was observed for gender (with a higher difference in MMR rate between asciminib and bosutinib in females than in males) and age (with a higher difference Novartis Confidential Page 64 of 146 in MMR rate between asciminib and bosutinib in patients below 65 years than in patients ≥65 years). The low number of patients with a baseline BCR::ABL1 <1% represents a limitation to interpret the results for this subgroup, however, the difference in MMR rates at Week 96 between asciminib and bosutinib in these patients was consistent with that in the patients with a baseline BCR::ABL1 ≥1%. These results support the clinical benefit of asciminib versus bosutinib in both groups of patients. Overall, the Week 96 efficacy subgroup analyses were consistent with the Week 24 efficacy subgroup analyses further supporting the long-term superior efficacy of asciminib versus bosutinib.

Figure 18 Forest plot of risk difference with 95% CI for MMR rate at 96 weeks from subgroup analysis (FAS)

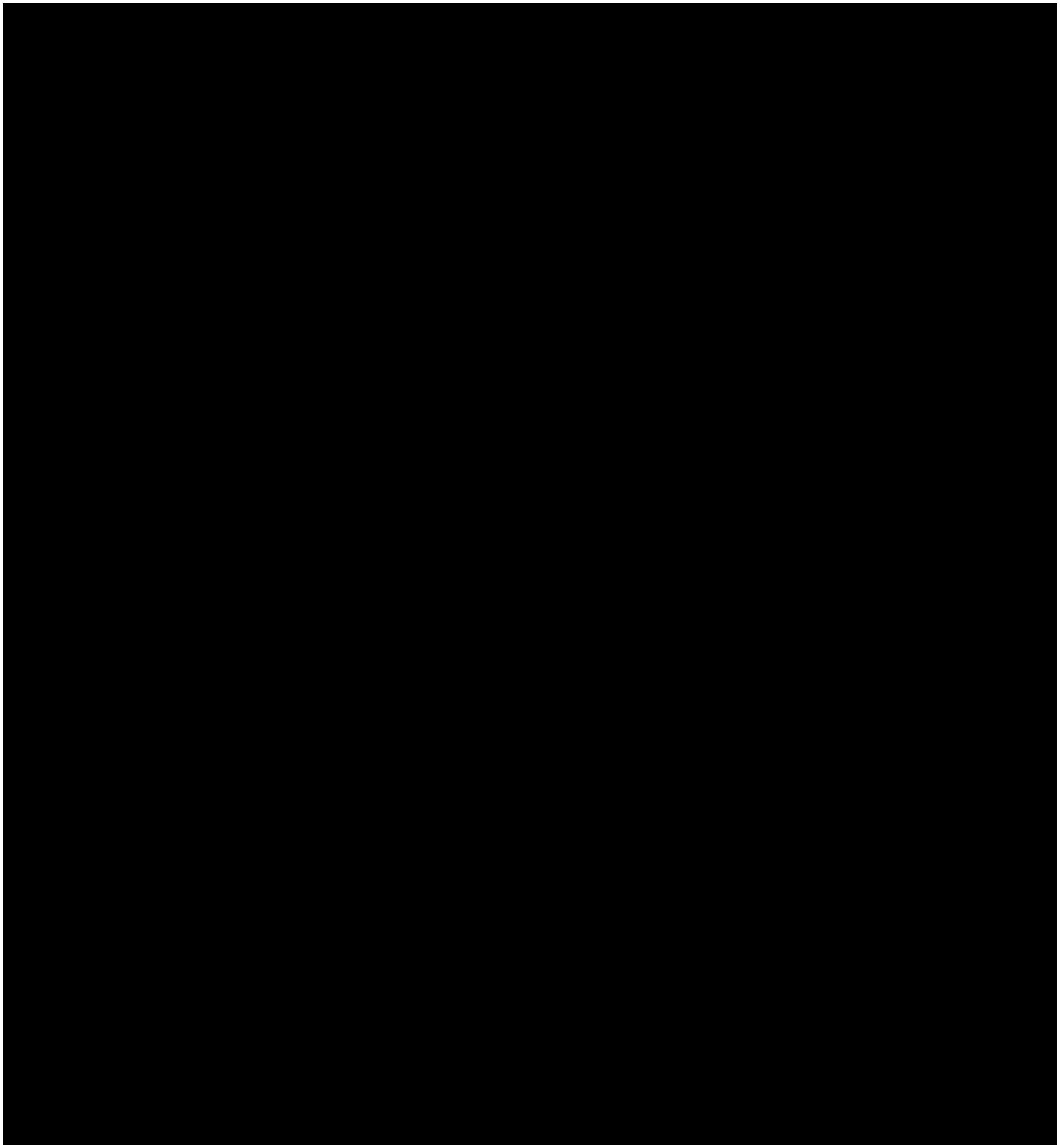
Subgroup	Subgroup	Asciminib n/N (%)	Bosutinib n/N (%)	Risk difference (95% CI)
All subjects	All subjects	59/157 (37.6)	12/76 (15.8)	21.8 (10.6 to 33.0)
Strata based on randomization data	Major cytogenetic response	25/46 (54.4)	3/22 (13.6)	40.7 (20.4 to 61.0)
	No major cytogenetic response	34/111 (30.6)	9/54 (16.7)	14.0 (0.8 to 27.1)
Strata based on CRF data	Major cytogenetic response	32/57 (56.16)	6/25 (24.0)	32.1 (11.0 to 53.3)
	No major cytogenetic response	27/100 (27.0)	6/51 (11.8)	15.2 (2.8 to 27.6)
Sex	Female	30/75 (40.0)	3/45 (6.7)	33.3 (20.1 to 46.6)
	Male	29/82 (35.4)	9/31 (29.0)	6.3 (-12.7 to 25.4)
Race	Asian	8/22 (36.4)	2/11 (18.2)	18.2 (-12.2 to 48.6)
	White	44/118 (37.3)	9/56 (16.1)	21.2 (8.2 to 34.2)
	Others	7/17 (41.2)	1/9 (11.1)	30.1 (-1.1 to 61.2)
Age category	18-65 years	48/128 (37.5)	7/61 (11.5)	26.0 (14.4 to 37.6)
	≥65 years	11/29 (37.9)	5/15 (33.3)	4.6 (-25.1 to 34.3)
	≥75 years	4/4 (100)	1/2 (50.0)	50.0 (-19.3 to 100.0)
Reason for discontinuation on last prior TKI	Failure	29/95 (30.5)	4/54 (7.4)	23.1 (11.5 to 34.7)
	Intolerance	30/59 (50.9)	8/22 (36.4)	14.5 (-9.3 to 38.3)
Number of prior TKI therapies	2	38/89 (42.7)	9/33 (27.3)	15.4 (-2.9 to 33.8)
	3	19/53 (35.9)	3/33 (9.1)	26.8 (10.5 to 43.0)
	≥4	2/15 (13.3)	0/10 (0.0)	13.3 (-3.9 to 30.5)
Line of therapy of randomization treatment	3	34/82 (41.5)	9/30 (30.0)	11.5 (-8.1 to 31.0)
	4	16/44 (36.4)	3/29 (10.3)	26.0 (8.0 to 44.0)
	≥5	9/31 (29.0)	0/17 (0.0)	29.0 (13.1 to 45.0)
BCR-ABL mutation at day 1 of week 1	Unmutated	47/125 (37.6)	10/63 (15.9)	21.7 (9.3 to 34.1)
	Mutated	7/17 (41.2)	2/8 (25.0)	16.2 (-21.9 to 54.2)
BCR-ABL transcript level at baseline	≥1%	49/142 (34.5)	10/72 (13.9)	20.6 (9.4 to 31.8)
	<1%	10/15 (66.7)	2/4 (50.0)	16.7 (-37.8 to 71.2)



n: The number of subjects who responded. N: The total number of subjects in the subgroup and treatment group with response variable defined. 95% Wald CI for Risk Difference. Risk Difference is Asciminib vs Bosutinib.
Strata based on CRF data: patients with missing baseline bone marrow aspirate and baseline BCR::ABL1 levels <=10% were considered in MCyR. BCR::ABL1 ratio at baseline <1%: Protocol amendment 3 allowed the inclusion of subjects intolerant to most recent TKI and BCR::ABL1 ratio > 01%. Disc.: discontinue, basel.: baseline. Patients with T315I and V299L BCR::ABL1 mutations or non-evaluable mutation assessment were excluded from subgroup mutation analysis

Subgroup analyses were performed to assess homogeneity of the treatment effect. A multivariate analysis using a logistic regression was performed to assess the treatment effect after adjusting for important demographic and disease characteristics between treatment groups. Secondary efficacy endpoints are described in the supplemental Appendix. These end points are reported descriptively for both treatment arms and no P values were calculated.

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety



ECOG, Eastern Cooperative Oncology Group; NA, not available. *The number of lines of prior TKI therapy was based on the sequence of treatments. †Lack of efficacy criteria were based on 2013 ELN recommendations (see supplemental Appendix for details). ‡Includes study medication wrongly assigned, lack of efficacy and tolerability, and optimal response not reached after 5 y of treatment. §All patients with BCR-ABL1IS ,1% at baseline were intolerant to the last TKI, except 1 in the asciminib arm (who deviated from the protocol)

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Number of previous TKI treatments in the two treatment arms.

Table 49 Number of prior TKI therapy by arm

[redacted]

Comparability of patients across studies

NA

Comparability of the study populations with Danish patients eligible for treatment

The study population is very much relevant to the Danish patient population for patients having tolerability issues with a previous 2G TKI. According to Danish guideline, ponatinib is reserved to the resistant patient population after 2 or more 2G TKIs.

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Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures [5]

Abbreviation / term	Definition	Meaning	Clinical relevance
CCyR	Complete cytogenetic response	No (or less than 1% of) cells in the bone marrow have the Philadelphia chromosome.	In line with ELN guideline (2020) and with Danish guideline [5, 24]
CMR	Complete Molecular Response	The PCR test does not find the BCR-ABL gene.	
DMR	Deep molecular response	A deep molecular response is commonly defined as BCR-ABL1 values of ≤0.01% IS, where Is described as various BCR-ABL1 cutoff values, where molecular response 4 (MR4) is ≤0.01% IS, MR4.5 ≤0.0032% IS, and MR5 <0.001%	
MCyR	Major cytogenetic response	No more than 35% of the cells in the bone marrow have the Philadelphia chromosome.	
MMR	Major molecular response	The amount of BCR-ABL gene in your blood or bone marrow is 1/1000th (or less) of what's expected in someone with untreated CML.	
MR	Molecular response	It is based on how much of the BCR-ABL gene (which is found in CML cells) can be detected by the PCR test. This test can be done on either your blood or bone marrow.	
PCyR	Partial cytogenetic response	Between 1% and 35% of the cells in the bone marrow still have the Philadelphia chromosome.	
TFR	Treatment-free remission	is achieved when a patient who has discontinued TKI therapy maintains a major molecular response (MMR) and does not need to restart therapy.	

Figure 19 Definition of the CML treatment level response

	Optimal response	Warning	Treatment failure
Baseline	NA	High Risk or CCA/Ph+, major route	NA
3 months	*BCR-ABL1*^{IS} ≤ 10% and/or Ph+ ≤ 35%	*BCR-ABL1*^{IS} > 10 % and/or Ph+ 36–95 %	Non-CHR and/or ph+ > 95 %
6 months	*BCR-ABL1*^{IS} < 1 % and/or Ph+ 0 % (CCyR)	*BCR-ABL1*^{IS} 1–10 % and/or Ph+ 1–35 %	*BCR-ABL1*^{IS} > 10 % and/or Ph+> 35 %
12 months	*BCR-ABL1*^{IS} ≤ 0,1 %	*BCR-ABL1*^{IS} > 0,1–1 %	*BCR-ABL1*^{IS} > 1 % and/or Ph+ > 0 %
Then, and at any time	*BCR-ABL1*^{IS} ≤ 0,1%	CCA/Ph- (-7 or 7q-)	Loss of CHR
			Loss of Ccyr
			Confirmed loss of MMR
			Mutations
			CCA/Ph+

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Results per study

All data used in the analysis are from 96 weeks data cut-off. 24- and 48-weeks data cut-off are only given as information

Table 50 Efficacy results in patients treated with two or more tyrosine kinase inhibitors (ASCEMBL)

	At time points *		By time points**	
	Asciminib N=157	Bosutinib N=76	Asciminib N=157	Bosutinib N=76
Week 24				
Response rate, % (95% CI)[1]	25,5 (18,87; 33,04)	13,2 (6,49; 22,87)	27,4 (20,58; 35,07)	14,5 (7,45; 24,42)
Un-stratified difference in response rate (vs. bosutinib) (%), 95% CI[2]	12,3 (2,11; 22,53)		12,9 (2,37; 23,46)	
Common risk difference (%), 95% CI[3]	12,2 (2,19; 22,30)		12,9 (2,40; 23,29)	
CMH test p-value[4]	0,029		0,027	
Week 48				
Response rate, % (95% CI)[1]	29,3 (22,32; 37,08)	13,2 (6,49; 22,87)	35,0 (27,60; 43,04)	19,7 (11,49; 30,46)
Un-stratified difference in response rate (vs. bosutinib)	16,1 (5,73; 26,55)		15,3 (3,64; 26,95)	
Common risk difference (%),	16,1 (5,69; 26,49)		15,2 (3,65; 26,83)	
CMH test p-value[4]	0,007		0,16[4]	
Week 96				
Response rate, % (95% CI)[1]	37,6 (29,99; 45,65)	15,8 (8,43; 25,96)	42,7 (34,83; 50,81)	23,7 (14,68; 34,82)
Un-stratified difference in response rate (vs. bosutinib)	21,8 (10,63; 32,95)		18,99 (6,69; 31,29)	
Common risk difference (%),	21,7 (10,53; 32,95)		18,9 (6,61; 31,25)	
CMH test p-value[4]	0,001		0,005	

[1]Pearson-Clopper 95% 2-sided CI
[2]Wald 95% 2-sided CI
[3]The common risk difference after adjusting for stratum: major baseline cytogenetic response status (based on randomization data) and its 95% CI were estimated using the Mantel-Haenszel method
[4]CMH 2-sided test was stratified by baseline major cytogenetic response status based on randomization data. Nominal p-values are presented for descriptive purpose only except for the 24-week and 96-week "AT" time points.
*At the time point = Value occurred at the exact time.
**By the time = Value occurred any time before the time you are talking about and up to X time

Table 51 Analysis sets (all randomized patients; 24-week, 48-week, and 96-week analysis)

Analysis sets, n (%)	24-week analysis (data cut-off May 25, 2020)			48-week analysis (data cut-off January 06, 2021)			96-week analysis (data cut-off October 06, 2021)		
	Asciminib (N=157)	Bosutinib (N=76)	All patients (N=233)	Asciminib (N=157)	Bosutinib (N=76)	All patients (N=233)	Asciminib (N=157)	Bosutinib (N=76)	All patients (N=233)
Full analysis set	157 (100.0)	76 (100.0)	233 (100.0)	157 (100.0)	76 (100.0)	233 (100.0)	157 (100.0)	76 (100.0)	233 (100.0)
Safety set	156 (99.4)	76 (100.0)	232 (99.6)	156 (99.4)	76 (100.0)	232 (99.6)	156 (99.4)	76 (100.0)	232 (99.6)
PAS	149 (94.9)	NA	NA	-	-	-	-	-	-
MMR responder set	54 (34.4)	14 (18.4)	68 (29.2)	62 (39.4)	18 (23.7)	80 (34.3)	69 (43.9)	18 (23.7)	87 (37.3)
CCyR analysis set	103 (65.6)	62 (81.6)	165 (70.8)	103 (65.6)	62 (81.6)	165 (70.8)	103 (65.6)	62 (81.6)	165 (70.8)

CCyR responder set	44 (28.0)	19 (25.0)	63 (27.0)	49 (31.2)	22 (28.9)	71 (30.5)	51 (32.5)	22 (28.9)	73 (31 .3)
Switch analysis set	NA	22 (28.9)	NA	NA	24 (31.6)	NA	NA	24 (31 .6)	NA
MMR responders Switch analysis set	-	-	-	-	-	-	NA	0	NA
CCyR Switch analysis set	-	-	-	-	-	-	NA	24 (31 .6)	NA
CCyR responders Switch analysis set	-	-	-	-	-	-	NA	4 (5.3)	NA
MR2 Analysis set	-	-	-	-	-	-	142 (90.4)	72 (94.7)	214 (91 .8)
MR2 Responder set	-	-	-	-	-	-	78 (49.7)	24 (31 .6)	102 (43.8)
MR2 Switch analysis set	-	-	-	-	-	-	NA	24 (31 .6)	NA
MR2 responders Switch analysis set	-	-	-	-	-	-	NA	2 (2.6)	NA

CCyR: Complete cytogenetic response; MR: Molecular response, MMR: Major molecular response; PAS: Pharmacokinetic analysis set

Table 52 Patient disposition (FAS) (24-week, 48-week, and 96-week analysis)

Patients, n (%)	24 week analysis (data cut-off May 25, 2020)			48-week analysis (data cut-off January 06, 2021)			96-week analysis (data cut-off October 06, 2021)		
	Asciminib (N=157)	Bosutinib (N=76)	All patients (N=233)	Asciminib (N=157)	Bosutinib (N=76)	All patients (N=233)	Asciminib (N=157)	Bosutinib (N=76)	All patients (N=233)
Patients randomized	**157**	**76**	**233**	**157**	**76**	**233**	**157**	**76**	**233**
Treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not treated*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment ongoing**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from treatment	**59 (37.6)**	**54 (71.1)**	**113 (48.5)**	**67 (42.7)**	**59 (77.6)**	**126 (54.1)**	**72 (45.9)**	**61 (80.3)**	**133 (57.1)**
<Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥Week 24 and <week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥Week 48 and <week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for discontinuation									
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AEs	[redacted]								
Patient/guardian decision	[redacted]								
Death	[redacted]								
Lost to follow-up	[redacted]								
Progressive disease	[redacted]								
Protocol deviation	[redacted]								

*Reasons for not being treated: Physician decision

**Ongoing at the time of respective data cut-off dates

Table 53 Reasons for discontinuations at different time points (24-week analysis and 48-week update analysis)

Patients, n (%)	<Week 24		≥Week 24 and <week 48		≥Week 48 and <week 96	
	Asciminib (N=157)	Bosutinib (N=76)	Asciminib (N=157)	Bosutinib (N=76)	Asciminib (N=157)	Bosutinib (N=76)
24-week analysis (data cut-off date May 25, 2021)						
AEs	[redacted]					
Lack of efficacy	[redacted]					
Physician decision	[redacted]					
Patient/guardian decision	[redacted]					
Progressive disease	[redacted]					
Death	[redacted]					
Protocol deviation	[redacted]					
Lost to follow-up	[redacted]					
48-week update analysis (data cut-off date January 06, 2021)						
AEs	[redacted]					
Lack of efficacy	[redacted]					
Physician decision	[redacted]					
Patient/guardian decision	[redacted]					
Progressive disease	[redacted]					
Death	[redacted]					
Protocol deviation	[redacted]					
Lost to follow-up	[redacted]					
96-week analysis (data cut-off date October 06, 2021)						
AEs	[redacted]					
Lack of efficacy	[redacted]					
Physician decision	[redacted]					
Patient/guardian decision	[redacted]					
Progressive disease	[redacted]					
Death	[redacted]					
Protocol deviation	[redacted]					
Lost to follow-up	[redacted]					

Handling of data in the analyses

Handling of missing values/censoring/discontinuations

Primary endpoint

Patients with missing PCR evaluations at 24 weeks were considered as non-responders. However, if the 24-week PCR evaluation was missing, but both a PCR evaluation at 16 weeks and a PCR evaluation at 36 weeks indicated MMR, the 24-week assessment was imputed as 'Response', assuming that MMR was maintained between 16 and 36 weeks.

Secondary endpoints

- MMR rates at specific time points: Patients discontinuing the randomized treatment prior to a specific time point due to any reason or patients without an available assessment at that time point were considered as non-responders for that time point.
- CCyR rates at specific time points: Patients discontinuing the randomized treatment prior to a specific time point due to any reason were considered as non-responders for that time point.
- MMR/CCyR rates by specific time points: Patients without any documented response for which an evaluable response assessment was never provided were considered as non-responders for the period of time up to that time point.
- Molecular/cytogenetic response at specific time points: The category "Missing" was assigned to:
    - Ongoing cases, i.e. patients without an evaluable response assessment at the specific time point who have not discontinued study treatment before that time point.
    - Discontinued due to lack of efficacy/progressive disease/death prior to a specific time point.
    - Discontinued due to other reasons prior to a specific time point.
- Molecular/cytogenetic response category by specific time points: The category "Missing" was assigned to patients for whom an evaluable response assessment was never provided.
- Time to MMR/CCyR: For patients in the FAS/CCyR analysis set who did not experience any MMR/CCyR, the time was censored as follows in the Kaplan-Meier analysis:
    - If a patient did not achieve the specified response before the cut-off date for the analysis, censoring time was the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.
    - If a patient experienced treatment failure prior to achieving a response without discontinuing study treatment, then the patient was censored at the last molecular assessment (PCR) date on treatment prior or on the treatment failure date.
    - If a patient discontinued study treatment prior to achieving a response for a reason other than disease progression or death, then the patient was censored at the last molecular assessment (PCR) date on treatment prior to the cut-off date or the EoT visit, whichever comes first.
    - If a patient discontinued study treatment prior to achieving a response due to progression or death, then the censoring time was set to the longest follow-up time in the treatment group.
    - In case no on-treatment response assessment was performed, the patient was censored at Day 1.
- Duration of MMR/CCyR: For patients in the MMR responder set/ CCyR responder set who have not experienced any event (loss of MMR/CCyR, progression to AP/BC, or CML-

related death), the duration was censored at the last molecular assessment (PCR) indicating MMR/or the last cytogenetic assessment date on treatment.

- TTF: For patients in the FAS who had not reached treatment failure, their TTFs were censored at the time of their last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date.
- PFS: For patients who had not experienced an event (disease progression to AP/BC or death from any cause), their PFS times was censored at the date of last study assessment (PCR, cytogenetic, hematologic or extramedullary) before the cut-off date, regardless of subsequent intake of treatment(s) after randomization.
- OS: Patients who were alive at the time of the analysis data cutoff date were censored at the date of last contact before the cut-off date, regardless of subsequent intake of treatment(s) after randomization.

Calculation of treatment discontinuation

Treatment discontinuation is calculated as the number of patients with ≥1 event divided by number of treated patients (Asciminib (N=156), Bosutinib (N=76)). In ASCEMBL study number of patients treated with asciminib and analysed is 157, where one patient has been excluded from the safety analysis (he developed cytopenia after randomization and was not treated with asciminib), that's why n=156 for treatment discontinuation.

Preferred term	24-week analysis (Data cut-off May 25, 2020)				96-week analysis (Data cut-off October 06, 2020)			
	Asciminib (N=156)		Bosutinib (N=76)		Asciminib (N=156)		Bosutinib (N=76)	
	All grades	Grade ≥3, n	All grades,	Grade ≥3, n (%)	All grades, n	Grade ≥3, n (%)	All grades, n	Grade ≥3, n (%)
Number of patients with ≥1 event	9 (5.8)	8 (5.1)	16 (21.1)	12 (15.8)	12 (7.7)	12 (7.7)	20 (26.3)	15 (19.7)

Appendix E Safety data for intervention and comparator(s)

The side effect frequencies used in our analysis are not based on the adjusted incidence but on the overall incidence.

Overview of adverse events

	Primary Analysis Results (Data cut-off: 25-May-2020)				Key secondary endpoint analysis Results (Data cut-off: 6-Oct-2021)			
	Asciminib 40mg BID N=156		Bosutinib 500mg QD N=76		Asciminib 40mg BID N=156		Bosutinib 500mg QD N=76	
Category, n(%)	All grades	Grade >=3	All grades	Grade >=3	All grades	Grade >=3	All grades	Grade >=3
Adverse events	140 (89.7)	79 (50.6)	73 (96.1)	46 (60.5)	142 (91.0)	88 (56.4)	74 (97.4)	52 (68.4)
SAEs	21 (13.5)	16 (10.3)	14 (18.4)	12 (15.8)	28 (17.9)	22 (14.1)	20 (26.3)	18 (23.7)
Fatal AEs	2 (1.3)	2 (1.3)	1 (1.3)	1 (1.3)	2 (1.3)	2 (1.3)	1 (1.3)	1 (1.3)
AEs leading to discontinuation*	9 (5.8)	8 (5.1)	16 (21.1)	12 (15.8)	12 (7.7)	12 (7.7)	20 (26.3)	15 (19.7)

*Most common AEs leading to treatment discontinuation (no changes since primary analysis): thrombocytopenia and neutropenia in 5 (3.2%) and 4 (2.6%) patients, respectively, on asciminib; increased ALT and neutropenia in 4 (5.3%) and 3 (3.9%) patients, respectively, on bosutinib.

Median duration of exposure with asciminib was 103.1 weeks (min-max: 0.1-201.1) vs 30.5 weeks (min-max: 1.0-188.3) for bosutinib.

No patients with fatal outcomes since primary analysis cut-off.

Most frequent all-grade AEs (occurring in ≥10% of patients in any treatment arm)

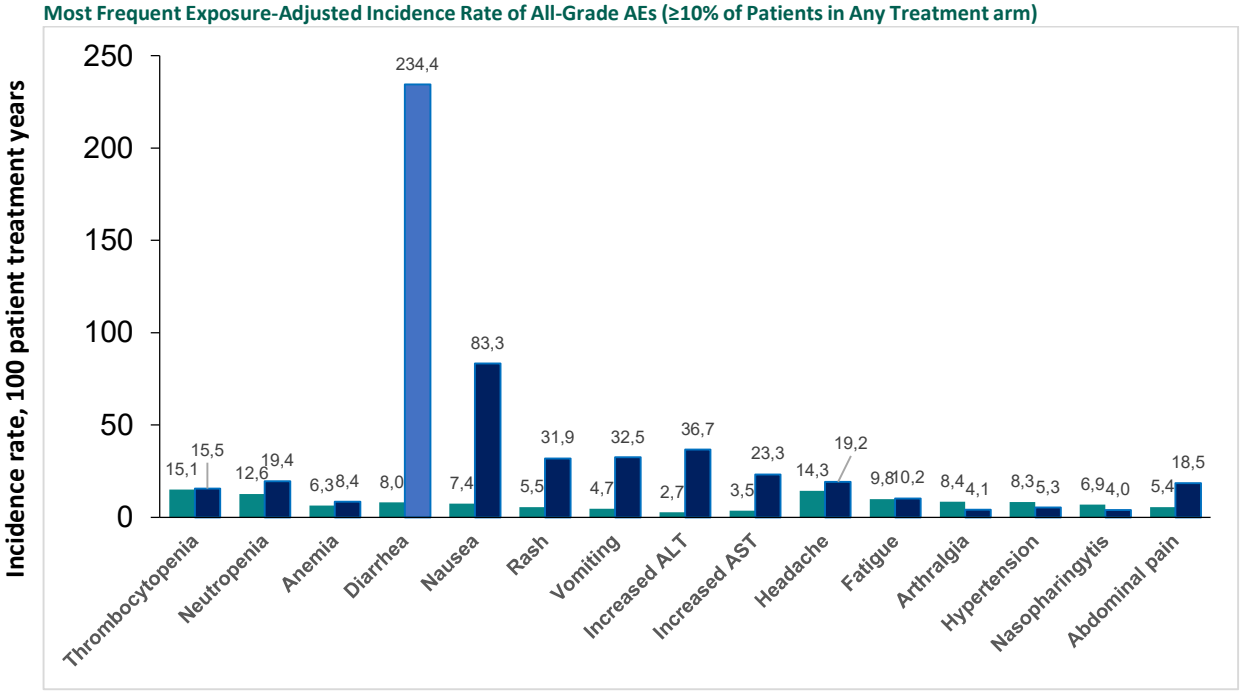
Key secondary endpoint analysis

Most frequent AEs recorded in the ASCEMBL study at the time of 96-week

Preferred term	AsciminibN=156 All grades n (%)	Grade >=3n (%)	Bosutinib N=76 All grades n (%)	Grade >=3 n (%)
Number of subjects with at least one event	**142 (91,0)**	**88 (56,4)**	**74 (97,4)**	**52 (68,4)**
Thrombocytopenia	36 (23,1)	28 (17,9)	11 (14,5)	5 (6,6)
Headache	31 (19,9)	3 (1,9)	12 (15,8)	0
Neutropenia	30 (19,2)	24 (15,4)	13 (17,1)	9 (11,8)
Fatigue	23 (14,7)	1 (0,6)	7 (9,2)	1 (1,3)
Hypertension	21 (13,5)	10 (6,4)	4 (5,3)	3 (3,9)
Arthralgia	20 (12,8)	1 (0,6)	3 (3,9)	0
Diarrhoea	20 (12,8)	0	55 (72,4)	8 (10,5)
Nausea	18 (11,5)	1 (0,6)	35 (46,1)	0
Nasopharyngitis	17 (10,9)	0	3 (3,9)	0
Anaemia	16 (10,3)	2 (1,3)	6 (7,9)	3 (3,9)
Abdominal pain	14 (9,0)	0	12 (15,8)	1 (1,3)
Pain in extremity	14 (9,0)	1 (0,6)	5 (6,6)	0
Rash	14 (9,0)	0	18 (23,7)	3 (3,9)
Asthenia	13 (8,3)	0	1 (1,3)	0
Cough	13 (8,3)	0	5 (6,6)	0
Back pain	12 (7,7)	1 (0,6)	3 (3,9)	1 (1,3)
Vomiting	12 (7,7)	2 (1,3)	20 (26,3)	0
Dizziness	11 (7,1)	0	2 (2,6)	0

Dyspepsia	11 (7,1)	0	3 (3,9)	0
Insomnia	11 (7,1)	0	1 (1,3)	0
Oedema peripheral	11 (7,1)	0	2 (2,6)	0
Upper respiratory tract infection	11 (7,1)	1 (0,6)	4 (5,3)	0
Myalgia	10 (6,4)	0	2 (2,6)	0
Platelet count decreased	10 (6,4)	7 (4,5)	4 (5,3)	2 (2,6)
Amylase increased	9 (5,8)	1 (0,6)	4 (5,3)	0
Aspartate aminotransferase increased	9 (5,8)	3 (1,9)	16 (21,1)	5 (6,6)
Muscle spasms	9 (5,8)	1 (0,6)	0	0
Constipation	8 (5,1)	0	4 (5,3)	0
Decreased appetite	8 (5,1)	0	6 (7,9)	0
Dry skin	8 (5,1)	0	6 (7,9)	0
Dyspnoea	8 (5,1)	0	4 (5,3)	0
Lipase increased	8 (5,1)	6 (3,8)	5 (6,6)	4 (5,3)
Neutrophil count decreased	8 (5,1)	7 (4,5)	4 (5,3)	3 (3,9)
Non-cardiac chest pain	8 (5,1)	2 (1,3)	1 (1,3)	0
Oropharyngeal pain	8 (5,1)	0	2 (2,6)	0
Pruritus	8 (5,1)	0	5 (6,6)	1 (1,3)
Rash maculo-papular	8 (5,1)	0	2 (2,6)	1 (1,3)
Abdominal pain upper	7 (4,5)	0	5 (6,6)	1 (1,3)
Alanine aminotransferase increased	7 (4,5)	1 (0,6)	23 (30,3)	11 (14,5)
Pyrexia	6 (3,8)	2 (1,3)	6 (7,9)	1 (1,3)
Blood creatinine increased	5 (3,2)	0	5 (6,6)	0
Influenza like illness	3 (1,9)	0	4 (5,3)	0
Hypophosphataemia	2 (1,3)	1 (0,6)	4 (5,3)	3 (3,9)

Most Frequent Exposure-Adjusted Incidence Rate of All-Grade AEs (≥10% of Patients in Any Treatment arm)



Incidence rate = exposure-adjusted incidence rate: number of subjects with an event divided by the corresponding sum of the exposure duration for all subjects, where duration of exposure in 100 Patient Treatment Years is counted up to the first qualifying event (or end of time at risk for subjects without event). MedDRA version 24.1, CTCAE version 4.03

Overview of Adverse Events by Reason for Discontinuation of Last Prior TKI

Category, n(%)	Resistance				Intolerance			
	Asciminib 40mg BID N=94		Bosutinib 500mg QD N=54		Asciminib 40mg BID N=59		Bosutinib 500mg QD N=22	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Adverse events	82 (87.2)	50 (53.2)	52 (96.3)	34 (63.0)	57 (96.6)	36 (61.0)	22(100.0)	18 (81.8)
Fatal AEs	2 (2.1)	2 (2.1)	1 (1.9)	1 (1.9)	0	0	0	0
AEs leading to discontinuation	4 (4.3)	4 (4.3)	12 (22.2)	10 (18.5)	8 (13.6)	8 (13.6)	8 (36.4)	5 (22.7)
AEs leading to dose adjustment/interruption	33 (35.1)	26 (27.7)	32 (59.3)	28 (51.9)	33 (55.9)	31 (52.5)	17 (77.3)	11 (50.0)
AEs requiring additional therapy	62 (66.0)	28 (29.8)	46 (85.2)	23 (42.6)	47 (79.7)	23 (39.0)	22(100.0)	12 (54.5)

- Patients intolerant of last TKI had more severe AEs and more dose modifications and discontinuations in both treatment arms
- Safety and tolerability with asciminib was better than that with bosutinib regardless of the reason for the discontinuation of the last prior TKI

Appendix F Comparative analysis of efficacy and safety

Not applicable

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Appendix G Extrapolation

TTD

Figure 20 and Figure 23 show the various parametric curves and Figure 22 and Figure 25 show splines curves fitted to asciminib and bosutinib time to treatment discontinuation curves respectively.

Figure 20 Parametric curves fitted to asciminib TTD curve

Figure 21 Hazard functions per parametric distribution for asciminib

Figure 22 Splines fitted to asciminib TTD curve

For Asciminib splines are on hazard and odd scale.

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Figure 23 Parametric curves fitted to bosutinib TTD curve

Figure 24 Hazard functions per parametric distribution for bosutinib

Figure 25 Splines fitted to bosutinib TTD curve

For Bosutinib splines are on hazard, odd and normal scale.

Figure 26 and Figure 27 shows asciminib and respectively bosutinib AIC and BIC statistics for each parametric distribution, ranked in order of the best statistical fit.

Figure 26 AIC and BIC values for TTD curve of asciminib

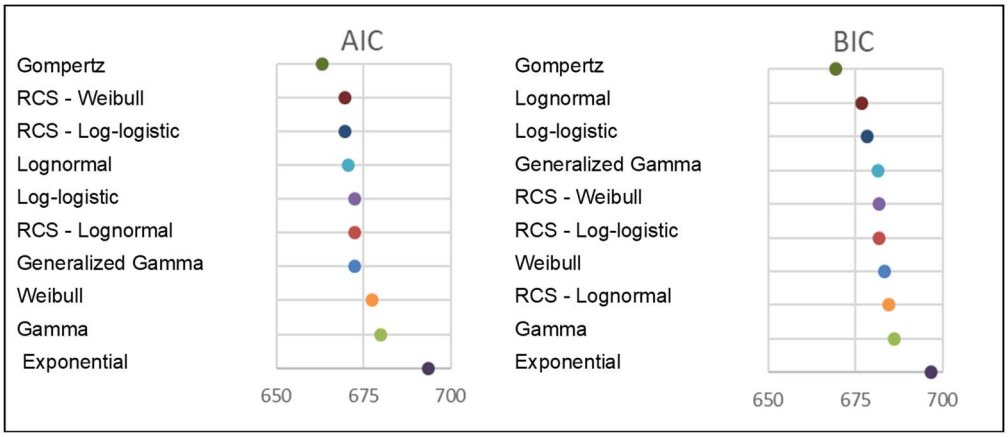

Figure 27 AIC and BIC values for TTD curve of bosutinib

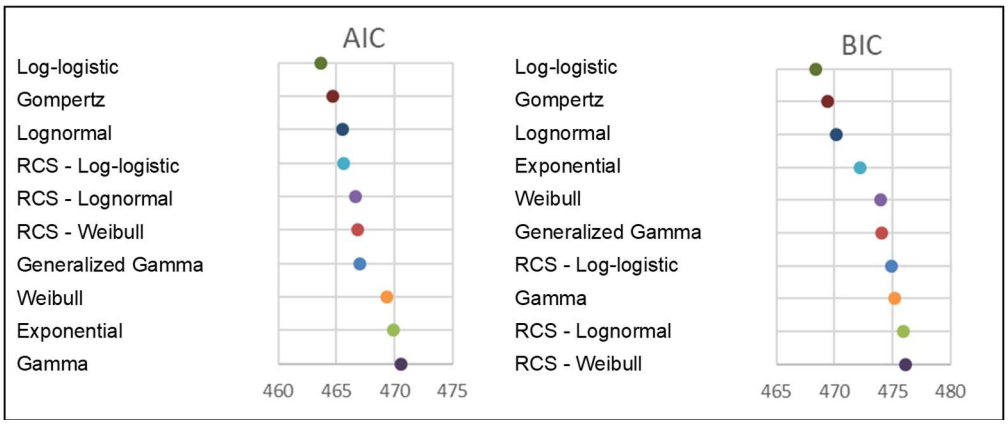

Figure 28 Extrapolation curves for KM data for TTD curves of asciminib in the ASCEMBL

[redacted]

Figure 29 Extrapolation curves for KM data for TTD curves of bosutinib in the ASCEMBL trial

[redacted]

[redacted]

Allo-SCT

The curves were digitized, and the IPD was reconstructed using the Guyot approach [76]. A number of parametric models were fitted to RFS (Relapse free survival) and OS curves for CP and progressed disease to examine best fit. Distribution selection for SCT (RFS or OS in either phase) made very little difference to the results.
Table 54 and Table 55 include the AIC and BIC statistics for each fitted parametric curve. The parametric curves can be visualized in Figure 30 and Figure 31.

Table 54 AIC and BIC values for Allo-SCT RFS and OS for CML

RFS and OS in Chronic Phase								
	Relapse free survival				Overall survival			
	AIC	Rank AIC	BIC	Rank BIC	AIC	Rank AIC	BIC	Rank BIC
Exponential	69,9	3	70,6	2	45,9	1	46,6	1
Weibull	71,3	9	72,8	6	47,7	6	49,2	6
Gompertz	70,0	4	71,5	4	46,4	3	48,0	2
Lognormal	69,9	2	71,4	3	46,8	4	48,4	3
Log-Logistic	70,6	8	72,1	5	47,4	5	48,9	5
Gamma	71,5	10	73,0	7	47,8	7	49,3	7
Gen. Gamma	68,3	1	70,6	1	46,1	2	48,4	4
RCS Weibull	70,4	7	73,5	10	48,5	10	51,6	10
RCS Log-Logistic	70,4	6	73,5	9	48,4	9	51,5	9
RCS Lognormal	70,1	5	73,2	8	48,2	8	51,3	8

The generalized gamma distribution had the best fit on both the AIC and BIC criteria to data on RFS for patients in the CP subgroup. This was supported by local clinical experts, that estimated approximately 50 % of patients would be alive and disease free at 5 years. This fit the extrapolation and thus the generalized gamma distribution was used in the base case for RFS following SCT in the chronic phase (Figure 30 to visualize the parametric curves).

For OS in the CP subgroup, the exponential model provided the best fit, followed by generalized gamma according to AIC, and Gompertz according to BIC. Clinical expert opinion was that the generalized gamma distribution had the best fit when compared to long term survival estimates in the disease area, therefore this was used as the base case (Figure 30 to visualize the parametric curves).
Figure 30 and Figure 31 show the various parametric curves tested for the Allo-SCT RFS and OS extrapolation in Chronic phase and progressed phase.

Figure 30 In chronic phase

[redacted]

Table 55 AIC and BIC values for Allo-SCT RFS and OS for progressed patients

RFS and OS in Progressed Disease								
	Relapse free survival				Overall survival			
	AIC	Rank AIC	BIC	Rank BIC	AIC	Rank AIC	BIC	Rank BIC
Exponential	152,1	10,0	153,5	5,0	120,1	9,0	121,5	8,0
Weibull	150,1	6,0	153,0	4,0	119,8	8,0	122,7	9,0
Gompertz	148,0	1,0	150,9	1,0	112,9	5,0	115,8	5,0
Lognormal	149,3	3,0	152,2	3,0	116,3	6,0	119,2	6,0
Log-Logistic	148,4	2,0	151,2	2,0	118,0	7,0	120,9	7,0
Gamma	150,9	7,0	153,8	6,0	120,5	10,0	123,4	10,0
Gen. Gamma	151,1	9,0	155,4	7,0	110,2	4,0	114,5	4,0
RCS Weibull	149,9	4,0	155,6	8,0	107,7	3,0	113,5	3,0
RCS Log-Logistic	150,0	5,0	155,7	9,0	107,6	2,0	113,3	2,0
RCS Lognormal	151,0	8,0	156,8	10,0	107,5	1,0	113,2	1,0

In the progressed phase, for RFS the Gompertz distribution had the best fit on both the AIC and BIC criteria. Clinical opinion noted that most mortality would occur within the first or two years and that survival would likely plateau beyond. Thus, the lognormal curve was therefore considered most clinically plausible, as this was a conservative compared to the Gompertz distribution.
For the OS for the progressed disease subgroup, the generalized gamma had the best statistical fit. However clinical opinion considered the log-normal the most clinical plausible, similar this had a plateau which is what is to be expected post SCT in clinical practice but was more conservative than the Gompertz and generalized gamma.

Figure 31 In progressed phase

The results are presented Figure 32 and Figure 33.

Figure 32 OS and RFS for patients who received SCT in chronic phase

Figure 33 OS and RFS for patients who received SCT in progressed disease

Again, distribution selection for SCT (RFS or OS in either phase) made very little difference to the results, therefore alternatives are not presented in sensitivity analysis for this submission. The extrapolations applied for each outcome for the different health states have been presented above. These were included in the base case as clinical experts had validated these and found these clinical plausible. Still, these were further tested in the sensitivity analysis.

Appendix H – Literature search for HRQoL data

Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	2000 to Feb 4, 2022	04.02.2022
Medline	Embase.com	2000 to Feb 4, 2022	04.02.2022
CENTRAL	Cochrane library interface	2000 to Feb 4, 2022	04.02.2022

Conference abstracts were hand searched to retrieve the latest studies that have not yet been published in journals as full text articles or supplement results of previously published studies. Abstracts from eleven conference proceedings were searched from 2018 till Feb 2022.
The following conferences were searched:

- American Society of Clinical Oncology (ASCO)
- American Society of Haematology (ASH)
- European Haematology Association (EHA)
- European Society for Medical Oncology (ESMO)
- European School of Haematology (ESH) John Goldman Conference on Chronic Myeloid Leukaemia
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) EU/USA
- Society of Hematologic Oncology (SOHO)
- European Leukaemia Network (ELN)
- European Society of Blood and Marrow Transplantation (EBMT)
- British Society of Haematology (BSH)
- Academy of Managed Care Pharmacy (AMCP)

Other sources:

1. The following websites were searched additionally:
   - The University of Sheffield Health Utilities Database (ScHARRHUD; available at www.scharrhud.org/)
   - The EQ-5D Publications Database (available at www.euroqol.org/search-for-eq-5d-publications/)
   - NICE Decision support unit: Utilities TSD series (available at http://nicedsu.org.uk/technical-support-documents/utilities-tsd-series/)
2. Bibliographic searching of selected relevant systematic reviews identified during screening was conducted to identify any additional published studies not identified during the database searching.

Search strategy

Search strategy was build using disease related and study design related terms. CML related disease terms were used in multiple cominations with different limits. Standard search filters such as ISSG search filter resource were used to limit the search hits for utility studies.

Search strategy for Embase®, MEDLINE®, MEDLINE® In-Process

No.	Query	Facet
#1	'chronic myeloid leukemia'/syn	Disease
#2	'chronic myelogenous leukemia':ab,ti OR 'chronic myelogenous leukaemia':ab,ti OR 'chronic myeloid leukaemia':ab,ti OR 'chronic myeloid leukemia':ab,ti OR 'cml':ab,ti OR 'cml-cp':ab,ti	
#3	'chronic myel*' NEAR/3 leuk?emia	

#4	(philadelphia OR ph1 OR 'bcr-abl') NEAR/3 myel* NEAR/3 leuk?emia?	
#5	#1 OR #2 OR #3 OR #4	
#6	'socioeconomics'/de	Study design (SD)
#7	(utilit* NEAR/2 (measure* OR outcome* OR state* OR health OR score* OR weight* OR analysis)):ab,ti	
#8	'health utility index' OR 'hui' OR 'hui1' OR 'hui2' OR 'hui3'	
#9	'hrqol' OR 'hqol' OR hql OR 'h qol' OR 'hr qol'	
#10	'quality-of-life'/exp	
#11	'quality of life' OR 'quality-of-life' OR qol OR pqol OR qls	
#12	(utilit* NEXT/1 (score* OR value* OR evaluation*)) OR (health NEXT/2 utilit*)	
#13	('health'/exp OR 'health') AND (state NEXT/1 utilit*)	
#14	'quality adjusted life year'/exp	
#15	'quality adjusted life year' OR 'quality adjusted life'	
#16	('quality adjusted' NEXT/1 survival*) OR qaly* OR qald* OR qale* OR qtime*	
#17	(health NEXT/1 state*) AND (state* NEXT/1 preference*)	
#18	'disability adjusted life' OR daly*	
#19	'health survey'/exp OR 'health survey'	
#20	hye* OR health*year*equivalent	
#21	health NEAR/2 utilit*	
#22	'wellbeing'/exp OR 'wellbeing'	
#23	(quality NEAR/2 well*being) OR qwb OR (willingness NEAR/2 pay)	
#24	(standard NEAR/2 gamble) OR (time NEAR/2 trade*off) OR tto OR ('discrete choice' NEXT/1 experiment*)	
#25	disutili*	
#26	'short form 36'/exp OR 'short form 36' OR 'sf36' OR 'sf-36' OR 'sf 36'	
#27	'short form 12'/exp OR 'short form 12' OR 'sf12' OR 'sf-12' OR 'sf 12'	
#28	'short form 6' OR 'sf6' OR 'sf-6' OR 'sf 6'	
#29	'euroqol' OR euro*qol	
#30	'eq5d' OR 'eq-5d' OR 'eq 5d' OR rosser	
#31	(visual NEXT/1 analog*) AND (analog* NEXT/1 scale*)	
#32	'health status indicator'/de	
#33	utilit* NEAR/3 (valu* OR measur* OR health OR life OR estimat* OR elicit* OR disease OR score* OR weight)	
#34	'nottingham health profile'/exp	
#35	((instrument OR instruments) NEAR/3 'quality of life'):ab,ti	
#36	'european organization for research and treatment of cancer quality of life questionnaire core 30'/syn OR 'eortc qlqc30' OR 'eortcqlq-c30' OR eortcqlqc30	
#37	'eortc qlq-cml24' OR 'eortc qlqcml24' OR 'eortcqlq-cml24' OR eortcqlqcml24	
#38	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	
#39	#5 AND #38	Disease + SD
#40	#39 AND [animals]/lim NOT ([animals]/lim AND [humans]/lim)	
#41	**#39 NOT #40**	

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Search strategy in CENTRAL

No.	Query	Facet
#1	MeSH descriptor: [Leukemia, Myelogenous, Chronic, BCR-ABL Positive] explode all trees	Disease
#2	'chronic myelogenous leukemia':ti,ab,kw OR 'chronic myelogenous leukaemia':ti,ab,kw OR 'chronic myeloid leukaemia':ti,ab,kw OR 'chronic myeloid leukemia':ti,ab,kw OR 'cml':ti,ab,kw OR 'cml-cp':ti,ab,kw	
#3	'chronic myel*' NEAR/3 leuk?emia	
#4	(philadelphia OR ph1 OR 'bcr-abl') NEAR/3 myel* NEAR/3 leuk?emia?	
#5	#1 OR #2 OR #3 OR #4	
#6	socioeconomic*	Study design (SD)
#7	((utilit* NEAR/2 (measure* OR outcome* OR state* OR health OR score* OR weight* OR analysis))):ti,ab,kw	
#8	health utility index OR hui OR hui1 OR hui2 OR hui3	
#9	hrqol OR hqol OR hql OR “h qol” OR “hr qol”	
#10	MeSH descriptor: [Quality of Life] explode all trees	
#11	quality of life OR quality-of-life OR qol OR pqol OR qls	
#12	(utilit* NEXT/1 (score* OR value* OR evaluation*)) OR (health NEXT/2 utilit*)	
#13	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	
#14	quality adjusted life year OR “quality adjusted life”	
#15	('quality adjusted' NEXT/1 survival*) OR qaly* OR qald* OR qale* OR qtime*	
#16	MeSH descriptor: [Health] explode all trees	
#17	health	
#18	#16 OR #17	
#19	(state NEXT/1 utilit*)	
#20	#18 AND #19	
#21	(health NEXT/1 state*) AND (state* NEXT/1 preference*)	
#22	'disability adjusted life' OR daly*	
#23	MeSH descriptor: [Health Surveys] explode all trees	
#24	health survey OR hye* OR health*year*equivalent OR health NEAR/2 utilit*	
#25	wellbeing OR (quality NEAR/2 well*being) OR qwb OR (willingness NEAR/2 pay)	
#26	(standard NEAR/2 gamble) OR (time NEAR/2 trade*off) OR tto OR ('discrete choice' NEXT/1 experiment*)	
#27	short form 36 OR sf36 OR sf-36 OR “sf 36”	
#28	short form 12 OR sf12 OR sf-12 OR “sf 12”	
#29	short form 6 OR sf6 OR sf-6 OR “sf 6”	
#30	euroqol OR euro*qol	
#31	'eq5d' OR 'eq-5d' OR 'eq 5d' OR rosser	
#32	(visual NEXT/1 analog*) AND (analog* NEXT/1 scale*)	
#33	MeSH descriptor: [Health Status Indicators] explode all trees	
#34	utilit* NEAR/3 (valu* OR measur* OR health OR life OR estimat* OR elicit* OR disease OR score* OR weight)	
#35	nottingham health profile	
#36	((instrument OR instruments) NEAR/3 "quality of life"):ti,ab,kw	
#37	("european organization for research and treatment of cancer quality of life questionnaire core 30" OR "eortc qlqc30" OR eortcqlq-c30 OR eortcqlqc30)	
#38	eortc qlq-cml24 OR eortc qlqcml24 OR eortcqlq-cml24 OR eortcqlqcml24	
#39	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OT #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	

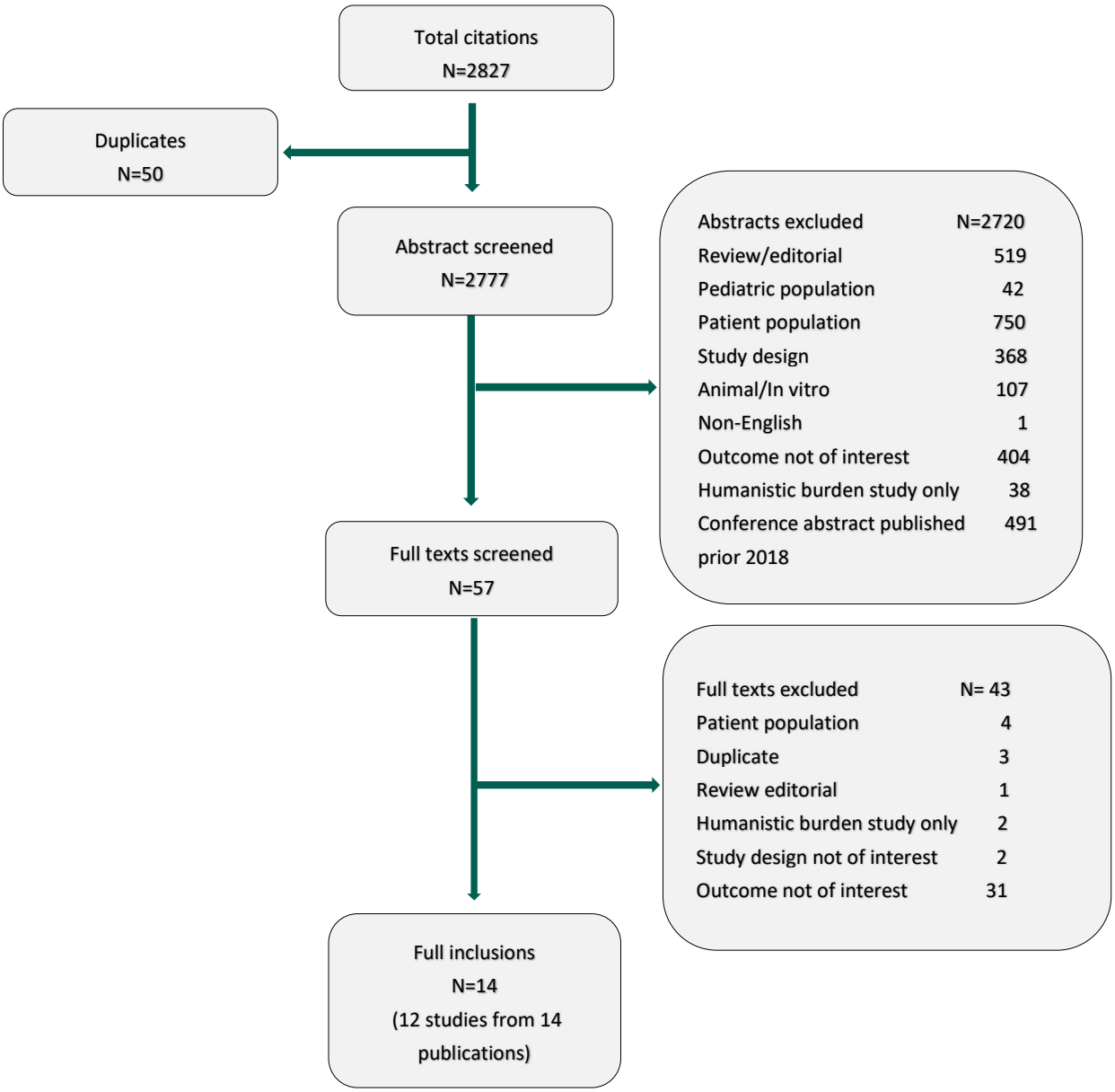
#40	#5 AND #39	Disease + SD
#41	#40 in Trials	
#42	**#41 with Publication Year from 2000 to 2022, in Trials**	

Studies were selected on the basis of following inclusion/exclusion criteria. Patient population was adult CML patients similar to ASCEMBL trial and studies reporting utilities/disutilities in CML during last 20 years were considered.

Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
Patient population Adults (aged ≥18 years) with CML	• Animal/in vitro studies • Studies in pediatric population
Intervention/Comparators	
• No interventional/ comparators study were included	• Not applicable
Outcomes*:*	
• Studies reporting utilities/disutilities in CML or mapping algorithms from HRQoL to utilities in CML	• Studies not reporting the relevant health state utilities
Study design	
• Original research studies (observational studies, surveys, post-hoc analysis of clinical trials, any other studies reporting utilities data)	
Language • English	• Non-English studies
Publication date • From 2000 – May 13, 2020 (last 20 years) • May 10, 2020 – June 7, 2021 (1st SLR update) • June 7, 2021- Feb 4, 2022 (2nd SLR update)	
Country • No limits	• Not applicable

PRISMA diagram of utility SLR (after Feb 2022 update)



Appendix J Sensitivity analyses

Deterministic

As named in chapter 6.1, we did a sensitivity analyses based on nilotinib and dasatinib price using efficacy data of bosutinib in ASCEMBL. The results are included in Table 56 and Table 57.

Table 56 Results for asciminib vs nilotinib

Per patient	Asciminib	Nilotinib	Difference
Life years gained (discounted)			
Total life years gained	[redacted]	[redacted]	[redacted]
QALYs (discounted)			
Total QALYs	[redacted]	[redacted]	[redacted]
Costs (discounted)			
Total costs	[redacted]	[redacted]	[redacted]
Incremental results	Intervention vs. Comparator		
ICER (per QALY)	[redacted]		

Result calculated by changing, in the sheet "Model Parameters", the drug acquisition costs for bosutinib in cell F201 by the drug acquisition costs for Nilotinib (S15 instead of S12 in cell F201) and adjust RDI in cell F204 (P15 instead of P12)

Table 57 Results for asciminib vs dasatinib

Per patient	Asciminib	Dasatinib	Difference
Life years gained			
Total life years gained	[redacted]	[redacted]	[redacted]
QALYs			
Total QALYs	[redacted]	[redacted]	[redacted]
Costs			
Total costs	[redacted]	[redacted]	[redacted]
Incremental results	Intervention vs. Comparator		
ICER (per QALY)	[redacted]		

Result calculated by changing, in the sheet "Model Parameters", the drug acquisition costs for bosutinib in cell F201 by the drug acquisition costs for Dasatinib(S14 instead of S12 in cell F201) and adjust RDI in cell F204 (P14 instead of P12)

Probabilistic

Table 58 Distribution used for various parameters in PSA

	Expected value	Standard error	Reason / Rationale / Source	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Probabilities							
Efficacy OS, - Post Discontinuation	3,5		Literature	normal	α:100	β:0,035	*Model Parameters!D59*
Utility							
Asciminib							
CP on 3L treatment Utility	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D508*
CP off 3L treatment Utility	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D509*
CP AlloSCT Relapse Free Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D510*
CP AlloSCT Relapsed Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D511*
AP Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D512*
BP Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D513*
PD AlloSCT Relapse free Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D514*
PD AlloSCT Relapsed Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	Model Parameters!D515
Bosutinib							
CP on 3L treatment Utility	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D519*
CP off 3L treatment Utility	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D520*
CP AlloSCT Relapse Free Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D510*
CP AlloSCT Relapsed Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D511*
AP Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D512*
BP Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D513*
PD AlloSCT Relapse free Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D514*
PD AlloSCT Relapsed Utility	[redacted]	[redacted]	Literature	beta	[redacted]	[redacted]	*Model Parameters!D515*
DRI							
Asciminib	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D200*
Bosutinib	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D201*
Drug costs							
Drug acquistion Asciminib - per day	[redacted]	[redacted]	Assumption	gamma	[redacted]	[redacted]	*Model Parameters!D197*

	Expected value	Standard error	Reason / Rationale / Source	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Drug acquistion Bosutinib - per day	[redacted]	[redacted]	Danish medicine agency	gamma	[redacted]	[redacted]	*Model Parameters!D198*
AE Incidence, Grade 3-4							
Asciminib							
Alanine aminotransferase increased	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D134*
Aspartate aminotransferase increased	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D135*
Hypertension	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D137*
Lipase increased	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D138*
Neutropenia	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D139*
Thrombocytopenia	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D140*
Bosutinib							
Alanine aminotransferase increased	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D166*
Aspartate aminotransferase increased	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D167*
Diarrhoea	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D168*
Hypertension	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D169*
Lipase increased	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D170*
Neutropenia	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D171*
Thrombocytopenia	[redacted]	[redacted]	ASCEMBL	beta	[redacted]	[redacted]	*Model Parameters!D172*