Simplified Single Technology Assessment

ID2019_029 Vitrakvi (larotrectinib) for the treatment of adult patients over 18 years of age with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options.

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Norwegian Medicines Agency

PREFACE

The regional health authorities (RHF) are responsible for *Nye* metoder, *the National System for the Managed Introduction of New Health Technologies* within the specialist health service. The principles for prioritization which *Nye Metoder* operates by are set out in the white paper on priority setting in the Norwegian health care sector (Meld. St. 34 (2015-2016)) by the Ministry of Health and Care Services. The *Nye Metoder* system has been legislated since 2019 and allows health technologies relevant for the specialist health service to be assessed in a systematic way, to ensure efficient allocation of resources within the health services. More details about the system can be found on the *Nye Metoder* website at nyemetoder.no.

As part of *Nye Metoder*, the Norwegian Medicines Agency has been given the responsibility to perform single technology assessments (STA). STA is a methodological framework for comparing the costs and benefits of a single (new) technology to the standard of care for the indication of interest. The severity of the disease in question is also considered. The objective of STAs is to inform decision-making through an overall evaluation of whether the new method meets the three principles for priority setting in health care: the benefit criterion, the resource criterion, and the severity criterion. The benefit and resource use associated with a health technology is assessed by estimating the additional cost for each "year of life spent in good health" the technology offers compared to the current standard of care. A “year of life spent in good health", indicates a year spent in "perfect" health, in other words without illness or any pain nor discomfort. "Perfect" health in a STA is defined as a quality-adjusted life-year (1 QALY), which is a standardized unit of measure allowing one to compare the benefit of different treatments across indications. The Norwegian Medicines Agency does not evaluate the risk-benefit ratio; this is assessed by the European Medicines Agency (EMA) during the marketing authorization process.

The pharmaceutical company holding the marketing authorization for the health technology in question is obligated to submit documentation for the STA. More specifically, the company submits a health economic model which is used for estimating the relationship between benefit and cost, expressed as the cost for an additional QALY. The Norwegian Medicines Agency can provide guidance for this. Subsequentially, the Norwegian Medicines Agency assesses the assumptions made in the submitted model by examining if the model reflects Norwegian clinical practice. If required, the Norwegian Medicines Agency may request additional information from the company, clinical experts and/or patients to perform additional calculations of the costs and cost-effectiveness using the submitted model.

A Decision Forum comprised of the four CEOs (one for each regional health authority) decides whether to introduce the method or not within the specialist health service through an overall assessment of the criteria for priority-setting. The Norwegian Medicines Agency does not have decision-making authority in the system of *Nye Metoder*, but the STA reports by the Norwegian Medicines Agency are used to inform decision-making. Sykehusinnkjøp HF negotiates the price of the new health technology in the system of *Nye Metoder*. How much society is willing to pay for a QALY is related to the severity of the disease. In addition, STAs associated with high uncertainty, low quality of available evidence, and/or with large budgetary consequences may be given a lower priority by the Decision Forum.

Some of the information in the Norwegian Medicines Agency's reports may be confidential. The Norwegian Medicines Agency assesses requests for exemption from public access by the pharmaceutical company and decides whether the information should be confidential (section 13.1 of the Public Administration Act, guideline in Norwegian can be found here). All HTA evaluation reports are published and are publicly available on the Norwegian Medicines Agency's website at legemiddelverket.no.

EXECUTIVE SUMMARY

Scope

A simplified single technology assessment (STA) of Vitrakvi (larotrectinib) for the treatment of adult patients with solid neurotrophic tyrosine receptor kinase (NTRK-) fusion positive tumours has been conducted. The Norwegian Medicines Agency (NoMA) has summarized the clinical efficacy, safety and costs in accordance with the Summary of Product Characteristics (SmPC) for larotrectinib, and the requested specifications from the Ordering Forum (ID2019_029).

The assessment is based primarily on the analysis submitted by Bayer, supported by clinical experts, SmPC and EPAR.

Background

The benefits and risks of larotrectinib have been documented through the approval of a conditional marketing authorisation. The main residual uncertainties at the time of the marketing authorization were subsequent to the uncontrolled nature of the pivotal trials, combined with a small sample size and a relatively short duration of follow up. Thus, at the time of the marketing authorization, non-comprehensive data were judged to be available for the precision and size of the efficacy estimates, histology based subgroup analysis, resistance mechanisms, the role of concomitant oncogenic drivers and the dose in small children where drug exposure at the recommended doses may be higher than in the adults. In addition, the size of the safety database was deemed to be small and the data on long-term safety were limited.

Bayer has committed to addressing these uncertainties through the submission of the final study report for the pivotal clinical trial LOXO-TRK-15002 (NAVIGATE, due date 30 June 2024) as well as the 5-year follow-up data from the pivotal clinical trial LOXO-TRK-13003 (SCOUT, due date 31 March 2027).

The current STA only covers the adult indication. The paediatric indication will be addressed in a separate STA (ID2020_115).

Solid tumours that display a NTRK gene fusion

NTRK gene fusions occur through chromosomal breakage and re-joining, leading to constitutive activation of the tropomyosin receptor kinases TRKA, TRKB, and TRKC causing unchecked cellular proliferation and tumour growth (1, 2). NTRK gene fusions have been identified in a wide range of commonly occurring tumours, such as lung cancer, breast cancer, colorectal cancer, thyroid cancer, sarcoma, and others, though at low frequencies. On the other hand, in certain very rare tumours, such as infantile fibrosarcoma (IFS), secretory/juvenile breast cancer, and mammary analogue secretory cancer of the salivary glands, NTRK gene fusions are the defining genetic feature occurring in approximately 90% to 100% (3). NTRK gene fusions are reported to be mutually exclusive of other oncogenic drivers when found in any given cancer (4, 5).

Number of patients in Norway
The number of patients with NTRK-fusion positive solid tumours eligible for treatment with larotrectinib in Norway given a positive decision regarding use, is so far unknown. The prevalence of NTRK-fusions is estimated to be about 0.3% of solid tumours (6). This implies that in order to identify one patient with NTRK-fusion, approximately 300 patients would have to be tested. Based on currently available evidence, patients with NTRK-fusions are expected to receive treatment with larotrectinib for about 18.6 months. Assuming that all eligible patients with NTRK-fusion would be identified and that patients will be distributed equally to treatment with larotrectinib and entrectinib (another recently approved NTRK inhibitor), approximately 3-25 individuals could potentially receive larotrectinib on a yearly basis.

NoMA's assessment is based on the assumption that all patients with tumours harbouring NTRK-positive fusions can be identified in the future, most likely through Next generation sequencing (NGS)-screening. Testing for NTRK-fusions is not yet standard procedure across all relevant indications but it is becoming increasingly available in Norwegian clinical practice. The Norwegian Institute of Public Health has evaluated the tests necessary to identify patients with NTRK-positive fusions (Tests for the detection of NTRK gene fusions in patients with locally advanced or metastatic solid tumours).

Treatment of solid tumours that display a NTRK gene fusion in Norwegian clinical practice
Until recently, there were no approved therapies targeting NTRK-fusions in use in Norway, and patients with tumours harbouring NTRK-fusions were treated with standard of care therapies for each specific tumour histology. Entrectinib was recently introduced by the Decision Forum (ID2019_119) for the same target adult population as that covered by the larotrectinib indication, i.e. patients with solid neurotrophic tyrosine receptor kinase (NTRK) fusion positive tumours who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options (i.e., for which clinical benefit has not been established, or where such treatment options have been exhausted). Albeit still under conditional approval, taking into account the very last line indication of both products, NoMA considers entrectinib to be the relevant comparator in this assessment. It should be noted, however, that similar to the current STA, due to the limited data available, cost-effectiveness over best standard of care has not been established for entrectinib.

Severity and absolute shortfall
NoMA has done a simplified assessment and has not quantified severity. In the assessment of entrectinib for a similar indication, NoMA estimates that patients with NTRK-fusion positive cancers who have exhausted all satisfactory treatment options loose on average about 20 quality-adjusted life years (QALYs). The patient population is very heterogeneous, which can lead to high variation in severity depending on the subpopulation.

Clinical efficacy
The clinical efficacy of Vitrakvi is based on a pooled analysis of three open label, phase I/II, uncontrolled trials (LOXO, SCOUT and NAVIGATE) using a data cut-off of July 2020. The efficacy analysis set, referred to as the ePAS5, includes 192 patients (122 adults) enrolled across the three studies with 1) an NTRK gene

fusion, 2) a non-CNS primary tumour, 3) measurable disease assessed by RECIST v1.1, and 4) who received at least one dose of Vitrakvi as of July 2020.

In the overall study population, ORR (primary endpoint) was 72% with 23% being complete responders (CR). Median duration of response (DOR) was 34.5 months. In the adult sub-population (n=122), the ORR was 64% with 19% being in CR. The observed ORR was highly variable across the studied tumour types, ranging from 0% to 100%. Estimates in individual histopathological subgroups are not robust due to the limited sample size. The extent to which the response rates translate into a survival benefit relative to best supportive care is not documented. It seems likely, however, that patients without other treatment options could achieve a clinically meaningful benefit of larotrectinib, at least in the patient cohorts where responses have been documented.

Costs
One year of treatment (365 days) costs 841 406 NOK (including VAT) per patient.

Budget estimate
The budget impact analyses for larotrectinib can only result in a very rough estimate due to the uncertain number of patients that will be identified in Norwegian clinical practice in the following years. Prevalence, testing strategy and competition with entrectinib will impact the number of patients treated. NoMA presents a wide range for budget estimate, which could be somewhere between 3,9 million NOK for 3 patients and 30,3 million NOK for 25 patients per year including VAT.

Recommendations by the Norwegian Medicines Agency
The uncontrolled, pivotal trials (LOXO, SCOUT and NAVIGATE) could not provide an estimate for the relative effectiveness of larotrectinib compared to neither entrectinib nor best standard of care. In line with the order from the Order forum, NoMA has conducted a simplified STA, providing a description of effect, safety and costs. Although not part of the order, Bayer also submitted a cost-minimizing analysis with entrectinib as comparator and relative effectiveness based on an unanchored matching-adjusted indirect treatment comparison (MAIC). The documentation was, however, not considered sufficient to allow an evaluation of relative effectiveness and was therefore not further assessed.

The benefit of larotrectinib has been established primarily through its antitumoral activity, i.e. response rates and duration of response. To which extent these response rates will translate into a survival benefit is not documented, although it seems likely that patients with no other treatment options could derive a clinically meaningful benefit of larotrectinib. As outlined in the European Public Assessment report (EPAR), there is substantial residual uncertainty, related to the precision and size of the efficacy estimates, particularly across individual histopathological tumour types, potential resistance mechanisms and the role of concomitant oncogenic drivers. Patients with NTRK-positive fusion cancers who have exhausted their treatment options have a severe prognosis. NoMA expects that such patients may loose

on average about 20 quality-adjusted life years. The number is, however, based on assumptions and it should be interpreted with caution.

The submitted documentation clearly shows the different requirements of the regulatory Marketing Authorization process and the Health Technology Assessment-process (HTA). The submitted documentation was deemed sufficient to establish a positive benefit/risk by The European Medicines Agency (EMA). However, it is not possible to establish relative effectiveness against neither entrectinib nor other best standard of care, as required for an HTA based on the clinical data available. NoMA identified three major evidence gaps that hinder establishment of relative effectiveness and evaluation of the cost-effectiveness of larotrectinib:

1. *Unknown prognostic value of NTRK-fusion:* Although there is emerging data on the prognostic value of NTRK-fusion, the effectiveness of standard of care in patients harbouring the NTRK-fusion is not considered established across all relevant indications (5).
2. *Unknown size of treatment effect:* The efficacy estimates are highly uncertain, given the heterogenous and small patient population studied, the uncontrolled nature of the pivotal clinical trials and the short duration of follow up. Furthermore, there is substantial residual uncertainty related to the precision and size of the efficacy estimates across individual histopathological tumour types (i.e., the agnostic potential of larotrectinib), potential resistance mechanisms and the role of concomitant oncogenic drivers.
3. *Unknown generalizability:* There is uncertainty regarding the generalizability of the patient population to Norwegian clinical practice.

NORSK SAMMENDRAG

Formål
Dette er en forenklet metodevurdering av legemiddelet Vitrakvi (larotrektinib). Legemiddelverket har oppsummert effekt, sikkerhet og ressursbruk ved bruk av Vitrakvi i henhold til bestilling ID2019_029 «Vitrakvi (larotrektinib) til behandling av pasienter over 18 år med solide tumorer med et nevrotrofisk tropomyosin-reseptorkinase (NTRK) fusjonsgen, som har en sykdom som er lokalavansert, metastatisk eller hvor kirurgisk reseksjon sannsynligvis vil føre til alvorlig morbiditet, og hvor det ikke finnes noen tilfredsstillende behandlingsalternativer», og godkjent preparatomtale. Vurderingen tar utgangspunkt i dokumentasjon innsendt av Bayer, kliniske eksperter, preparatomtale og EPAR.

Bakgrunn
Nytten og risikoen til larotrektinib har blitt dokumentert gjennom en betinget markedsføringstillatelse. De største usikkerhetene med dokumentasjonen som lå til grunn for den betingede markedsføringstillatelsen, er relatert til det ukontrollerte studiedesignet til de pivotale studiene, kombinert med lavt pasientantall i studiene og relativt kort oppfølgingstid. Ved tidspunktet for markedsføringstillatelsen ble det påpekt usikkerhet knyttet til størrelsen på effektestimatene, histologiske subgruppeanalyser, resistensmekanismer, betydningen av koeksisterende onkogene drivere og riktig dose i små barn, der legemiddeleksponeringen kan være høyere enn hos voksne. I tillegg er sikkerhetsdata foreløpig begrenset, inkludert data på langsiktig sikkerhet.

Bayer har forpliktet seg til å adressere disse usikkerhetene gjennom innsending av den endelige studierapporten for den pivotale kliniske studien LOXO-TRK-15002 (NAVIGATE, forventet avsluttet 30. juni 2024) samt innsending av 5 års oppfølgingsdata fra den pivotale kliniske studien LOXO-TRK-13003 (SCOUT, forventet avsluttet 31. mars 2027).

Denne metodevurderingen dekker kun bruk hos voksne pasienter. Den pediatriske indikasjonen vil bli vurdert i en egen metodevurdering (ID2020_115).

Solide tumorer med NTRK genfusjoner
NTRK genfusjoner oppstår gjennom kromosomale brudd og spleisinger, noe som leder til kontinuerlig aktivering av tropomysinreseptorkinasene TRKA, TRKB, og TRKC. Dette leder i sin tur til ukontrollert celleproliferasjon og tumorvekst (1, 2). NTRK genfusjoner har blitt identifisert i et bredt spektrum av vanlig forekommende kreftformer, slik som lungekreft, brystkreft, kolorektalkreft, thyroideakreft og sarkom, men med lav frekvens. I veldig sjeldne krefttyper, derimot, slik som infantil fibrosarkom (IFS), sekretorisk/juvenil brystkreft, og sekretorisk (mamary analogue) spyttkjertelkarsinom, er NTRK genfusjoner det definerende genetiske trekket, og forekommer i ca. 90% til 100% av tilfellene (3). NTRK genfusjoner er gjensidig ekskluderende for andre onkogene drivermutasjoner (4, 5).

Pasientgrunnlag
Det er ikke kjent hvor mange pasienter med NTRK-fusjonspositive solide svulster som vil bli behandlet med laroktrektinib dersom det blir innført i Norge. Forekomsten av NTRK-fusjoner anslås til omtrent 0,3 % av alle solide tumorer. Dette innebærer at omtrent 300 pasienter må testes for å finne én pasient med NTRK-fusjon. Basert på de tilgjengelige data, antar vi at pasienter med NTRK-fusjoner vil bli behandlet med larotrektinib i omtrent 18,6 måneder. Dersom alle pasienter med NTRK-fusjoner egnet for behandling blir identifisert og ca. halvparten av pasientene får behandling med larotrektinib mens den andre halvparten får behandling med entrektinib (en NTRK-hemmer som har blitt nylig innført midlertidig), antar Legemiddelverket at mellom 3 og 25 pasienter vil kunne motta larotrektinib årlig.

Behandling av svulster som har NTRK-fusjoner i norsk klinisk praksis
Folkehelseinstituttet har vurdert testene som er nødvendige for å indentifisere pasienter med NTRK-fusjoner (Tester for deteksjon av NTRK genfusjoner hos pasienter med lokalt avanserte eller metastatiske solide svulster). Beslutningsforum har innført entrektinib midlertidig som monoterapi til behandling av voksne og pediatriske pasienter fra 12 års alder som har solide tumorer som uttrykker nevrotrofisk tyrosinreseptor kinase (NTRK)-genfusjon og som har en lokalavansert eller metastatisk sykdom, eller der kirurgisk reseksjon forventes å kunne resultere i alvorlig morbiditet, og som ikke har mottatt tidligere behandling med NTRK-hemmer, og som ikke har noen tilfredsstillende behandlingsalternativer. Legemiddelverket mener derfor at entrektinib er relevant komparator i denne saken. I likhet med i denne metodevurderingen, er det begrensede tilgjengelige data for entrektinib, noe som har medført at kostnadseffektiviteten sammenliknet med beste standardbehandling heller ikke ble etablert for entrektinib.

Alvorlighet og helsetap
Legemiddelverket har utført en forenklet metodevurdering, og ikke utført tentative beregninger av alvorlighetsgrad. I metodevurderingen av entrektinib til behandling av tilsvarende pasientpopulasjon, har Legemiddelverket estimert et absolutt prognosetap på ca. 20 QALYs. Pasientpopulasjonen er heterogen, og alvorlighet vil derfor variere avhengig av subpopulasjon.

Effektdokumentasjon
Den kliniske effekten av larotrektinib er basert på en «poolet» analyse av tre åpne, fase I/II, ukontrollerte studier (LOXO, SCOUT and NAVIGATE) med et datakutt fra juli 2020. Analysesettet for effekt refereres til som ePAS5, og inkluderer 192 pasienter (122 voksne) innrullert fra de tre studiene med 1) en NTRK genfusion, 2) en ikke-CNS primær tumor, 3) målbar sykdom vurdert basert på RECIST v1.1, og 4) som har mottatt minst en dose larotrektinib tidligere enn juli 2020.

I den totale studiepopulasjonen var resultatet for utfallsmålet ORR (primær endepunktet) 72%, hvorav 23% var komplette responser (CR). Median responsvarighet var 34,5 måneder. I den voksne sub-populasjonen (n=122) var ORR 64%, hvorav 19% var komplette responser. Det var stor variasjon i

observert ORR (fra 0% til 100%) for de ulike tumortypene, men estimatene for de individuelle histopatologiske undergruppene er imidlertid ikke robuste pga. det begrensede pasientantallet.

I hvilken grad responsratene vil medføre overlevelsesgevinst sammenlignet med beste støttebehandling er ikke dokumentert. Det anses likevel som rimelig at pasienter uten andre behandlingsalternativer kan få en klinisk relevant effekt av larotrektinib, i hvert fall i de kohorter der responser er dokumentert.

Kostnader
Et års behandling (365 dager) koster 841 406 NOK (maksimal AUP inkl. mva.) per pasient.

Budsjettestimat
Usikkerhet rundt antallet pasienter som vil få larotrektinib påvirker klart budsjettkonsekvensen. Prevalensen, teststrategien og konkurranse mot entrektinib vil påvirke antallet pasienter som behandles. Vi viser derfor et stort spenn i budsjettestimatene, som kan være mellom 3,9 millioner kroner for 3 pasienter, til 30,3 millioner for 25 pasienter.
På grunn av usikkerheten i antall pasienter som vil bli identifisert i norsk klinisk praksis i årene som kommer, kan Legemiddelverket bare gi et veldig grovt budsjettestimat.

Legemiddelverkets vurdering
De ukontrollerte, pivotale studiene (LOXO, SCOUT and NAVIGATE) kunne ikke gi et estimat på relativ effekt for larotrektinib sammenliknet med hverken entrektinib eller beste standardbehandling. I tråd med bestillingen fra Bestillingsforum, har Legemiddelverket gjennomført en forenklet metodevurdering, med en beskrivelse av effekt, sikkerhet og kostnader. Bayer har også sendt inn en kostnadsminimaliseringsanalyse med entrektinib som komparator basert på en uankret justert indirekte sammenlikning (MAIC), til tross for at dette ikke var del av bestillingen. Dokumentasjonen var imidlertid ikke tilstrekkelig for å kunne gjennomføre en evaluering av relativ effekt, og ble derfor ikke videre vurdert.

Den kliniske effekten av larotrektinib er dokumentert primært gjennom den antitumorale aktiviteten, dvs. gjennom utfallsmål knyttet til responsrater og responsvarighet. I hvilken grad disse vil medføre overlevelsesgevinst er ikke dokumentert, selv om det vurderes som sannsynlig at pasienter uten andre behandlingsalternativer trolig kan få en klinisk relevant gevinst av larotrektinib. Som beskrevet i den Europeiske utredningsrapporten (EPAR) gjenstår det betydelig usikkerhet knyttet til størrelsen på effektestimatene, spesielt i de ulike histopatologiske tumortypene, potensielle resistensmekanismer og rollen til konkomitante onkogene drivere. Pasienter med NTRK-fusjonspositiv kreft uten annen tilgjengelig behandling har en alvorlig prognose, og det er i en tidligere metodevurdering estimert et prognosetap på 20 QALYs for den aktuelle pasientgruppen. Dette estimatet er usikkert og må brukes med varsomhet.

Denne metodevurderingen illustrerer tydelig forskjellen på hvilken dokumentasjon som er tilstrekkelig for en markedsføringstillatelse og hva som er nødvendig for metodevurderingen. Den innsendte dokumentasjonen ble vurdert av EMA som tilstrekkelig til å etablere et positivt forhold mellom nytte og risiko. Det er derimot utfordrende å etablere den relative effekten for larotrektinib sammenlignet med både entrektinib og annen standard behandling, noe som kreves for en metodevurdering. Legemiddelverket identifiserte tre vesentlige mangler ved dokumentasjonsgrunnlaget i denne

metodevurderingen som hindrer etablering av relativ effekt og vurdering av kostnadseffektiviteten til larotrektinib:

1. *Ukjent prognostisk verdi av NTRK-fusjoner:* Selv om det begynner å komme data om prognose av NTRK-fusjon, effekten av dagens standardbehandling i pasienter som har en NTRK-fusjon er ikke ansett som godt dokumentert for alle relevante indikasjoner (5).
2. *Ukjent størrelse på behandlingseffekten:* Effektestimatene er svært usikre på grunn av den lille og heterogene pasientpopulasjonen som ble studert, den korte oppfølgingstiden og det ukontrollerte designet på de pivotale studiene. Videre er det stor usikkerhet knyttet til presisjonen og størrelsen på effekten for de individuelle histopatologiske tumor typene (dvs. det agnostiske potensiale for larotrektinib), potensielle resistensmekanismer og rollen til eventuelle koeksisterende onkogene drivere.
3. *Ukjent overførbarhet til norsk klinisk praksis:* Det er usikkerhet knyttet til om data fra pasientene i studiene kan overføres til norsk klinisk praksis.

VURDERING AV VITRAKVI TIL BEHANDLING AV KREFT MED NTRK-GENFEIL

Hva er Vitrakvi?
Vitrakvi er et legemiddel som kan benyttes med formål om å hindre kreftsvulster med genfeil i NTRK-reseptoren i å vokse ukontrollert.

NTRK-reseptoren som kalles for neurotrofisk tropomyosin reseptor tyrosinkinase finnes i kreftsvulster flere ulike steder i kroppen, for eksempel i tarm, lunger, og skjoldbruskkjertel.

Hva er en metodevurdering? Du kan lese om Legemiddelverkets arbeid med metodevurderinger *her*.

Hva menes med et godt leveår? Du kan lese mer om hva som menes med et godt leveår *her*.

Vitrakvi er et legemiddel som virker mot flere krefttyper, uavhengig av hvor i kroppen kreftsykdommen har oppstått. Fellesnevneren for svulstene er genfeil i NTRK-reseptoren og derfor kalles Vitrakvi for et vevs-uavhengig legemiddel. Vitrakvi er en tablett som pasienten skal svelge to ganger daglig.

Dagens behandling for pasienter med genfeil i NTRK-reseptoren (NTRK-fusjonspositiv kreft) er Rozlytrek.

NTRK genfeil er sjeldne, og man antar at så få som 3 av 1000 pasienter som får kreft har denne genfeilen.

Hvor alvorlig er sykdommen?
NTRK-fusjonspositiv kreft er en alvorlig sykdom. Pasientene lever kortere enn og har nedsatt helserelatert livskvalitet. Prognosen til de pasientgruppene som kan behandles med Vitrakvi er dårlig, men varierer litt mellom pasientgruppene.

Hvem kan få behandling med Vitrakvi?
Pasienter over 18 år med kreftsvulster som er forårsaket av en forandring i nevrotrofisk tyrosinreseptor kinase (NTRK)-genet kan behandles med Vitrakvi. Det er vanskelig å si hvor mange norske pasienter som vil kunne få behandling med Vitrakvi hvis det blir bestemt at behandlingen kan tas i bruk på norske sykehus. Det er fordi kreftsvulsten må testes for genfeil i NTRK-reseptoren før en pasient kan få Vitrakvi, og denne testen er per i dag ikke en rutinetest for alle relevante indikasjoner i norske sykehus, men tilgjengeligheten øker stadig. Det kan være aktuelt å behandle mellom 3 til 25 pasienter årlig i Norge med Vitrakvi.

Hvilken nytte har Vitrakvi?
NTRK-fusjonspositiv kreft oppstår når celler begynner å dele seg og vokse uten hemning. Hos pasienter med endringer i NTRK-genene vil Vitrakvi blokkere virkningen av de resulterende unormale TRK-proteinene, og dermed forsinke eller stoppe veksten av kreften.

Hvordan er nytten av behandlingen undersøkt?
Flere kliniske studier har sett på nytten av, og risikoen ved, behandling med Vitrakvi ved ulike typer NTRK-fusjonspositiv kreft. For denne metodevurderingen har disse studiene blitt sammenslått i én analyse som omfatter 192 pasienter med NTRK-fusjonspositiv kreft.

Ingen av studiene har sammenlignet Vitrakvi med andre behandlinger og det er derfor vanskelig å si om Vitrakvi virker bedre, like bra eller dårligere enn dagens behandling som er Rozlytrek.

I den sammenslåtte analysen opplevde ca. 7 av 10 pasienter at kreftsvulstene krympet og hos ca. 2 av 10 pasienter forsvant kreftsvulsten helt. Effekten varierte avhengig av hvor kreften var lokalisert. Vi vet ikke hvor lenge pasienter som behandles med Vitrakvi lever, da studien var for kort til å si noe om dette. De mest vanlige bivirkningene var økning i leverenzymer, kvalme og oppkast, forstoppelse, trøtthet, anemi, svimmelhet og muskelsmerter.

Legemiddelverkets vurdering av dokumentasjonen

Studiene viste at Vitrakvi kan gi krymping av kreftsvulsten hos en andel av pasientene og i noen tilfeller kan svulsten forsvinne helt. Siden studien har fulgt pasientene bare i en begrenset tidsperiode, vet vi ikke hvor lenge pasienter som får Vitrakvi har effekt av behandlingen. Det er imidlertid rimelig å anta at Vitrakvi kan gi en klinisk relevant behandlingseffekt sammenliknet med beste støttebehandling. Vi vet ikke hvor godt eller dårlig Vitrakvi virker sammenliknet med dagens standardbehandling (Rozlytrek) for samme pasientgruppe.

Legemiddelverket konkluderer derfor med at det ikke er mulig å si hvilken effekt pasienter i norsk klinisk praksis vil få av å ta Vitrakvi sammenlignet med Rozlytrek.

Det er flere grunner til at Legemiddelverket ikke kan sammenligne effekten av Vitrakvi med dagens standardbehandling (Rozlytrek) eller med annen standardbehandling/støttebehandling:

- *Ukjent prognostisk verdi av NTRK-fusjon:* Fordi vi ikke tester for NTRK-mutasjon for alle relevante indikasjoner i dag vet vi ikke hvordan sykdomsforløpet til pasientene som har NTRK-fusjonspositiv kreft ser ut sammenlignet med pasienter som har samme krefttype uten genfeil i NTRK-reseptoren.
- *Usikker effekt av Vitrakvi*: Tallene som beskriver effekt fra studiene er veldig usikre, siden studien omfatter små pasientgrupper med stor variasjon i prognose og egenskaper.
- *Ukjent overførbarthet av studiedata til norsk klinisk praksis*: Det er ukjent i hvilken grad resultatene fra studiene kan brukes til å forutsi hvordan det ville ha gått med pasienter i norsk klinisk praksis dersom de får behandling med Vitrakvi.

Hva koster Vitrakvi?

En måneds legemiddelbehandling med Vitrakvi for en pasient koster i dag omtrent 70 117 kroner med maksimalpris, inkludert merverdiavgift. Dette tilsvarer 841 406 kroner i legemiddelkostnader dersom pasienten behandles i ett år. Kostnadene relatert til gentesting er ikke tatt med siden testkostnadene har blitt vurdert av Folkehelseinstituttet i en separat rapport (Tester for deteksjon av NTRK genfusjoner hos pasienter med lokalt avanserte eller metastatiske solide svulster).

Hva er forholdet mellom nytte og kostnad?

For å kunne vurdere om behandling med Vitrakvi gir en merverdi må Legemiddelverket vite hvordan det ville ha gått med pasientene med samme sykdom som får en annen behandling enn Vitrakvi. Studiene som ble gjennomført belyser bare nytten av Vitrakvi isolert sett. Legemiddelverket har derfor ikke kunnet

vurdere nytten av Vitrakvi sammenlignet med behandlingen disse pasientene får i dag i norsk klinisk praksis.

I en metodevurdering regner vi vanligvis om prisen til det vi kaller kostnaden for et «godt leveår» (på fagspråket kalt «kvalitetsjustert leveår»). Med et godt leveår mener vi ett år helt uten sykdom. Dette er en standardisert måte å regne på som gjør det mulig å sammenlikne nytten av ulike behandlinger som brukes mot ulike sykdommer. På grunn av manglende data på hvordan Vitrakvi virker sammenlignet med Rozlytrek kunne ikke Legemiddelverket beregne «kvalitetsjustert leveår» i denne metodevurderingen.

Hvem bestemmer om Vitrakvi skal tas i bruk?
Basert på denne rapporten og andre hensyn fatter Beslutningsforum, bestående av direktørene for de regionale helseforetakene, en endelig beslutning om innføring av nye behandlinger i norske sykehus.

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Bestilling:	*ID-nr ID2019_029: Larotrectinib (Vitrakvi) til behandling av pasienter over 18 år med solide tumorer med et nevrotrofisk tropomyosin-reseptorkinase (NTRK) fusjonsgen, som har en sykdom som er lokalavansert, metastatisk eller hvor kirurgisk reseksjon sannsynligvis vil føre til alvorlig morbiditet og som det ikke finnes noen tilfredsstillende behandlingsalternativer for.*
Bestillingsordlyd:	En forenklet metodevurdering med oppsummering av effekt, sikkerhet og kostnader (D) gjennomføres ved Statens legemiddelverk for Larotrectinib (Vitrakvi) til behandling av pasienter over 18 år med solide tumorer med et nevrotrofisk tropomyosin-reseptorkinase (NTRK) fusjonsgen, som har en sykdom som er lokalavansert, metastatisk eller hvor kirurgisk reseksjon sannsynligvis vil føre til alvorlig morbiditet og som det ikke finnes noen tilfredsstillende behandlingsalternativer for.
Forslagstiller:	Statens legemiddelverk
Legemiddelfirma:	Bayer
Preparat:	Vitrakvi
Virkestoff:	Larotrektinib
Indikasjon:	VITRAKVI, som monoterapi, er indisert til behandling av voksne pasienter med solide tumorer med et nevrotrofisk tropomyosin-reseptorkinase (NTRK)-fusjonsgen - som har en sykdom som er lokalavansert, metastatisk eller hvor kirurgisk reseksjon sannsynligvis vil føre til alvorlig morbiditet og - som det ikke finnes noen tilfredsstillende behandlingsalternativer for
ATC-nr:	L01EX12

Prosess

Tidspunkt for MT for legemiddelet evt. indikasjonsutvidelsen	19-09-2019
Dokumentasjon bestilt av Legemiddelverket	26-08-2019
Fullstendig dokumentasjon mottatt hos Legemiddelverket	21-12-2021
Klinikere kontaktet for første gang	16-05-2022
LIS kontaktet for første gang av Legemiddelverket.	08-03-2022

Legemiddelverket bedt om ytterligere dokumentasjon	17.02.2022 28.03.2022 16.05.2022
Ytterligere dokumentasjon mottatt av Legemiddelverket	28.02.2022 13.04.2022 24.05.2022
Rapport ferdigstilt:	26-09-2022
Saksbehandlingstid:	273 dager hvorav 35 dager i påvente av ytterligere opplysninger fra legemiddelfirma. Dette innebærer en reel saksbehandlingstid hos legemiddelverket på 238 dager.
Saksutredere:	Beatriz Luís Helga Haugom Olsen Randi Krontveit Yvonne Anne Michel
Kliniske eksperter:	Anne Siri Gløersen Martin Petersen Elin Hallan Naderi Odd Terje Brustugun
Kliniske eksperter har bidratt med avklaringer av sentrale forutsetninger i analysen (bl.a. sammenlignende behandling, pasientgrunnlag og overførbarhet av studiedata til norsk klinisk praksis). Legemiddelverket er ansvarlig for rapportens innhold. Kliniske eksperter har ikke vært involvert i noen konsensusprosess eller hatt noen «peer-review» funksjon ved utarbeidelse av rapporten.	

GLOSSARY

AE	Adverse events
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
BID	Twice a day
BRCA	BReast CAncer gene
BSA	Body surface area
BSC	Best supportive care
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CT	Computed tomography
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
FISH	Fluorescence in situ hybridization
FMI	Foundation Medicine Inc.
FOLFIRI	5FU + irinotecan + calcium folinate
IC50	Half-maximal inhibitory concentration
IRC	Independent review committee
H2H	Head-to-Head
HRQoL	Health Related Quality of Life
HTA	Health technology assessment
KM	Kaplan Meier

MA	Marketing authorization
MAA	Marketing authorization application
MAIC	Matching adjusted indirect treatment comparison
MAH	Market Authorisation Holder
MASC	Mammary analogue secretory carcinoma
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NET	Neuroendocrine tumours
NGS	Next generation sequencing
NoMA	Norwegian Medicines Agency
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PET	Positron emission tomography
PFS	Progression free survival
PR	Partial response
QALY	Quality-adjusted life year
RECIST	Response evaluation criteria in solid tumors
ROS1	Proto-oncogene tyrosine-protein kinase 1
SmPC	Summary of Product Characteristics
SOC	Standard of care
STA	Single Technology Assessment
T-vec	Imlygic, talimogene laherparepvec
TRK	Tropomyosin receptor kinase

1 BACKGROUND

1.1 SCOPE

This descriptive single technology assessment concerns the treatment of adult (above 18 years of age) patients with solid neurotrophic tyrosine receptor kinase (NTRK) fusion positive tumours with Vitrakvi (Larotrectinib) in Norway. According to the order ID2019_029, NoMA has evaluated the clinical efficacy, safety and costs for the treatment with larotrectinib in patients 18 years of age or older with locally advanced or metastatic solid tumours harbouring NTRK gene fusion where surgical resection is likely to result in severe morbidity and who have no satisfactory treatment options.

Larotrectinib received a condtional marketing authorisation 19 Sept 2019. The main residual uncertainties at the time of the marketing authorization were subsequent to the uncontrolled nature of the pivotal trial, combined with a small sample size and a relatively short duration of follow up. Thus, non-comprehensive data were judged to be available for the precision and size of the efficacy estimates, subgroup analysis based on histology, resistance mechanisms, the role of concomitant oncogenic drivers and the dose in small children where drug exposure at the recommended doses may be higher than in the adults. In addition, the size of the safety database was deemed to be small and the data on long-term safety were limited.

Bayer has committed to address these uncertainties through the submission of the final study report for the pivotal clinical trial LOXO-TRK-15002 (NAVIGATE, due data 30 June 2024) and the 5 years follow up data for the pivotal clinical trial LOXO-TRK-13003 (SCOUT, due date 31 March 2027).

In May 2019 Bayer sent a proposal to the Order Forum and requested a STA covering the adult and the paediatric population. In August 2019, the Order Forum issued an order (ID2019_029) with the adult and paediatric indications being addressed in one STA. Bayer submitted a cost-utility-analysis and documented relative effect based on a naive indirect comparison in March 2020. In early April 2020, NoMA started to assess the delivered documentation and arrived at the conclusion that the submitted documentation was not sufficient to 1) establish relative effect and 2) that the adult and paediatric subpopulations should be assessed separately due to different value propositions in the two subpopulations.

In December 2020 the Order forum issued updated orders requesting two simplified STAs (D-track), with the adult and paediatric indications being addressed separately, both describing the clinical efficacy, safety and costs for the treatment with larotrectinib (ID2019_029 & ID2020_115).

Between December 2020 and November 2021 NoMA provided guidance to Bayer to support the submission of two documentation packages, corresponding to the ordered D-track assessments (ID2019_029 & ID2020_115). July 2021, Bayer sent a request to the Order forum and asked to update the age range of the orders using a cut-off age of 18 years. This request was approved by the Order forum in August 2021.

Bayer submitted documentation for the simplified D-Track assessment on the adult indication in December 2021 (ID2019_029).

The order for the current STA on the adult indication is

En forenklet metodevurdering med oppsummering av effekt, sikkerhet og kostnader (D) gjennomføres ved Statens legemiddelverk for Larotrectinib (Vitrakvi) til behandling av pasienter over 18 år med solide tumorer med et nevrotrofisk tropomyosin-reseptorkinase (NTRK) fusjonsgen, som har en sykdom som er lokalavansert, metastatisk eller hvor kirurgisk reseksjon sannsynligvis vil føre til alvorlig morbiditet og som det ikke finnes noen tilfredsstillende behandlingsalternativer for. Prisnotat utarbeides av Sykehusinnkjøp HF, LIS. Folkehelseinstituttet har ansvar for å gjøre vurderingen av relevante diagnostiske tester.

In addition, Bayer submitted a cost-minimizing analysis with entrectinib as comparator and relative effectiveness based on an unanchored matching adjusted indirect treatment comparison (MAIC). The submitted documentation was not considered sufficient to allow an evaluation of relative effect. NoMA has thus assessed the submitted documentation in line with the simplified order, providing a description of effect, safety and costs. Parts of the documentation package that are not in line with the order given by the Order forum have not been further evaluated.

The paediatric indication will be assessed in a separate STA (ID2020_115) as soon as Bayer has provided documentation.

1.2 SOLID NEUROTROPHIC TYROSINE RECEPTOR KINASE (NTRK) FUSION POSITIVE TUMOURS

The population eligible for treatment with larotrectinib is defined based on the presence of a specific genomic alteration (NTRK-fusion), irrespective of tumour type (tumour-agnostic). Patients with any type of locally advanced or metastatic solid tumour, who test positive for an NTRK-fusion, fall into the scope of this assessment. The tropomyosin receptor kinase (TRK) family includes TRK A, B and C, which are encoded by the neurotrophic tyrosine kinase (NTRK) receptor genes 1, 2 and 3, respectively (7). They are expressed in neuronal tissues, where they play a critical role in the development and function of neurons of the central and peripheral nervous systems, as well as a variety of non-neuronal tissues throughout development, including the cardiovascular, endocrine, reproductive, and immune systems (8). Gene fusions involving NTRK1/2/3 (when the 3' region of the NTRK gene is joined with a 5' sequence of a fusion partner gene) result in a constitutive activation or overexpression of TRK-receptors, potentially leading to oncogenesis (9); multiple fusion partners have been identified in NTRK1/2/3-rearranged tumours to date (7).

1.2.1 Number of patients in Norway

NTRK gene fusions have been identified in a wide range of tumours in both the paediatric and adult population, and is rare in commonly occurring tumours, such as lung cancer, breast cancer, colorectal cancer, thyroid cancer, sarcoma and others (e.g., frequency of <1% - 3% in NSCLC and 1 - 2% in CRC). On the other hand, in certain very rare tumours, such as infantile fibrosarcoma (IFS), secretory/juvenile breast cancer, and mammary analogue secretory cancer of the salivary glands, NTRK gene fusions are the defining genetic feature occurring in approximately 90% to 100% of tumours (3, 10-12). NTRK gene fusions are reported to be mutually exclusive of other oncogenic drivers when found in any given cancer (4, 5). Distribution of NTRK-fusions across some cancer types are shown in Table 1.

Table 1: Detection of NTRK gene fusion in various types of cancer (13)

	NTRK 1	NTRK 2	NTRK 3
NSCLC		<1-3%	
Sarcoma	<1%		
MASC			91-100%
Papillary thyroid	<12%		2-21%
CRC		<1-2%	
Secretory breast			92%
Head and Neck cancer		<1%	<1%
Melanoma	21%		
Neuroendocrine			<1%
Glioblastoma (adult)	1%	1%	1%
Low-grade gliomas		<1%	
Cholangiocarcinoma	4%		

Abbreviations: AML, acute myeloid lymphoma; CRC, colorectal cancer; MASC, mammary analogue secretory carcinoma; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase.

Based on NGS profiling of 116,398 adult and paediatric tumour samples using the Foundation Medicine Inc. (FMI) NGS platform, an estimated prevalence of 0.32% has been observed (12).

1.3 SEVERITY AND SHORTFALL

Patients with NTRK-fusion positive cancers who have exhausted all satisfactory treatment options have poor prognosis. The patient population potentially eligible for larotrectinib is necessarily diverse due to the histology independent indication. Severity and shortfall of patients with solid NTRK-fusion positive tumours is consequently likely to differ by histology. For patients with solid NTRK-fusion positive tumours who do not have other suitable treatment options at current or when surgical resection is likely to result in severe morbidity, prognosis is especially poor.

Given that this is a simplified assessment with the aim of summarizing clinical efficacy, safety and costs, NoMA has not calculated the severity for patients with solid NTRK-fusion positive tumours. In the single technology assessment of entrectinib, NoMA estimated that patients with NTRK-fusion positive cancers who have exhausted all satisfactory treatment options loose about 20 QALYs. However, this estimation is based on assumptions and it should be interpreted with caution (13).

1.4 TREATMENT OF SOLID NEUROTROPHIC TYROSINE RECEPTOR KINASE (NTRK) FUSION POSITIVE TUMOURS

1.4.1 Treatment with larotrectinib

- Therapeutic indication

  Larotrectinib as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion,

  - who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
  - who have no satisfactory treatment options

- Mechanism of action

  Larotrectinib is an adenosine triphosphate (ATP)-competitive and selective tropomyosin receptor kinase (TRK) inhibitor that was rationally designed to avoid activity with off-target kinases. The target for larotrectinib is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by NTRK1, NTRK2 and NTRK3 genes, respectively. In a broad panel of purified enzyme assays, larotrectinib inhibited TRKA, TRKB, and TRKC with IC50 values between 5-11 nM. The only other kinase activity occurred at 100-fold higher concentrations. In *in vitro* and *in vivo* tumour models, larotrectinib demonstrated anti-tumour activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression.

- Posology

  The recommended dose in adults is 100 mg larotrectinib twice daily, until disease progression or until unacceptable toxicity occurs.
  Dosing in paediatric patients is based on body surface area (BSA). The recommended dose in paediatric patients is 100 mg/m2 larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs.

- Undesirable effects

  The most common adverse drug reactions (≥ 20%) of Vitrakvi in order of decreasing frequency were increased ALT (31%), increased AST (29%), vomiting (29%), constipation (28%), fatigue (26%), nausea (25%), anaemia (24%), dizziness (23%), and myalgia (20%).

1.4.2 Treatment guidelines

Until recently, there were no approved therapies for NTRK-fusion positive cancers, and treatment guidelines generally recommend standard of care as appropriate for each individual tumour type.

1.4.3 Position of larotrectinib in the treatment pathway

According to the SmPC, larotrectinib should only be used if there are no satisfactory treatment options (i.e., for which clinical benefit has not been established, or where such treatment options have been exhausted). Until recently, treatment modalities for such patients would mainly be best supportive care (BSC) or last line palliative chemotherapy. However, recently another NTRK inhibitor, entrectinib, was granted a conditional approval in an overlapping patient population, i.e. as monotherapy for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, who have not received a prior NTRK inhibitor, and who have no satisfactory treatment options. In Norway entrectinib was subsequently temporarily introduced by the Decision forum, condition on an alternative pricing arrangement.

Bayer did not submit sufficient documentation to establish the treatment effect of larotrectinib relative to other treatments (see section 2.2). Cost-effectiveness has also not been established for entrectinib, due to the same limitations as those outlined for larotrectinib. It is, however, anticipated that larotrectinib will constitute an alternative to entrectinib in clinical practice. A discussion of the potential positioning of larotrectinib in the treatment pathway is presented in Appendix 1: Discussion on comparators.

1.4.4 Comparator

Despite the non-comprehensiveness of the clinical efficacy and safety data supporting the regulatory decisions for both entrectinib and larotrectinib, taking into account the last-line indication granted for both products, NoMA considers entrectinib to be the relevant comparator for this assessment.

1.4.5 Treatment with entrectinib

- Therapeutic indication

  Entrectinib as monotherapy is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,

  o who have a disease that is locally advanced, metastatic or where surgical resection is likely to
  o result in severe morbidity, and
  o who have not received a prior NTRK inhibitor
  o who have no satisfactory treatment options

  Entrectinib as monotherapy is also indicated for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors.

- Mechanism of action

  Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases TRKA, TRKB and TRKC (encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes NTRK1, NTRK2 and NTRK3,

respectively), proto-oncogene tyrosine-protein kinase ROS (ROS1), and anaplastic lymphoma kinase (ALK).

Fusion proteins that include TRK, ROS1 or ALK kinase domains drive tumorigenic potential through hyperactivation of downstream signalling pathways leading to unconstrained cell proliferation. Entrectinib demonstrated in vitro and in vivo inhibition of cancer cell lines derived from multiple tumour types, including subcutaneous and intracranial tumours, harbouring NTRK, ROS1, and ALK fusion genes.

- Posology

  The recommended dose for adults is 600 mg entrectinib once daily. For adults, the dose of entrectinib may be reduced up to 2 times, based on tolerability. Entrectinib treatment should be permanently discontinued if patients are unable to tolerate a dose of 200 mg once daily. For adolescents with a body surface area (BSA) between 1.11 m2 and 1.50 m2 a dose of 400 mg daily is recommended. For adolescents with a BSA over 1.50 m2, the recommended dose is 600 mg. For adolescents and children ≥12 years of age, the dose of entrectinib may be reduced up to 2 times, based on tolerability, see separate table in SmPC.

- *Undesirable effects*

  The most common adverse reactions (≥20%) were fatigue, constipation, dysgeusia, oedema, dizziness, diarrhoea, nausea, dysesthesia, dyspnoea, anaemia, increased weight, increased blood creatinine, pain, cognitive disorders, vomiting, cough, and pyrexia. The most frequent serious adverse reactions (≥2%) were lung infection (5.2%), dyspnoea (4.6%), cognitive impairment (3.8%), and pleural effusion (2.4%). Permanent discontinuation due to an adverse reaction occurred in 4.4% of patients.

2 SUBMITTED DOCUMENTATION TO PROVE THE RELATIVE EFFECTIVENESS

2.1 OVERVIEW OF RELEVANT CLINICAL STUDIES

The efficacy and safety of larotrectinib in paediatric and adult patients with NTRK-fusion positive cancer is evaluated in three multi-centre open label, phase I/II, single arm trials. Two of these studies are still recruiting patients and all studies are ongoing:

• LOXO-study TRK-14001 (NCT-02122913): adults (recruitment ended) phase-I

• SCOUT-study LOXO-TRK-15003 (NCT-02637687): paediatric patients, phase-I/II (SCOUT)

• NAVIGATE-study LOXO-TRK-15002 (NCT-02576431): adult and adolescent, phase II (NAVIGATE)

Results are based on a pooled analyses of efficacy and safety data for both paediatric and adult patients. The marketing authorization application (MAA) used a data cut-off from July 2018 (n=93). For the purpose of this application a later data cut-off (July 2020) has been submitted. The efficacy analysis set, referred to as the ePAS5, includes 192 patients enrolled across the three studies with 1) an NTRK gene fusion, 2) a non CNS primary tumour, 3) measurable disease assessed by RECIST v1.1, and 4) who received at least one dose of Vitrakvi as of July 2020.

The current application only concerns the adult subpopulation (n=122). Bayer was, however, unable to provide separate data on the adult population for all study results. This section therefore presents data for the overall study population (n=192), followed by data from the adult subpopulation where available.

In addition, 33 patients with primary CNS tumours and measurable disease at baseline were treated in two of the three studies (NAVIGATE and in SCOUT). Results for these 33 patients are presented as the SAS3 analysis set. Results from a post-hoc analyses including patients with primary CNS tumours, resulting in a pooled population of 225 patients, are also presented where available.

The three ongoing clinical trials pivotal to the marketing authorization (MA) are summarized in Table 2 below.

Table 2: Overview of the pivotal clinical trials for larotrectinib

Study 1	LOXO-study TRK-14001 (NCT-02122913): adults (recruitment ended) phase-I: A Study to Test the Safety of the Investigational Drug Larotrectinib in Adults That May Treat Cancer. 12 MAY 2014–Study ongoing, closed to further enrollment
Sample size (n)	75 participants
Study design	Multicenter, Phase 1, open-label, 3 + 3 dose escalation study, with expansion phase in adult patients with NTRK gene fusions only
Patient population	Adult patients with advanced solid tumors (all comers) not selected for NTRK gene fusion cancer
Intervention(s)	Test the safety of the investigational drug larotrectinib in adults that may treat cancer
Comparator(s)	N/A Single arm trial
Follow-up period	Up to 60 months

Is the study used in the health economic model?	Yes
Reasons for use / non-use of the study in model	The efficacy and safety of Vitrakvi in pediatric and adult patients with TRK fusion cancer is studied in three multi-centre open label, phase I/II and single arm trials. Based on agreements with regulatory agencies these 3 studies constitue the marketing authorisation studies
Primary endpoints reported* include results	Safety, MTD, recommended dose for Phase 2
Other outcomes reported * include results	ORR (CR + PR), Duration of response, PK profile

* Provide a definition for the endpoints when relevant

** Explain why these are more relevant for the assessment if they replace the primary endpoints of the study

Study 2	SCOUT-study LOXO-TRK-15003 (NCT-02637687): pediatric patients, phase-I/II: A study to test the safety and efficacy of the drug larotrectinib for the treatment of tumors with NTRK-fusion in children (SCOUT) 15 OCT 2015–Study ongoing
Sample size (n)	174
Study design	Multicenter, Phase 1/2, open-label, study in pediatric patients (1 month to <21 years) with advanced solid or primary CNS tumors. Phase 1, a sequential-cohort, dose escalation study to identify the MTD dose Phase 2, treatment with larotrectinib in 3 cohorts of pediatric patients with IFS, other extracranial solid tumors, and primary CNS tumors
Patient population	Patients aged 1 month to 21 years with advanced solid or primary central nervous system (CNS) tumors
Intervention(s)	Dose escalation study to identify the MTD dose (Phase 1); Treatment with larotrectinib in 3 cohorts of pediatric patients with IFS, other extracranial solid tumors, and primary CNS tumors (Phase 2)
Comparator(s)	N/A single arm trial
Follow-up period	Up to 112 months
Is the study used in the health economic model?	Yes
Reasons for use / non-use of the study in model	The efficacy and safety of Vitrakvi in pediatric and adult patients with TRK fusion cancer is studied in three multi-centre open label, phase I/II and single arm trials. Based on agreements with regulatory agencies these 3 studies constitue the marketing authorisation studies
Primary endpoints reported* include results	Phase 1 Primary: Safety, DLT; Phase 2 Primary: ORR (CR + PR)
Other outcomes reported * include results	Phase 1 Secondary: Best overall response, Duration of response, Quality of life Safety; Phase 2 Secondary: Duration of response Safety

* Provide a definition for the endpoints when relevant

** Explain why these are more relevant for the assessment if they replace the primary endpoints of the study

Study 3	NAVIGATE-study LOXO-TRK-15002 (NCT-02576431): adult and adolescent, phase II: A study to test the effect of the drug larotrectinib in adults and children with NTRK-fusion positive solid tumors. 13 OCT 2015–Study ongoing
Sample size (n)	200
Study design	Multicenter, Phase 2, open-label "basket" study in patients 12 years of age or older with an advanced cancer bearing an *NTRK* gene fusion
Patient population	Patients 12 years of age or older with an advanced cancer bearing an *NTRK* gene fusion
Intervention(s)	Basket study of the Oral TRK Inhibitor Larotrectinib in patients with NTRK fusion-positive tumors
Comparator(s)	N/A single arm trial
Follow-up period	Up to 120 months
Is the study used in the health economic model?	Yes
Reasons for use / non-use of the study in model	The efficacy and safety of Vitrakvi in pediatric and adult patients with TRK fusion cancer is studied in three multi-centre open label, phase I/II and single arm trials. Based on agreements with regulatory agencies these 3 studies constitue the marketing authorisation studies
Primary endpoints reported* include results	ORR (CR + PR)
Other outcomes reported * include results	Best overall response, duration of response, Clinical benefit rate (disease control rate), PFS, OS, Exploratory Quality of life, Safety

2.1.1 Methods

2.1.1.1 Study participants

All three trials enroll patients with a locally advanced, or metastatic evaluable (by RECIST v. 1.1.) solid tumour who have an ECOG PS of 0 to 3, with an adequate major organ function. All patients must have received prior standard therapy or would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy (NAVIGATE); or must have progressed on prior therapy or be nonresponsive to available therapies and for which no standard or available systemic curative therapy existed (Studies LOXO and SCOUT). Studies LOXO (14001) and SCOUT (15003) included patients with or without documented NTRK gene fusions while NAVIGATE (15002) required all patients to have an NTRK gene fusion. Furthermore, primary CNS malignancy was specifically mentioned and allowed in Studies NAVIGATE and SCOUT. As specified above, however, only patients with an NTRK gene fusion and a non-CNS primary malignancy were included in the primary efficacy analyses set (ePAS5).

Identification of NTRK gene fusions mainly relied upon next generation sequencing (NGS), however polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), Nanostring, Sanger sequencing, and Chromosome Microarray were also used in a minority of patients (n=30).

2.1.1.2 Treatments

Larotrectinib was administered in two different forms: capsule or oral solution at a target adult dose of 100 mg BID, continuously in 28-day cycles, until disease progression or intolerable toxicity. However, as patients from dose-finding studies are included in the pooled efficacy analysis, not all patients received this dose.

In at least two of the studies (LOXO and NAVIGATE) patients with progressive disease were allowed to continue larotrectinib if, in the opinion of the Investigator, the patient was deriving clinical benefit from continuing study drug and continuation of treatment was approved by the Sponsor.

Median time on treatment was 16.8 months (range: 0.10 to 60.4 months).

2.1.1.3 Endpoints

The primary endpoint for the pooled efficacy analyses was ORR by IRC assessment, defined as the proportion of patients with best overall response of confirmed complete response (CR) or confirmed partial response (PR).

Best overall response was defined as the best response designation as of the data cut-off date for each patient recorded between the date of the first dose of larotrectinib and the date of documented disease progression per RECIST v1.1, the date of subsequent therapy or cancer related surgery, or the data cut-off date, whichever occurred first. Patients who underwent surgical resection on therapy with no viable tumour cells and negative margins on postsurgical pathology report were considered a CR by surgery/pathology.

Study success was to be claimed if a lower limit of 30% for ORR was ruled out. This was considered clinically meaningful and consistent with the estimated response rates seen with approved targeted therapies in genetically-defined patient populations who had progressed on prior therapies.

Across the 3 studies, disease assessment was performed by computed tomography (CT), positron emission tomography (PET), and/or magnetic resonance imaging (MRI) performed at screening, every other cycle on or around day 1 of odd-numbered cycles, and at the end-of-treatment.

The main secondary endpoints for the pooled analyses were time to response and time to best response, duration of response (DOR), time on treatment, disease-control rate, progression-free survival (PFS) and overall survival (OS).

2.1.2 Results

2.1.2.1 Patient characteristics

The main baseline patient and disease characteristics for the overall ePAS5 population and the SAS3 population are summarized in Table 3 and Table 4 below, whereas the number and percentage of prior treatment line for the overall populations (ePAS5 and SAS3) and by tumour type and presented in Table 5 and Table 6.

Table 3: Main baseline characteristics ePAS5-Dataset

Dataset	ePAS5
Data cut-off	July 2020
Total patient population	192
Median age, years	38 (0.1-75+)
Number of children, %	36.5
Number of women, %	49
Performance status, %	ECOG
0 or 1	87
>=2	13
Primary tumour location	Soft tissue sarcoma, Salivary gland, Lung, Colon, Infantile fibrosarcoma, Thyroid, Melanoma, Breast, GIST, Pancreas, Bone sarcoma, Cholangiocarcinoma, Appendix, Hepatic, Congenital mesoblastic nephroma, Cervix, Prostate, Rectal, External auditory canal, Uterus, Esophageal

Table 4: Main disease characteristics ePAS5- and SAS3 Datasets

	ePAS5	**SAS3**
N	192	33
Primary tumor type, n (%)		
Soft tissue sarcoma	48 (25)	0
Salivary gland	22 (11)	0
Lung	15 (8)	0
Colon	8 (4)	-
Infantile fibrosarcoma	40 (21)	0
Thyroid	28 (15)	0
Melanoma	7 (4)	-
Breast	7 (4)	0
Non-secretory	3 (2)	-
Secretory	4 (2)	-
Gastrointestinal stromal	4 (2)	-
Pancreas	2 (1)	-
Bone sarcoma	2 (1)	-
Cholangiocarcinoma	2 (1)	-
Appendix	1 (1)	-
Congenital mesoblastic nephroma	2 (1)	-
Hepatic	1 (1)	-
Cancer of unknown primary	1 (1)	-
Cervix	1 (1)	0
Prostate	1 (1)	-
Primary CNS	-	33 (100)
Time from diagnosis, years		
Median	1.3	2.0
Range	0.02 – 31.5	0.13 – 9.6
Disease extent at enrollment, n (%)		
Locally advanced	55 (29)	0
Metastatic	137 (71)	0
Other	0	33 (100)
NTRK gene fusion, n (%)		
NTRK1	82 (43)	5 (15)
NTRK2	6 (3)	24 (73)
NTRK3	95 (49)	4 (12)
Inferred *NTRK*3	9 (5)	0

Table 5: Number and percentage of patients who received 0, 1, 2, or 3+ prior treatment lines presented for ePAS5 and SAS3

Number of Prior Systemic Regimens	ePAS5 (N=192)	SAS3 (N=33)
0	51 (27%)	6 (18%)
1	54 (28%)	12 (36%)
2	37 (19%)	8 (24%)
3 or more	50 (26%)	7 (21%)

Table 6: Number and percentage of patients who received 0, 1, 2, or 3+ prior treatment lines presented separately for each tumour type, Investigator assessed (INV) thereby 218 patients. Data cut of July 2020.

	Number of prior lines of therapy*				Total (n=218)
	0 (n=58)	1 (n=59)	2 (n=42)	≥3 (n=57)	
Tumor type, n (%)					
Soft tissue sarcoma	15 (26)	19 (32)	11 (26)	10 (18)	56 (26)
Infantile fibrosarcoma	15 (26)	15 (25)	8 (19)	6 (11)	44 (20)
Thyroid	7 (12)	7 (12)	4 (10)	10 (18)	29 (13)
Salivary gland	13 (22)	6 (10)	2 (5)	3 (5)	24 (11)
Lung	1 (2)	6 (10)	3 (7)	10 (18)	20 (9)
Colon	1 (2)	2 (3)	6 (14)	0	9 (4)
Melanoma	0	1 (2)	3 (7)	3 (5)	7 (3)
Breast	2 (3)	0	0	5 (9)	7 (3)
Other†	4 (7)	3 (5)	5 (12)	10 (18)	22 (10)

2.1.2.2 Efficacy results

2.1.2.2.1 Overall response rate (ORR) and duration of response (DOR)

Response rates and DoR in the overall study population excluding and including patients with CNS primary malignancies are presented in Table 7 and response rates and DoR by tumour type are summarized in Table 8 and Table 9. In the ePAS5, ORR was 72% (CI: 65-79%) with 23% being Complete Responders (CR) and 7% of the patients being in pathological CR. Median duration of response (DOR) was 34.5 months (range 1.6 – 58.5) at a median follow-up time of 20.3 months. The median time to response was 1.8 months. In the post-hoc analyses including patients with primary CNS tumours, the point estimate for ORR was lower, as only 8 of the 33 patients (24%) with a CNS primary achieved a response (Table 7).

In the adult sub-population (n=122), the ORR was 64% (95% CI: 55-72%) of whom 19% were in CR and 1% in pathological CR. In the 33 patients with primary CNS malignancies, the overall response rate was 24% (95% CI: 11, 42), and the DoR could not be estimated (data not shown).

Table 7: Pooled efficacy results in solid tumours including and excluding primary CNS tumours

Efficacy parameter	**Analysis in solid tumours excluding primary CNS tumours (n=192)**[a]	**Analysis in solid tumours including primary CNS tumours (n=225)**[a, b]
Overall response rate (ORR) % (n) [95% CI]	72% (139) [65, 79]	65% (147) [59, 72]
Complete response (CR)	23% (44)	21% (47)
Pathological complete response[c]	7% (13)	6% (13)
Partial response (PR)	43% (82)	39% (87)[d]
Time to first response (median, months) [range]	1.84 [0.89, 16.20]	1.84 [0.89, 16.20]
Duration of response (median, months) [range] % with duration ≥ 12 months % with duration ≥ 24 months	34.5 [1.6+, 58.5+] 79% 66%	34.5 [1.6+, 58.5+] 79% 66%

+ denotes ongoing, a Independent review committee analysis by RECIST v1.1 for solid tumours except primary CNS tumours (192 patients). b Investigator assessment using either RANO or RECIST v1.1 criteria for primary CNS tumours (33 patients). c A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumour cells and negative margins on post-surgical pathology evaluation. The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v.1.1. d An additional 1% (2 patients with primary CNS tumours) had partial responses, pending confirmation.

Table 8: Overall response rate and duration of response by tumour type.

Tumour type	Patients (n=225)	ORR[a]		DOR		
		%	95% CI	months		Range (months)
				≥ 12	≥ 24	
Soft tissue sarcoma	48	69%	54%, 81%	78%	63%	1.9+, 54.7
Infantile fibrosarcoma	40	93%	80%, 98%	80%	62%	1.6+, 38.5+
Primary CNS	33	24%	11%, 42%	75%	NR	3.8, 22.0+
Thyroid	28	64%	44%, 81%	94%	76%	2.8+, 39.2+
Salivary gland	22	86%	65%, 97%	89%	84%	7.4, 58.5+
Lung	15	87%	60%, 98%	64%	64%	1.9+, 45.1+
Colon	8	38%	9%, 76%	67%	67%	5.6, 27.3
Melanoma	7	43%	10%, 82%	50%	NR	1.9+, 23.2+
Breast	7					
Secretory[b]	4	75%	19%, 99%	0%	0%	9.4+, 11.1
Non-secretory[c]	3	67%	9%, 99%	100%	NR	15.2, 23.0+
Gastrointestinal stromal tumour	4	100%	40%, 100%	75%	38%	9.5, 31.1+
Bone sarcoma	2	50%	1%, 99%	0%	0%	9.5
Cholangiocarcinoma[d]	2	0%	NA	NA	NA	NA
Pancreas	2	0%	NA	NA	NA	NA
Congenital mesoblastic nephroma	2	100%	16%, 100%	100%	100%	6.4+, 24.2+
Unknown primary cancer	1	100%	3%, 100%	0%	0%	7.4
Appendix	1	0%	NA	NA	NA	NA
Hepatic[d]	1	0%	NA	NA	NA	NA
Prostate	1	0%	NA	NA	NA	NA
Cervix	1	0%	NA	NA	NA	NA

DOR: duration of response, NA: not applicable due to small numbers or lack of response, NR: not reached,+ denotes ongoing response a evaluated per independent review committee analysis by RECIST v1.1 for all tumour types except patients with a primary CNS tumour who were evaluated per investigator assessment using either RANO or RECIST v1.1 criteria b with 2 complete, 1 partial response c with 1 complete, 1 partial response d one patient who is not evaluable.

Table 9: Duration of Response by Primary Diagnosis Based on IRC Assessment (Subgroup of Extended Primary Analysis Set 5 with Confirmed CR, sCR, or PR)

	Number of Patients with CR/sCR/PR[1,2]	Median (Range) Duration of Response in Months[3]
Primary Diagnosis		
Overall	139	34.46 (1.58+, 58.48+)
IFS	37	31.31 (1.58+, 38.54+)
Soft tissue sarcoma	33	34.46 (1.87+, 54.70)
Salivary gland	19	41.49 (7.39, 58.48+)
Thyroid	18	NE (2.79+, 39.16+)
Lung	13	NE (1.87+, 45.11+)
Breast	5	15.18 (9.40+, 23.03+)
GIST	4	17.35 (9.46, 31.05+)
Colon	3	27.33 (5.55, 27.33)
Melanoma	3	NE (1.87+, 23.20+)
Congenital mesoblastic nephroma	2	NE (6.44+, 24.21+)
Bone sarcoma	1	9.49 (9.49, 9.49)
Cancer of unknown primary	1	7.39 (7.39, 7.39)
Breast Cancer		
Secretory	3	11.10 (9.40+, 11.10)
Non-secretory	2	NE (15.18, 23.03+)

In 198 patients with wide molecular characterisation before larotrectinib treatment, the ORR in 95 patients who had other genomic alterations in addition to NTRK gene fusion was 55%, and in 103 patients without other genomic alterations ORR was 70% (data not shown).

2.1.2.2.2 Progression free survival (PFS)

The KM curves for PFS for the ePAS5 and for the adult subpopulation of the ePAS5 are shown in Figure 1 and Figure 2, respectively, whereas the progression status for the ePAS5 are presented in Table 10.

In the overall study population, at a median follow-up of 22.1 months, median PFS was documented to be 33.4 months. The PFS rate at 24 months was 57%.

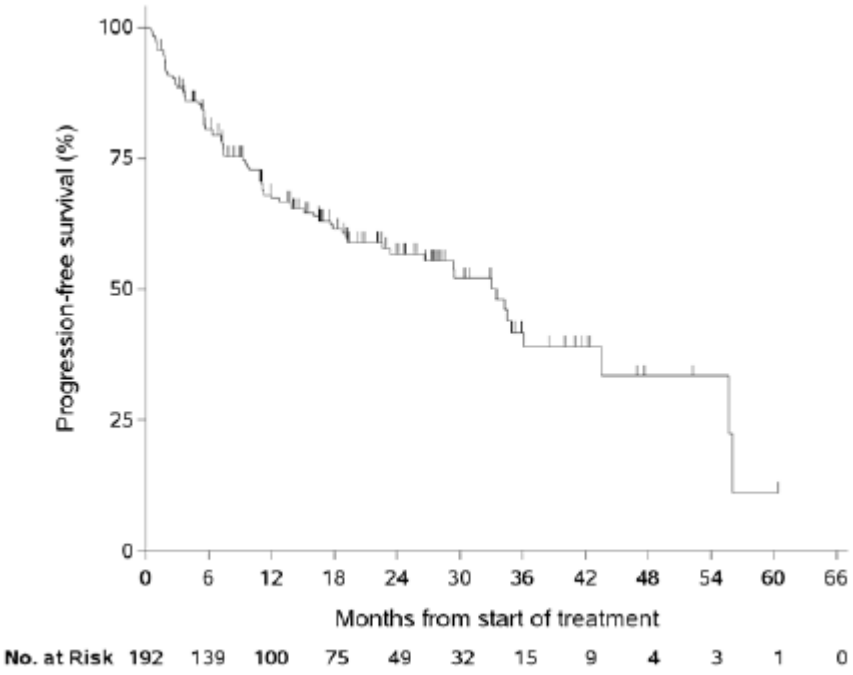

Figure 1: Kaplan Meier curve of PFS for patients with TRK-fusion cancer (ePAS5, July 2020)

Table 10: Progression status based on IRC Assessments for the Extended Primary Analysis Set 5

[redacted]

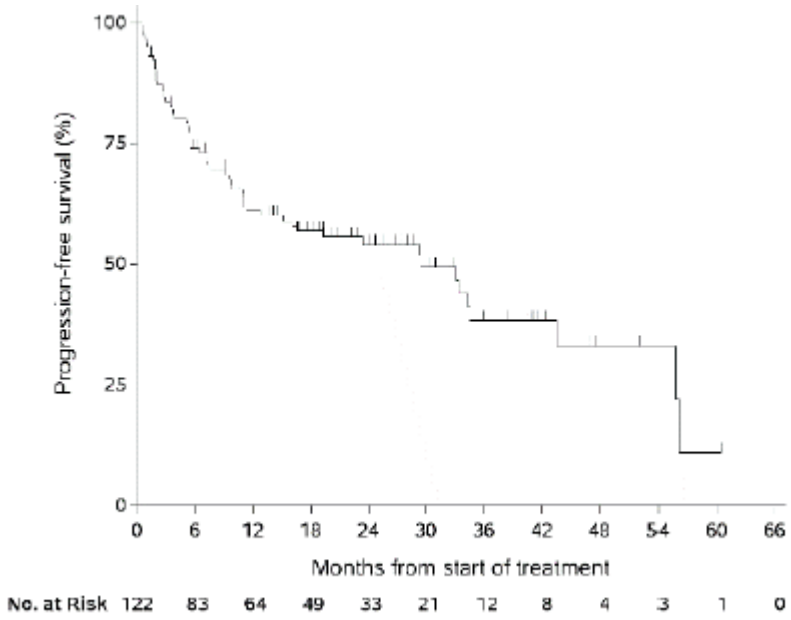

Figure 2: Kaplan Meier curve of PFS for adults (n=122)

2.1.2.2.3 Overall survival (OS)

The KM-curves for overall survival in the ePAS5 and adult subpopulation of the ePAS5 are shown in Figure 3 and Figure 4, respectively. In the overall study population, at a median follow-up time of 24 months, median OS was not reached. At 12 and 24 months, 89% and 82% of the patients were alive.

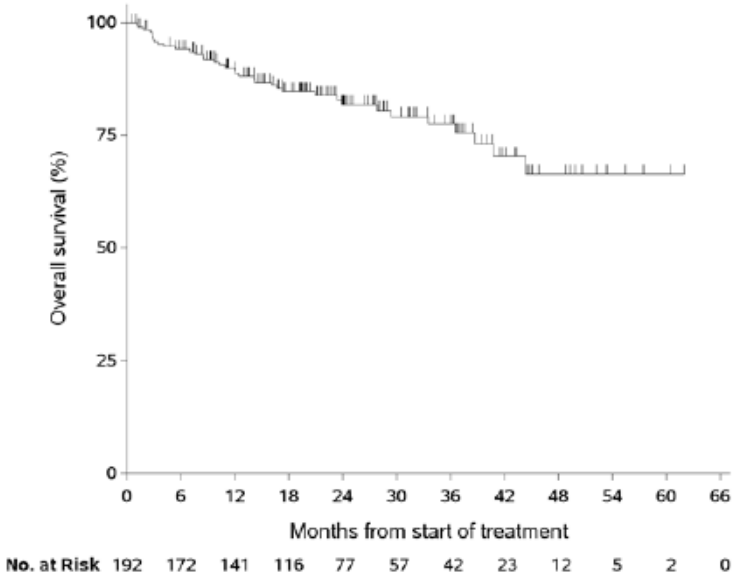

Figure 3: Kaplan Meier curve of OS for patients with TRK-fusion cancer (ePAS5, July 2020)

In the adult sub-population, median OS was not reached at a median follow-up time of 25 months. The OS landmark at 24-months was 74% for adults.

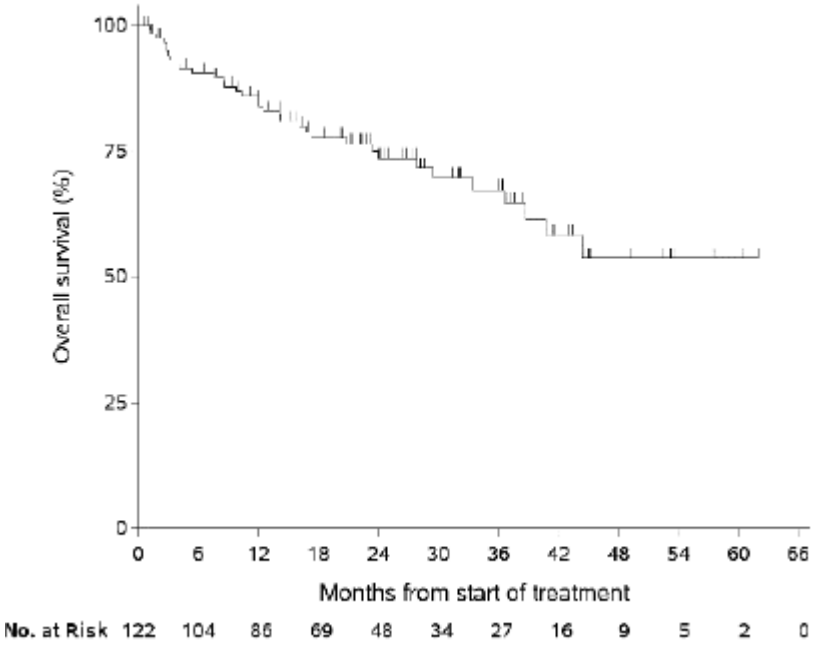

Figure 4: Kaplan Meier curve of OS for adults (n=122)

2.1.2.2.4 Contextualisation of the larotrectinib study results

Due to the limited sample size, short study durations and uncontrolled nature of both the pivotal larotrectinib and entrectinib trials, the relative effectiveness of larotrectinib over best standard of care (other than entrectinib) and over entrectinib cannot be established. To contextualize the larotrectinib study results, data on clinical outcomes as reported in the literature (SOC, Table 11) and in the SmPC (entrectinib, Table 12 and Table 13) have been included below. These data are intended to provide a high-level overview of expected outcomes in the current treatment landscape. Any comparisons of larotrectinib to these data constitute naïve comparisons with no adjustment for important confounding factors (including NTRK status for SOC). Furthermore, information concerning the internal and external validity of the comparator trials, the definition and timing of endpoint etc. has not been evaluated. NoMA would therefore generally advice against such comparisons.

Table 11: Outcomes as reported for Larotrectinib and Available Systemic Treatment for Cancer (by Tumour Type), data cut-off 20 Jul 2020 (source: Bayer, (14))

Tumour Site	Available Treatments (range of data across available publications)					Larotrectinib (ePAS5)		
	Treatment line	N	CR+PR (%)	PFS (months)	OS (months)	N	CR+PR (%)	PFS range (months)
Soft tissue sarcoma	First[a]	30-228	8 - 26	3.0-7.4	8-26.5	48	69	0.03+ to 55.69
	Second [b]	16-345	1.6 - 45.8	1.5-6.6	11.5-19.5			
Salivary gland carcinoma	First/ second [c]	8-45	0 - 60	2.1-64	4-35	22	86	0.72 to 60.39+
Infantile fibrosarcoma	Vincristine- dactinomycin[d]	56	71	NR	NR	40	93	3.22+ to 42.12+
Colorectal	First [e]	122-701	18 – 65.1	4.2 – 12.1	12 – 31.0	8	38	1.48+ to 29.37
	Second [f]	109-650	3.3 - 35	2.6 – 14.2	10.0-21.5			
	Further [g]	111-534	0.4 – 22.9	1.5 – 4.1	5.0 – 10.4			
Thyroid cancer	Any [h]	2 - 231	0 – 64.8	1.6 - 61	3.0 - 35	28	64	0.03+ to 42.41+
Gastrointestinal Stromal tumour	First (imatinib)	147-473	51.0 – 68.1	20.4 – 24.0	46.8 - 57	4	100	11.14 to 32.79+
	Second (sunitib)	61- 207	7 – 13.0	5.5 – 7.8	24.6			
	Further (regorafenib)	34-133	4.5 – 11.8	4.8 – 10.0	NR			
Lung cancer (EGFR and ALK negative)	First [i]	88 - 290	9.9 – 22.7	3.1 – 5.5	6.4 – 14.3	15	87	5.32 to 46.92+
	Second [j]	104 - 659	3 – 22.9	1.9 – 10.6	4.6 – 12.7			
Lung cancer (EGFR mutated)	Any [k]	75 - 723	23 – 72.5	2.2 – 16.0	6.9 – 245			
Lung cancer (ALK mutated)	Any [l]	83 - 189	20 – 82.9	1.6 – 25.7	16.7 – 26.0			
Malignant melanoma	First [m]	47 - 655	11 - 61	2.2 – 11.5	9.1 – 37.6	7	43	0.03+ to 24.84+
	Second [n]	133 - 272	10.6 – 31.7	2.86 – 4.7	10.1			
Malignant melanoma (BRAF mutated)	First [o]	63 - 338	5 - 69	1.5 – 12.3	10.3 – 25.1			
	Second [p]	23 - 132	10 - 57	3.0 – 6.8	10.0 – 15.9			

Data cut-off 20Jul2020
+ patient still ongoing
The different treatment options used for each histology type are shown in the following footnotes.
a Doxorubicin, Doxorubicin+Olaratumab, Doxorubicin+Ifosfamide, Gemcitabine+docetaxel, Gemcitabine, Paclitaxel. Paclitaxel both first and second line.
b Trabectedin, Dacarbazine, Pazopanib, Eribulin, Paclitaxel + bevacizumab, Paclitaxel.
c Paclitaxel, Gemcitabine, Epirubicin + Plat + 5FU, Cisplatin + vinorelbine first line, Cisplatin + vinorelbine second line, Mitoxantrone+Cisplatin,
Plat + Gemcitabine, Cyclophosphamide, doxorubicin + cisplatin, Cisplatin + Imatinib, Cetuximab + Cis + 5FU
Pembrolizumab, Sorafenib, Dovitinib, Imatinib, Lapatinib, Sunitinib, Everolimus, Nelfinavir, Bortezomib, Gefitinib
d Limited data available from case series only
e IFL, fluorouracil, leucovorin, Irinotecan, FOLFOX, Oxiplatin + irinotecan, FOLFIRI, XELOX, FUOX, FOLFOXFIRI, IFL + bevacizumab, FOLFIRI + bevacizumab,
FOLFOXIRI + bevacizumab, FOLFOX/XELOX + bevacizumab, FOLFOX/XELOX, FOLFIRI + cetuximab, FOLFOX + panitumumab
f Capecitabine + irinotecan, FOLFIRI, FOLFOX, Fluoropyrimidines, Fluoropyrimidine+ irinotecan, Fluoropyrimidine + oxaliplatin, Oxaliplatin + bevacizumab,Bevacizumab, oxaliplatin + fluoropyrimidine
g Cetuximab, Cetuximab + irinotecan, Panitumumab, Regorafenib + best supportive care, Placebo + best supportive care, Trifluridine/tipiracil + best supportive care
h Doxorubicin, Doxorubicin + cisplatin, Sorafenib, Lenvatinib, Doxorubicin + cisplatin + bleomycin, Paclitaxel, Docetaxel, Axitinib, Lenvatinib, Dabrafenib + trametinib, Everolimus, Imatinib, Lenvatinib, Pazopanib, Sorafenib, Vandetanib, Vemurafenib, Fosbretabulin + paclitaxel + carboplatin, Paclitaxel + Efatutazone, Efatutazone
i Cisplatin +paclitaxel, Cisplatin + gemcitabine, Cisplatin + docetaxel, Carboplatin and paclitaxel, Vinorelbine, gemcitabine, Vinorelbine + gemcitabine, Docetaxel

j Pemetrexed, Docetaxel, Best supportive care, Nivolumab, Pembrolizumab, Ramucirumab + docetaxel, Nintedanib + docetaxel, Afatinib, Erlotinib
k Gefitinib, Carboplatin + paclitaxel, Docetaxel, Erlotinib, Cisplatin + docetaxel, Erlotinib and bevacizumab, Afatinib, Gefitinib, Cisplatin + Pemetrexed, Osimertinib mesylate
l Crizotinib, Pemetrexed, Docetaxel, Pemetrexed+ cisplatin, Pemetrexed + carboplatin, Alectinib, Ceritinib
m Pembrolizumab, Pembrolizumab + reduced dose ipilimumab, Nivolumab, Dacarbazine, Ipilimumab + dacarbazine, Ipilimumab, Novilumab + ipilimumab
n Nivolumab, Dacarbazine or paclitaxel + carboplatin, Ipilumab
o Vemurafenib, Dacarbazine, Dabrafenib, Dacarbazine, Trametinib, Dacarbazine or paclitaxel, Vemurafenib, Vemurafenib + cobimetinib, Dabrafenib + trametinib
p Vemurafenib, Dabrafenib + trametinib
Abbreviations: 5-FU = fluorouracil; ALK = anaplastic lymphoma kinase; CR = complete response; EGFR = epidermal growth factor receptor; ePAS = extended primary analysis set; FOLFIRI = folinic acid (leucovorin calcium) + fluorouracil + irinotecan; FOLFOX = folinic acid (leucovorin calcium) + fluorouracil + oxaliplatin ; FOLFOXFIRI = folinic acid (leucovorin calcium) + fluorouracil + oxaliplatin + irinotecan; FUOX = fluorouracil and oxaliplatin; IFL = folinic acid (leucovorin calcium) + fluorouracil + irinotecan; NR = not reported; OS = overall survival; PFS = progression-free survival; PR = partial response; XELOX = capecitabine + oxaliplatin

Table 12: Responses and duration of response by BICR in adults with NTRKgene fusion-positive solid tumours as reported for entrectinib

Efficacy endpoint	**Rozlytrek N = 74**
Primary endpoints *(BICR assessed; RECIST 1.1)*	
Objective Response Rate	
Number of Responses	47/74
ORR% (95% CI)	63.5% (51.5, 74.4)
Complete Response, n (%)	5 (6.8%)
Partial Response, n (%)	42 (56.8%)
Duration of Response*	
Number (%) of patients with events	21/47 (44.7%)
Median, months (95% CI)	12.9 (9.3, NE)
6-month durable response % (95% CI)	71% (58, 85)
9-month durable response % (95% CI)	65% (51,80)
12-month durable response % (95% CI)	55% (39,72)
NE = not estimable. Confidence Intervals (CI) calculated using the Clopper-Pearson method. *Median and percentiles based on Kaplan-Meier estimates	

Table 13: Efficacy of entrectinib by tumour type, in adults with NTRK gene fusion-positive solid tumours.

Tumour type	Patients (N = 150)	ORR		DOR
		n (%)	95% CI	Range (months)
Sarcoma	32	19 (59.4)	(40.6, 76.3)	2.8, 44.6*
Non-small cell lung cancer	31	20 (64.5)	(45.4, 80.8)	3.7, 58.8*
Salivary (MASC)	26	22 (84.6)	(65.1, 95.6)	2.8, 49.7*
Breast cancer (secretory)	6	5 (83.3)	(35.9, 99.6)	5.5, 53.4*
Breast cancer (non-secretory)	2	NE, PR	NA	4.2
Breast cancer (NOS)	1	NE	NA	NA
Thyroid cancer	16	10 (62.5)	(35.4, 84.8)	5.6, 44.2*
Colorectal cancer	11	3 (27.3)	(6.0, 61.0)	1.9*, 20.0
Neuroendocrine cancers	5	2 (40.0)	(5.3, 85.3)	11.1, 31.1
Head and neck	5	3 (60.0)	(14.7, 94.7)	4.0, 32.6*
Pancreatic cancer	4	3 (75.0)	(19.4, 99.4)	7.1, 12.9
Unknown primary cancer	3	1 (33.3)	(0.8, 90.6)	9.1
Ovarian cancer	1	Non CR/PD	NA	NA
Endometrial carcinoma	1	PR	NA	38.2
Cholangiocarcinoma	1	PR	NA	9.3
Gastrointestinal cancer (other)	1	CR	NA	30.4
Neuroblastoma	1	NE	NA	NA
Prostate	1	PD	NA	NA
Penile	1	PD	NA	NA
Adrenal cancer	1	PD	NA	NA

*Censored
ORR: Objective Response Rate; DOR: Duration of Response; MASC: mammary analogue secretory carcinoma; NA: not applicable due to small number or lack of response; CR: complete response; PR: partial response; PD: progressive disease; NE: not estimable.

2.1.2.2.5 Health related quality of life (HRQoL)

Patient reported outcome data were collected as exploratory endpoints to evaluate disease related symptoms and health related quality of life using validated instruments (EORTC QLQC-30). EORTC Core Quality of Life Questionnaire (EORTC QLQC-30) is a non-preference based cancer-specific HRQoL instrument. The results of these analyses have not been presented in the submitted documentation.

2.1.2.3 Safety results

The majority of adverse events (AE) reported with larotrectinib were Grade 1 or 2. Grade 3 AEs, were reported for anaemia, weight increased, fatigue, dizziness, paraesthesia, muscular weakness, nausea, myalgia, gait disturbance, and vomiting. All the reported Grade 3 AEs occurred in 5% or less of patients except for anaemia (7%) (Table 14). Grade 4 AEs were reported for neutrophil count decreased (2%), ALT increased (1%), AST increased, leucocyte count decrease and blood alkaline phosphatase increase (each in < 1%). Permanent discontinuation of larotrectinib for treatment emergent adverse reactions, regardless of attribution occurred in 2% of patients (Table 14). The majority of adverse reactions leading to dose reduction occurred in the first three months of treatment.

Table 14: Summary of safety (Gr ≥3 AEs) in TRK fusion-positive cancer patients, adult and pediatric, treated with larotrectinib at recommended dose (overall safety population, n=248)

Gr ≥3 AEs	• **ALT increased (5%)** • **AST increased (5%)** • **anaemia (7%)** • neutropenia (4%) • leukopenia (2%) • dizziness (1%) • paraesthesia (1%) • gait disturbance (<1%) • vomiting (<5%) • nausea (<5%) • myalgia (<5%) • muscular weakness (<5%) • fatigue (<5%) • weight increase (<5%) • blood alkaline phosphatase increase (3%)
Tx. Disc.	2%
AEs leading to death	0%

2.1.3 Ongoing studies

Ongoing studies for larotrectinib are summarized in Table 15 below.

Table 15: Summary of ongoing studies for larotrectinib.

Title of the study and RCT (clinical-trials.gov)	Objective of the study (patient pop., etc.)	Intervention	Comparator	Outcome	Starting date	Expected end date
ON-TRK (NCT04142437)	Prospective non-interventional Phase 4 study is being conducted to prospectively follow patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib in order to gather safety and efficacy data in a large population in real-life setting.	observational study to learn more about the safty and efficacy of larotrectinib in patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib in real-life setting	N/A, single arm trial	The primary endpoint is safety, with an evaluation of the incidence of treatment-emergent adverse events (TEAEs), including severity, seriousness, outcome, and causality assessment. Secondary endpoint includes ORR, DCR, DOR, OS	April 2020	March 2030

Specific Obligation to complete post-authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the histology-independent efficacy of larotrectinib and to investigate the primary and secondary resistance mechanisms, the MAH should submit a pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002 (NAVIGATE).	30 June 2024
In order to further investigate the long-term toxicity and developmental effects of larotrectinib in paediatric patients, with particular focus on neurodevelopment including cognitive function, the MAH should submit the final report of study LOXO-TRK-15003 (SCOUT) including 5 year follow up data.	31 March 2027
In order to further confirm the appropriate dose recommended in paediatric patients, the MAH should submit an updated pop PK model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT).	30 September 2021

2.1.4 NoMA's assessment of the submitted evidence

The efficacy assessment is based on the pooled interim data from three ongoing trials; a dose-finding phase 1/2 study in adults with or without NTRK gene fusions (LOXO-TRK-14001), a phase 2 basket trial in adolescent and adult patients with NTRK fusions (NAVIGATE, 15002), and a dose-finding phase 1/2 study in paediatric patients with or without NTRK fusions (SCOUT, 15003). Data for the adult population comes from LOXO and NAVIGATE. Pooling within or between studies were not planned in the original protocols, which were amended several times during the course of the clinical trials. This impacts the internal validity of the studies, and a data-driven approach cannot be excluded. The main limitation, however, is the lack of comparative data combined with a small sample size, a heterogeneous patient population and a relatively short duration of follow up. This is particularly problematic as the study population is selected based on a gene fusion (NTRK) for which the prognostic significance in a pan-tumour setting remains unclear.

Patient population

The efficacy analyses set (ePAS5) consists of patients from the three studies who met the following criteria 1) documented NTRK gene fusion, 2) non-CNS primary tumour, 3) at least one measurable lesion at baseline as assessed by RECIST v1.1 and 4) received at least one dose of Larotrectinib. A subgroup analysis of the adult population (122 of 192 patients from the ePAS5) constitute the relevant population for this STA.

All patients were to have a locally advanced, or metastatic solid tumour, adequate major organ function and previously having received standard therapy. ECOG PS 0-3 was allowed, although the majority of patients enrolled had ECOG PS 0-1 (87%).

Compared to Norwegian clinical practice, the study population may be enriched for patients with a better prognosis (i.e., mostly ECOG 0-1 and no organ dysfunction). Furthermore, whereas primary CNS tumours are covered by the approved indication, these patients were excluded from the primary efficacy analyses set (ePAS5), mainly based on non-clinical data indicating lack of sufficient drug penetration to the CNS. Although responses were observed also in patients with CNS primaries, the point estimate for ORR was

substantially lower (ORR of 24% (investigator assessed) vs 64% in adult ePAS5). Compared to the target population, the efficacy estimates from the adult ePAS5 are thus somewhat overestimated. The main concern regarding the external validity of the study results for the Norwegian patient population is however related to the discrepancy between the study population and the approved indication. Whereas the indication is restricted to treatment of patients with no satisfactory treatment options, the inclusion criteria for the clinical trials were less strict, and a proportion of the study population had received fewer previous treatments than that required by the approved indication. As previous treatment lines may affect both prognosis and response to therapy, the study results could present an overestimate of clinical efficacy compared to what can be expected in clinical practice.

The external validity of other patient characteristics for Norwegian clinical practice cannot be determined, given that patients are currently not routinely tested for NTRK-fusions across all relevant indications. Comparisons to an overall patient population with the same primary malignancy could be misleading, as it is not clear if NTRK gene fusions are also associated with distinct patient characteristics across the different tumour types. The distribution of NTRK-positive patients across different histologies in Norwegian clinical practice is also difficult to estimate, due to limited data.

Treatment

The target adult dose for larotrectinib is 100 mg BID, administered continuously in 28-day cycles, until disease progression or intolerable toxicity. NoMA anticipates that dosing in clinical practice will be in line with the approved posology. Duration of therapy will be determined by duration of response, which may differ according to prognosis and histopathological subtype.

Endpoints

The primary endpoint for the pooled data analysis was objective response rate (ORR). This is standard for uncontrolled clinical oncology trials. Analyses by an independent review committee (IRC) reduces the risk of bias due to the open-label trial design. The observed ORR of 64% in the adult population is considered clinically compelling and is supported by durable responses in a proportion of patients. Compared to the overall study population, the point estimate for response in adults is somewhat lower. It should be noted, however, that age groups co-vary with type of tumour.

In the adult sub-population, the median PFS was 29.4 months. Data on OS were immature, with median OS not being reached at a median follow-up time of 25 months. PFS and OS are important for supporting the clinical relevance of the observed ORR and DoR results, and for the contextualization with other anticancer products normally approved based on PFS and/or OS. However, due to the pooling of many different types of primary malignancies with inherently different prognosis, the data should be interpreted with caution. Furthermore, the immaturity of these data with a high level of early censoring lends considerable uncertainty to the KM estimates. Perhaps most importantly, however, is that the uncontrolled study design makes it impossible to disentangle the treatment effect from the effect of patient related factors on the clinical outcome measures. This hampers the interpretation of time-to-event endpoints and clinical efficacy is mainly established through the documented response rates supported by DOR.

Tumour agnostic indication

Data from the NTRK negative vs. NTRK positive populations included in LOXO and SCOUT, show high response rates in NTRK fusion-positive groups and essentially no responses in NTRK fusion-negative patients. This provides clinical support for the proposed mechanism of action and the selectivity of the treatment effect to patients harbouring the drug target. Nevertheless, the objective response rates were highly variable across the studied tumour types, ranging from no responses among single patients with appendix-, prostate-, cervix-, hepatic-, pancreas cancer and cholangiocarcinoma to 100% in 4 patients with GIST. Tumour types where NTRK gene fusions are characteristic (or even pathognomonic) of the disease, such as Infantile fibrosarcoma (IFS, n=40), salivary gland (n=22), and congenital mesoblastic nephroma (n=2), tended to have higher ORRs (93%, 86%, and 100%, respectively). Patients with other genomic alterations in addition to NTRK gene fusion (n=95) also had a somewhat lower point estimate for ORR (55%), compared to patients without other genomic alterations (n=103, ORR = 70%). However, these estimates are not robust due to the small sample sizes of individual subgroups. The small sample sizes are reflective of the original exploratory nature of the studies. However, despite pooling of data across the three trials, sample sizes are still small.

Thus, although a tumour agnostic indication has been granted by the EU Commission, the small samples in most of the histological cohorts does not allow conclusions regarding the homogeneity of possible effects between tumour types. Particularly in common tumour types where NTRK fusions are rare, there is still limited information on the level of efficacy. Generally, the observed ORRs were lower and DOR shorter in these patients and for several primary malignancies efficacy data are lacking.

Safety

In general, larotrectinib appears to be reasonably well-tolerated and the safety profile is overall in line with what is observed for other tyrosine kinase inhibitors. The safety database is small and data on long-term safety are still limited.

Conclusion

Favourable effects of larotrectinib have been shown on the basis of overall response rate and response duration in a limited number of tumour types. Responses are likely overestimated compared to what could be expected in Norwegian clinical practice, as the study population may be enriched for patients with a better prognosis (i.e., no organ dysfunction, ECOG 0-1 and less heavily pre-treated). Furthermore, efficacy may be quantitatively different depending on the primary malignancy, as well as on the concomitant genetic alterations, and for several primary malignancies data to support efficacy is lacking. Due to the inherently different prognosis and options for SOC treatment in different primary malignancies, relative efficacy would usually need to be established separately for every mutation/histology combination. The lack of comparative data as well as the small sample sizes across individual tumour types, does not allow conclusions regarding the relative efficacy of larotrectinib compared to best standard of care. For these reasons, larotrectinib was granted an indication in patients where there are no satisfactory treatment options available.

Overall, the data on ORR and DoR are considered compelling in the target patient population. Also, in patients with CNS primary malignancies, durable responses were observed. The immaturity of the time-

to-event outcomes and the non-comparative nature of the data hampers the interpretation of the time-to-event endpoints, and it is not clear to what extent the observed response rates will translate into a benefit on PFS and OS. It is, however, considered likely that larotrectinib may provide a clinically relevant benefit in patients who have exhausted all other treatment options, particularly in the tumour types where responses have been observed.

It is anticipated that use in clinical practice will reflect the approved indication and posology. It is noted, however, that the "last-line" indication is not well defined (i.e., patients should have exhausted all satisfactory treatment options, however, what constitutes a "satisfactory" treatment option may be a subjective decision). The exact placement in the treatment algorithm may therefore depend on physician and patient preference, and there may be a "drift" towards use in earlier treatment lines as more data and clinical experience becomes available.

2.2 INDIRECT COMPARISONS

Bayer submitted a protocol describing which type of unanchored matching adjusted indirect (MAIC) comparison of efficacy of larotrectinib compared to entrectinib that could be performed. In the submission, Bayer has only included a table with an overview of which factors from the larotrectinib-study where matched to the entrectinib studies and tables with the results.

2.2.1 NoMA's assessment

An unanchored MAIC should include the following Philippo et al (15):

- *unanchored forms of population adjustment must provide evidence on the likely extent of error due to unaccounted covariates, in relation to the observed relative treatment effect.*
- *unanchored population adjustment methods should adjust for all effect modifiers and prognostic variables.*
- *be carried out on the usual linear predictor scale used for evidence synthesis of that outcome*
- *The target population for the decision problem must be explicitly stated, and*
- *the population adjustment must deliver treatment effect estimates for that target population.*
- *Strict reporting requirements are recommended, including the*
    - *assessment of covariate distributions*
    - *evidence for effect modifier status*
    - *distribution of weights (if applicable)*
    - *appropriate measures of uncertainty*
    - *reporting of effective sample size after matching*

Neither of this is submitted, and NoMA has therefore not assessed the submitted MAIC. The submission is not in accordance with the order of ID2019_029 where indirect comparison with entrectinib is not described.

3 ECONOMIC ANALYSIS

As described in chapter 2.2.1, NoMA considers the information provided by Bayer as insufficient to conclude whether the clinical efficacy of larotrectinib is equal, better, or worse than the efficacy of entrectinib. Therefore, the health economics model submitted by Bayer is not used in this simplified track D-assessment. This chapter presents a summary of treatment costs with larotrectinib.

The Norwegian Hospital Procurement Trust (Sykehusinnkjøp HF) will make a comparison of treatment costs between larotrectinib and entrectinib in a separate report.

3.1 APPROXIMATION OF THE NUMBER OF PATIENTS POTENTIALLY SUITABLE FOR THE TREATMENT

NoMA considers the number of patients expected to be treated with Vitrakvi (larotrectinib) as highly uncertain. While NoMA assumed throughout this report that all patients with NTRK-fusion can be identified, the budget estimates are based on the expected number of patients that actually can be identified in current clinical practice in Norway. The number of treated patients depends on the ability to identify patients with NTRK-fusions and on how many patients will receive treatment with entrectinib rather than larotrectinib. Due to these uncertainty factors, the budget impact analyses for Vitrakvi (larotrectinib) need to be considered to be a rough estimate associated with considerable uncertainty.

To reflect this uncertainty, NoMA presents the budget impact as a range. Table 16 presents a lower and upper range for patients to be treated with Vitrakvi every year if the treatment is recommended. The range is based on NoMA's evaluation of entrectinib, where an estimate of 5-50 patients was used, with the upper range increasing over time due to more testing practice (13). Although the indication for entrectinib includes patients over 12 years, the vast majority are adults (16). According to clinicians working in Norwegian clinical practice, it is difficult to define a precise number of patients eligible for treatment with larotrectinib. Nevertheless, their estimates tend towards an average of 0 – 1 eligible patients with thyroid cancer and 2 – 15 eligible patients with lung cancer each year. NoMA does not have an estimate of patients eligible for NTRK inhibitors with other cancer types but assumes it is included in the range. Moreover, Norwegian clinicians suppose that the market share of larotrectinib and entrectinib will be driven by the treatment prices as well as further data and clinical experience of the two comparators that may become available in the future. Hence, NoMA considers the patients range from the evaluation of entrectinib and assumes a market share of 50% for Vitrakvi, which was also assumed by Bayer. The resulting numbers do not differ greatly from Bayer's estimation of 1-9 eligible patients per year.

Table 16: Number of new-diagnosed patients expected to start treatment with Vitrakvi (larotrectinib) in the next 5 years – scenario where treatment is recommended.

	Year 1	Year 2	Year 3	Year 4	Year 5
Total NTRK positive cancer patients expected to be treated with Vitrakvi (lower range)	3	3	3	3	3
Total NTRK positive cancer patients expected to be treated with Vitrakvi (upper range)	5	10	15	20	25

To illustrate the uncertainty in the budget impact analyses NoMA presents budget impact in the fifth year after introduction for 3, 10 and 25 patients. The presented budget impact is highly uncertain due to the aspects listed above in addition to the unknown numbers of patients with NTRK-fusions that can be identified in Norwegian clinical practice.

3.2 COST ESTIMATION

The cost estimate in NoMA's simplified budget impact analyses is based on the drug acquisition costs for Vitrakvi (larotrectinib).
Costs related to testing for NTRK-fusion are of relevance. However, they have not been included in this budget impact analyses due to the fact that The Norwegian Institute of Public Health is in charge of providing information on testing (17).

For this budget impact analysis NoMA considers all other costs beyond drug costs of Vitrakvi (larotrectinib) to be negligible. Consequently, NoMA has not included wastage, compliance rate and dose adjustments in the simplified budget estimate.

Table 17 shows the drug acquisition costs for Vitrakvi (larotrectinib).

Table 17: Drug acquisition costs. List price, including VAT (NOK) (source: Legemiddelsøk)

Product	Pack volume	Cost per package	Price per mg	Price per year
Vitrakvi 100 mg pack	56	64 546,20	11,53	841 406
Vitrakvi 25 mg pack	56	16 163,70	11,55	842 822

Patients receive treatment until progression or until unacceptable toxicity occurs.

NoMA used the following parameters to estimate the drug costs for Vitrakvi (larotrectinib) per patient per year:

- Dose: 200 mg per day
- Treatment duration: mean observed time on treatment is 18.6 months
- Price 100mg-pack: 64 546,20 NOK

3.3 BUDGET ESTIMATES

The budget analyses for Vitrakvi (larotrectinib) can only result in a very rough estimate due to the unknown number of identified patients. Consequently, NoMA chose to simplify the following parameters used in the budget impact analyses:

- Time on treatment: NoMA uses 18.6 months for time on treatment.
- Compliance rate: NoMA assumed 100% compliance rate for Vitrakvi (larotrectinib).
- Wastage and dose adjustments: NoMA has not included wastage and dose adjustments in this simplified budget impact analysis.

The estimated budget in NOK as a result of drug costs for lower and upper ranges of eligible patients is presented in Table 18.

Table 18: The expected budget impact in MNOK of drug costs for the eligible patient population for a lower and upper range. List price, including VAT and undiscounted

	Year 1 (3-5 patients)	Year 2 (3-10 patients)	Year 3 (3-15 patients)	Year 4 (3-20 patients)	Year 5 (3-25 patients)
Total drug costs if larotrectinib is adopted	2,5 mil – 4,2 mil	3,9 mil – 10,7 mil	3,9 mil – 17,3 mil	3,9 mil – 23,8 mil	3,9 mil – 30,3 mil

Conclusion

To illustrate the uncertainty in the budget impact analyses NoMA presents budget impact in the fifth year after introduction for 3, 10 and 25 patients. The presented budget impact is highly uncertain due to the aspects listed above in addition to the unknown numbers of patients with NTRK-fusions that can be identified in Norwegian clinical practice.
In the fifth year after introduction, a rough estimate of the budget impact of a positive recommendation for Vitrakvi (larotrectinib) for eligible patient populations of different size are estimated to be around:

- 30,3 million NOK including VAT for 25 patients
- 10,7 million NOK including VAT for 10 patients
- 3,9 million NOK including VAT for 3 patients.

4 SUMMARY AND DISCUSSION

Larotrectinib is a selective TRK inhibitor, conditionally approved for the treatment of NTRK positive cancers, independent of histopathological tumour type (i.e., a tumour agnostic indication). One similar product, entrectinib, was recently conditionally approved and introduced by the Decision Forum for the same target adult population (ID ID2019_119).

Originally, the Order Forum requested a full STA (C-track) covering both the adult and paediatric patient population. However, following a preliminary assessment it was concluded that the submitted data was insufficient to establish relative efficacy. Furthermore, it was proposed that the adult and paediatric indications were addressed separately, due to different value propositions in the two populations.

An updated order was issued in December 2020, requesting simplified STAs (D-track) to be conducted separately for the adult and paediatric populations. In accordance with this order Bayer submitted a description of efficacy, safety and costs for larotrectinib. In addition, Bayer submitted a cost-minimization analysis with entrectinib as comparator and a high-level description of an unanchored MAIC, along with the relative efficacy results. These latter analyses were not part of the order. Furthermore, it was concluded that the submitted data were not sufficient to allow an evaluation of relative efficacy. Therefore, these analyses were not further assessed.

NoMAs assessment of the benefit criterion:

Evidence for the efficacy of larotrectinib is based on a pooled interim analysis of patients from three ongoing phase 1 / 2 trials (LOXO, NAVIGATE and SCOUT), with LOXO and NAVIGATE providing data for the adult population. The extended primary analyses set (ePAS5) includes 122 adult patients with NTRK positive, locally advanced or metastatic, non-CNS primary solid tumours, who have received at least one dose of larotrectinib prior to the July 2020 data cut-off. In addition, a post-hoc analysis of patients with primary CNS tumours (n=33) was submitted.

In the adult ePAS5 patient population, an ORR of 64% was observed. DoR was not reported separately for the adult population, but median DoR was 34.5 months in the overall population (ePAS5). Response rates were highly variable across the studied tumour types, ranging from 0% in single patients with appendix cancer, prostate cancer and cervix cancer to 100% in 4 patients with GIST. Tumour types where NTRK gene fusions are characteristic (or even pathognomonic) of the disease, such as Infantile fibrosarcoma (IFS, n=40), salivary gland (n=22), and congenital mesoblastic nephroma (n=2), tended to have higher ORRs (93%, 86%, and 100%, respectively). However, these estimates are not robust due to the small sample sizes of individual subgroups. In patients with a CNS primary (excluded from the ePAS5) response rates were lower (24%), but durable responses were observed in a proportion of patients (75% at 12 months). The median PFS in the adult ePAS5 population was 29.4 months, data on OS was immature, with median OS not being reached at a median follow-up time of 25 months.

The external validity of the trial results for Norwegian clinical practice cannot be readily determined, given that patients are currently not routinely tested for NTRK-fusions. It can be anticipated, however, that compared to Norwegian clinical practice, the efficacy results are overestimated, as the inclusion criteria

might have enriched the study population for patients with a better prognosis (i.e., no major organ dysfunction, mostly ECOG 0-1) and as the study population was generally less heavily pre-treated than that required by the approved indication.

Nevertheless, overall the data on ORR and DoR are considered compelling in the target patient population. The antitumoural activity of larotrectinib is further supported by the comparative data in the NTRK negative population, where essentially no responses were observed (data not shown), thus providing evidence for the proposed mechanism of action. To which extent these response rates will translate into a survival benefit is not documented, although it seems likely that patients with no other treatment options could derive a clinically meaningful benefit of larotrectinib.

NoMAs assessment of the resource criterion:

The documentation submitted on the relative effectiveness and cost-effectiveness of larotrectinib submitted by Bayer does not allow NoMA to evaluate the resource criterion.

The cost-effectiveness of larotrectinib could not be assessed with the submitted health economic model. While the model type chosen by Bayer might have been appropriate, NoMA cannot approve the input used in the model as sufficient to establish relative effectiveness. Consequently, NoMA could not estimate an ICER to quantify cost-effectiveness of introducing larotrectinib.

NoMAs assessment of the severity criterion:

Metastatic solid tumours without satisfactory treatment options are clearly severe conditions, regardless of the mutational status of the tumour.

NoMA lacks a credible estimate remaining QALYs for patients with NTRK-positive fusions that receive currently available treatment (BSC) and could not quantify severity in terms of absolute shortfall. Describing severity based on average age of the patient population in the clinical trials and the corresponding expected remaining QALYs in the general Norwegian population, NoMA assumes that patients with NTRK-positive fusions lose on average around 20 QALYs, as described in entrectinib's assessment (13). This description of severity is based on assumptions, and it should be interpreted with caution.

NoMAs assessment of the data quality and uncertainty in the provided documentation:

Pooling within or between studies were not planned in the original study protocols, which were amended several times during the course of the clinical trials. This impacts the internal validity of the studies, and a data-driven approach cannot be excluded. The main limitations, however, are related to the small sample size, the short duration of follow-up, the heterogeneity of the patient population and the lack of comparative data.

Due to the small sample size the precision of the efficacy estimates for individual tumour cohorts is low, with a substantial variability in response rates across different tumour types. Particularly, in patients with common tumour types where NTRK fusions are rare, the individual tumour cohorts are poorly populated and the observed ORRs are lower and DOR shorter. Only 6 cohorts (overall population, n=192) include

more than 10 patients, and there are 6 cohorts with 1-2 patients, reporting a response rate of 0%. Thus, although the antitumour activity of larotrectinib is considered established for the overall study population, there is considerable uncertainty as to the homogeneity of treatment effect in different histopathological subgroups, and in several types of tumour evidence for a treatment effect is lacking. Furthermore, the treatment effect may be quantitatively different for patients with and without concomitant genetic alterations.

Concerning PFS and OS, the short duration of follow-up with subsequent high rates of early censoring lends uncertainty to the KM estimates. Furthermore, due to the uncontrolled study design it is not possible to disentangle the effect of patient related factors from the treatment effect, thus precluding interpretation of these endpoints. This is particularly problematic as the study population is selected based on a gene fusion (NTRK) for which the prognostic significance in a pan-tumour setting remains unclear. In addition, the pooling of many different types of primary malignancies with inherently different prognosis, means the data should be interpreted with caution, and the clinical relevance of the overall efficacy estimate for the individual tumour sub-types is not clear. Thus, the benefit of larotrectinib is primarily established based on the demonstration of an antitumoral activity (ORR and DOR) and it is not clear to what extent this will translate into a clinically relevant benefit on PFS and/or OS.

NoMAs assessment of the budget estimate:

There is high uncertainty about how many patients will be tested for NTRK-fusions, and which criteria will be used for testing in Norwegian clinical practice. The testing of tumours for NTRK-fusions has been assessed by The Norwegian Institute of Public Health in a separate report (17).

Uncertainty about the number of patients clearly influences the budget analyses. The prevalence, the testing strategy and competition with entrectinib will impact the number of patients treated. We therefore present a simplified budget estimate with a wide range, which could be somewhere between 3,9 million NOK for 3 patients and for 30,3 million NOK for 25 patients per year in a stable market.

Norwegian Medicines Agency, 26-09-2022

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APPENDIX 1: DISCUSSION ON COMPARATORS

According to the approved indication, larotrectinib and entrectinib should be used in patients with no other satisfactory treatment options. The exact placement in the treatment algorithm for larotrectinib and entrectinib will vary by the histology of the tumour, and there are no clear guidelines available. It is anticipated that, in Norwegian clinical practice, larotrectinib (if introduced), will be an alternative to entrectinib. Based on the available guidelines, and some feedback from clinical experts, the placement of entrectinib in different histologies was discussed in the assessment of entrectinib (13) as follows:

Breast cancer
According to the Norwegian guidelines, patients with triple negative breast cancer who are BRCA-negative are treated with chemotherapy. Based on the guidelines, patients seem likely to benefit from at least two lines of chemotherapy, and there are several available treatment options, including regimens containing antracyclins and taxans. Given the multitude of available chemotherapy regimens available for breast cancer, the exact placement of chemotherapy is depending on patient preference. Roche placed entrectinib in the 3rd and later treatment lines which NoMA considers as appropriate. However, NoMA considers the provided comparator data in breast cancer as little representative for the breast cancer patient population in Norwegian clinical practice as 4 of the 6 patients with breast cancer had secretory breast cancer, which has a different prognosis from non-secretory breast cancer.

Non-small lung cancer
According to feedback from Norwegian clinicians, patients with non-small cell lung cancer may benefit from treatment with platinum-based chemotherapy, either sequentially or in combination with immunotherapy. The benefit of docetaxel is rather limited, and the clinicians assume that entrectinib will be used before docetaxel in eligible patients. Nintedanib is not used in Norwegian clinical practice.

Colorectal cancer
Norwegian guidelines on colorectal cancer recommend two lines of chemotherapy, while the benefit of a third line and beyond is considered to be limited. Consequently, it seems reasonable that patients with colorectal cancer who have received two lines of chemotherapy would be considered candidates for treatment with entrectinib.

Neuroendocrine tumours (NET)
According to the Norwegian guidelines, everolimus is recommended as first or second line treatment for gastroenteropancreatic NET, and sunitinib might be used in the same line in patients who have a tumour with origin in the pancreas. Patients with NET would probably have received one or two lines of treatment before receiving entrectinib. The proposed comparator for entrectinib is best supportive care in patients with no previous treatment. While best supportive care is in general appropriate, it is considered problematic that the patients were less heavily pre-treated than the patients should be according to the approved indication.

Pancreatic cancer
Roche proposed gemcitabine with or without paclitaxel, or FOLFORI, in previously untreated patients as comparator for patients with pancreatic cancer. The Norwegian guidelines mention either of these

therapies as first-line treatment and consider them well documented alternatives. It seems appropriate to position entrectinib after first line chemotherapy in these patients.

Thyroid cancer
Roche used best supportive care in second line after radioactive iodine as the comparator for patients with thyroid cancer. According to Norwegian guidelines, lenvatinib is considered first line treatment and sorafenib is second line treatment in patients refractive to radioactive iodine. Thus, patients have at least two satisfactory treatment lines, that should be used before entrectinib.

Soft tissue sarcoma
Roche proposed doxorubicin or trabectedin as comparator. Both of these treatments are recommended by ESMO, with an anthracyclins including doxorubicin recommended in the first line, and trabectedin considered a position in the second line and beyond (34). Soft tissue sarcomas are heterogenous, and the exact treatment given will depend on the specific subgroup. However, it seems that patients have at least two satisfactory treatment lines, that should be used before entrectinib.

MASC
Given the high prevalence of NTRK-fusions it seems likely that entrectinib will be used as first-line treatment for these patients. It is noted that despite the clear histological definition of MASC, Roche submitted a control arm containing different forms of salivary gland histologies.

Others
Patients with other histologies (5 different histologies) are included in the submitted comparator data. For those patients, the same comparator effect as the average of the other patients included in the comparator arm, have been assumed. This approach excludes these patients from the analysis. As these patients are still included in the intervention arm, NoMA is concerned about the imbalance regarding histology this generates in the arms.

VEDLEGG 1 KOMMENTARER FRA PRODUSENT

Cost-effectiveness has not been established as this is out of the scope of the STA order. Thus, CUA was not submitted to the Norwegian Medicine Agency.

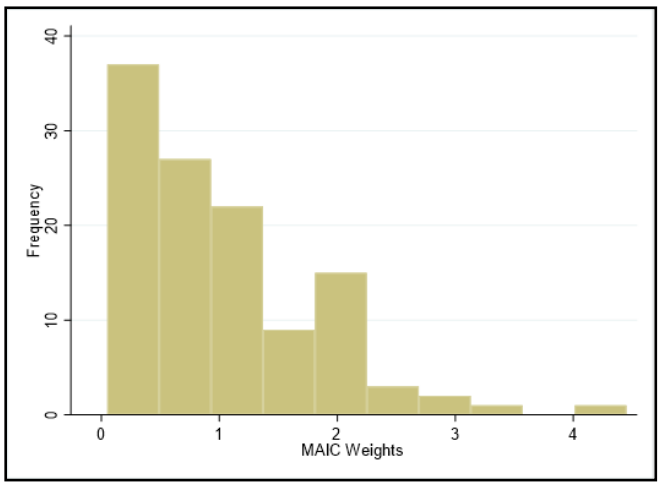
On the 26th of April 2022 TLV concluded - based on Bayer's CUA, same MAIC submitted to NoMA and existing data - that Vitrakvi has better efficacy advantage compared to Rozlytrek (in adult patients with NTRK gene fusion-positive tumor). Also, Rozlytrek was found cost effective by TLV.

MAIC Methodology

Bayer is aware that the MAIC submitted was not requested and therefore it was summarised in a descriptive and concise way. MAIC methodology is based on Signorovitch et al.[1] which is similar to Philippo et al. and in accordance with NICE DSU TSD-18. The error is reflected in the weighted hazard ratio (robust Std. Err). Bayer also provided the distribution of weights and the differences in covariate distributions pre and post matching.

Without a common comparator arm for the outcome comparisons, it was not feasible to validate whether the adjustments fully balance the characteristics of the study populations. However, MAIC and STC have been established as valid approaches for comparing single-arm trials. The effect of observed (but missing) and unobserved covariates on the outcome could not be quantified. However, the MAIC accounted for all known/important prognostic factors.

Regarding *"unanchored population adjustment methods should adjust for all effect modifiers and prognostic variables"*, Bayer adjusted for all variables that were reported for entrectinib and could be matched on, that were felt to be predictive or prognostic of outcomes. The MAIC comparison matched on available baseline characteristics known or suspected to be confounding factors for the outcomes of interest. It should be also noted that the MAIC was carried out on the usual linear predictor scale used for evidence synthesis of that outcome and in line with Philippo et al. Furthermore, the target population was explicitly stated.



Evidence for effect modifier status was not applicable. Patients treated with larotrectinib were assigned weights so that the weighted average of selected baseline characteristics matched those of the entrectinib patient population. The weights were obtained based on a logistic regression model for the propensity of enrollment in the larotrectinib trials vs. the entrectinib trials.

Because only summary data were available for the entrectinib trials, the logistic regression model was estimated using the method of moments. Furthermore, appropriate measures of uncertainty are presented by robust standard error (using sandwich estimator) as stated in Philippo et al.[2] Weight histogram is provided in the figure.

While MAIC and STC adjust for differences in baseline characteristics that are available and similarly measured across trial populations, the comparisons may be biased by differences in unobserved baseline characteristics that affect

outcomes. Adjusting for additional baseline characteristics not yet included in the analysis could further improve the estimate of the relative treatment effects. The current analysis already includes a wide range of key baseline characteristics, and so it is unclear whether additional baseline characteristics may significantly affect the results. Ultimately, only a well-conducted, head-to-head randomized trial comparison can avoid the potential bias due to unobserved baseline differences.

The effective sample size after matching included 117 patients from the larotrectinib efficacy population and 147 from the safety population, and 74 patients from the entrectinib trials. ESS (Effective Sample size) for efficacy = 71.8; ESS for safety= 90.7 – both after matching. It should be noted that the ESSs and observed MAIC weights indicated good statistical power even after adjusting for observed for differences between the trial populations of entrectinib and larotrectinib.

Unknown prognostic value of NTRK-fusion

The Voyager 1 study and GMI data were discussed in the dossier and provide insides on the prognostic value and NTRK-fusions and clinical outcomes for TRK fusion patients not treated with TRK inhibitors in comparison to receiving TRK inhibitor treatment. It is not clear from NoMA's assessment why this was not valid enough and/ or to which extend they were considered together.

Unknown size of treatment effect

The main heterogeneity is coming from mixing paediatrics and adults together which it is not discussed in the documentation submitted.

Unknown size of treatment effect can be addressed in several ways. Yet, some of the following approaches are not

in line with this STA's order and for this reason were not discussed in Bayer's application:

- Bayer can update the bayesian hierarchical modelling to show the uncertainty is not large
- Bayer can use ePAS2 (regulatory approval datacut and use the 2022 datacut to show new KM curve following parametric model)
- Bayer can show that although ORR looks different by tumour type, OS curves look similar between tumour type
- MAIC vs. SoC published in ASCO 2022

The relative effectiveness of larotrectinib over best standard of care (other than entrectinib) and over entrectinib cannot be established.

This statement is partially correct. Bayer has applied the following methods to establish the relative effectiveness of larotrectinib against SoC and entrectinib:

- MAIC larotrectinib vs entrectinib
- The intra patient comparison (GMI) is also an established/published methodology to assess comparative effectiveness
- The ASCO 2022 publication for comparison against SoC is controlled for important confounding factors

[1] Signorovitch, J.E., Sikirica, V., Erder, M.H., Xie, J., Lu, M., Hodgkins, P.S., Betts, K.A. and Wu, E.Q., 2012. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value in Health*, *15*(6), pp.940-947.

[2] Garcia-Foncillas, J.; Bokemeyer, C.; Italiano, A.; Keating, K.; Paracha, N.; Fellous, M.; Marian, M.; Fillbrunn, M.; Gao, W.; Ayyagari, R.; et al. Indirect Treatment Comparison of Larotrectinib versus Entrectinib in Treating Patients with TRK Gene Fusion Cancers. Cancers 2022, 14, 1793. pp.4