Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende bictegravir/emtricitabin/ tenofovir alafenamid som mulig standardbehandling til hiv-1-infektion

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om lægemidlets samlede pris er rimelig, når man sammenligner den med den kliniske værdi.

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	30. januar 2019
Ikrafttrædelsesdato	30. januar 2019
Dokumentnummer	39101
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 30. januar 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Biktarvy
Generisk navn	Bictegravir/emtricitabin/tenofovir alafenamid
Firma	Gilead
ATC-kode	J05AR20
Virkningsmekanisme	Kombinationspræparat af tre antiretrovirale midler: hiv-integrasehæmmer (bictegravir), nukleosid-revers-transkriptasehæmmer (emtricitabin) og nukleotid-revers-transkriptasehæmmer (tenofovir alafenamid).
Administration/dosis	50 mg/200 mg/25 mg bictegravir/emtricitabin/tenofovir alafenamid kombinationstablet én gang dagligt.
EMA-indikation	Biktarvy er indiceret til behandling af voksne, der er inficeret med human immundefekt virus 1 (hiv 1) uden nuværende eller tidligere påvist viral resistens overfor integrasehæmmerklassen, emtricitabin eller tenofovir.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** bictegravir/emtricitabin/tenofovir alafenamid som mulig standardbehandling til patienter med hiv-1-infektion, som ikke har aktuel eller tidligere påvist viral resistens overfor integrasehæmmerklassen, emtricitabin eller tenofovir.

Medicinrådet finder, at der er et rimeligt forhold mellem lægemidlets kliniske merværdi og omkostningerne ved behandling med bictegravir/emtricitabin/tenofovir alafenamid sammenlignet med dolutegravir i kombination med to antiretrovirale midler af klassen nukleosid- og nukleotid-revers-transkriptasehæmmere.

Medicinrådet har besluttet, at der i 2019 udarbejdes en fælles regional behandlingsvejledning for hiv. Indtil Medicinrådet har udarbejdet en behandlingsvejledning, anbefales det, at regionerne, under hensyntagen til den godkendte indikation og population, vælger det regime, der er forbundet med de laveste omkostninger.

Det kliniske spørgsmål, som ligger til grund for anbefalingen, er som følger:

Hvad er den kliniske merværdi af bictegravir/emtricitabin/tenofovir alafenamid til behandlingsnaive patienter med hiv-1-infektion sammenlignet med dolutegravir og to NRTI'er?

3 Formål

Formålet med baggrundsrapporten for Medicinrådets anbefaling vedrørende bictegravir/emtricitabin/tenofovir alafenamid som mulig standardbehandling til hiv-1-infektion er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Hiv-1-infektion er en kronisk virusinfektion, som angriber immunforsvaret og kan være dødelig, hvis patienten ikke behandles.

Ifølge Statens Serum Institut diagnosticeres mellem 200 og 300 danskere årligt med hiv-infektion. I 2016 var der ca. 250 nye tilfælde. I 2016 blev 5.268 patienter fulgt hos en behandler (Det Danske HIV Kohorte Studie).

Yderligere information findes i "Medicinrådets vurdering af klinisk merværdi for bictegravir/emtricitabin/tenofovir alafenamid til behandling af hiv-1-infektion", bilag 4.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådet modtog den foreløbige ansøgning den 26. februar 2018, og protokollen blev sendt til Gilead den 18. maj 2018.

Den endelige ansøgning blev modtaget den 6. december 2018, og Medicinrådet har gennemført vurderingen af bictegravir/emtricitabin/tenofovir alafenamid på 7 uger og 6 dage.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at bictegravir/emtricitabin/tenofovir alafenamid til behandling af hiv-1-infektion giver **ingen klinisk merværdi** sammenlignet med dolutegravir givet sammen med to antiretrovirale midler af klassen nukleosid- og nukleotid-revers-transkriptasehæmmere. Evidensens kvalitet er moderat.

6 Høring

Den 19. december 2018 indsendte ansøger et høringssvar, som ikke gav anledning til at ændre Medicinrådets vurdering af klinisk merværdi. Høringssvaret er vedlagt som bilag 3.

7 Resumé af økonomisk beslutningsgrundlag

Behandling med bictegravir/emtricitabin/tenofovir alafenamid er forbundet med begrænsede meromkostninger sammenlignet med dolutegravir/lamivudin/abacavir.

Med den nuværende SAIP på bictegravir/emtricitabin/tenofovir alafenamid vurderer Amgros, at omkostningerne er rimelige sammenlignet med den kliniske merværdi, som lægemidlet tilbyder.

8 Overvejelser omkring alvorlighed/forsigtighed

Medicinrådet har ikke fundet anledning til at inddrage forhold vedrørende alvorlighed eller forsigtighed i anbefalingen.

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende hiv/aids

Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	**Indstillet af**
Ann-Brit Eg Hansen *Overlæge, klinisk lektor*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
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Olav Ditlevsen Larsen *Overlæge, ph.d.*	Region Syddanmark
Toke Barfoed *Overlæge, lektor*	Region Sjælland
Jan Gerstoft *Professor, overlæge, dr.med.*	Region Hovedstaden
Marianne Kjettrup-Jensen *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Bjarne Ørskov Lindhardt *Ledende overlæge, klinisk lektor*	Udpeget af formanden
Paul Thomsen *Patient/patientrepræsentant*	Danske Patienter
Bent Hansen *Patient/patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
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10 Versionslog

Version	Dato	Ændring
1.0	30.01.2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag
- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Vurdering af den kliniske merværdi af bictegravir/emtricitabin/tenofovir alafenamid
- Ansøgers endelige ansøgning
- Protokol for vurdering af den kliniske merværdi af bictegravir/emtricitabin/tenofovir alafenamid

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) som mulig standardbehandling af HIV-1-infektion hos voksne patienter. Vurderingen er baseret på lægemidlets meromkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	30-01-2019
Firma	Gilead (ansøger)
Lægemiddel	Bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy)
Indikation	Biktarvy er indiceret til behandling af voksne, der er inficeret med human immundefekt virus 1 (HIV-1) uden nuværende eller tidligere evidens for viral resistens over for integrasehæmmerklassen, emtricitabin eller tenofovir

Amgros' vurdering

- Amgros vurderer, at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) ved behandling af HIV-1-infektion hos voksne patienter

Overordnet konklusion

Medicinrådet har vurderet, at bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) giver:

- **Ingen klinisk merværdi** til patienter med HIV-1-infektion sammenlignet med dolutegravir, der gives sammen med to nukleosid- og nukleotid-revers-transkriptasehæmmere (NRTIs)

Med den nuværende SAIP på bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) vurderer Amgros, at meromkostningerne **er** rimelige sammenlignet med den kliniske værdi, som lægemidlet tilbyder.

Amgros har indgået en aftale med Gilead om indkøb af bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) til en aftalepris, som er lavere end AIP. Konklusionen er baseret på SAIP for bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy).

Konklusion for populationen

Tabel 1 Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP)

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
Behandlingsnaive patienter med HIV-1-infektion	Dolutegravir + to NRTIs	Ingen klinisk merværdi	Moderat evidenskvalitet	Acceptabelt

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Amgros' afrapportering af omkostnings- og budgetkonsekvensanalyser er baseret på AIP for bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy). Foretages analyserne på baggrund af SAIP, og ikke på baggrund af AIP, reduceres de inkrementelle omkostninger. Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Amgros' afrapportering - Inkrementelle omkostninger per patient (AIP)

Behandling med bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) er forbundet med begrænsede meromkostninger sammenlignet med de valgte komparatorer.

I tabel 2 illustreres de estimerede omkostninger ved behandling med bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) sammenlignet med de valgte komparatorer for patienter med HIV-1-infektion.

Tabel 2 Estimerede gennemsnitlige omkostninger per patient, DKK, AIP

	Lægemiddel	Pris per patient per år	Totale lægemiddelomkostninger	Inkrementelle omkostninger
	Biktarvy	118.755	118.755	-
Komparatorer				
1	Epivir®	13.423	102.033	**16.722**
	Tenofovir disoproxil "Teva"	37.743		
	Tivicay	50.867		
2	Abacavir/Lamivudin ”Mylan”	33.866	84.733	**34.022**
	Tivicay	50.867		
3	Emtricitabin/Tenofovir disoproxil "Mylan"	70.452	121.319	**-2.564**
	Tivicay	50.867		
4	Triumeq	88.537	88.537	**30.218**
5	Epivir®	13.423	87.595	**31.160**
	Ziagen®	23.305		
	Tivicay	50.867		
6	Emtriva	20.052	109.727	**9.028**
	Viread®	38.808		
	Tivicay	50.867		
7	Emtriva	20.052	94.224	**24.531**
	Ziagen®	23.305		
	Tivicay	50.867		
8	Descovy	50.843	101.710	**17.045**
	Tivicay	50.867		

Amgros' afrapportering – Budgetkonsekvenser (AIP)

Amgros vurderer, at anbefaling af bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) som mulig standardbehandling vil resultere i budgetkonsekvenser ca. 4 mio. DKK i år 5.

I tabel 3 ses de estimerede budgetkonsekvenser over 5 år.

Tabel 3 Amgros' hovedanalyse for totale budgetkonsekvenser, mio. DKK., ikke-diskonterede tal, baseret på AIP.

AIP	År 1	År 2	År 3	År 4	År 5
Biktarvy anbefales ikke	4,2	7,0	8,9	9,7	10,8
Biktarvy anbefales	5,9	9,9	12,5	13,7	15,1
Totale budgetkonsekvenser	**1,7**	**2,8**	**3,6**	**3,9**	**4,3**

Kontrakt- og markedsforhold

Amgros har indgået aftale med Gilead om indkøb af bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) til en pris, der er lavere end AIP. Aftalen er gældende fra 30.01.2019 indtil 30.06.2019 med mulighed for forlængelse.

Der findes et aktivt udbud på HIV-området, hvor bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) ikke er inkluderet. Udbuddet udløber 30.06.2019, men har mulighed for forlængelse.

Desuden skal Medicinrådet vurdere terapiområdet HIV i 2019-2020. I forhold til den kommende behandlingsvejledning er det Amgros' vurdering, at det vil være hensigtsmæssigt, at bictegravir/emtrictabin/tenofoviralafenamid (Biktarvy) anbefales som standardbehandling, så den i fremtiden kan konkurrenceudsættes på lige fod med de øvrige første-linje behandlinger.

BICTEGRAVIR/EMTRICTABIN/ TENOFOVIRALAFENAMID (BIKTARVY)

HIV-1-INFEKTION HOS VOKSNE

AMGROS 14. januar 2019

AMGROS

OPSUMMERING

Baggrund

Biktarvy (bictegravir/emtricitabin/tenofoviralafenamid) er en tablet indiceret til behandling af HIV-1 infektion uden nuværende eller tidligere tegn på resistens over for integrasehæmmere, emtricitabin eller tenofovir. Det forventes, at ca. 200 nye patienter per år diagnosticeres med HIV-1-infektion. Derudover forventes det, at patienter, der skal skifte behandling også kan behandles med Biktarvy. Amgros' vurdering tager udgangspunkt i dokumentationen indsendt af Gilead.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med Biktarvy sammenlignet med behandling med dolutegravir + to nukleosid- og nukleotid-revers-transkriptasehammere (NRTIs) til voksne patienter.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige inkrementelle omkostninger per patient ved brug af Biktarvy sammenlignet med komparatorer. De inkrementelle omkostninger er angivet i AIP.

I analysen, som Amgros mener er mest sandsynlig, er de gennemsnitlige inkrementelle omkostninger for Biktarvy ca. -2.500 kr. til 34.000 kr. per patient. De inkrementelle omkostninger varierer alt efter, hvilken kombinationsmulighed af dolutegravir + 2 NRTIs, der benyttes som komparator.

Amgros vurderer, at budgetkonsekvenserne for regionerne per år ved anbefaling af Biktarvy som standardbehandling vil være ca. 4 mio. kr.

Konklusion

Amgros kan konkludere, at behandling med Biktarvy er forbundet med begrænsede meromkostninger sammenlignet med komparator. Meromkostningerne er i denne analyse udelukkende drevet af lægemiddelomkostninger for Biktarvy og komparator.

Liste over forkortelser

AIDS	Aquired immunodeficiency syndrome
AIP	Apotekernes indkøbspris
DKK	Danske kroner
HIV	Human immundefektvirus
NRTIs	Nukleosid- og nukleotid-revers-transkriptasehæmmere
SAIP	Sygehusapotekernes indkøbspris
SPC	Summary of Product Characteristics

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Gilead
Handelsnavn:	Biktarvy
Generisk navn:	Bictegravir/emitricitabin/tenofoviralafenamid
Indikation:	Biktarvy er indiceret til behandling af voksne, der er inficeret med human immundefekt virus 1 (HIV-1) uden nuværende eller tidligere evidens for viral resistens over for integrasehæmmerklassen, emtricitabin eller tenofovir
ATC-kode:	J05AR20

Proces	
Ansøgning modtaget hos Amgros:	06-12-2018
Endelig rapport færdig:	04-01-2019
Sagsbehandlingstid fra endelig ansøgning:	29 dage
Arbejdsgruppe:	**Line Brøns Jensen** Pernille Winther Johansen Louise Greve Dal Lianna Christensen Mark Friborg

Priser

Alle lægemiddelpriser i denne afrapportering er på AIP-niveau. Amgros har ofte aftaler om rabatter på de analyserede lægemidler. Derfor vil analyser på AIP-niveau ikke altid afspejle regionernes faktiske omkostninger til anskaffelse af lægemidlerne. Da rabatterne varierer betragteligt på tværs af lægemidler, vil prisforskellene i afrapporteringen, ikke altid afspejle de faktiske prisforskelle.

Anbefalingerne i Amgros' beslutningsgrundlag, som sendes sammen med denne afrapportering, bygger på regionernes faktiske anskaffelsespriser (SAIP).

1 BAGGRUND

Biktarvy er en kombinationsbehandling indiceret til behandling af HIV-1-infektion uden nuværende eller tidligere tegn på resistens over for integrasehæmmere, emtricitabin eller tenofovir. Gilead (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af Biktarvy og har den 06.12.2018 indsendt en ansøgning til Medicinrådet om anbefaling af Biktarvy som standardbehandling på danske sygehuse af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de inkrementelle omkostninger forbundet med behandling af HIV-1-infektion, i form af de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af Biktarvy som standardbehandling på danske sygehuse af den nævnte indikation. I analysen sammenlignes behandling med Biktarvy med behandling med dolutegravir + 2 NRTIs, der er defineret i Medicinrådets protokol som nuværende standardbehandling.

1.2 Patientpopulation

HIV-infektion er en kronisk infektion med human immundefektvirus (HIV), som primært overføres seksuelt og via blod. HIV angriber immunforsvaret ved at inficere CD4-positive T-hjælperlymfocytter (kaldet CD4-celler), som er en type af hvide blodlegemer og en del af immunforsvaret. Behandles infektionen ikke, vil virus forårsage, at CD4-cellerne ødelægges, og mængden af CD-4 celler vil falde. En aftagende mængde af CD4-celler vil medføre en tiltagende svækkelse af immunforsvaret, som vil resultere i, at den inficerede person udvikler aquired immunodeficiency syndrome (AIDS) og slutteligt dør.(1)

HIV er særlig prævalent blandt mænd, som har sex med mænd, personer med blødersygdom, stofmisbrugere og personer fra Afrika syd for Sahara.(2)

Der findes to typer af HIV; type 1 og 2. Den langt overvejende del af den danske patientpopulation har HIV-1-infektion. Der lever kun få personer med HIV-2-infektion i Danmark. Incidensen af nydiagnosticerede HIV-patienter i Danmark har i mange år ligget stabilt mellem 200 og 300.(3,4) I 2016 fik 182 personer i Danmark diagnosen HIV. Herudover blev der anmeldt 62 personer, som allerede var diagnosticeret i udlandet.(3)

Det estimeres, at der ved udgangen af 2016 levede omkring 6.200 mennesker med HIV i Danmark.(3) Ifølge data fra Det Danske HIV Kohorte Studie var i alt 5.502 af de HIV-inficerede personer på dette tidspunkt under antiretroviral behandling.(2)

De antiretrovirale lægemidler virker på de proteiner, som HIV-partiklen indeholder, og som er nødvendig for HIV-partiklens syntese og fortsatte evne til at inficere nye CD4-celler. De mest hyppigt anvendte antiretrovirale midler kan inddeles i fire forskellige grupper efter virkningsmekanisme(4–6):

1. Nukleosid- og nukleotid-revers-transkriptasehæmmere (NRTIs) hæmmer HIV revers-transkriptase
2. Non-nukleosid-revers-transkriptasehæmmere nedsætter ligesom NRTIs også aktiviteten af HIV revers-transkriptase
3. Intergrasehæmmere inhiberer aktiviteten af den HIV-kodede integrase
4. Proteasehæmmere inhiberer den HIV-specifikke protease

1.3 Behandling med Biktarvy

Indikation
Bictegravir/emtricitabin/tenofoviralafenamid har EMA-indikationen behandling af voksne patienter med HIV-1-infektion uden nuværende eller tidligere tegn på resistens over for integrasehæmmere, emtricitabine eller tenofovir.

Virkningsmekanisme
Bictegravir/emtricitabin/tenofoviralafenamid er en kombinationstablet bestående af tre antiretrovirale midler: Det nye lægemiddel bictegravir som er en andengenerationsintegrasehæmmer og de i forvejen godkendte og markedsførte NRTIs emtricitabin og tenofoviralafenamid.

Dosering
Biktarvy administreres som én tablet indeholdende 50 mg bictegravir, 200 mg emtricitabin og 25 mg tenofoviralafenamid en gang dagligt.

1.3.1 Komparator
Medicinrådet har defineret komparator som dolutegravir + 2 NRTIs.

1.4 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af behandling med Biktarvy sammenlignet med dolutegravir + 2 NRTIs for følgende population:

- Behandlingsnaive patienter med HIV-1-infektion

Den godkendte indikation omfatter også patienter, som skal skifte behandling, der ikke er resistente overfor integrasehæmmere, emtricitabine eller tenofovir. Fagudvalget vurderer, at sammenligningen med komparator for behandlingsnaive kan ekstrapoleres til denne patientgruppe.(7)

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af gennemsnitlige behandlingsomkostninger per patient sammenlignes behandling med Biktarvy med behandling med dolutegravir i kombination med to NRTI'er (Triumeq) til voksne patienter med HIV-1-infektion.

2.1 Model, metode og forudsætninger

2.1.1 Modelbeskrivelse
Ansøger har indsendt en simpel omkostningsmodel for behandling af patienter i den nævnte population.

Ansøger har valgt at sammenligne Biktarvy med Triumeq, eftersom Triumeq har været komparator til Biktarvy i to head-to-head studier. Ansøger mener derfor, at Triumeq er en relevant repræsentant for kombinationen dolutegravir i kombination med to NRTIs, som angivet i Medicinrådets protokol.

Ansøger antager, at behandlingsforløbene for Biktarvy og Triumeq er identiske, og at effekt- og bivirkningsprofilen er helt ens. Frafald inkluderes således ikke i analysen. Der er derfor tale om en forsimplet analyse, der udelukkende inkluderer lægemiddelomkostninger for Biktarvy og Triumeq.

I modellen antages, at alle behandlingsnaive patienter, der starter i behandling med enten Biktarvy eller Triumeq fortsætter med behandlingen resten af deres liv.

Amgros' vurdering

Amgros vurderer, at modellens grundlæggende struktur er nogenlunde rimelig, om end forsimplet i forhold til det naturlige sygdomsforløb. Modellen inkluderer blandt andet ikke bivirkningsomkostninger, omkostninger

forbundet med ressourcetræk på sundhedsvæsenet eller betydningen af behandlingsskift i tidshorisonten. Modellen er derfor blot en simpel beregning på lægemiddelomkostninger.

Amgros vurderer, at Triumeq er en relevant repræsentant for den valgte komparator, men tilføjer dog de resterende kombinationsmuligheder for dolutegravir + 2 NRTIs i Amgros' hovedanalyse, jf. den seneste behandlingsvejledning.(8)

Amgros har bedt regionerne udpege klinikere med ekspertise indenfor det relevante område, og bedt de valgte klinikere om at validere ansøgers grundlæggende antagelser og estimater. Regionerne udpegede 4 klinikere, der svarede på spørgsmål angående ansøgers modelstruktur og estimater. På baggrund af deres svar har Amgros ikke fundet grund til at ændre i modeltilgangen.

Amgros accepterer den forsimplede modeltilgang, men tilføjer dog de resterende kombinationsmuligheder for komparatoren i Amgros' hovedanalyse.

2.1.2 Analyseperspektiv

Analysen inkluderer udelukkende lægemiddelomkostninger. Tidshorisonten i analysen er 1 år.

Amgros' vurdering

Analysens perspektiv er i tråd med Amgros' retningslinjer, Jf. Amgros Metodevejledning om, hvad der må inkluderes i en økonomisk analyse.

Amgros vurderer, at tidshorisonten er tilstrækkeligt lang til at opfange betydelige relevante forskelle mellem de sammenlignede interventioner i analysen for den angivne population, da patienterne antages at få behandlingen resten af deres liv, grundet HIV-1-infektionens kroniske karakter. Det antages ikke, at omkostningerne skifter per år over livstidsbehandlingen, hvorfor 1 år anses som en relevant tidshorisont.

Amgros godtager analysens perspektiv og tidshorisonten.

2.1.3 Omkostninger

Det følgende afsnit om omkostninger redegør for hvordan og hvilke omkostninger ansøger har inkluderet i analysen.

Lægemiddelomkostninger

Ansøger har for Biktarvy og Triumeq anvendt SPC'erne for lægemidlerne.(9,10) Alle anvendte lægemiddelpriser er på AIP-niveau.

Tabel 1 illustrerer de lægemiddelpriser, som anvendes i analysen.

Tabel 1: Anvendte lægemiddelpriser, DKK, AIP (juli 2018)

Lægemiddel	Styrke	Pakningsstørrelse	Pris pr pakning	Kilde
Bictegravir/emitricitabin/tenofo-viralafenamid (Biktarvy)	25/200/25 mg	30 tabletter	9.754,00	Medicinpriser.dk (Biktarvy)
Lamivudin/abacavir/dolutegravir (Triumeq)	50/600/300 mg	30 tabletter	7.272,04	Medicinpriser.dk (Triumeq)

Ansøger antager, at patienter behandles med én tablet dagligt over hele tidshorisonten – uanset behandlingsregime.

Tabel 2 illustrerer administreringen af lægemidlerne, som anvendes i analysen og prisen per dag.

Tabel 2: Lægemiddelomkostninger per dag, AIP (juli 2018)

Behandlingsregime	Antal doseringer	Pris pr. pakning	Pris pr. dag
Bictegravir/emitricitabin/tenofovir alafenamid (Biktarvy)	365,25 per år	9.754,00 kr.	325,13 kr.
Lamivudin/abacavir/dolutegravir (Triumeq)	365,25 per år	7.272,04 kr.	242,40 kr.

Amgros' vurdering

Ansøger har valgt at benytte Triumeq som repræsentant for alle de mulige kombinationer af dolutegravir + 2 NRTIs. Amgros vurderer, at Triumeq er en acceptabel repræsentant for denne gruppe, men inkluderer dog de resterende kombinationsmuligheder i Amgros' hovedanalyse.

Doseringen og administration af lægemidlerne er i tråd med lægemidlernes SPC'er.(9,10)

Amgros accepterer den valgte tilgang, men inkluderer alle kombinationsmuligheder med dolutegravir + 2 NRTIs som komparatorer i Amgros' hovedanalyse.

2.2 Følsomhedsanalyser

Ansøger har ikke udarbejdet følsomhedsanalyser.

Amgros' vurdering

Amgros accepterer, at ansøger ikke har udarbejdet følsomhedsanalyser, eftersom den forsimplede modeltilgang ikke giver anledning til usikkerheder omkring omkostninger for behandlingerne.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Ansøgers hovedanalyse resulterer i gennemsnitlige meromkostninger per patient for Biktarvy sammenlignet med Triumeq på ca. 30.000 kr.

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 3.

Tabel 3: Resultat af ansøgers hovedanalyse, gns. omkostninger per patient, kr., AIP

	Biktarvy	Triumeq	Inkrementelle omkostninger (DKK)
Lægemiddelomkostninger	118.755	88.537	**30.218**

3.2 Amgros' hovedanalyse

3.2.1 Antagelser i Amgros hovedanalyse

- *Amgros tilføjer de resterende kombinationsmuligheder af dolutegravir + 2 NRTIs som komparatorer*

3.2.2 Resultat af Amgros hovedanalyse

Resultaterne fra Amgros hovedanalyse præsenteres i tabel 4.

Tabel 4: Anvendte lægemiddelpriser, AIP (december 2018)

Lægemiddel	Styrke	Pakningsstørrelse	Pris pr pakning	Kilde*
Bictegravir/emtricita-bin/tenofoviralafenamid (Biktarvy)	50/200/25 mg	30 stk.	9.754,00	Medicinpriser.dk (Biktarvy)
Lamivudin (Epivir®)	300 mg	30 stk.	1.102,52	Medicinpriser.dk (Epivir®)
Tenofovir disoproxil (Tenofovir disoproxil "Teva")	245 mg	30 stk.	3.100,00	Medicinpriser.dk (Tenofovir disoproxil "Teva")
Dolutegravir (Tivicay)	50 mg	30 stk.	4.178,00	Medicinpriser.dk (Tivicay)
Lamivudin og abacavir (Abacavir/Lamivudin "Mylan")	600/300 mg	30 stk.	2.781,59	Medicinpriser.dk (Abacavir/Lamivudin "Mylan")
Tenofovir disoproxil og emtricitabin (Emtricita-bin/Tenofovir disoproxil "Mylan")	200/245 mg	30 stk.	5.786,59	Medicinpriser.dk (Emtricitabin/Tenofovir disoproxil "Mylan")
Lamivudin, abacavir og dolutegravir (Triumeq)	50/600/300 mg	30 stk.	7.272,04	Medicinpriser.dk (Triumeq)
Abacavir (Ziagen®)	300 mg	60 stk.	1.914,14	Medicinpriser.dk (Ziagen®)
Emtricitabin (Emtriva)	200 mg	30 stk.	1.647,00	Medicinpriser.dk (Emtriva)
Tenofovirdisoproxil (Vi-read®)	245 mg	30 stk.	3.187,50	Medicinpriser.dk (Viread®)
Emtricitabin og tenofovi-ralafenamid (Descovy)	200/10 mg	30 stk.	4.176,00	Medicinpriser.dk (Descovy)

*Tilgået 14.12.2018

I tabel 5 ses resultatet af Amgros' hovedanalyse for Biktarvy sammenlignet med de tilgængelige kombinations-muligheder af dolutegravir + 2 NRTIs, der er inkluderet i behandlingsvejledningen og lægemiddelrekommandati-onen for terapiområdet HIV/AIDS.(4)

De inkrementelle omkostninger forbundet med behandling med Biktarvy vil være ca. -2.500 – 34.000 kr. per år afhængig af de valgte komparatorer.

Tabel 5 Resultat af Amgros' hovedanalyse, kr., AIP.

	Lægemiddel	Pris per patient per år	Totale lægemiddel-omkostninger	Inkrementelle omkostninger
	Biktarvy	118.755	118.755	-
Komparatorer				
1	Epivir®	13.423	102.033	**16.722**
	Tenofovir disoproxil "Teva"	37.743		
	Tivicay	50.867		
2	Abacavir/Lamivudin ”Mylan”	33.866	84.733	**34.022**
	Tivicay	50.867		
3	Emtricitabin/Tenofovir diso-proxil "Mylan"	70.452	121.319	**-2.564**
	Tivicay	50.867		
4	Triumeq	88.537	88.537	**30.218**
5	Epivir®	13.423	87.595	**31.160**
	Ziagen®	23.305		
	Tivicay	50.867		
6	Emtriva	20.052	109.727	**9.028**
	Viread®	38.808		
	Tivicay	50.867		
7	Emtriva	20.052	94.224	**24.531**
	Ziagen®	23.305		
	Tivicay	50.867		
8	Descovy	50.843	101.710	**17.045**
	Tivicay	50.867		

4 BUDGETKONSEKVENSER

Budgetkonsekvenserne per år er baseret på antagelsen om, at Biktarvy vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

- Biktarvy bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler
- Biktarvy bliver ikke anbefalet som standardbehandling

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Medicinrådet angiver i protokollen for vurdering af den kliniske merværdi af Biktarvy til HIV-1-infektion, at ca. 200 patienter i 2016 blev diagnosticeret med HIV. Ansøger har antaget, at ingen nydiagnosticerede patienter vil blive behandlet med Biktarvy. Til gengæld vil en del da de patienter, der allerede er i behandling skifte til Biktarvy.

Ansøgers estimerede patientantal er vist i tabel 6.

Tabel 6 Ansøgers estimat af antal nye patienter per år

Antal patienter	År 1	År 2	År 3	År 4	År 5
Biktarvy anbefales ikke					
Biktarvy	0	0	0	0	0
Triumeq	50	83	105	115	127
Biktarvy anbefales					
Biktarvy	50	83	105	115	127
Triumeq	0	0	0	0	0

Amgros' vurdering af estimeret patientantal

Amgros vurderer, at ansøgers estimater virker rimelige.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen.

Med de indlagte antagelser estimerer ansøger, at anvendelse af Biktarvy vil resultere i budgetkonsekvenser på ca. 4 mio. kr. per år ved år 5.

Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 7.

Tabel 7 Ansøgers hovedanalyse for totale budgetkonsekvenser, mio. kr., ikke-diskonterede tal, baseret på AIP.

AIP	År 1	År 2	År 3	År 4	År 5
Biktarvy anbefales ikke	4,4	7,3	9,3	10,2	11,2
Biktarvy anbefales	5,9	9,9	12,5	13,7	15,1
Totale budgetkonsekvenser	**1,5**	**2,5**	**3,2**	**3,5**	**3,8**

Amgros' vurdering

Amgros vurderer, at ansøgers analyse er acceptabel, omend forsimplet. Amgros udarbejder en budgetkonsekvens-analyse baseret på den billigst tilgængelige komparator benyttet i Amgros' hovedanalyse.

4.2 Amgros' estimat af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- *Omkostningerne fra Amgros' hovedanalyse anvendes*
- *Amgros beregner budgetkonsekvenserne baseret på omkostningen forbundet med den billigste tilgængelige kombinationsmulighed af dolutegravir + 2 NRTIs som komparator, dvs. Abacavir/Lamivudin "Mylan" + Tivicay*

Med de indlagte antagelser estimerer Amgros, at anvendelse af Biktarvy vil resultere i budgetkonsekvenser på ca. 4 mio. kr. per år. Budgetkonsekvenserne er meget usikre.

Amgros' estimat af budgetkonsekvenserne fremgår af tabel 8.

Tabel 8 Amgros' hovedanalyse for totale budgetkonsekvenser, mio. kr., ikke-diskonterede tal, baseret på AIP.

AIP	År 1	År 2	År 3	År 4	År 5
Biktarvy anbefales ikke	4,2	7,0	8,9	9,7	10,8
Biktarvy anbefales	5,9	9,9	12,5	13,7	15,1
Totale budgetkonsekvenser	**1,7**	**2,8**	**3,6**	**3,9**	**4,3**

5 DISKUSSION

Ansøger har kun inkluderet lægemiddelomkostninger, eftersom de er antager, at behandlingerne er ligeværdige med hensyn til effekt og bivirkningsprofil. Alle lægemidler administreres oralt, og derfor antages ens administrations- og monitoreringsomkostninger.

Amgros vurderer, at de inkrementelle omkostninger forbundet med behandling med Biktarvy vil være ca. -2.500 – 34.000 kr. afhængig af de valgte komparatorer.

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AMGROS

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Høringssvar fra Gilead i forbindelse med udkast til Medicinrådets vurdering af klinisk merværdi for Biktarvy til behandling af hiv-1-infektion.

Til Medicinrådet 19. december 2018

I forbindelse med modtagelsen af vurderingsrapporten af 12. december 2018 har Gilead følgende bemærkninger:

- Gilead tager beslutningen om klassificering til efterretning.
- Gilead har dog enkelte bemærkninger om udkastet til Medicinrådets vurdering af klinisk merværdi, der har generel interesse for offentligheden og speciel interesse for patienter i antiretroviral behandling.

I protokollen blev patientpopulationen begrænset til "kun" at omfatte behandlingsnaive patienter.

Gilead er som udgangspunkt skuffet over begrænsningen i patientpopulationen. Primært fordi antiretroviral behandling skal følges livslangt. Der vil med behandlingstiden opleves forskellige bivirkninger eller tilstødende ko-morbiditeter. Endelig ekskluderer begrænsningen i patientpopulationen halvdelen af den kliniske dokumentation i form af kliniske studier på behandlingserfarne patienter som har deltaget i fase 3 studier.

I Gilead anerkender vi at kritiske effektmål må være viral suppression og viral svigt indenfor HIV behandling. Omvendt ser vi det nødvendigt at fremhæve at andre effektmål er blevet tiltagende vigtige i en livslang behandling når man er en kronisk syg patient. HIV patientpopulationen i Danmark har en hurtigt stigende gennemsnitsalder, øget risiko for ko-morbiditeter, en ændret tolerabilit profil, risiko for drug-drug-interaktion og oplevet livskvalitet gennem livslang behandling etc.

Vi noterer os at Biktarvy tildeles en lille klinisk merværdi sammenlignet med dolutegravir + 2 NRTI'er, hvad angår ikke alvorlige bivirkninger – stadig kun evalueret på behandlingsnaive patienter.

Vi noterer os at fagudvalget konkluderer; "Men da behandlingen er livslang, finder fagudvalget, at også ikkealvorlige bivirkninger er af stor betydning for patienten." og "at der ikke er grund til at tro at behandlingsregimernes påvirkning af blandt andet livkvalitet er afhængig af om patienten tidligere har modtaget behandling og at disse studier, der undersøger patienter som skifter behandling, ikke tilføjer yderligere information, som er relevant for sammenligningen af behandlingsregimerne i vurderingen af merværdi".

For behandlingserfarne patienter opleves oftest flere forskellige typer af bivirkninger, som ud over kvalme er dårlig søvn og bivirkninger relateret til central nerve systemet.

Gilead beklager at den kliniske dokumentation som findes for behandlingserfarne patienter er blevet ekskluderet alene fordi patientpopulationen blev begrænset til behandlingsnaive patienter.

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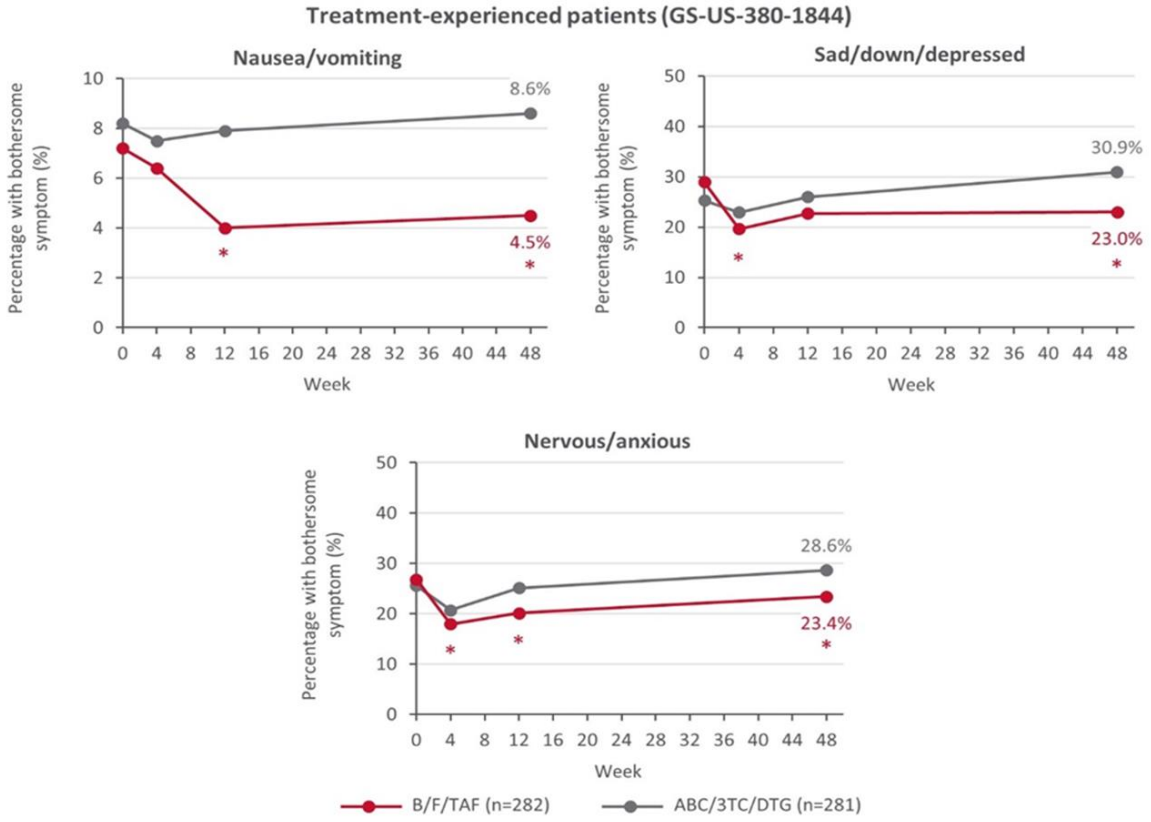
At patienter som har været i stabil behandling og er fuld supprimeret forventes det at behandlingen tåles godt og de fleste bivirkninger er overstået. Derfor tillader vi os at inkludere nedenstående figur som dokumenterer Biktarvys signifikant positive effekt med hensyn til bivirkninger i behandlingserfarne patienter.

Patient-reported outcomes in study GS-US-380-1844: A double-blind, randomized, phase III study comparing B/F/TAF with DTG/ABC/3TC in virologically suppressed adults



Kilde: Wohl 2018

I Gilead ser vi meget frem til at dele resultaterne med fagudvalget når vi får publiceret data med 96 og 144 ugers opfølgningstid for Biktarvy.

Sluttelig vil vi fremhæve at der er god dokumentation for at der findes et udækket medicinsk behov for HIV patienter i dagens Danmark. Dette gælder især for subgruppen af patienter med høj risiko for hjerte/kar sygdomme, nyresygdom (EGFR> 30 ml / min) og/eller osteopeni/osteoporose hvor Biktarvy er et velegnet alternativ.

Med venlig hilsen

Flemming Axelsen
Sundhedsøkonom

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Medicinrådet den 21. december 2018

Fagudvalgsformanden for fagudvalget vedrørende hiv/aids og Medicinrådets sekretariatet har vurderet høringssvar fra Gilead og har følgende bemærkning til ansøgers høringssvar:

Medicinrådets vurdering er ikke begrænset til behandlingsnaive patienter, men dækker over patienter med hiv-1 infektion, som ikke har aktuel eller tidligere påvist resistens overfor indholdsstofferne, og hvor der er indikation for at skifte behandling, som det også fremgår på side 19 i vurderingsrapporten.

Medicinrådet

Medicinrådets vurdering af klinisk merværdi for bictegravir/emtricitabin/tenofovir alafenamid til behandling af hiv-1-infektion

Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at bictegravir/emtricitabin/tenofovir alafenamid til behandling af hiv-1-infektion giver **ingen klinisk merværdi** sammenlignet med dolutegravir givet sammen med to antiretrovirale midler af klassen nukleosid- og nukleotid-revers-transkriptasehæmmere. Evidensens kvalitet er moderat.

Handelsnavn	Biktarvy
Generisk navn	Bictegravir/emtricitabin/tenofovir alafenamid
Firma	Gilead
ATC-kode	J05AR20
Virkningsmekanisme	Kombinationspræparat af tre antiretrovirale midler: hiv-integrasehæmmer (bictegravir), nukleosid-revers-transkriptasehæmmer (emtricitabin) og nukleotid-revers-transkriptasehæmmer (tenofovir alafenamid).
Administration/dosis	50 mg/200 mg/25 mg bictegravir/emtricitabin/tenofovir alafenamid kombinationstablet én gang dagligt.
EMA-indikation	Biktarvy er indiceret til behandling af voksne, der er inficeret med human immundefekt virus 1 (hiv 1) uden nuværende eller tidligere påvist viral resistens overfor integrasehæmmerklassen, emtricitabin eller tenofovir.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	12. december 2018 12. december 2018 33921 1.0

Fagudvalgets sammensætning og sekretariatets arbejdsgruppe, se bilag 1

Definition af klinisk merværdi:

Medicinrådet kategoriserer lægemidlets kliniske merværdi i en af følgende kategorier:

Kategori 1. Stor merværdi: Vedvarende og stor forbedring i effektforhold der ikke tidligere er opnået med et relevant behandlingsalternativ. Eksempler herpå er sygdomsremission, markant stigning i overlevelsestid, langvarigt fravær af alvorlige sygdomssymptomer eller udtalt fravær af alvorlige bivirkninger.

Kategori 2. Vigtig merværdi: Markant forbedring, eksempelvis lindring af sygdomstilstand, moderat stigning i overlevelsestid, lindring af alvorlige symptomer, fravær af alvorlige bivirkninger og væsentligt fravær af andre bivirkninger.

Kategori 3. Lille merværdi: Moderat forbedring, f.eks. reduktion i ikkealvorlige sygdomssymptomer eller fravær af bivirkninger.

Kategori 4. Ingen merværdi: Ingen merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 5. Negativ merværdi: Negativ merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 6. Ikkedokumenterbar merværdi: Ikkedokumenterbar merværdi sammenlignet med standardbehandling/ andre behandlinger. Effektforskellen kan ikke kvantificeres ud fra det videnskabelige datagrundlag.

Om Medicinrådet:

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Forkortelser

3TC:	Lamivudin
ABC:	Abacavir
AE:	*Adverse event* (uønsket hændelse)
aids:	*Acquired immunodeficiency syndrome* (Erhvervet Immundefekt syndrom)
BIC:	Bictegravir
DGT:	Dolutegravir
FTC:	Emtricitabin
GRADE:	*Grading of Recommendations Assessment, Development and Evaluation*
Hiv:	Human immundefektvirus
HR:	*Hazard Ratio*
IQR:	*Interquatile range*
ITT:	*Intention-to-treat*
NRTI	Nukleosid- og nukleotid-revers-transkriptasehæmmere
RR:	Relativ Risiko
TAF:	Tenofovir alafenamid

Indhold

1 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af bictegravir/emtricitabin/tenofovir alafenamid til voksne med human immundefektvirus (hiv) -1-infektion er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparatorer).

Med udgangspunkt i den kliniske merværdi og en omkostningsanalyse udarbejdet af Amgros vurderer Medicinrådet, om bictegravir/emtricitabin/tenofovir alafenamid anbefales som mulig standardbehandling.

2 Baggrund

Hiv-1-infektion

Hiv-infektion er en kronisk infektion med human immundefektvirus (hiv), som primært overføres seksuelt og via blod. Hiv angriber immunforsvaret ved at inficere de hvide blodlegemer, som kaldes CD4-positive T-hjælper lymfocytter (også kaldet CD4-celler). Hvis infektionen ikke behandles, dræber hiv-virussen CD4-cellerne, og mængden af CD4-celler falder. Det medfører, at den inficerede persons immunforsvar gradvist svækkes og kan resultere i, at personen udvikler aids, som er en dødelig sygdom.[1].

Der findes to typer af hiv, type 1 og 2. Den langt overvejende del af den danske patientpopulation har hiv-1-infektion. Antallet af nydiagnosticerede patienter med hiv-infektion i Danmark har i mange år ligget stabilt mellem 200 og 300 personer [2,3]. I 2016 blev 182 personer i Danmark diagnosticeret med hiv. Herudover blev 62 personer, som allerede var diagnosticeret i udlandet, anmeldt i Danmark [2].

Ifølge Statens Seruminstitut levede ca. 6.200 mennesker med hiv i Danmark i 2016 [3], og ifølge data fra Det Danske HIV Kohorte Studie blev 5.268 patienter samme år fulgt hos en behandler [4].

Nuværende behandling

Målet med den nuværende behandling er at hæmme, at virus formerer sig, og herved forhindre at immunsystemet svækkes, og sygdommen udvikles. Effektiv behandling nedsætter risikoen for, at patienten udvikler aids og dør som følge heraf. En vellykket behandling eliminerer også hiv-smitte [1,3].

Danske patienter behandles som standard med en kombinationsbehandling af tre antiretrovirale midler. Den såkaldte "*backbone"* af behandlingen består af to nukleosid- og nukleotid-revers-transkriptasehæmmere (NRTI'er). Backbone gives med et tredje stof, som enten er en non-nukleosid-revers-transkriptasehæmmer, en proteasehæmmer eller en integrasehæmmer [3,5]. De antiretrovirale lægemidler virker på de proteiner, som hiv-partiklen indeholder, og som er nødvendige for hiv-partiklens syntese og fortsatte evne til at inficere nye CD4-celler.

De stofklasser, der er relevante for denne vurdering, er NRTI'erne og integrasehæmmerne.
NRTI-klassen inkluderer lægemidlerne lamivudin, abacavir, tenofovir disoproxil, tenofovir alafenamid og emtricitabin [6]. Integrasehæmmerklassen inkluderer dolutegravir, raltegravir, elvitegravir. Elvitegravir gives i kombination med boosteren cobicistat, som forøger den tid, elvitegravir er i blodet [7]. Det nye lægemiddel, bictegravir, tilhører integrasehæmmerklassen.

Der er ikke en bestemt kombination af lægemidlerne, som betragtes som standardbehandling, da valg af behandlingsregime er afhængig af flere faktorer, og mange patienter skifter regime i behandlingsforløbet. Behandlingen skiftes, hvis der optræder resistensudvikling, bivirkninger, betydelige interaktioner eller adhærensproblemer. Op til 50 % af patienterne skifter medicin inden for det første år [3]. Når der skal vælges et alternativt regime, tages der hensyn til patientens medicinhistorie og resistensudvikling, som kan være meget kompleks [3,5]. Der tages også hensyn til nemhed for patienten ved medicinindtaget.

Anvendelse af bictegravir/emtricitabin/tenofovir alafenamid

Bictegravir/emtricitabin/tenofovir alafenamid er en kombinationstablet bestående af det nye lægemiddel, bictegravir, som er en andengenerations-integrasehæmmer, og NRTI'erne emtricitabin og tenofovir alafenamid, der begge allerede er godkendt og markedsført.

Bictegravir/emtricitabin/tenofovir alafenamid er godkendt til behandling af voksne patienter med hiv-1-infektion uden aktuel eller tidligere påvist viral resistens over for integrasehæmmerklassen, emtricitabin eller tenofovir.

Bictegravir/emtricitabin/tenofovir alafenamid er tilgængelig som kombinationstablet á 50 mg bictegravir, 200 mg emtricitabin og 25 mg tenofovir alafenamid. Tabletten doseres én gang i døgnet. Behandlingen er som udgangspunkt livslang.

3 Metode

Ansøgningen er valideret af Medicinrådets sekretariat. Ansøger har anvendt og fulgt den metode, der er præspecificeret i protokollen, som er godkendt den 18. maj 2018.

Fagudvalget har bedt om, at bictegravir/emtricitabin/tenofovir alafenamid sammenlignes med en kombination af tre antiretrovirale lægemidler, hvor dolutegravir gives som tredjestof sammen med en valgfri backbone af to NRTI'er. Ansøger har sammenlignet med dolutegravir/abacavir/lamivudin og dolutegravir + emtricitabin/tenofovir alafenamid.

Metodiske opmærksomhedspunkter er beskrevet under afsnit 4 (Litteratursøgning) og afsnit 5 (Databehandling).

Som efterspurgt i protokollen har ansøger kun leveret data for behandlingsnaive patienter.

Fagudvalget vurderer, at der ikke er grund til at tro, at behandlingsregimernes effekt, bivirkningsprofil og påvirkning af livskvalitet er afhængig af, om patienten tidligere har modtaget behandling. Antagelsen gælder kun for patienter, som ikke har aktuel eller tidligere påvist resistens overfor indholdsstofferne. Fagudvalget vurderer således, at studier, der undersøger patienter, som skifter behandling, ikke tilføjer yderligere information, som er relevant for sammenligningen af behandlingsregimerne i vurderingen af merværdi [8].

Fagudvalget vurderer derfor, at sammenligningen med komparator for behandlingsnaive patienter kan ekstrapoleres til behandlingserfarne patienter som ikke har aktuel eller tidligere påvist resistens.

4 Litteratursøgning

Ansøger har foretaget en systematisk litteratursøgning. Her fandt de to studier, GS-US-380-1489 og GS-US-380-1490, som opfylder kriterierne opstillet i protokollen. Begge studier er fase 3-studier og danner grundlag for Medicinrådets vurdering af den kliniske merværdi af bictegravir/emtricitabin/tenofivor. Hovedresultaterne og livskvalitetsdata er publiceret i 3 referencer (tabel 1).

Tabel 1. Publikationer inkluderet i analysen af den kliniske merværdi af bictegravir/emtricitabin/tenofovir alafenamid

Reference	Klinisk forsøg	NCT-nummer
Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. **Gallant et al. 2017. The Lancet**. [9]	GS-US-380-1489, hovedanalyse	NCT02607930
Patient-Reported Symptoms Over 48 Weeks Among Participants in Randomized, Double-Blind, Phase III Non-inferiority Trials of Adults with HIV on Co-formulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide versus Co-formulated Abacavir, Dolutegravir. **Wohl et al. 2018. The Patient** [10]	GS-US-380-1489, analyse af livskvalitetsdata	NCT02607930
Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiori**. Sax et al. 2017. The Lancet**. [11]	GS-US-380-1490, hovedanalyse	NCT02607956

Ansøger identificerede desuden et fase 2-studie [12], som undersøger bictegravir/emtricitabin/tenofovir alafenamid. Studiet blev ekskluderet, fordi bictegravir blev givet i en anden dosis end den, der blev godkendt i EMA, og som er defineret i protokollen.

Ansøger har både søgt efter referencer om bictegravir/emtricitabin/tenofovir alafenamid, og referencer som kun omhandler komparator. Ansøger identificerer derfor flere artikler, end de medtager i analysen. Ansøger har søgt efter litteratur i to forskellige databaser med tre måneders mellemrum, og søgestrengene afveg fra hinanden. Desuden er ansøgers angivelse af antallet af inkluderede referencer ikke fuldt gennemskuelig. Medicinrådets sekretariat har eftertjekket ansøgers litteratursøgning og screening og har konkluderet, at al relevant litteratur er medtaget.

Fra evidens til kategori. Medicinrådet vurderer den kliniske merværdi af et lægemiddel ud fra den indsendte endelige ansøgning, evt. suppleret med andet materiale. I protokollen blev effektmålene angivet som "kritiske", "vigtige" og "mindre vigtige". I vurderingen af klinisk merværdi vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Den kliniske merværdi kategoriseres først enkeltvis pr. effektmål, hvorefter der foretages en vurdering af den samlede kategori for lægemidlet på tværs af effektmålene. Kategoriseringen pr. effektmål foretages på baggrund af absolutte og relative værdier for det enkelte effektmål. Den relative effekt beskrives med et estimat og et konfidensinterval, der sammenholdes med generiske væsentlighedskriterier. Den absolutte effekt sammenholdes med den i protokollen beskrevne "mindste klinisk relevante forskel". Den endelige kategorisering af lægemidlets kliniske merværdi er en delvis kvalitativ proces, hvor der foretages en vurdering af det samlede datagrundlag på tværs af effektmålene.

Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk merværdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

5 Databehandling

Medicinrådets sekretariat har valideret databehandlingen i ansøgningen og har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger.

Da studierne stadig er i gang, er data for opfølgning ved uge 96 og 144 ikke opgjort endnu. Ansøger har således kun angivet data for opfølgning på 48 uger.

Alle anførte konfidensintervaller er angivet som 95 %-konfidensintervaller.

Absolutte effektforskelle for viral suppression er justeret for baseline hiv-RNA (≤ 100.000 vs. > 100.000 kopier/ml) og region (USA vs. ikke USA), som det fremgår i publikationerne. De resterende effektmål er ikke justeret for baselinekarakteristika.

Medicinrådets sekretariat har bemærkninger til ansøgningen påfølgende punkter:

- Ansøger har ikke foretaget metaanalyser, men har medtaget en alternativ poolet analyse. Fagudvalget har ikke benyttet denne analyse, fordi ansøger ikke har poolet resultater for komparatorarmene.
- Fagudvalget vurderer, at det er forsvarligt at foretage metaanalyser for effektmålene "viral suppression" og "viralt svigt", da design, population og komparator i de to studier er sammenlignelige. Medicinrådets sekretariat og fagudvalget har derfor udarbejdet metaanalyser for effektmålene. Effektestimaterne i metaanalyserne er ikke justeret for stratificerende faktorer. Metaanalyserne vil fungere som supplerende beslutningsgrundlag for fagudvalget.
- Ansøgningen indeholder data for effektmål, der ikke er efterspurgt i protokollen. Fagudvalget har ikke anvendt de data i vurderingen af behandlingsregimet.
- For effektmålet "ikkealvorlige bivirkninger" har ansøger leveret data for "alle bivirkninger", hvilket fagudvalget har accepteret.
- Data fra hiv-symptom index, som måler patienternes livskvalitet, er ikke opgjort på den måde, fagudvalget definerede i protokollen. Derfor inddrages det fulde datasæt for Hiv Symptom Index-skalaen ikke i vurderingen.

6 Klinisk merværdi

6.1 Konklusion klinisk spørgsmål

Hvad er den kliniske merværdi af bictegravir/emtricitabin/tenofovir alafenamid til behandlingsnaive patienter med hiv-1-infektion sammenlignet med dolutegravir og to NRTI'er?

Fagudvalget vurderer, at bictegravir/emtricitabin/ tenofovir alafenamid til patienter med hiv-1-infektion giver **ingen klinisk merværdi** (moderat evidenskvalitet) sammenlignet med dolutegravir og to NRTI'er.

6.1.1 Gennemgang af studier

Karakteristika

GS-US-380-1489
GS-US-380-1489 (NCT02607930) er et randomiseret, dobbeltblindet, kontrolleret fase 3-studie, der er udformet til at påvise klinisk sammenlignelighed (non-inferioritet med en grænse på 12 %) for det primære effektmål. Studiet inkluderede patienter fra 122 centre i 9 forskellige lande.

Patienterne er randomiseret 1:1 til behandling med henholdsvis 50 mg bictegravir/200 mg emtricitabin/35 mg tenofovir alafenamid som kombinationstablet eller 50 mg dolutegravir/600 mg abacavir/300 mg lamivudin som kombinationstablet. Begge blev doseret én gang i døgnet. Randomisering er stratificeret efter antal hiv-RNA kopier per ml plasma, CD4-celletal og region (USA eller ikke-USA). I alt blev 631 patienter inkluderet.

Studiets blindede fase er stadig i gang og er planlagt at vare 144 uger. Dataindsamling for kontrolbesøg ved uge 48 er komplet.

Studiets primære effektmål er andelen af patienter, der opnår hiv-RNA/ml < 50 ved 48 uger defineret ved FDA's snapshotanalyse.

GS-US-380-1490
GS-US-380-1490 (NCT02607956) er er et randomiseret, dobbeltblindet, kontrolleret fase 3-studie, der er udformet til at påvise non-inferioritet for det primære effektmål. Studiet inkluderede patienter fra 126 centre i 10 forskellige lande.

Patienterne er randomiseret 1:1 til behandling med henholdsvis 50 mg bictegravir/200 mg emtricitabin/35 mg tenofovir alafenamid som kombinationstablet eller 50 mg dolutegravir i kombination med 200 mg emtricitabin/25 mg tenofovir alafenamid. Begge blev doseret én gang i døgnet. Randomisering var stratificeret efter hiv-RNA/ml, CD4 celletal og region. I alt blev 657 patienter inkluderet.

Studiets blindede fase er stadig i gang og er planlagt at vare 144 uger. Dataindsamling for kontrolbesøg ved uge 48 er komplet.

Studiets primære effektmål er andelen af patienter, der opnår hiv-RNA/ml < 50 ved 48 uger defineret ved FDA's snapshotanalyse

Population

I studierne GS-US-380-1489 og GS-US-380-1490 indgik behandlingsnaive patienter over 18 år med hiv-RNA/ml ≥ 500. Ingen af patienterne havde dekompenseret cirrose.

Patienterne i GS-US-380-1489 havde en glomerular filtrationsrate ≥ 50 ml/min og var negative for *HLA-B*5701*-allelen, som er forbundet med hypersensitivitet overfor abacavir. Ingen af patienterne havde hepatitis B.

Patienterne i GS-US-380-1490 havde en glomerular filtrationsrate ≥ 30 ml/min. Se tabel 1 for baselinekarakteristika for studiepopulationen.

Tabel 2. Patientkarakteristika for GS-US-380-1489 og GS-US-380-1490

	GS-US-380-1489 [8]		**GS-US-380-1490** [11]	
Intervention	B/F/TAF (N = 314)	DGT/ABC/3TC (N = 315)	B/F/TAF (N = 320)	DGT/F/TAF (N = 325)
Alder, år, median (IQR)	31 (18-71)	32 (18-68)	33 (27-46)	34 (27-46)
Kvinder, n (%)	29 (9 %)	33 (10 %)	40 (13 %)	37 (11 %)
Etnicitet: kaukasiere n (%)	180 (57 %)	179 (57 %)	183 (57 %)	195 (60 %)
BMI, median (IQR)	25,1 (22,4-28,7)	24,9 (22,5-29,1)	25,0 (22,2-28,3)	24,6 (22,2-28,0)
Hiv-RNA kopier, $\log_{10}$ c/ml, median (IQR)	4,42 (4,03-4,87)	4,51 (4,04-4,87)	4,43 (3,95-4,90)	4,45 (4,03-4,84)
CD4-celletal, celler/µl, median (IQR)	443 (299-590)	450 (324-608)	440 (289-591)	411 (297-597)
CD4-celletal, celler/µl ≥ 200 n (%)	278 (89 %)	283 (90 %)	276 (86 %)	291 (90 %)
CD4-celletal, celler/µl ≥ 350 (%)	209 (67 %)	225 (72 %)	209 (65 %)	214 (66 %)
Asymptomatisk hiv-infektion, CDC kategori, n (%)	286 (91 %)	286 (91 %)	286 (89 %)	288 (89 %)
Patienter med aids n, (%)	12 (4 %)	15 (5 %)	24 (8 %)	26 (8 %)

IQR: *interquartile range* dvs. interkvartilafstanden, B: bictegravir, F: emtricitabin, TAF: tenofovir alafenamid, DGT: dolutegravir, 3TC: lamivudin.

Fagudvalget finder, at studiepopulationerne er sammenlignelige og at der for begge studier ikke er nogen betydende forskelle i baselinekarakteristika mellem behandlingsarmene. Sammenlignet med den danske patientpopulation er der lidt større andel, som har CD4-celletal under 350 celler/µl. Jf. opgørelse fra Statens Serum Institut er der også en større andel af patienter med aids-definerende symptomer ved diagnose i den danske patientpopulation sammenlignet med studiepopulationen [2,13]. Der er tale om små forskelle, og fagudvalget vurderer, at studiepopulationerne kan overføres til den danske population.

6.1.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som henholdsvis kritiske og vigtige, følger nedenfor.

Viral suppression (kritisk)

Ved tidlig behandling med moderne effektive antiretrovirale behandlingsregimer forventes det ikke, at en patient med hiv-infektion oplever alvorlige kliniske symptomer inden for tidsrammen af et klinisk forsøg. Måling af hiv-RNA er et etableret surrogatmål for forbedring af kliniske endepunkter [14–16]. Både FDA og EMA anbefaler at benytte andelen af patienter, der opnår og fortsat har viral suppression, til at måle effekten af antiretrovirale behandlingsregimer [14,15]. Effektmålet er jævnfør FDA's snapshotalgoritme opgjort ved, hvor stor en andel af patienterne der opnår hiv-RNA < 50 kopier/ml ved uge 48.

Tabel 3. Vurdering af klinisk merværdi: andel af patienter, der opnår plasma hiv RNA < 50 kopier/ml iht. til FDA's snapshotanalyse efter 48 uger

	Forhåndsdefineret grundlag for vurdering		Resultater	
			GS-US-380-1489 BIC/FTC/TAF vs. DTG/ABC/3TC	GS-US-380-1490 BIC/FTC/TAF vs. DTG+ FTC/TAF
Absolutte forskelle	5 procentpoint		-0,6 procentpoint [-4,8; 3,6]	-3,5 procentpoint [-7,9; 1,0]
Relative forskelle	Stor merværdi	Nedre konf.gr. > 1,33		
	Vigtig merværdi	Nedre konf.gr. > 1,11		
	Lille merværdi	Nedre konf.gr. > 1,00		
	Ingen merværdi	Nedre konf.gr. ≤ 1,00	RR = 0,99 [0,95; 1,04]	RR = 0,96 [0,92; 1,01]
	Negativ merværdi	Øvre konf.gr. < 1,00		
Evidensens kvalitet	Moderat (se punkt 10.1.3)			

Første kolonne indeholder det i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder absolutte og relative effektforskelle [95 % konfidensinterval], som indgår i Medicinrådets vurdering. Medicinrådets metodehåndbog indeholder for nuværende ikke retningslinjer for merværdikategorisering af positive effektmål som dette, men ud fra vejledningen for negative effektmål kan grænserne for merværdi ved positive effektmål udregnes. (fx er 1,33 den reciprokke værdi af 0,75). BIC: bictegravir, FTC: emtricitabin, TAF: tenofovir alafenamid, DTG: dolutegravir, ABC: abacavir, 3TC: lamivudin. RR; relativ risiko.

Generelt viser studierne høje rater af viral suppression, og derved at patienterne responderer på behandlingen.

For sammenligningen bictegravir/emtricitabin/tenofovir alafenamid vs. dolutegravir/abacavir/lamivudin opnår henholdsvis 92,4 % og 93 % af patienterne hiv-RNA < 50 kopier/ml. Den absolutte effektforskel er -0,6 procentpoint. For sammenligningen bictegravir/emtricitabin/tenofovir alafenamid vs. dolutegravir + emtricitabin/tenofovir alafenamid opnår henholdsvis 89 % og 93 % af patienterne hiv-RNA < 50 kopier/ml. Den absolutte effektforskel er -3,5 procentpoint. De absolutte effektforskelle overstiger ikke den mindste klinisk relevante forskel på 5 procentpoint.

Den relative risiko (RR) sammenlignet med dolutegravir/abacavir/lamivudin er 0,99 [0,95; 1,04], og den relative risiko sammenlignet med dolutegravir + emtricitabin/tenofovir alafenamid er 0,96 [0,92; 1,01]. De relative effektforskelle indplacerer bictegravir/emtricitabin/tenofovir alafenamid i kategorien for ingen merværdi, da konfidensintervallernes nedre grænse er ≤ 1,00.

Som supplerende information har Medicinrådets sekretariat foretaget en metaanalyse (figur 1). Det relative effektestimat på RR = 0,98 [0,95; 1,01] indplacerer også bictegravir/emtricitabin/tenofovir alafenamid i kategorien for ingen merværdi. Den absolutte risikoreduktion udregnes ud fra det relative effektestimat og medianen (og i dette tilfælde gennemsnittet) af incidensraten i komparatorarmen, som er 93 %. Den absolutte risikoreduktion bliver da 1,86 procentpoint (93 % - (0,98 * 93 %). Det betyder, at raten af patienter, der opnår viral suppression er 1,86 procentpoint lavere hos patienter, der behandles med bictegravir/emtricitabin/tenofovir alafenamid. Denne forskel overstiger heller ikke den mindste klinisk relevante forskel.

Figur 1. Metaanalyse for andelen af patienter, der opnår plasma hiv RNA < 50 kopier/ml iht. til FDA's snapshot-analyse efter 48 uger.

Baseret på det tilgængelige data vurderer fagudvalget, at bictegravir/emtricitabin/tenofovir alafenamid har **ingen** klinisk merværdi sammenlignet med dolutegravir + 2 NRTI'er, hvad angår viral suppression.

Viralt svigt (kritisk)

Viralt svigt er defineret som hiv-RNA > 50 kopier/ml ved uge 48. Effektmålet er opgjort for per-protokolpopulationen, altså for de patienter, som har fået målt hiv-RNA ved uge 48, og som fortsat er i behandling. Dvs. opgørelsen inkluderer ikke patienter, som skifter eller ophører behandling pga. manglende effekt før uge 48, eller patienter der er udtrådt af studiet før uge 48 af andre årsager, og hvor deres sidste måling viser hiv-RNA > 50 kopier/ml.

Tabel 4. Vurdering af klinisk merværdi: andel af patienter, der har hiv RNA > 50 kopier/ml ved uge 48 (i per protokolanalyse)

	Forhåndsdefineret grundlag for vurdering		Resultater	
			GS-US-380-1489 BIC/FTC/TAF vs. DTG/ABC/3TC	**GS-US-380-1490** BIC/FTC/TAF vs. DTG+ FTC/TAF
Absolutte forskelle	3 procentpoint		-1,36 procentpoint [-3,24; 0,53]	0,73 procentpoint [-0,64; 2,09]
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75		
	Vigtig merværdi	Øvre konf.gr. < 0,90		
	Lille merværdi	Øvre konf.gr. < 1,00		
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	RR = 0,34 [0,07; 1,66]	RR = 3,16 [0,33; 30,2]
	Negativ merværdi	Nedre konf.gr. > 1,00		
Evidensens kvalitet	Moderat (se punkt 10.1.3)			

Første kolonne indeholder det i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder absolutte og relative effektforskelle [95 % konfidensinterval], som indgår i Medicinrådets vurdering. BIC: bictegravir, FTC: emtricitabin, TAF: tenofovir alafenamid, DTG: dolutegravir, ABC: abacavir, 3TC: lamivudin RR; relativ risiko.

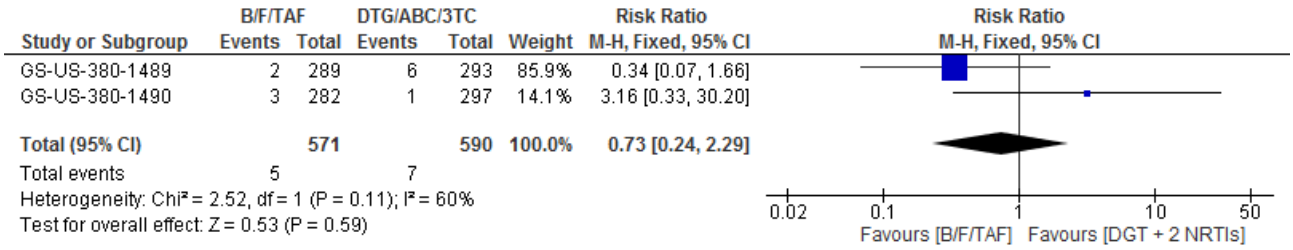
Generelt viser studierne, at meget få patienter oplever svigt.

For sammenligningen bictegravir/emtricitabin/tenofovir alafenamid vs. dolutegravir/abacavir/lamivudin oplever henholdsvis 2 (0,6 %) og 6 (1,9 %) patienter svigt defineret som målt hiv-RNA > 50 kopier/ml ved uge 48. Det vil sige, at 1,36 procentpoint færre patienter oplever viralt svigt i gruppen behandlet med bictegravir/emtricitabin/tenofovir alafenamid. Omvendt er det for sammenligningen bictegravir/emtricitabin/tenofovir alafenamid vs. dolutegravir + emtricitabin/tenofovir alafenamid, hvor henholdsvis 3 (1 %) og 1 (0,3 %) patienter oplever svigt. Det betyder, at der er 0,73 procentpoint færre i gruppen behandlet med dolutegravir + emtricitabin/tenofovir alafenamid, der oplever behandlingssvigt. De absolutte effektforskelle overstiger ikke den mindste klinisk relevante forskel på 3 procentpoint.

Den relative risiko sammenlignet med dolutegravir/abacavir/lamivudin er 0,34 [0,07; 1,66], og den relative risiko sammenlignet med dolutegravir + emtricitabin/tenofovir alafenamid er 3,16 [0,33; 30,2]. De relative effektforskelle indplacerer bictegravir/emtricitabin/tenofovir alafenamid i kategorien for ingen merværdi, da konfidensintervallernes nedre grænse er ≤ 1,00.

Som supplerende information har Medicinrådets sekretariat foretaget en metaanalyse (figur 2). Det relative effektestimat er 0,73 [0,24; 2,29]. Den absolutte forskel udregnes ud fra det relative effektestimat og medianen (som i dette tilfælde også er gennemsnittet) af incidensraten i komparatorarmen, som er 1,2 %. $\left(\frac{0,34+2,09}{2}\right)$. Den absolutte risikoreduktion bliver da 0,3 procentpoint (1,2 % - (0,73 * 1,2 %)), hvilket betyder, at raten for viralt svigt er 0,3 procentpoint lavere hos patienter, der behandles med bictegravir/emtricitabin/tenofovir alafenamid.

Figur 2. Metaanalyse for andelen af patienter, der opnår plasma hiv RNA > 50 kopier/ml efter 48 uger



Baseret på det tilgængelige data vurderer fagudvalget, at bictegravir/emtricitabin/tenofovir alafenamid har **ingen** klinisk merværdi sammenlignet med dolutegravir + 2 NRTI'er, hvad angår viralt svigt.

Resistensudvikling (kritisk)

Resistens måles ved en genotypisk og fænotypisk test af viral integrase, protease og revers-transkriptase hos patienter, der oplever viralt svigt. Fagudvalget har ønsket effektmålet opgjort som andelen af patienter, der har udviklet resistens ved 48 uger.

En subgruppe af patienter med hiv-RNA ≥ 50 kopier/ml opfyldte kriterierne for at blive testet for resistens (under 10 patienter i hver studiearm). Kun patienter, hvor der var biologisk rationale for, at patienten kunne have udviklet resistens, blev testet. Ingen af de testede patienter havde udviklet resistens, hvilket tyder på, at det gælder for begge regimer, at patienterne ikke udvikler resistens, som medfører, at behandlingen svigter.

Baseret herpå vurderer fagudvalget, at bictegravir/emtricitabin/tenofovir alafenamid har **ingen** klinisk merværdi sammenlignet med dolutegravir + 2 NRTI'er, hvad angår resistensudvikling.

Alvorlige bivirkninger (kritisk)

Alvorlige bivirkninger er ikke opgjort i studiet GS-US-380-1490 (bictegravir/emtricitabin/tenofovir alafenamid vs. dolutegravir + emtricitabin/tenofovir alafenamid), og ansøger har derfor kun leveret data for GS-US-380-1489 (bictegravir/emtricitabin/tenofovir alafenamid vs. dolutegravir/abacavir/lamivudin).

Tabel 5. Vurdering af klinisk merværdi: andel af patienter med alvorlige bivirkninger af studiemedicinen

	Forhåndsdefineret grundlag for vurdering		Resultater	
			GS-US-380-1489 BIC/FTC/TAF vs. DTG/ABC/3TC	**GS-US-380-1490** BIC/FTC/TAF vs. DTG+ FTC/TAF
Absolutte forskelle	2 procentpoint		0 procentpoint [-0,88;0,88]	Ikke rapporteret
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75		
	Vigtig merværdi	Øvre konf.gr. < 0,90		
	Lille merværdi	Øvre konf.gr. < 1,00		
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	RR= 1,00 [0,06; 16,00]	
	Negativ merværdi	Nedre konf.gr. > 1,00		
Evidensens kvalitet	Lav (se punkt 10.1.3)			

Første kolonne indeholder det i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder absolutte og relative effektforskelle [95 % konfidensinterval], som indgår i Medicinrådets vurdering. BIC: bictegravir, FTC: emtricitabin, TAF: tenofovir alafenamid, DTG: dolutegravir, ABC: abacavir, 3TC: lamivudin RR; relativ risiko.

Kun én patient i hver studiearm oplever alvorlige bivirkninger relateret til studiemedicinen. Den absolutte forskel er estimeret til 0 procentpoint. Den absolutte effektforskel overstiger ikke den mindste klinisk relevante forskel på 2 procentpoint.

Den relative effektforskel (RR: 1,00 [0,06; 16,00]) lever op til kriteriet for ingen klinisk merværdi, da konfidensintervallets øvre grænse er ≥ 1,00.

På baggrund af det tilgængelige data vurderer fagudvalget, at bictegravir/emtricitabin/tenofovir alafenamid har **ingen** klinisk merværdi sammenlignet med dolutegravir + 2 NRTI'er, hvad angår alvorlige bivirkninger.

Behandlingsophør pga. uønskede hændelser (vigtig)

Tabel 6. Vurdering af klinisk merværdi: andel af patienter med behandlingsophør pga. uønskede hændelser ved 48 uger

	Forhåndsdefineret grundlag for vurdering		Resultater	
			GS-US-380-1489 BIC/FTC/TAF vs. DTG/ABC/3TC	**GS-US-380-1490** BIC/FTC/TAF vs. DTG+ FTC/TAF
Absolutte forskelle	5 procentpoint		-1,3 procentpoint [-2,65; 0,11]	1,25 procentpoint [-0,23; 2,74]
Relative forskelle	Stor merværdi	Øvre konf.gr. < 0,75		
	Vigtig merværdi	Øvre konf.gr. < 0,90		
	Lille merværdi	Øvre konf.gr. < 1,00		
	Ingen merværdi	Øvre konf.gr. ≥ 1,00	RR= 0,11 [0,01; 2,06]	RR= 5,08 [0,60; 43,23]
	Negativ merværdi	Nedre konf.gr. > 1,00		
Evidensens kvalitet	Moderat (se punkt 10.1.3)			

Første kolonne indeholder det i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder absolutte og relative effektforskelle [95 % konfidensinterval], som indgår i Medicinrådets vurdering. BIC: bictegravir, FTC: emtricitabin, TAF: tenofovir alafenamid, DTG: dolutegravir, ABC: abacavir, 3TC: lamivudin RR; relativ risiko.

I studiet GS-US-380-1489 ophører fire patienter med behandling, fordi de oplever uønskede hændelser. Alle fire patienter behandles med dolutegravir/abacavir/lamivudin, hvilket svarer til en absolut risikoreduktion på -1,3 procentpoint til fordel for bictegravir/emtricitabin/tenofovir alafenamid. I studiet GS-US-380-1490 ophører seks patienter med behandling, fordi de oplever uønskede hændelser. Fem af patienterne behandles med bictegravir/emtricitabin/tenofovir alafenamid. Det vil sige, at der er en absolut risikoreduktion på 1,25 procentpoint til fordel for dolutegravir + emtricitabin/tenofovir alafenamid. De absolutte effektforskelle overstiger ikke den mindste klinisk relevante forskel på 5 procentpoint.

Den relative risiko sammenlignet med dolutegravir/abacavir/lamivudin er 0,11 [0,01; 2,06], og den relative risiko sammenlignet med dolutegravir + emtricitabin/tenofovir alafenamid er 5,08 [0,60; 43,23]. De relative effektforskelle indplacerer bictegravir/emtricitabin/tenofovir alafenamid i kategorien for ingen merværdi, da konfidensintervallernes nedre grænse er ≤ 1,00.

På baggrund af det tilgængelige data vurderer fagudvalget, at bictegravir/emtricitabin/tenofovir alafenamid har **ingen** klinisk merværdi sammenlignet med dolutegravir + 2 NRTI'er, hvad angår behandlingsophør pga. uønskede hændelser.

Ikkealvorlige bivirkninger (vigtig)

Ansøger har ikke leveret data for andelen af patienter, som får ikkealvorlige bivirkninger, da disse ikke er opgjort i de inkluderede studier. I stedet har ansøger leveret data for alle bivirkninger, der vurderes at være relateret til studiemedicinen. Da ganske få patienter (< 1%) oplever alvorlige bivirkninger relateret til studiemedicinen, vurderer fagudvalget, at det leverede data vil afspejle andelen af patienter, som oplever ikkealvorlige bivirkninger. Fagudvalget vurderer derfor, at den forhåndsbestemte mindste klinisk relevante forskel ikke skal justeres

Tabel 7. Vurdering af klinisk merværdi: andel af patienter med ikkealvorlige bivirkninger af studiemedicinen

	Forhåndsdefineret grundlag for vurdering		Resultater	
			GS-US-380-1489 BIC/FTC/TAF vs. DTG/ABC/3TC	**GS-US-380-1490** BIC/FTC/TAF vs. DTG+ FTC/TAF
Absolutte forskelle	10 procentpoint		-14,2 [-21,5; -6,93]	-7,73 [-14,05; -1,40]
Relative forskelle	Stor merværdi	Ikke muligt		
	Vigtig merværdi	Øvre konf.gr. < 0,80		
	Lille merværdi	Øvre konf.gr. < 0,90	RR= 0,65 [0,51; 0,81]	
	Ingen merværdi	Øvre konf.gr. ≥ 0,90		RR=0,70 [0,52; 0,94]
	Negativ merværdi	Nedre konf.gr. > 1,00		
Evidensens kvalitet	Moderat (se punkt 10.1.3)			

Første kolonne indeholder det i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder absolutte og relative effektforskelle [95 % konfidensinterval], som indgår i Medicinrådets vurdering. BIC: bictegravir, FTC: emtricitabin, TAF: tenofovir alafenamid, DTG: dolutegravir, ABC: abacavir, 3TC: lamivudin RR; relativ risiko.

I studiet GS-US-380-1489 oplever 26 % og 40 % af patienterne behandlet med henholdsvis bictegravir/emtricitabin/tenofovir alafanamid og dolutegravir/abacavir/lamivudine ikkealvorlige bivirkninger. Den absolutte forskel er -14 procentpoint til fordel for bictegravir/emtricitabin/tenofovir alafanamid. Resultatet overstiger den mindste klinisk relevante forskel på 10 procentpoint. Den relative risiko er 0,65 [0,51; 0,81]. Det indplacerer bictegravir/emtricitabin/tenofovir alafanamid i kategorien for lille klinisk merværdi, da konfidensintervallets øvre grænse er < 0,90. Forskellen på frekvensen er hovedsagelig drevet af, at flere patienter behandlet med dolutegravir/abacavir/lamivudine får kvalme. Baseret på klinisk erfaring vurderer fagudvalget, at det kan skyldes, at regimet indeholder abacavir.

I studiet GS-US-380-1490 er der også færre patienter, der oplever ikkealvorlige bivirkninger ved behandling med bictegravir/emtricitabin/tenofovir alafanamid. Ca. 18 % af patienterne behandlet med bictegravir/emtricitabin/tenofovir alafanamid oplever bivirkninger, mens ca. 26 % af patienterne behandlet med dolutegravir + emtricitabin/tenofovir alafenamid oplever bivirkninger. Den absolutte forskel er -8 procentpoint til fordel for bictegravir/emtricitabin/tenofovir. Dette overstiger ikke den mindste klinisk relevante forskel. Den relative risiko er 0,70 [0,52; 0,94]. Det relative effektestimat indplacerer bictegravir/emtricitabin/tenofovir i kategorien for ingen klinisk merværdi, da konfidensintervallets øvre grænse er ≥ 0,90.

For begge studier var resultaterne for både de absolutte og relative forskelle mellem de to grupper signifikant forskellige. Da den absolutte forskel GS-US-380-1490 er tæt på den forhåndsdefinerede mindste klinisk relevante forskel, indikerer resultaterne samlet set for begge studier, at frekvensen af ikkealvorlige bivirkninger er lavere, når patienter behandles med bictegravir/emtricitabin/tenofovir.

Afhængig af hvilken backbone der vælges sammen med dolutegravir, nedsætter bictegravir/emtricitabine/tenofovir muligvis frekvensen af bivirkninger i forskellig grad.

På baggrund af det tilgængelige data vurderer fagudvalget, at bictegravir/emtricitabin/tenofovir giver en **lille** klinisk merværdi sammenlignet med dolutegravir + 2 NRTI'er, hvad angår ikkealvorlige bivirkninger.

Kvalitativ vurdering af bivirkninger, knogletæthed og lipidprofil (vigtig)

Fagudvalget har bedt ansøger om at beskrive lægemidlernes bivirkningsprofil, og hvordan behandlingerne påvirker patienternes knogletæthed og lipidprofil.

Baseret på observerede bivirkninger fra studierne, lipidprofiler og knoglemineraldensiteter i de to studier vurderer fagudvalget, at regimerne er sammenlignelige. Effektmålet tildeles ikke en merværdikategori.

Bivirkninger

Generelt gælder det, at størstedelen af de rapporterede bivirkninger er lette eller moderate (sværhedsgrad 1 eller 2). Men da behandlingen er livslang, finder fagudvalget, at også ikkealvorlige bivirkninger er af stor betydning for patienten.

I studierne var de mest frekvente bivirkninger hovedpine, diarré, træthed, øvre luftvejsinfektioner og kvalme.

I GS-US-380-1489-studiet var der 13 procentpoint færre, der fik kvalme, når de blev behandlet med bictegravir/emtricitabin/tenofovir alafenamid sammenlignet med dolutegravir/lamivudin/abacavir. Baseret på klinisk erfaring vurderer fagudvalget, at det kan skyldes, at regimet indeholder abacavir.

Patientens rapportering af kvalme indgår i Hiv Symptom Index-skalaen, der måler patienternes livskvalitet baseret på patienternes oplevelse af bivirkninger. Fagudvalget bemærker, at data for denne skala tyder på, at kvalmen er forbigående for en andel af patienterne. Ved uge 4 og 12 er der signifikant forskel mellem studiearmene for patienter, der oplever kvalme. Ved uge 48 er forskellen ikke længere signifikant.

Udover kvalme var frekvensen af bivirkningerne sammenlignelig mellem de to studiearme. Fagudvalget finder, at bictegravir/emtricitabin/tenofovir alafenamid kan tilbyde en merværdi sammenlignet med dolutegravir/lamivudin/abacavir alene baseret på frekvensen af kvalme.

Fagudvalget finder overordnet, at der ikke er væsentlige forskelle i bivirkningsprofilerne for bictegravir/emtricitabin/tenofovir alafenamid og dolutegravir + 2 NRTI'er.

Knogletæthed

Knogletæthed er opgjort i studiet GS-US-380-1489. Den gennemsnitlige procentvise ændring fra baseline af knogletæthed i hofte og rygsøjle var sammenlignelig mellem de to regimer. Hvad angår knogletæthed vurderer fagudvalget derfor, at bictegravir/emtricitabin/tenofovir alafenamid ikke er klinisk betydende forskellig fra dolutegravir/lamivudin/abacavir. Denne vurdering er i overensstemmelse med Biktarvys EPAR. Regimet dolutegravir/lamivudin/abacavir er ikke tidligere blevet forbundet med knogletoksicitet [17].

Lipid profil

Patienters lipidprofil er opgjort i GS-US-380-1489 og GS-US-380-1490. Ved 48 uger var medianværdien for totalt kolesterol, LDL, triacylglycerider og HDL sammenlignelige mellem studiearmene i de to studier. Fagudvalget finder derfor, at der ikke er klinisk betydende forskelle mellem de to regimer, hvad angår deres påvirkning af patienters lipidprofil.

Livskvalitet (vigtig)

Ansøger har leveret data for SF-36, som fagudvalget har efterspurgt.

Tabel 8. Vurdering af klinisk merværdi: forskelle i ændring fra baseline i global scores på SF-36 efter 48 uger

	Forhåndsdefineret grundlag for vurdering	Medicinrådets vurdering BIC/FTC/TAF vs. DTG/ABC/3TC
Absolutte forskelle fra baseline ved uge 48	0,5 SD point	Median (IQR) SF-PCS: 0,1 (-3,3 - 3,1) vs. 0,2 (-2,6 - 2,8) Median (IQR): SF-MCS: 2,3 (-1,6 - 9,0) vs. 2,1 (-4,0 - 7,0)
Evidensens kvalitet	lav	

Første kolonne indeholder det i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering. IQR: *interquatile range*, SF-PSC: *physical component summary score* i SF-36 spørgeskemaet. SF-MCS: *mental component summary score* i SF-36 spørgeskemaet.

Ansøger har leveret data for SF-36 som medianen af ændring fra baseline og interkvartilafstanden ved 48 uger. Dette indikerer, at data ikke er normalfordelt, og den mindste klinisk relevante forskel ikke kan udregnes. En stigning på SF-36-skalaen indikerer bedre livskvalitet. For behandling med bictegravir/emtricitabin/tenofovir alafenamid og dolutegravir/lamivudin/abacavir var medianændringen fra baseline henholdsvis 0,1 og 0,2 for den fysiske score og 2,3 og 2,1 point for den mentale score. Ændringerne er ikke signifikant forskellige mellem grupperne (p-værdi henholdsvis 0,85 og 0,09).

Fagudvalget vurderer, at data indikerer, at livskvaliteten ikke er forskellig mellem behandlingerne.

På baggrund af det spinkle datagrundlag vurderer fagudvalget, at bictegravir/emtricitabin/tenofovir alafenamid har **ikke dokumenterbar** klinisk merværdi, hvad angår livskvalitet.

6.1.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 1 er samlet set **moderat**. Overvejelser vedrørende vurdering af evidensens kvalitet kan ses i bilag 2.

Evidensens kvalitet er bestemt ud fra den laveste vurdering af evidensens kvalitet for de kritiske effektmål. Evidensens kvalitet er ikke vurderet for effektmål, der har ikkedokumenterbar merværdi.

6.1.4 Konklusion

Fagudvalget vurderer, at bictegravir/emtricitabin/tenofovir alafenamid giver **ingen klinisk merværdi** for patienter med hiv-1-infektion sammenlignet med dolutegravir + 2 NRTI'er (moderat evidenskvalitet).

Nedenfor ses et overblik over den kliniske merværdi af bictegravir/emtricitabin/tenofovir alafenamid for hvert effektmål.

Effektmål	Vigtighed	Klinisk merværdi	Evidensens kvalitet
Viral suppression	Kritisk	Ingen	Høj
Viralt svigt	Kritisk	Ingen	Høj
Resistensudvikling	Kritisk	Ingen	Moderat
Alvorlige bivirkninger	Kritisk	Ingen	Lav
Behandlingsophør pga. AE	Vigtig	Ingen	Moderat
Ikkealvorlige bivirkninger	Vigtig	Lille	Moderat
Kvalitativ vurdering af bivirkninger	Vigtig	Ikke vurderet	Ikke vurderet
Livskvalitet	Vigtig	Ikkedokumenterbar	Lav
Samlet vurdering		Ingen	Moderat

Fagudvalget har lagt vægt på, at begge regimer viser en god effekt, og at de ikke er forbundet med udvikling af resistens. Dertil er begge lægemidler forbundet med få alvorlige bivirkninger. Fagudvalget bemærker, at der kan være forskel i frekvensen af kvalme, afhængigt af hvilken backbone dolutegravir gives med, men ikke i sådan grad at det påvirker den samlede merværdi-kategorisering. Evidensens kvalitet er moderat.

Baseret på data for behandlingsnaive patienter har fagudvalget tildelt bictegravir/emtricitabin/tenofovir alafenamid **ingen** klinisk merværdi. Fagudvalget finder, at den kliniske merværdi kan overføres til patienter, der skal skifte behandling, så længe de ikke har aktuel eller tidligere påvist resistens overfor integrasehæmmere eller NRTI'er.

7 Andre overvejelser

Nemhed for patienten

Bictegravir/emtricitabin/tenofivor alafenamid tages som en tablet én gang dagligt. Dolutegravir kan både administreres som enkeltstoftablet eller i kombinationstabletten lamivudin/abacavir/dolutegravir én gang dagligt. Både bictegravir/emtricitabin/tenofivor alafenamid og lamivudin/abacavir/dolutegravir kan tages med eller uden mad. Lamivudin/abacavir/dolutegravir kombinationstabletten er større end bictegravir/emtricitabin/tenofivor alafenamid kombinationstabletten og har en størrelse, som bevirker, at nogle patienter foretrækker en anden behandling.

Fordelen ved både intervention og komparator er, at de ikke kræver farmakologisk boostning, hvilket betyder, at der er få interaktioner.

Praktiske forhold

Før abacavir administreres, skal patienten screenes for *HLA*B5701*-allelen, som er forbundet med overfølsomhedsreaktioner overfor abacavir. Indtil prøvesvaret foreligger, behandles patienten med et regime, der ikke indeholder abacavir. Hvis patienten ikke har HLA*B5701-allelen, skiftes behandlingen. På kort sigt kan skiftet have betydning for nemhed af behandlingen for patienten og behandler.

Patienter med hepatitis B kan behandles med bictegravir/emtricitabin/tenofivor alafenamid.

Bictegravir/emtricitabin/tenofivor alafenamid kan ikke anvendes til gravide kvinder eller kvinder med graviditetsønske.

Længden og mængden af observationstid

Behandling med antiretrovirale lægemidler er som udgangspunkt livslang. For andre antiretrovirale lægemidler har fagudvalget erfaring med, at den fulde bivirkningsprofil først er fuldt afdækket efter flere års observationstid. Da der endnu kun er 48 ugers opfølgningstid for bictegravir/emtricitabin/tenofivor alafenamid, er langtidseffekterne ukendte.

8 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at bictegravir/emtricitabin/tenofovir alafenamid giver **ingen klinisk merværdi** for patienter med hiv-1-infektion sammenlignet med dolutegravir + 2 NRTI'er (moderat evidenskvalitet).

9 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at bictegravir/emtricitabin/tenofovir alafenamid giver **ingen klinisk merværdi** for patienter med hiv-1-infektion sammenlignet med dolutegravir + 2 NRTI'er (evidenskvaliteten er moderat).

10 Relation til eksisterende behandlingsvejledning

RADS har udarbejdet en behandlingsvejledning for behandling af patienter med hiv-1-infektion.

Fagudvalget vurderer, at bictegravir/emtricitabin/tenofovir alafenamid på nuværende tidspunkt ikke kan ligestilles med de behandlingsregimer, der er ligestillede i RADS' behandlingsvejledning. Denne vurdering er baseret på, at der endnu kun er studier med kort opfølgningstid for bictegravir/emtricitabin/tenofivor alafenamid, og at langtidseffekterne, specielt hvad angår bivirkningsprofil, derfor ikke er fuldt afdækkede. For andre antiretrovirale lægemidler har fagudvalget erfaring med, at den fulde bivirkningsprofil først er fuldt afdækket efter flere års observationstid.

Fagudvalget finder det vigtigt, at der tages stilling til spørgsmålet om ligestilling, når der er længere opfølgningsdata for bictegravir/emtricitabin/tenofivor alafenamid fra de kliniske studier. På det tidspunkt forventer fagudvalget også, at der foreligger data fra lægemidlets anvendelse i klinisk praksis.

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12 Bilag 1: Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende hiv/aids

Formand	*Indstillet af*
Ann-Brit Eg Hansen *Overlæge, klinisk lektor*	Lægevidenskabelige Selskaber
Medlemmer	*Udpeget af*
Christian Wejse *Afdelingslæge, lektor, ph.d.*	Region Midtjylland
Olav Ditlevsen Larsen *Overlæge, ph.d.*	Region Syddanmark
Toke Barfoed *Overlæge, lektor*	Region Sjælland
Jan Gerstoft *Professor, overlæge, dr.med.*	Region Hovedstaden
Marianne Kjettrup-Jensen *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Bjarne Ørskov Lindhardt *Ledende overlæge, klinisk lektor*	Udpeget af formanden
Paul Thomsen *Patient/patientrepræsentant*	Danske Patienter
Bent Hansen *Patient/patientrepræsentant*	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe Thea Christensen (projekt- og metodeansvarlig) Ditte Marie Irwin-Clugston (projektdeltager) Ilse Linde (koordinator) Jan Odgaard-Jensen (biostatistiker) Bettina Fabricius Christensen (informationsspecialist) Kirsten Holdt Henningsen (teamleder)

13 Bilag 2: GRADE-evidensprofiler

13.1 Cochrane Risk of Bias

Studie: GS-US-380-1489

Risk of bias	Vurdering	Begrundelse
Random sequence generation (selection bias)	• Lav risiko for bias	Patienter blev blockrandomiseret 1:1 vha. en computergenereret allokeringsekvens i en blokstørrelse på 4. Randomisering var stratificeret efter de vigtigste confoundere (HIV-1 RNA (≤100 000 kopier/mL, >100 000 til ≤400 000 kopier/mL, eller >400 000 kopier/mL), CD4 celletal (<50 celler/µL, 50–199/per µL, eller ≥200 celler/µL), og region (USA eller ex-USA).
Allocation concealment (selection bias)	• Lav risiko for bias	Sekvensen var computergenereret. Det er ikke angivet, om allokeringen var centraliseret.
Blinding of participants and personnel (performance bias)	• Lav risiko for bias	
Viral-suppression/viralt svigt (Hiv-RNA)	• Lav risiko for bias	Laboratorie-værdien vil ikke være påvirket af blinding.
Bivirkninger/AE	• Lav risiko for bias	Studiet var dobbeltblindet. Blindingen er forsøgt holdt, ved at patienter i begge behandlingsarme har fået aktiv behandling og matchende placebobehandling. Det fremgår specifikt, at patienter var blindet (*participants will continue masked treatment with visits every 12 weeks until week 144.).* Da studiet er dobbeltblindet, formodes det, at den læge, som kontrollerer patienten, også var blindet.
Livskvalitet	• Lav risiko for bias	Patienter var blindet som beskrevet for bivirkninger/AE ovenfor.
Bone mineral density	• Lav risiko for bias	Det forventes ikke, at måden scanningen udføres, bliver påvirket af blinding.
Blinding of outcome assessment (detection bias)	• Lav risiko for bias	
Viral-suppression/viralt svigt (hiv-RNA)	• Lav risiko for bias	Laboratorieværdien vil ikke være påvirket af blinding.
Bivirkninger/AE	• Lav risiko for bias	Studiet var dobbeltblindet. Blindingen er forsøgt holdt, ved at patienter i begge behandlingsarme har fået aktiv behandling og matchende placebobehandling. Det fremgår specifikt, at patienter var blindet (*participants will continue masked treatment with visits every 12 weeks until week 144.).* Da studiet er dobbeltblindet, formodes det, at den læge, som kontrollerer patienten, også var blindet.
Livskvalitet	• Lav risiko for bias	Patienter var blindet som beskrevet for bivirkninger/AE ovenfor.
Bone mineral density	• Lav risiko for bias	Et centraliseret center blindet for behandlingsallokering evaluerede scanningerne.
Incomplete outcome data (attrition bias)	• Lav risiko for bias	To patienter i interventionsarmen, som blev randomiseret, modtog ikke behandling og er ikke

		medtaget i analyserne. Det er under 1 % af antallet af patienter i hver arm.
Selective reporting (reporting bias)	• Uklar risiko for bias	Absolutte effektforskelle for virologisk respons er justeret for stratificering. De resterende effektestimater, som fagudvalget har benyttet i deres vurdering, er udregnet ved en ikke-stratificeret metode. Det kan ikke forudsiges, om dette vil skævvride resultatet og i givet fald i hvilken retning. Dog er der lille forskel mellem justerede og ikke justerede resultater for virologisk respons.
Other bias	• Lav risiko for bias	

Studie: GS-US-380-1490

Risk of bias	**Vurdering**	**Begrundelse**
Random sequence generation (selection bias)	• Lav risiko for bias	Patienter blev blockrandomiseret 1:1 vha. en computergenereret allokeringsekvens i en blokstørrelse på 4. Randomisering var stratificeret efter de vigtigste confoundere (HIV-1 RNA (≤100 000 kopier/mL, >100 000 til ≤400 000 kopier/mL, eller >400 000 kopier/mL), CD4 celletal (<50 celler/µL, 50–199/per µL, eller ≥200 celler/µL), og region (USA eller ex-USA).
Allocation concealment (selection bias)	• Lav risiko for bias	Sekvensen var computergenereret. Det er ikke angivet, om allokeringen var centraliseret.
Blinding of participants and personnel (performance bias)	• Lav risiko for bias	
Viral-suppression/viralt svigt (Hiv-RNA)	• Lav risiko for bias	Laboratorie-værdien vil ikke være påvirket af blinding.
Bivirkninger/AE	• Lav risiko for bias	Studiet var dobbeltblindet. Blindingen er forsøgt holdt, ved at patienter i begge behandlingsarme har fået aktiv behandling og matchende placebobehandling. Det fremgår specifikt, at patienter var blindet (*..participants will continue masked treatment with visits every 12 weeks until week 144.).* Da studiet er dobbeltblindet, formodes det, at den læge, som kontrollerer patienten, også var blindet.
Livskvalitet	• Lav risiko for bias	Patienter var blindet som beskrevet for bivirkninger/AE ovenfor.
Bone mineral density	• Lav risiko for bias	Det forventes ikke, at måden, scanningen udføres, bliver påvirket af blinding.
Blinding of outcome assessment (detection bias)	• Lav risiko for bias	
Viral-suppression/viralt svigt (hiv-RNA)	• Lav risiko for bias	Laboratorieværdien vil ikke være påvirket af blinding.
Bivirkninger/AE	• Lav risiko for bias	Studiet var dobbeltblindet. Blindingen er forsøgt holdt ved, at patienter i begge behandlingsarme har fået aktiv behandling og matchende placebobehandling. Det fremgår specifikt, at patienter var blindet (*.participants will continue masked treatment with visits every 12 weeks until week 144.).* Da studiet er dobbeltblindet, formodes det, at den læge, som kontrollerer patienten, også var blindet.

Livskvalitet	• Lav risiko for bias	Patienter var blindet som beskrevet for bivirkninger/AE ovenfor.
Bone mineral density	• Lav risiko for bias	Et centraliseret center blindet for behandlingsallokering evaluerede scanningerne.
Incomplete outcome data (attrition bias)	• Lav risiko for bias	Syv patienter i interventionsarmen og fem patienter i kontrolarmen, som blev randomiseret, modtog ikke behandling og er ikke medtaget i analyserne. Det er under 5% af antallet af patienter i hver arm.
Selective reporting (reporting bias)	• Uklar risiko for bias	Absolutte effektforskelle for virologisk respons er justeret for stratificering. De resterende effektestimater, som fagudvalget har benyttet i deres vurdering, er udregnet ved en ikke-stratificeret metode. Det kan ikke forudsiges, om dette vil skævvride resultatet og i givet fald i hvilken retning. Dog er der lille forskel mellem justerede og ikke justerede resultater for virologisk respons.
Other bias	• Lav risiko for bias	

13.2 GRADE-evaluering af evidenskvaliteten til vurdering af den kliniske merværdi af bictegravir/emtricitabin/tenofovir alafenamid

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsi-stency**	**Indirect-ness**	**Impreci-sion**	**Other conside-rations**	**B/F/TAF**	**NRTIs og dolu-tegravir**	**Relative (95% CI)**	**Absolute (95% CI)**		
Viral suppression (follow up: mean 48 weeks)												
2	randomised trials	not serious	not serious	not serious	not serious	none	576/634 (90.9%)	595/640 (93.0%)	**RR 0.98** (0.95 to 1.01)	**19 fewer per 1.000** (from 9 more to 46 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Viralt svigt (follow up: mean 48 weeks)												
2	randomised trials	not serious	not serious	not serious	not serious	none	5/571 (0.9%)	7/590 (1.2%)	**RR 0.73** (0.24 to 2.29)	**3 fewer per 1.000** (from 9 fewer to 15 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Alvorlige bivirkninger (follow up: mean 48 weeks)												
1	randomised trials	not serious	serious [a]	not serious	serious [b]	none	1/314 (0.3%)	1/315 (0.3%)	**RR 1.00** (0.06 to 16.00)	**0 fewer per 1.000** (from 3 fewer to 48 more)	⊕⊕◯◯ LOW	CRITICAL
Resistensudvikling ikkepoolede analyser (follow up: mean 48 weeks) – antaget at dem der ikke testes er negative for resistens												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	GS-US-380-1489 0/314 (0%)	GS-US-380-1489 0/315 (0%)	GS-US-380-1489 **OR 1.00** (0.02 to 50.70)	-	⊕⊕⊕◯ MODERATE	CRITICAL
							GS-US-380-1490 0/320 (0%)	GS-US-380-1490 0/325 (0%)	GS-US-380-1490 **OR 1.01** (0.02 to50.70)	-		
Behandlingsophør pga. uønskede hændelser: ikke-poolede analyser (follow up: mean 48 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsi-stency**	**Indirect-ness**	**Impreci-sion**	**Other conside-rations**	**B/F/TAF**	**NRTIs og dolu-tegravir**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	not serious	not serious	not serious	serious [b]	none	GS-US-380-1489 0/314 (0.0%)	GS-US-380-1489 4/315 (1.3%)	GS-US-380-1489 **RR 0.11** (0.01 to 2.06)	GS-US-380-1489 **11 fewer per 1.000** (from 13 fewer to 13 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
							GS-US-380-1490 5/320 (1.6%)	GS-US-380-1490 1/325 (0.3%)	GS-US-380-1490 **RR 5.08** (0.60 to 43.23)	GS-US-380-1490 **13 more per 1.000** (from 1 fewer to 130 more)		
ikkealvorlige bivirkninger: ikke-poolede analyser (follow up: mean 48 weeks)												
2	randomised trials	not serious	not serious	not serious	serious [c]	none	GS-US-380-1489 82/314 (26.1%)	GS-US-380-1489 127/315 (40.3%)	GS-US-380-1489 **RR 0.65** (0.51 to 0.81)	GS-US-380-1489 **141 fewer per 1.000** (from 77 fewer to 198 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
							GS-US-380-1490 57/320 (17.8%)	GS-US-380-1490 83/325 (25.5%)	GS-US-380-1490 **RR 0.70** (0.52 to 0.94)	GS-US-380-1490 **77 fewer per 1.000** (from 15 fewer to 123 fewer)		
Livskvalitet												
Ikke vurderet												

CI: Confidence interval; **RR:** Risk ratio, **OR**: Odds ratio

Forklaringer
a. Da der kun er data fra et studie, er det usikkert, om dette studie estimerer den sande størrelse af effekten.
b. Kriterierne for "optimal information size" er ikke opfyldt for at undersøge, om der er en forskel mellem de to grupper, der er så stor som den mindste klinisk relevante forskel.
c. De to forskellige studier kvalificerer til to forskellige kategoriseringer af klinisk merværdi.

Application for the assessment of clinical added value of B/F/TAF (Biktarvy®) for HIV

Contents

General information

This is a template of the application form to be submitted to the Danish Medicines Council (*Medicinrådet*) for the assessment of the clinically added value of new medicines and new indications. The purpose of the form is to provide an overview of the basic information, literature search, study, and analysis results that will serve as the basis for the assessment. It indicates the minimum required information needed for the assessment.

The assessment of the pharmaceutical will be based on the outcomes defined in the protocol. Results for all critical and important outcomes (*kritiske og vigtige effektmål*) must be addressed in the application. The results of less important outcomes (*mindre vigtige effektmål*) do not need to be addressed. For all the data provided, a reference is mandatory.

During the completion of this form, elements should not be removed from the document. All sections should be filled in (if a section is not applicable, state "not applicable" and explain why). Table examples are provided in the form. Layout may deviate from the template to accommodate data; however, all requested information must be stated. We accept submission of appendices. Audits of data analyses and literature searches will occur.

In order to minimize any translation errors between the application and the assessment report, submission in the Danish language is preferred.

If confidential data are submitted, highlight the data in yellow and write the expected publication date in a comment. If confidential data are submitted in an appendix, the document must in addition be watermarked as "confidential."

The application will be published simultaneously with the final assessment and recommendation report on the Danish Medicines Council's web page (www.medicinraadet.dk). Any data that will be considered in the assessment report will be published with the final application.

Checklist before submitting the application form:

- Are all relevant fields in the application form filled in?
- Is the application explicit and self-explanatory?
- Does the application meet the general requirements defined in the *Process and Methods Guide* of the Danish Medicines Council for new medicines and new indications?
- Does the application meet the specific requirements in the protocol?
- Are deviation(s) from the protocol (if any) described?
- Are deviation(s) from the protocol (if any) justified?

1 Basic information

Contact information

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Overview of the pharmaceutical

Proprietary name	Biktarvy
Generic name	Bictegravir/emtricitabine/tenofovir alafenamide referred to in this application as B/F/TAF
Marketing authorization holder in Denmark	Gilead Sciences Denmark Aps Arne Jacobsens Alle 7, 5th floor DK-2300 Copenhagen S Denmark
ATC code	J05AR20
Pharmacotherapeutic group	Integrase inhibitors
Active substance(s)	Bictegravir/emtricitabine/tenofovir alafenamide
Pharmaceutical form(s)	Film-coated tablet, purplish-brown, capsule-shaped debossed on one side “GSI” and “9883” on the other side
Mechanism of action	B/F/TAF are three drugs in a single tablet regimen of bictegravir, a second generation HIV-1 integrase strand transfer inhibitor (INSTI), and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside/nucleotide analog reverse transcriptase inhibitors (NRTIs). • Bictegravir (BIC) is an inhibitor of the HIV-1 integrase (IN) that is required for viral cDNA integration into the host cell genome. • Emtricitabine (FTC) a nucleoside analogue that inhibits reverse transcriptase, the enzyme that copies HIV RNA into new viral DNA. • Tenofovir alafenamide (TAF) a nucleotide analogue that inhibits reverse transcriptase, the enzyme that copies HIV RNA into new viral DNA.
Dosage regimen	Biktarvy is a single table regimen (STR), taken orally, once daily without regard of food
Therapeutic indication relevant for assessment (as defined by the European	B/F/TAF is indicated for the treatment of adults infected with HIV-1 without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir

Medicines Agency, EMA)	
Other approved therapeutic indications	Biktarvy contains tenofovir alafenamide which is active against hepatitis B virus (HBV) and approved as Vemlidy
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Not applicable
Packaging – types, sizes/number of units, and concentrations	Biktarvy comes in bottles of 30 tablets and in packs made up of 3 bottles each containing 30 tablets. Each bottle contains a silica gel desiccant that must be kept in the bottle to help protect the tablets. The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed. Not all pack sizes may be marketed
Orphan drug designation	Not applicable

2 Abbreviations

3TC	Lamivudine
ABC	Abacavir
ATV	Atazanavir
BMI	Body mass index
BSAP	Bone-specific alkaline phosphatase
CDC	Center for Disease Control and Prevention
CI	Confidence interval
CTx	Type 1 collagen crosslinked C-telopeptide
DMC	Danish Medicines Council
DRV	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
FTC	Emtricitabine
NA	Not applicable
NR	Not reported
NRTI	Nucleoside reverse transcriptase inhibitor
P1NP	Procollagen type 1 N-terminal propeptide
RAL	Raltegravir
RTV	Ritonavir

SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate

3 Summary

In June 2018, marketing authorization for Biktarvy (B/F/TAF) was issued by the European Commission for the treatment of HIV-1 infection.

One medical question was outlined *"what is the added clinical value of B/F/TAF in treatment naivee HIV-1 infected patients compared to dolutegravir plus 2 NRTIs"* in the Medicine Council (DMC) protocol of 18th May 2018 to guide the assessment of the added clinical value of B/F/TAF.

The systematic literature review (SLR) found 9 publications of which 8 presented relevant clinical efficacy/safety data whereas the ninth publication investigated patient reported outcomes (PROs). Only two of eight studies found, compared B/F/TAF head-to-head to dolutegravir-based regimens; GS-US-380-1489 and GS-US-380-1490. The other 6 publications were either dose finding (phase II) or studies comparing DTG-based regimens to alternative regimens.

The PRO study compared head-to-head, biktarvy vs. triumeq in a double-blinded manner. The data were based on study GS-US-380-1489 but were published separately.

Since head-to-head studies between bictegravir and dolutegravir do exist and a cross-study comparison is not appreciated, only those providing direct evidence (GS-US-380-1489, GS-US-380-1490, PROs) were included in the comparative analyses.

The two head-to-head comparison studies (GS-US-380-1489; GS-US-380-1490) were randomized, double blind and active-controlled. The populations outlined in those studies were treatment naïve HIV-1 infected adults (≥18 years).

The intervention outlined in the direct head-to-head studies was:

- GS-US-380-1489: B/F/TAF compared to DTG/ABC/3TC in naïve treated patients [4].
- GS-US-380-1490: B/F/TAF compared to DTG plus FTC/TAF in naïve treated patients [7].

The outcomes outlined in the head-to-head comparisons were efficacy and safety and PRO only in GS-US-380-1489 [5]:

- B/F/TAF was non inferior to DTG based treatment in naïve patients
- Significantly less treatment related AEs has been reported to bictegravir compared to dolutegravir
- Bictegravir was associated with a significantly lower prevalence of multiple bothersome symptoms across gastrointestinal disorders, neuropsychiatric events, and sleep compared to dolutegravir.

What is the added clinical value of B/F/TAF in treatment naive HIV-1 infected patients compared to dolutegravir plus 2 NRTIs

The added clinical value of the fixed dose combination of Biktarvy (B/F/TAF) compared to the combination of Triumeq (DTG/ABC/3TC) are as follows:

- Both DTG and ABC are associated with hypersensitivity reactions. Initiation of treatment with DTG/ABC/3TC must be delayed pending HLA B*5701 testing. Coformulated B/F/TAF does not require HLA B*5701 might lend itself to rapid or same-day initiation of treatment in the clinical setting.
- Coformulated B/F/TAF can be given to individuals with an eGFR of 30 mL/min or more, whereas use of DTG/ABC/3TC is limited to those with an eGFR of more than 50 mL/min.
- PRO in naive patients show less bothersome symptoms associated with Biktarvy compared to Triumeq [5].
- Triumeq contains ABC and some, but not all, studies have shown an association between ABC use and an increased risk of myocardial infarction, although a pathophysiological underlying mechanism has not been defined [35-41].
- Biktarvy contains TAF:
    - TAF is active against hepatitis B virus and is approved for treatment of hepatitis B as a single drug (VEMLIDY). HIV treatment guidelines recommend TAF or TDF as components of regimens for treatment of people coinfected with HIV and hepatitis B virus [42]. While B/F/TAF is suitable for a rapid initiation even without prior knowledge of the patient's HBV status, initiating DTG/ABC/3TC is not recommended until HBV coinfection has been ruled out.
    - TAF has shown significant improvements in clinical categories of osteopenia and osteoporosis [43-45].
    - TAF has shown significant decrease in renal biomarkers in patients with renal impairment – 144 weeks data – study 112 [46].
- Biktarvy is the smallest integrase-containing STR which make it easier to swallow (Biktarvy 721mg vs Triumeq 1750mg)

4 Literature search

A systematic literature review (SLR) was performed in accordance with a pre-specified protocol. This involved searching electronic databases, manual hand-searching of the reference lists of any systematic reviews or (network) meta-analyses identified in the course of the review and manual hand-searching of websites, including the European Medicines Agency (EMA) and ClinicalTrials.gov.

Databases and search strategy

Electronic databases

The following electronic databases were searched on 29th of May 2018 to identify relevant published literature:

- MEDLINE, including MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and Versions (via Ovid SP; 1946 to present)
- Cochrane Central Register of Controlled Trials (CENTRAL; via the Cochrane Library Wiley Online platform; Issue 4 of 12, April 2018)

Full details of the search strategies for the electronic database searches are presented in Appendix 1.

Website searches

A manual search of European Public Assessment Reports (EPAR) from the EMA website was conducted to ensure any additional relevant evidence was identified for inclusion.

Hand-searching of reference lists
As well as searching the electronic databases and website listed above, the bibliographies of all relevant SLRs and meta-analyses identified during the review were manually hand-searched, in order to identify any additional, relevant studies for inclusion.

Clinical trial registry searching
Finally, a search of ClinicalTrials.gov, using the Advanced Search function, was conducted for trials of B/F/TAF and its comparators in patients with HIV. Relevant studies were cross-checked against the results obtained from the electronic database searches and the manual hand-searches, to ensure that no relevant studies with published results were missed. Full details of the search strategy for ClinicalTrials.gov are presented in Table 5.

Study selection

Review process
The following review process was followed:

- Each abstract was reviewed against the inclusion/exclusion criteria by two independent reviewers for inclusion using an eligibility flowchart (Figure 2, Appendix 2) alongside the full eligibility criteria detailed in Table 1. Where the applicability of the inclusion criteria was unclear, the article was included at this stage to ensure that all potentially relevant studies were captured. The independent reviewers then compared their results and any disagreements were resolved by discussion until a consensus was met. If necessary, a third independent reviewer made the final decision.
- Each full text article was then assessed for inclusion in line with a second eligibility flowchart (Figure 3, Appendix 2) alongside the full eligibility criteria detailed in Table 1. In cases where the article did not give enough information to be sure that it met the inclusion criteria, the article was excluded to ensure that only relevant articles were included in the systematic review. The results of the two reviewers were compared and any disagreements resolved by discussion until a consensus was met. If necessary, a third independent reviewer made the final decision.

Eligibility criteria
TABLE 1. ELIGIBILITY CRITERIA FOR THE REVIEW

Domain	Inclusion	Exclusion
Population	Humans aged ≥18 years with HIV-1 infection, who are treatment-naïve	• Treatment-experienced, HIV-infected patients • HIV-infected patients aged <18 years • HIV-infected pregnant women • Uninfected individuals (e.g. studies of prophylatic use) • Studies in populations where all eligible participants had to meet a specific comorbidity-related criterion such as HCV infection
Intervention and comparator(s)	• B/F/TAF • Triple therapy regimens consisting of a relevant backbone (TDF/FTC,	• Any other treatments

Domain	Inclusion	Exclusion
	TAF/FTC or ABC/3TC) with DTG	• Any other treatments
Outcomes	Any of the following outcomes at week 48, 96 or 144 (or at the latest possible timepoint for resistance, safety and tolerability outcomes): <u>Efficacy</u> • Virologic response: percentage of patients with plasma HIV RNA <50 c/mL (FDA Snapshot analysis) • Virologic failure: percentage of patients with HIV RNA >50 c/mL (per protocol analysis) <u>Resistance</u> • Proportion of patients developing resistance <u>Safety and tolerability</u> • Percentage of patients with serious treatment-related adverse events • Percentage of patients discontinuing due to adverse events • Percentage of patients with non-serious treatment-related adverse events • Incidence of known side effects (to be specified in each product's Summary of Product Characteristics) <u>Other</u> • Change from baseline in global SF-36 score • Change from baseline in HIV Symptom Index Score (only if global SF-36 score is not available)	Any other outcomes
	Publications reporting study protocols or baseline characteristics only, without any outcomes of interest, were included at the title/abstract stage. At the full-text review stage, they were linked to other publications reporting on the same study. If there was at least one publication reporting relevant outcomes (efficacy, safety, resistance or HRQoL) for the trial, the protocol or baseline characteristics were included as a secondary publication for the trial. However, if there were no publications with relevant outcomes, the protocol or baseline characteristics were excluded.	
Study design	All Phases	
	SLRs, meta-analyses or NMAs of relevant RCTs were included at the title/abstract stage for the purpose of identifying any additional studies not identified in the database searches, but were subsequently excluded at the full-text review stage.	
Publication type	-	Case reports, editorials, review articles

Abbreviations: 3TC, lamivudine; ABC, abacavir; B/F/TAF, bictegravir/emtracitabine/tenofovir alafenimide; DTG, dolutegravir; FDA, Food and Drug Administration; FTC, emtricitabine; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; NMA, network meta-analysis; RCT, randomised controlled trial, RNA, ribonucleic acid; SF-36, 36-item Short Form Health Survey; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Data extraction

The methods and results of all included studies were extracted into pre-specified data extraction tables and contained the following information:

- Characteristics of the included patient population (for example, population size, age, sex, baseline viral load)
- Efficacy outcomes:
  - Virologic response: percentage of patients with plasma HIV RNA <50 c/mL (FDA Snapshot analysis) at weeks 48, 96 or 144
  - Virologic failure: percentage of patients with HIV RNA >50 c/mL at week 48 (per protocol analysis)
  - The proportion of patients developing resistance at the latest available timepoint
- Safety outcomes:
  - Percentage of patients with serious treatment-related adverse events at the latest available timepoint
  - Percentage of patients discontinuing due to adverse events at week 48 and the latest available timepoint
  - Percentage of patients with non-serious treatment-related adverse events at the latest available timepoint
  - Incidence of known side effects at the latest available timepoint. Known side effects for the intervention and comparators of interest were selected for extraction by review of the Summary of Product Characteristics (SPCs) for Triumeq and Tivicay, the SPC for B/F/TAF and the European AIDS Clinical Society guidelines (version 9.0, October 2017). Side effects designated as 'very common' in any of the three SPCs were selected, along with any side effects that are noted in the EACS guidelines for any component of the regimen:
    - Treatment-related adverse events:
      - Diarrhoea (noted as "very common" in both the Triumeq and Tivicay SPCs)
      - Fanconi syndrome (the EACS guidelines note Fanconi syndrome in relation to TDF)
      - Fatigue (noted as "very common" in the Triumeq SPC)
      - Fractures (the EACS guidelines note fractures in relation to TDF)
      - Headache (noted as "very common" in both the Triumeq and Tivicay SPCs, and the EACS guidelines note headache in relation to DTG)
      - Hepatitis (the EACS guidelines note hepatitis in relation to TDF)
      - Hypersensitivity (the EACS guidelines note hypersensitivity in relation to ABC and DTG)
      - Insomnia (noted as "very common" in the Triumeq SPC, and the EACS guidelines note headache in relation to DTG)

        - Nausea (noted as “very common” in both the Triumeq and Tivicay SPCs, and the EACS guidelines note headache in relation to DTG)
        - Osteomalacia (the EACS guidelines note osteomalacia in relation to TDF)
        - Rash (the EACS guidelines note rash in relation to DTG)
        - Sleep disturbances (the EACS guidelines note sleep disturbances in relation to DTG)
    - Other safety outcomes
        - Change from baseline in measures of bone mineral density (the EACS guidelines note bone mineral density in relation to TDF)
        - Change from baseline in eGFR (the EACS guidelines note eGFR in relation to TDF)
        - Evidence of ischaemic heart disease (IHD), (as noted by the EACS guidelines note IHD in relation to ABC)
- Quality of life outcomes:
    - Change from baseline in global SF-36 score at weeks 48, 96, 144
    - Change from baseline in HIV Symptom Index Score at weeks 48, 96, 144 (only if global SF-36 score is not available)

Data for baseline characteristics and outcomes were extracted separately by line of treatment if they were reported separately in the publication.

Data extraction was performed by a single reviewer for each included study. When the initial extraction was complete, a second reviewer then independently verified the extracted information and checked that no relevant information had been missed. Any discrepancies or missing information identified by the second reviewer was discussed by both reviewers until a consensus was reached on the information that should be presented in the extraction grid. When necessary, a third reviewer was enlisted to arbitrate the final decision.

Quality assessment

The quality of all included RCTs was assessed using the criteria provided by the Cochrane Collaboration’s tool for assessing risk of bias [1]. The quality of each study was assessed by a single individual in the first instance, with the conclusions confirmed independently by a second individual, and any discrepancies resolved through discussion. If necessary, a third individual was enlisted to arbitrate the final decision.

4.1 Relevant studies

On May 29th 2018 a total of 126 records were found through the database searches. After de-duplication of results, 99 unique records were suitable for review. After title and abstract review, 31 records were selected to be reviewed in full. Of these, 14 were found to fulfil the eligibility criteria.

Supplementary searches of websites and bibliographies yielded an additional 43 records and of these, 6 fulfilled the eligibility criteria.

This lead to a total of 20 records, representing 6 unique clinical trials included in the review; 14 from database searches and 6 from supplementary searches. Studies included after the full-text review are listed in Appendix 3 – Included Studies

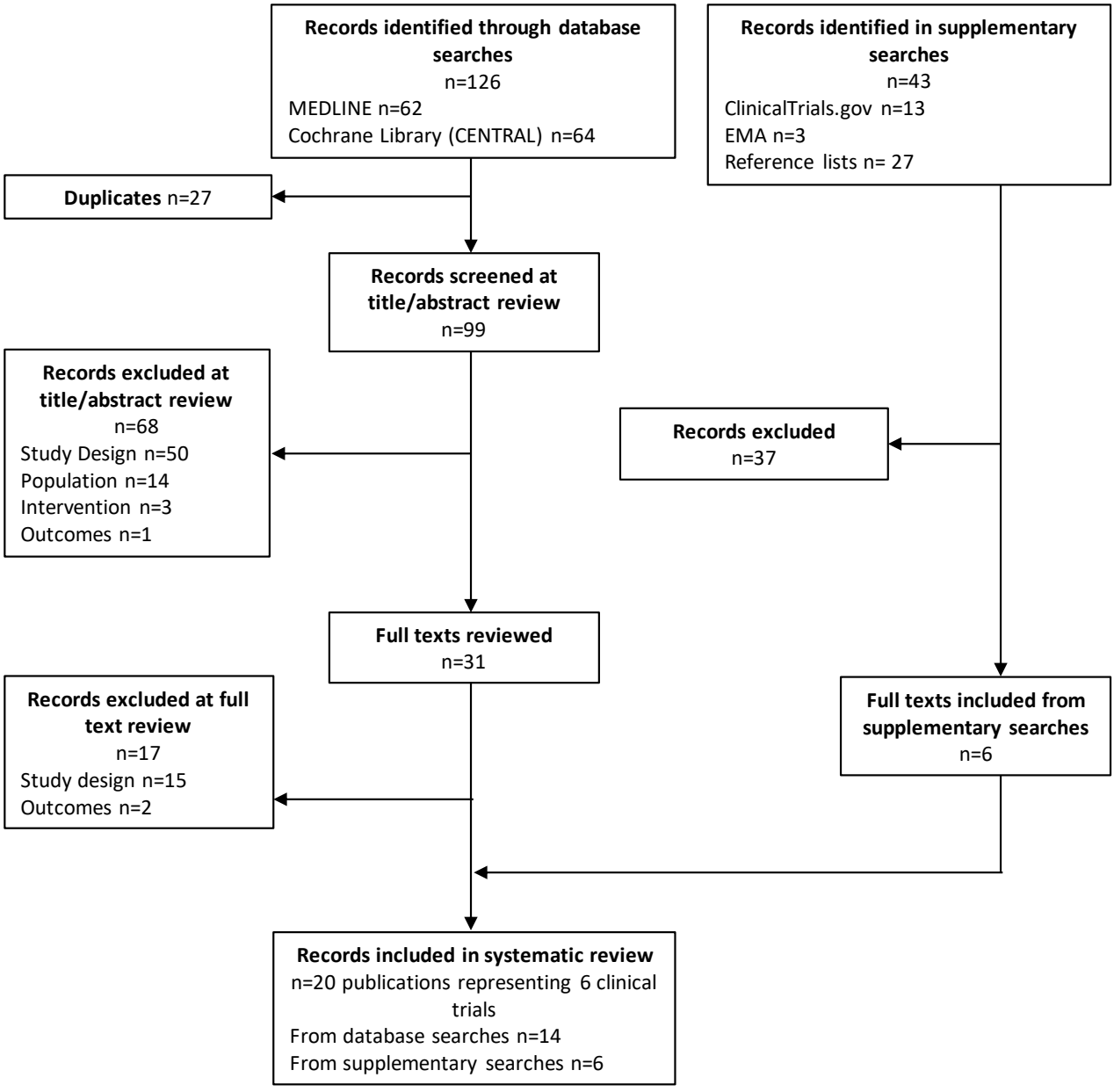
4.2 These details are presented in the main report.

Appendix 4 – Excluded Studies

Table 6 along with the reasons for exclusion.

The flow of records through the various review stages is presented in the PRISMA diagram in Figure 1.

FIGURE 1. PRISMA DIAGRAM



Note: A new search were performed September 6th 2018 based on request from Danish Medicines Council to include phase I and II studies resulted in three new publications – these were added to the literature list.

4.3 Study details

GS – 9883

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Bictegravir versus dolutegravir, each with emtricitabine, and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomized, double-blind, phase 2 trial, Sax et al., Lancet, 2017 [2]	GS- 9883	NCT02397694	Start: 23 March 2015 Expected completion: January 2019	Viral suppression Resistance development Side effects
Safety and Efficacy of Bictegravir + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults. ClinicalTrials.gov record, accessed September 2018 [3]	GS- 9883	NCT02397694	Start: 23 March 2015 Expected completion: January 2019	NA

GS-US-380-1489

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial, Gallant et al., Lancet, 2017 [4]	GS-US-380-1489	NCT02607930	Start: 13th November 2015 Expected completion: April 2019	Viral suppression Resistance development Side effects
Patient‐Reported Symptoms Over 48 Weeks Among participants in Randomized, Double‐Blind, Phase III Non‐inferiority Trials of Adults with HIV on Co‐formulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide versus Co‐formulated Abacavir, Dolutegravir, and Lamivudine. Wohl et al., The patient 2018 [5]	GS-US-380-1489	NCT02607930	Start: 13th November 2015 Expected completion: April 2019	SF-36 HIV-SI
Safety and Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults, ClinicalTrials.gov record, accessed June 2018 [6]	GS-US-380-1489	NCT02607930	Start: 13th November 2015 Expected completion: April 2019	NA

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable.

GS-US-380-1490

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Sax et al., Lancet, 2017 [7]	GS-US-380-1490	NCT02607956	Start: 11th November 2015 Expected completion: April 2020	Viral suppression Viral failure Resistance development Side effects
Safety and Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naivee Adults, ClinicalTrials.gov record, accessed June 2018 [8]	GS-US-380-1490	NCT02607956	Start: 11th November 2015 Expected completion: April 2020	NA

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable.

ARIA

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Orrell et al., Lancet, 2017 [9]	ARIA	NCT01910402	Start: 22nd August 2013 Expected completion: 31st December 2020	Viral suppression Viral failure Resistance development Side effects
Efficacy of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) fixed-dose combination (FDC) compared with ritonavir-boosted atazanavir (ATV/r) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in treatment-naïve women with HIV-1 infection (ARIA study): subgroup analyses. Johnson et al., JIAS Abstract Supplement, 2016 [10]	ARIA	NCT01910402	Start: 22nd August 2013 Expected completion: 31st December 2020	NA
A study to determine safety and efficacy of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) in Human Immunodeficiency Virus (HIV)-1 infected antiretroviral therapy (ART) naïve women (ARIA). ClinicalTrials.gov, accessed June 2018 [11]	ARIA	NCT01910402	Start: 22nd August 2013 Expected completion: 31st December 2020	Resistance development

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable.

FLAMINGO

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naivee adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study, Clotet et al., Lancet, 2014 [12]	FLAMINGO	NCT01449929	Start: 31st October 2011 End: 26 December 2016	Viral suppression Resistance development Side effects Health outcomes
Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naivee adults with HIV-1 infection (FLAMINGO): 96-week results from a randomised, open-label, phase 3b study, Molina et al., Lancet HIV, 2015 [13]	FLAMINGO	NCT01449929	Start: 31st October 2011 End: 26 December 2016	Viral suppression Resistance development Side effects Health outcomes
Dolutegravir: Clinical and Laboratory Safety in Integrase Inhibitor–Naivee Patients, Curtis et al., HIV Clin Trials, 2014 [14]	Integrated safety summary, including FLAMINGO	Various	NA	Side effects
Dolutegravir compared to darunavir/ritonavir, each in combination with dual nucleoside reverse transcriptase inhibitors (NRTIs) in ART-naivee subjects (FLAMINGO). ClinicalTrials.gov, accessed June 2018 [15]	FLAMINGO	NCT01449929	Start: 31st October 2011 End: 26 December 2016	NA
Triumeq: EPAR – Public assessment report, European Medicines Agency, 2014 [16]	FLAMINGO	NCT01449929	Start: 31st October 2011 End: 26 December 2016	Viral suppression Side effects

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable.

SINGLE

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection, Walmsley et al., NEJM, 2013 [17]	SINGLE	NCT01263015	Start: 1st February 2011 End: 3rd December 2015	Viral suppression Resistance development
Dolutegravir plus abacavir/lamivudine for the treatment of hiv-1	SINGLE	NCT01263015	Start: 1st February 2011	Viral suppression

infection in antiretroviral therapy-naivee patients: Week 96 and Week 144 results from the SINGLE randomized clinical trial, Walmsley et al., J AIDS 2015 [18]			End: 3rd December 2015	Resistance development Side effects
Greater change in bone turnover markers for efavirenz/emtricitabine/tenofovir disoproxil fumarate versus dolutegravir + abacavir/lamivudine in antiretroviral therapy-naivee adults over 144 weeks, Tebas et al., AIDS, 2015 [19]	SINGLE	NCT01263015	Start: 1st February 2011 End: 3rd December 2015	Side effects
A trial comparing GSK1349572 50mg plus abacavir/lamivudine once daily to Atripla (also called the SINGLE Trial), ClinicalTrials.gov record, accessed June 2018 [20]	SINGLE	NCT01263015	Start: 1st February 2011 End: 3rd December 2015	Health outcomes

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable.

SPRING-1

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. Stellbrink et al., AIDS 2013 [21]	SPRING-1	ING112276	Start: 30 July 2009 Completed: 22 December 2016	Viral suppression Viral failure Resistance development Side effects
A Dose Ranging Trial of GSK1349572 and 2 NRTI in HIV-1 infected, Therapy Naive Subjects (ING112276). ClinicalTrials.gov record, accessed September 2018 [22]	SPRING-1	ING112276	Start: 30 July 2009 Completed: 22 December 2016	NA

SPRING-2

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Once-daily dolutegravir versus raltegravir in antiretroviral-naivee adults with HIV-1 infection: 48-week results from the randomised, double-blind, non-inferiority SPRING-2 study, Raffi et al., Lancet, 2013 [23]	SPRING-2	NCT01227824	Start: 19th October 2010 End: 27th December 2016	Viral suppression Viral failure Resistance development Side effects
Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naivee adults with HIV-1 infection (SPRING-2 study): 96-week results	SPRING-2	NCT01227824	Start: 19th October 2010 End: 27th December 2016	Viral suppression Resistance

from a randomised, double-blind, non-inferiority trial, Raffi et al., Lancet Infect Dis, 2013 [24]				development Side effects
A trial comparing GSK1349572 50mg once daily to raltegravir 400mg twice daily (SPRING-2), ClinicalTrials.gov, accessed June 2018 [25]	SPRING-2	NCT01227824	Start: 19th October 2010 End: 27th December 2016	NA
Triumeq - assessment report, European Medicines Agency, 26 June 2014 [16]	SPRING-2	NCT01227824	Start: 19th October 2010 End: 27th December 2016	Side effects

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable.

4.4 Main characteristics of included studies

GS - 9883

Trial name	GS – 9883	
NCT number	NCT02397694	
Objective	To evaluate the efficacy, safety and tolerability of bictegravir (BIC) + emtricitabine/tenofovir alafenamide (F/TAF) fixed dose combination (FDC) versus dolutegravir (DTG) + F/TAF in HIV-1 Infected, antiretroviral treatment-naive adults	
Publications – title, author, journal, year	Bictegravir versus dolutegravir, each with emtricitabine, and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomized, double-blind, phase 2 trial, Sax et al., Lancet, 2017 [2] Safety and Efficacy of Bictegravir + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults. ClinicalTrials.gov record, accessed September 2018 [3]	
Study type and design	Double-blinded, randomised, phase 2 study. Enrolled patients were randomly assigned 2:1 centrally with a third-party interactive web response system and stratified by HIV-1 RNA (≤100 000 c/mL, >100 000 to ≤400 000 c/mL, or >400 000 c/mL). There was no crossover. Patiwnts recived placebo tablets matching either bictegravir or dolutegravir. Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to treatment assignment. Emtricitabine and tenofovir alafenamide were given in an open-label fashion	
Follow-up time	48 weeks	
Population (inclusion and exclusion criteria)	**Inclusion criteria**: • Antiretroviral naive (≤ 10 days of prior therapy with any antiretroviral agent) • Plasma HIV-1 RNA levels ≥ 1,000 copies/mL at screening • Screening genotype report provided by Gilead Sciences must show sensitivity to tenofovir (TFV)	**Exclusion criteria**: • A new AIDS-defining condition diagnosed within the 30 days prior to screening as defined in the study protocol • Prior use of antiretrovirals in the setting of pre-exposure prophylaxis (PrEP) or post exposure prophylaxis (PEP)

<table>
<tr>
<td></td>
<td>and FTC
• Adequate renal function as measured by estimated glomerular filtration rate ≥ 70 mL/min according to the Cockcroft-Gault formula
• CD4+ cell count > 200 cells/µL at screening</td>
<td>• Chronic hepatitis B virus (HBV) infection
• Hepatitis C infection (Individuals who are hepatitis C virus (HCV) Ab positive, but have a documented negative HCV RNA, are eligible)
• Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to baseline
• Participation in any other clinical trial without prior approval from the sponsor is prohibited while participating in this trial</td>
</tr>
<tr>
<td>Intervention</td>
<td colspan="2">Intervention: B/F/TAF single tablet 75 mg/200 mg/25 mg with matching bictegravir placebo (N=65)
Comparator: DTG + TAF/FTC tablets 50 mg +200 mg/25 mg with matching Dolutegravir placebo (N=33)</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td colspan="2">
<table>
<tr><th>Characteristic</th><th>B/F/TAF (n=314)</th><th>DTG + TAF/FTC (n=315)</th></tr>
<tr><td>Age, years, median (range)</td><td>30 (25–41)</td><td>36 (26–51)</td></tr>
<tr><td>Female sex, n (%)</td><td>1 (2)</td><td>3 (9)</td></tr>
<tr><td>White race, n (%)</td><td>38 (58)</td><td>18 (55)</td></tr>
<tr><td>BMI kg/m^2, median (IQR)</td><td>25.1 (22.5–27.8)</td><td>25.8 (23.5–27.4)</td></tr>
<tr><td>Viral load, HIV RNA $\log_{10}$ c/mL, median (IQR)</td><td>4.41 (4.01–4.78)</td><td>4.48 (3.94–4.82)</td></tr>
<tr><td>CD4 cell count, cells/µL, median (IQR)</td><td>441 (316–574)</td><td>455 (273–677)</td></tr>
<tr><td colspan="3">CDC category of HIV-1 infection, n (%)</td></tr>
<tr><td>Asymptomatic</td><td>61 (94)</td><td>31 (94)</td></tr>
<tr><td>Symptomatic</td><td>4 (6)</td><td>2 (6)</td></tr>
</table>
</td>
</tr>
</table>

Primary and secondary endpoints	**Primary endpoint**: • Proportion of participants with plasma HIV-1 RNA less than 50 c/mL at week 48, as defined by the US Food and Drug Administration (FDA) snapshot algorithm **Secondary outcomes**: • Proportion of participants with plasma HIV-1 RNA less than 50 c/mL at week 12 and 48, as defined by the US Food and Drug Administration (FDA) snapshot algorithm • Proportion of participants with plasma with HIV-1 RNA less than 20 copies per mL at week 48, as defined by the US Food and Drug Administration (FDA) snapshot algorithm • The change From baseline in CD4+ Cell Count at week 48 • Number of participants with treatment emergent adverse events (TEAEs) • Number of participants with treatment emergent laboratory abnormalities
Method of analysis	This phase 2 trial was not powered for non-inferiority, and the proposed sample size provided only a 32% power to assess non-inferiority, assuming a response of 88% for both groups and a non-inferiority margin of 0·12. Actual enrolment was 98 participants, which increased the power to assess non-inferiority to 40%. In the snapshot analysis using the full analysis set that included all participants randomly assigned and receiving at least one dose of study drug. The safety population included all randomly assigned patients who received at least one dose of study drug.
Subgroup analyses	NA

GS-US-380-1489

Trial name	GS-US-380-1489
NCT number	NCT02607930
Objective	To compare the efficacy and safety of coformulated bictegravir, FTC, and TAF with coformulated DTG, ABC, and 3TC in HIV-1-infected, previously untreated adults.
Publications – title, author, journal, year	• Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Gallant et al., Lancet, 2017 [4] • Safety and Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults, ClinicalTrials.gov record, accessed June 2018 [6]
Study type and design	Double-blinded, randomised, active-controlled, phase 3, non-inferiority study. Enrolled patients were randomly assigned 1:1 using a computer-generated allocation sequence (block size of four) and stratified by HIV-1 RNA (≤100 000 c/mL, >100 000

	to ≤400 000 c/mL, or >400 000 c/mL), CD4 count (<50 cells/µL, 50–199 cells/µL, or ≥200 cells/µL), and region (USA or ex-USA). There was no crossover. Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to treatment assignment.	
Follow-up time	48 weeks	
Population (inclusion and exclusion criteria)	**Inclusion criteria**: • Antiretroviral treatment naïve (≤ 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection) except the use for PrEP (pre-exposure prophylaxis) or PEP (post-exposure prophylaxis), up to one month prior to screening • Plasma HIV-1 RNA levels ≥ 500 c/mL at screening • Adequate renal function: Estimated glomerular filtration rate ≥ 50 mL/min (≥ 0.83 mL/sec) according to the Cockcroft-Gault formula • Negative screening test for HLA-B*5701 allele provided by Gilead Sciences	**Exclusion criteria**: • An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening (refer to study protocol) • Decompensated cirrhosis (e.g. ascites, encephalopathy, or variceal bleeding) • Current alcohol or substance use judged by the Investigator to potentially interfere with subject study compliance • Females who are pregnant (as confirmed by positive serum pregnancy test) • Females who are breastfeeding • Chronic HBV infection
Intervention	**Intervention**: B/F/TAF single tablet 50 mg/200 mg/25 mg once daily with matching placebo (N=314) **Comparator**: DTG/ABC/3TC single tablet 50 mg/600 mg/300 mg once daily with matching placebo (N=315)	

<table>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristic</th><th>B/F/TAF (n=314)</th><th>DTG/ABC/3TC (n=315)</th></tr>
<tr><td>Age, years, median (range)</td><td>31 (18–71)</td><td>32 (18–68)</td></tr>
<tr><td>Female sex, n (%)</td><td>29 (9)</td><td>33 (10)</td></tr>
<tr><td>White race, n (%)</td><td>180 (57)</td><td>179 (57)</td></tr>
<tr><td>BMI kg/m^2, median (IQR)</td><td>25.1 (22.4–28.7)</td><td>24.9 (22.5–29.1)</td></tr>
<tr><td>Viral load, HIV RNA log_{10} c/mL, median (IQR)</td><td>4.42 (4.03–4.87)</td><td>4.51 (4.04–4.87)</td></tr>
<tr><td>CD4 cell count, cells/µL, median (IQR)</td><td>443 (299–590)</td><td>450 (324–608)</td></tr>
<tr><td colspan="3">CDC category of HIV-1 infection, n (%)</td></tr>
<tr><td>Asymptomatic</td><td>286 (91)</td><td>286 (91)</td></tr>
<tr><td>Symptomatic</td><td>16 (5)</td><td>14 (4)</td></tr>
<tr><td>AIDS</td><td>12 (4)</td><td>15 (5)</td></tr>
<tr><td colspan="3">Known HIV risk factors, n (%)</td></tr>
<tr><td>Heterosexual contact</td><td>61 (19)</td><td>62 (20)</td></tr>
<tr><td>Homosexual contact</td><td>251 (80)</td><td>250 (79)</td></tr>
<tr><td>Injectable drug use</td><td>5 (2)</td><td>4 (1)</td></tr>
<tr><td>Transfusion</td><td>NR</td><td>NR</td></tr>
<tr><td>Haemophilia-associated injections</td><td>NR</td><td>NR</td></tr>
<tr><td>Occupational exposure</td><td>NR</td><td>NR</td></tr>
<tr><td>Vertical/perinatal transmission</td><td>NR</td><td>NR</td></tr>
<tr><td>Other</td><td>NR</td><td>NR</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>
Primary endpoint:
• Proportion of participants with plasma HIV-1 RNA less than 50 c/mL at week 48, as defined by the US Food and Drug Administration (FDA) snapshot algorithm
Secondary outcomes:
• Virological efficacy by subgroups of age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, geographical region, and study medication adherence
• Proportion of participants with plasma HIV-1 RNA less than 50 c/mL at week 48 after imputation of missing-as-failure and missing-as-excluded values
• Participants with HIV-1 RNA less than 20 c/mL at week 48 by the snapshot algorithm
• Change in HIV-1 RNA and CD4 cell count from baseline to week 48
• Percentage changes from baseline in hip and lumbar spine bone mineral density at week 48
</td></tr>
</table>

	• Change from baseline in serum creatinine and eGFR at week 48 • Percentage changes from baseline in urine retinol binding protein to creatinine ratio, urine β2-microglobulin to creatinine ratio, and urine albumin to creatinine ratio at week 48
Method of analysis	The primary endpoint was analysed in the full analysis set (all participants who were randomly assigned and had received at least one dose of the study drug, regardless of whether they returned for post-baseline assessments) and also in the per protocol set (excluded participants in the full analysis set analysis who did not have an HIV-1 RNA value in the week 48 window and those who had low adherence i.e. adherence ≤25th percentile). Change from baseline in log_{10} HIV-1 RNA was analysed in the full analysis set. Safety and demographic data was assessed in the safety analysis set (all randomly assigned participants who received at least one dose of study drug).
Subgroup analyses	NA

Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; ART, antirteroviral therapy; ATV, atazanavir; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CrCl, creatinine clearance; DTG, dolutegravir; FDA, Food and Drug Administration; FDC, fixed-dose combination; FTC, emtricitabine; HBV, Hepatitis B Virus; HDL, high-density lipoprotein; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IP, investigational product; IQR, interquartile range; ITT-E, intention-to-treat exposed; LDL, low-density lipoprotein; NA, not applicable; NC, North Carolina; NR, not reported; RNA, ribonucleic acid; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; US, United States; USA, United States of America.

GS-US-380-1490

Trial name	GS-US-380-1490	
NCT number	NCT02607956	
Objective	To compare the efficacy and safety of B/F/TAF as a fixed-dose combination versus DTG+TAF/FTC.	
Publications – title, author, journal, year	• Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial, Sax et al., Lancet, 2017 [7] • Safety and Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults, ClinicalTrials.gov record, accessed June 2018 [8]	
Study type and design	Double-blinded, randomised, active-controlled, phase 3, non-inferiority study. Enrolled patients were randomly assigned 1:1 using a computer-generated allocation sequence (block size of four) and stratified by HIV-1 RNA (≤100 000 c/mL, >100 000 to ≤400 000 c/mL, or >400 000 c/mL), CD4 count (<50 cells/µL, 50 to 199 cells/µL, or ≥200 cells/µL), and region (USA or outside the USA). There was no crossover. Investigators, participants, and study staff giving treatment, assessing outcomes, and collecting data were masked to treatment assignment.	
Follow-up time	48 weeks	
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • Antiretroviral treatment naivee (≤10 days of prior	**Exclusion criteria:** • An opportunistic illness indicative of stage 3 HIV

<table>
<tr><td></td><td>therapy with any antiretroviral agent following a diagnosis of HIV-1 infection) except the use for PrEP or PEP, up to one month prior to screening
• Plasma HIV-1 RNA levels ≥500 c/mL at screening
• Adequate renal function: Estimated glomerular filtration rate ≥30 mL/min (≥0.50 mL/sec) according to the Cockcroft-Gault formula</td><td>diagnosed within the 30 days prior to screening
Decompensated cirrhosis (e.g. ascites, encephalopathy, or variceal bleeding)
• Current alcohol or substance use judged by the Investigator to potentially interfere with subject study compliance
• Females who are pregnant (as confirmed by positive serum pregnancy test)
• Females who are breastfeeding</td></tr>
<tr><td>Intervention</td><td colspan="2">Intervention: B/F/TAF single tablet 50 mg/200 mg/25 mg with matching placebo (N=320)
Comparator: DTG+TAF/FTC tablets 50 mg/25 mg/200 mg with matching placebo (N=325)</td></tr>
<tr><td>Baseline characteristics</td><td colspan="2">
<table>
<tr><th>Characteristic</th><th>B/F/TAF (n=320)</th><th>DTG/ABC/3TC (n=325)</th></tr>
<tr><td>Age, years, median (IQR)</td><td>33 (27–46)</td><td>34 (27–46)</td></tr>
<tr><td>Female sex, n (%)</td><td>40 (13)</td><td>37 (11)</td></tr>
<tr><td>White race, n (%)</td><td>183 (57)</td><td>195 (60)</td></tr>
<tr><td>BMI kg/m^2, median (IQR)</td><td>25.0 (22.2–28.3)</td><td>24.6 (22.2–28.0)</td></tr>
<tr><td>Viral load, HIV RNA $\log_{10}$ c/mL, median (IQR)</td><td>4.43 (3.95–4.90)</td><td>4.45 (4.03–4.84)</td></tr>
<tr><td>CD4 cell count, cells/µL, median (IQR)</td><td>440 (289–591)</td><td>441 (297–597)</td></tr>
<tr><td colspan="3">CDC category of HIV-1 infection, n (%)</td></tr>
<tr><td>Asymptomatic</td><td>286 (89)</td><td>288 (89)</td></tr>
<tr><td>Symptomatic</td><td>10 (3)</td><td>11 (3)</td></tr>
<tr><td>AIDS</td><td>24 (8)</td><td>26 (8)</td></tr>
<tr><td colspan="3">Known HIV risk factors, n (%)</td></tr>
<tr><td>Heterosexual contact</td><td>81 (25)</td><td>77 (24)</td></tr>
<tr><td>Homosexual contact</td><td>237 (74)</td><td>250 (77)</td></tr>
<tr><td>Injectable drug use</td><td>3 (1)</td><td>6 (2)</td></tr>
<tr><td>Transfusion</td><td>NR</td><td>NR</td></tr>
<tr><td>Haemophilia-associated injections</td><td>NR</td><td>NR</td></tr>
<tr><td>Occupational exposure</td><td>NR</td><td>NR</td></tr>
<tr><td>Vertical/perinatal transmission</td><td>NR</td><td>NR</td></tr>
<tr><td>Other</td><td>NR</td><td>NR</td></tr>
</table>
</td></tr>
</table>

Primary and secondary endpoints	**Primary outcome**: • Proportion of participants who had plasma HIV-1 RNA of less than 50 c/mL at week 48 as defined by the US Food and Drug Administration (FDA) snapshot algorithm **Secondary outcomes**: • Virological efficacy by age (<50 vs ≥50 years), sex (male vs female), race (black vs non-black), baseline HIV-1 RNA (≤100 000 c/mL vs >100 000 c/mL), baseline CD4 count (<200 vs ≥200 cells per mL), geographical region (USA vs outside the USA), and study medication adherence (<95% vs ≥95%) • Proportion of participants with plasma HIV-1 RNA of less than 50 c/mL at week 48 when imputing missing data as failure (M = F) and missing as excluded (M = E) • Changes in log_{10} HIV-1 RNA and CD4 count from baseline at week 48 • Safety outcomes were assessed by changes from baseline in fasting glucose, lipid panels, serum creatinine, and eGFR at week 48
Method of analysis	The primary endpoint was analysed in the full analysis set (all participants who were randomly assigned and had received at least one dose of the study drug, regardless of whether they returned for post-baseline assessments) and also in the per protocol set (excluded participants in the full analysis set who were off study drug at week 48 or had low adherence (i.e. adherence at or below the 25^{th} percentile of those in the study). Change from baseline in log_{10} HIV-1 RNA was analysed in the full analysis set. Safety and demographic data was assessed in the safety analysis set (all randomly assigned participants who received at least one dose of study drug).
Subgroup analyses	NA

Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; ART, antirteroviral therapy; ATV, atazanavir; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CrCl, creatinine clearance; DTG, dolutegravir; FDA, Food and Drug Administration; FDC, fixed-dose combination; FTC, emtricitabine; HDL, high-density lipoprotein; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IP, investigational product; IQR, interquartile range; ITT-E, intention-to-treat exposed; LDL, low-density lipoprotein; NA, not applicable; NC, North Carolina; NR, not reported; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; RNA, ribonucleic acid; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; US, United States; USA, United States of America.

ARIA

Trial name	ARIA
NCT number	NCT01910402
Objective	To assess safety and efficacy of a fixed-dose combination of DTG plus ABC and 3TC in previously untreated women with HIV-1 compared with ATV with RTV plus a fixed-dose combination of TDF/FTC.
Publications – title, author, journal, year	• Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Orrell et al., Lancet, 2017 [9]

	• Efficacy of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) fixed-dose combination (FDC) compared with ritonavir-boosted atazanavir (ATV/r) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in treatment-naïve women with HIV-1 infection (ARIA study): subgroup analyses. Johnson et al., JIAS Abstract Supplement, 2016 [10] • A study to determine safety and efficacy of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) in Human Immunodeficiency Virus (HIV)-1 infected antiretroviral therapy (ART) naïve women (ARIA). ClinicalTrials.gov [11]	
Study type and design	Randomised, open-label, multi-centre, non-inferiority Phase 3b study. Randomisation and identifier code assignment were allocated centrally with a validated computerised system (RandAll; GlaxoSmithKline, Research Triangle Park, NC, USA). Random treatment group assignment was stratified by screening plasma HIV-1 RNA viral loads (≤100 000 c/mL or >100 000 c/mL) and CD4 counts (≤350 cells per µL or >350 cells per µL). As an open-label study, the protocol did not include procedures for masking.	
Follow-up time	48 weeks	
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • HIV-1 infected females (gender at birth) ≥18 years of age • Women capable of becoming pregnant must use appropriate contraception during the study (as defined by the protocol) • HIV-1 infection as documented by screening plasma HIV-1 RNA ≥500 c/mL • Documentation that the subject is negative for the HLA-B*5701 allele • Antiretroviral-naïve (≤10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection) • Signed and dated written informed consent is obtained from the subject or the subject's legal representative prior to screening	**Exclusion criteria:** • Women who are pregnant or breastfeeding • Women who plan to become pregnant during the first 48 weeks of the study • Any subject who has had a medical intervention for gender reassignment • Any evidence of an active CDC Category C disease • Subjects with any degree of hepatic impairment • Subjects positive for hepatitis B at screening, or anticipated need for HCV therapy during the study • History or presence of allergy to the study drugs or their components or drugs of their class • Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia • Poses a significant suicidality risk • History of osteoporosis with fracture or requiring pharmacologic therapy • Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of screening • Treatment with any of the following agents within 28 days of screening: radiation therapy; cytotoxic chemotherapeutic agents; any immunomodulators

<table>
<tr><td></td><td></td><td>that alter immune responses;
• Treatment with any agent, with documented activity against HIV-1 in vitro within 28 days of first dose of IP
• Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of IP
• Any evidence of primary viral resistance based on the presence of any major resistance-associated mutation in the screening result or, if known, any historical resistance test result
• Any verified Grade 4 laboratory abnormality, with the exception of Grade 4 lipid abnormalities (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol)
• Any acute laboratory abnormality at screening, which, in the opinion of the Investigator, would preclude the subject's participation in the study of an investigational compound
• ALT ≥5 times the ULN, or ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin)
• Subject has CrCL of <50 mL/min via Cockcroft-Gault method
• Corrected QT interval (QTc (Bazett) ≥450msec or QTc (Bazett) ≥480msec for subjects with bundle branch block</td></tr>
<tr><td>Intervention</td><td colspan="2">Intervention: DTG/ABC/3TC FDC tablets, 50 mg/600 mg/300 mg once daily (n=248)
Comparator: ATV/RTV 300 mg/100 mg + TDF/FTC 300/200 mg once daily (n=247)</td></tr>
<tr><td>Baseline characteristics</td><td colspan="2"><table>
<tr><th>Characteristic</th><th>DTG group (n=248)</th><th>ATV/r group (n=247)</th></tr>
<tr><td>Age, years, mean (SD)</td><td>38.1 (11.15)</td><td>37.8 (10.14)</td></tr>
<tr><td>Female sex, n (%)</td><td>248 (100)</td><td>247 (100)</td></tr>
<tr><td>White race, white, n (%)</td><td>115 (46)</td><td>107 (43)</td></tr>
<tr><td>BMI, kg/m^2</td><td>NR</td><td>NR</td></tr>
</table></td></tr>
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<table>
<tr><td></td><td>
<table>
<tr><td>Viral load, HIV RNA log_{10} c/mL, median*</td><td>4.410 (3.91-5.09)</td><td>4.430 (3.92-5.05)</td></tr>
<tr><td>CD4 cell count, cells/µL, median*</td><td>340.0 (197.0–497.5)</td><td>350.0 (241.0–487.0)</td></tr>
<tr><td colspan="3">CDC category of HIV-1 infection</td></tr>
<tr><td>Asymptomatic</td><td>210 (85)</td><td>208 (84)</td></tr>
<tr><td>Symptomatic, not AIDS</td><td>27 (11)</td><td>30 (12)</td></tr>
<tr><td>AIDS</td><td>11 (4)</td><td>9 (4)</td></tr>
<tr><td colspan="3">Known HIV risk factors</td></tr>
<tr><td>Heterosexual contact</td><td>233 (94)</td><td>233 (94)</td></tr>
<tr><td>Homosexual contact</td><td>1 (<1)</td><td>2 (1)</td></tr>
<tr><td>Injectable drug use</td><td>12 (5)</td><td>8 (3)</td></tr>
<tr><td>Transfusion</td><td>5 (2)</td><td>2 (1)</td></tr>
<tr><td>Haemophilia-associated injections</td><td>NR</td><td>NR</td></tr>
<tr><td>Occupational exposure</td><td>NR</td><td>NR</td></tr>
<tr><td>Vertical/perinatal transmission</td><td>NR</td><td>NR</td></tr>
<tr><td>Other</td><td>5 (2)</td><td>5 (2)</td></tr>
</table>
*Unit not reported but assumed to be range or IQR
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoint:
Proportion of participants with plasma HIV-1 RNA of less than 50 c/mL at week 48 assessed with the US FDA snapshot algorithm for the ITT-E population
Secondary endpoints:
Proportion of participants with plasma HIV-1 RNA of less than 50 c/mL and less than 400 c/mL over time
Absolute values and change from baseline in plasma HIV-1 RNA over time
CD4 lymphocyte cell counts and changes from baseline
Incidence of disease progression (HIV-associated conditions, AIDS, and death)
Serious adverse events
Incidence of suicidal intent according to the Columbia Suicide-Severity Rating Scale
Incidence of treatment-emergent genotypic and phenotypic resistance in patients who met confirmed virological withdrawal criteria
Health outcome measures of quality of life and treatment satisfaction.</td></tr>
<tr><td>Method of analysis</td><td>All efficacy analyses were performed in the ITT-E population, which was defined as all participants who received at least one dose of study medication. Analyses were on planned treatment rather than the actual treatment received. Efficacy analyses were also performed in the per-protocol population which included participants in the ITT-E, but excluded participants with major protocol violations that could have affected the assessment of antiviral activity, including those known to have less than 90% adherence to study medication. Safety outcomes were analysed in all participants who received at least one dose</td></tr>
</table>

	of study medication.
Subgroup analyses	NA

Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; ART, antirteroviral therapy; ATV, atazanavir; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CrCl, creatinine clearance; DTG, dolutegravir; FDA, Food and Drug Administration; FDC, fixed-dose combination; FTC, emtricitabine; HDL, high-density lipoprotein; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IP, investigational product; IQR, interquartile range; ITT-E, intention-to-treat exposed; LDL, low-density lipoprotein; NA, not applicable; NC, North Carolina; NR, not reported; RNA, ribonucleic acid; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; US, United States; USA, United States of America.

FLAMINGO

Trial name	FLAMINGO	
NCT number	NCT01449929	
Objective	To assess the efficacy, safety, and tolerability of DTG versus a guideline-recommended boosted protease inhibitor-based regimen (DRV plus RTV), in combination with two widely recommended NRTI backbones, as first-line treatment for adults with HIV-1 who were naïve for antiretroviral therapy.	
Publications – title, author, journal, year	• Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naivee adults with HIV-1 infection (FLAMINGO): 48-week results from the randomised open-label phase 3b study, Clotet et al., Lancet, 2014 [12] • Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naivee adults with HIV-1 infection (FLAMINGO): 96-week results from a randomised, open-label, phase 3b study, Molina et al., Lancet HIV, 2015 [13] • Dolutegravir compared to darunavir/ritonavir, each in combination with dual nucleoside reverse transcriptase inhibitors (NRTIs) in ART-naivee subjects (FLAMINGO). ClinicalTrials.gov, accessed June 2018 [15] • Triumeq: EPAR – Public assessment report, European Medicines Agency, 2014 [16]	
Study type and design	Phase 3b, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study. Patients were randomly assigned (1:1) via a central interface to receive either DTG 50 mg once daily or DRV 800 mg plus RTV 100 mg once daily. Randomisation was stratified by HIV-1 RNA (>100,000 c/mL or ≤100,000 c/mL) and NRTI backbone. No masking was done in this study.	
Follow-up time	96 weeks Median time of exposure to both DTG and DRV/r in the ABC/3TC subgroup was 337 days.	
Population (inclusion and exclusion criteria)	**Inclusion criteria**: • HIV-1 infected adults greater than or equal to 18 years of age. Females are eligible to enter and participate in the study if she is (1) non-childbearing potential, (2) child bearing potential with negative pregnancy test at screening and Day 1 and agrees to	**Exclusion criteria**: • Women who are pregnant or breastfeeding • Any evidence of an active CDC Category C disease [CDC, 1993], except cutaneous Kaposi's sarcoma not requiring systemic therapy • Subjects with moderate to severe hepatic

	use protocol-specified methods of birth control while on study. • HIV-1 infection with a screening plasma HIV-1 RNA greater than or equal to 1000 c/mL • Antiretroviral-naïve (less than or equal to 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection) • Signed and dated written informed consent is obtained from the subject or the subject's legal representative prior to screening	impairment (Class B or C) as determined by Child-Pugh classification • Anticipated need for HCV therapy during the study • History or presence of allergy or intolerance to the study drugs or their components or drugs of their class • History of malignancy within the past 5 years or ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma; other localized malignancies require agreement between the investigator and the Study medical monitor for inclusion of the subject • Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of screening • Treatment with any of the following agents within 28 days of screening: radiation therapy; cytotoxic chemotherapeutic agents; any immunomodulators • Treatment with any agent, except recognized ART as allowed above, with documented activity against HIV-1 in vitro within 28 days of first dose of investigational product • Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of investigational product • Any evidence of primary viral resistance based on the presence of any major resistance-associated mutation [IAS-USA, 2010] in the screening result or, if known, any historical resistance test result • Any verified Grade 4 laboratory abnormality. Any acute laboratory abnormality at screening, which, in the opinion of the Investigator, would preclude the subject's participation in the study of an investigational compound is exclusionary

<table>
<tr><td></td><td></td><td>• ALT greater than 5 times the upper limit of normal
• ALT greater than 3 times the upper limit of normal and bilirubin greater than or equal to 1.5 times the upper limit of normal (with greater than 35% direct bilirubin)
• Subject has creatinine clearance of less than 50 mL/min via Cockroft-Gault method
• Recent history (less than or equal to 3 months) of any upper or lower gastrointestinal bleed, with the exception of anal or rectal bleeding</td></tr>
<tr><td>Intervention</td><td colspan="2">Intervention: DTG 50 mg once daily (N=242) with investigator-selected NRTI backbone
Comparator: DRV 800mg once daily in combination with RTV 100mg once daily (N=242) with investigator selected NRTI backbone 159 (33%) of subjects were prescribed ABC/3TC as background NRTI, with the remainder 325 (67%) receiving TDF/FTC (67%)</td></tr>
<tr><td>Baseline characteristics</td><td colspan="2">
<table>
<tr><th>Characteristic</th><th>DTG group (n=242)</th><th>DRV/r group (n=242)</th></tr>
<tr><td>Age, years, median (range)</td><td>34 (18-67)</td><td>34 (19-67)</td></tr>
<tr><td>Female sex, n (%)</td><td>31 (12.8)</td><td>41 (16.9)</td></tr>
<tr><td>White race, n (%)</td><td>173 (71)</td><td>176 (73)</td></tr>
<tr><td>BMI kg/m^2</td><td>NR</td><td>NR</td></tr>
<tr><td>Viral load, HIV RNA $\log_{10}$ c/mL, median (IQR)</td><td>4.49 (4.02-5.02)</td><td>4.48 (4.01-5.01)</td></tr>
<tr><td>CD4 cell count, cells/µL, median (IQR)</td><td>390 (290–500)</td><td>400 (300–530)</td></tr>
<tr><td colspan="3">CDC category of HIV-1 infection, n (%)</td></tr>
<tr><td>Asymptomatic</td><td>203 (84)</td><td>204 (84)</td></tr>
<tr><td>Symptomatic, not AIDS</td><td>30 (12)</td><td>32 (13)</td></tr>
<tr><td>AIDS</td><td>9 (4)</td><td>6 (2)</td></tr>
<tr><td colspan="3">Known HIV risk factors</td></tr>
<tr><td>Heterosexual contact</td><td>NR</td><td>NR</td></tr>
<tr><td>Homosexual contact</td><td>NR</td><td>NR</td></tr>
<tr><td>Injectable drug use</td><td>NR</td><td>NR</td></tr>
<tr><td>Transfusion</td><td>NR</td><td>NR</td></tr>
<tr><td>Haemophilia-associated injections</td><td>NR</td><td>NR</td></tr>
<tr><td>Occupational exposure</td><td>NR</td><td>NR</td></tr>
<tr><td>Vertical/perinatal transmission</td><td>NR</td><td>NR</td></tr>
<tr><td>Other</td><td>NR</td><td>NR</td></tr>
</table>
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</table>

Primary and secondary endpoints	**Primary endpoint:** • Proportion of patients with a concentration of HIV-1 RNA lower than 50 c/mL at week 48, using the US FDA snapshot (missing, switch, or discontinuation equals failure; MSDF) algorithm **Secondary endpoints:** • Changes from baseline in CD4 cell counts • Incidence and severity of adverse events • Changes in laboratory variables (such as fasting LDL cholesterol) • Time to virological suppression • Treatment-emergent genotypic or phenotypic evidence of resistance • Disease progression • Proportion of patients who discontinued treatment because of adverse events • Health outcomes measures, including the EuroQol five dimension (EQ-5D), HIV Treatment Satisfaction Questionnaire, and Symptom Distress Module
Method of analysis	The analyses were conducted on the mITT-E or modified safety populations, which consisted of all patients randomly assigned to treatment groups who received at least one dose of study drug, excluding one patient at one study site in Russia that was closed early after the sponsor became aware of issues of non-compliance to good clinical practice in another ViiV Healthcare-sponsored study.
Subgroup analyses	Data for the backbone-specific subgroups are presented for the primary endpoint of virologic response. These analyses were prespecified; randomisation was stratified by backbone choice (and by baseline HIV RNA). The backbone was investigator-selected and therefore the analyses are subject to selection bias. In addition, the backbone was not blinded so the results may be subject to performance bias or detection bias. The study was not fully powered for subgroup analyses.

Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; ART, antirteroviral therapy; ATV, atazanavir; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CrCl, creatinine clearance; DTG, dolutegravir; FDA, Food and Drug Administration; FDC, fixed-dose combination; FTC, emtricitabine; HDL, high-density lipoprotein; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IP, investigational product; IQR, interquartile range; ITT-E, intention-to-treat exposed; LDL, low-density lipoprotein; mITT-E, modified intention-to-treat exposed; MSDF, missing, switch, or discontinuation equals failure; NA, not applicable; NC, North Carolina; NR, not reported; NRTI, nucleoside reverse transcriptase inhibitor; RNA, ribonucleic acid; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; US, United States; USA, United States of America.

SINGLE

Trial name	SINGLE
NCT number	NCT01263015

Objective	Assess the safety and efficacy of DTG at a dose of 50 mg plus a fixed-dose combination of ABC/3TC, as compared with fixed-dose EFV/TDF/FTC.	
Publications – title, author, journal, year	• Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection, Walmsley et al., NEJM, 2013 [17] • Dolutegravir plus abacavir/lamivudine for the treatment of hiv-1 infection in antiretroviral therapy-naivee patients: Week 96 and Week 144 results from the SINGLE randomized clinical trial, Walmsley et al., J AIDS 2015 [18] • Greater change in bone turnover markers for efavirenz/emtricitabine/tenofovir disoproxil fumarate versus dolutegravir + abacavir/lamivudine in antiretroviral therapy-naivee adults over 144 weeks, Tebas et al., AIDS, 2015 [19] • A trial comparing GSK1349572 50mg plus abacavir/lamivudine once daily to Atripla (also called the SINGLE trial), ClinicalTrials.gov record, accessed June 2018 [20]	
Study type and design	Randomised, multi-centre, double-blind, Phase 3 study. Enrolled patients were randomly assigned 1:1. Randomisation was performed in block sizes of six, with the use of a central procedure. The trial was double-blind and double-dummy until Week 96, after which the trial became open-label until completion at Week 144. No crossover was allowed. Patients, care providers and the sponsor were masked to treatment assignment until Week 96.	
Follow-up time	144 weeks Average follow-up time of 877.4 study days for DTG + ABC/3TC; average of 788.8 study days for EFV/TDF/FTC	
Population (inclusion and exclusion criteria)	**Inclusion criteria**: • Screening plasma HIV-1 RNA ≥1000 c/mL • Antiretroviral-naïve (≤10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection) • Ability to understand and sign a written informed consent form • Willingness to use approved methods of contraception to avoid pregnancy (women of child bearing potential only) • Age equal to or greater than 18 years • A negative HLAB*5701 allele assessment	**Exclusion criteria**: • Women who are pregnant or breastfeeding • Active CDC Category C disease • Hepatic impairment • HBV co-infection • Anticipated need for HCV therapy during the study • Allergy or intolerance to the study drugs or their components or drugs of their class • Malignancy within the past 5 years • Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of screening • Treatment with radiation therapy, cytotoxic chemotherapeutic agents or any immunomodulator within 28 days of screening • Exposure to an agent with documented activity against HIV-1 in vitro or an experimental vaccine or drug within 28 days of first dose of study medication • Primary viral resistance in the screening result • Verified Grade 4 laboratory abnormality

<table>
<tr><td></td><td></td><td>• ALT >5x ULN
• ALT ≥3x ULN and bilirubin ≥1.5xULN (with >35% direct bilirubin)
• Estimated creatinine clearance <50 mL/min
• Recent history (≤3 months) of upper or lower gastrointestinal bleed</td></tr>
<tr><td>Intervention</td><td colspan="2">Intervention: DTG 50 mg once daily with ABC/3TC in a fixed-dose combination of 600 mg and 300 mg, respectively, also once daily (N=414). In addition, participants received a placebo matching the EFV/TDF/FTC tablet (i.e., all participants received three tablets each day).
Comparator: EFV/TDF/FTC as a single tablet once daily at fixed doses of 600 mg, 300 mg, and 200 mg, respectively (N=419). In addition, participants received placebos matching the DTG and ABC/3TC tablets (i.e., all participants received three tablets each day).</td></tr>
<tr><td>Baseline characteristics</td><td colspan="2">
<table>
<tr><th>Characteristic</th><th>DTG + ABC/3TC (N=414)</th><th>EFV/TDF/FTC (N=419)</th></tr>
<tr><td>Age, years, mean (SD)</td><td>36.5 (10.74)</td><td>36.4 (10.43)</td></tr>
<tr><td>Female sex, n (%)</td><td>67 (16)</td><td>63 (15)</td></tr>
<tr><td>White race, n (%)</td><td>284 (69)</td><td>285 (68)</td></tr>
<tr><td>BMI, kg/m^2</td><td>NR</td><td>NR</td></tr>
<tr><td>Viral load, HIV RNA log10 c/mL, median</td><td>4.67</td><td>4.70</td></tr>
<tr><td>CD4 cell count, cells/µL, median (range)</td><td>334.5 (19, 1027)</td><td>339.0 (19, 1123)</td></tr>
<tr><td colspan="3">CDC category, n (%)</td></tr>
<tr><td>A: Asymptomatic or lymphadenopathy or acute HIV</td><td>343 (83)</td><td>350 (84)</td></tr>
<tr><td>B: Symptomatic, not AIDS</td><td>53 (13)</td><td>52 (12)</td></tr>
<tr><td>C: AIDS</td><td>18 (4)</td><td>17 (4)</td></tr>
<tr><td>HIV risk factors known, yes, n (%)</td><td>403 (97)</td><td>408 (97)</td></tr>
<tr><td>Homosexual contact</td><td>268 (67)</td><td>289 (71)</td></tr>
<tr><td>Heterosexual contact</td><td>133 (33)</td><td>111 (27)</td></tr>
<tr><td>Injectable drug use</td><td>20 (5)</td><td>9 (2)</td></tr>
<tr><td>Transfusion</td><td>2 (<1)</td><td>1 (<1)</td></tr>
<tr><td>Haemophilia-associated injections</td><td>0</td><td>2 (<1)</td></tr>
<tr><td>Occupational exposure</td><td>0</td><td>0</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td>Vertical/perinatal transmission</td><td>0</td><td>1 (<1)</td></tr><tr><td>Other</td><td>5 (1)</td><td>12 (3)</td></tr></table>
Primary and secondary endpoints	**Primary endpoint**: Proportion of participants with a plasma HIV-1 RNA level of less than 50 c/mL at week 48, as determined with the use of the Snapshot algorithm from the Food and Drug Administration (FDA) **Secondary endpoints**: • Time to viral suppression (i.e., an HIV-1 RNA level of <50 c/mL) • Change from baseline in the CD4+ T-cell count • Safety profile • Health outcomes • Incidence of the development of genotypic and phenotypic resistance to DTG, EFV, and the respective backbone therapy components (ABC/3TC and TDF/FTC) during the treatment period
Method of analysis	Efficacy and safety analyses were performed in the intention-to-treat population and safety population, respectively; both populations included all participants who underwent randomisation and received at least one dose of study drug. The two populations were identical in this study.
Subgroup analyses	NA

Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; ART, antirteroviral therapy; ATV, atazanavir; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CrCl, creatinine clearance; DTG, dolutegravir; FDA, Food and Drug Administration; FDC, fixed-dose combination; FTC, emtricitabine; HDL, high-density lipoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IP, investigational product; IQR, interquartile range; ITT-E, intention-to-treat exposed; LDL, low-density lipoprotein; NA, not applicable; NC, North Carolina; NR, not reported; RNA, ribonucleic acid; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; US, United States; USA, United States of America.

SPRING-1

Trial name	SPRING-1
NCT number	ING112276
Objective	To evaluate the efficacy and safety/tolerability of dolutegravir (DTG, S/GSK1349572), a potent inhibitor of HIV integrase, through the full 96 weeks of the SPRING-1 study
Publications – title, author, journal, year	• Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. Stellbrink et al., AIDS 2013 [21] • A Dose Ranging Trial of GSK1349572 and 2 NRTI in HIV-1 Infected, Therapy Naive Subjects (ING112276), ClinicalTrials.gov, accessed September 2018 [22]
Study type and design	a phase IIb, multiicenter, partially blinded, dose-ranging study of DTG (10, 25, and 50 mg) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) in treatment-naive individuals. Participants were randomized (1 : 1 : 1 : 1)

	to treatment with DTG 10, 25, or 50 mg once daily (q.d.) or EFV 600 mg q.d. that was blinded to dose of DTG but not study drug. At 96 weeks, participants randomized to the DTG arms were switched to the selected 50 mg q.d. dose, and participants randomized to EFV were discontinued from further study follow-up	
Follow-up time	96 weeks	
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • HIV-1 infected male or female adults at least 18 years of age. Women capable of becoming pregnant must use appropriate contraception during the study (as defined by the protocol) • HIV-1 infection with a screening plasma HIV-1 RNA greater than or equal to 1000copies/mL • CD4+ cell count greater than or equal to 200cells/mm3 (or higher as local guidelines dictate) • ART-naive (less than or equal to 10 days of prior therapy with any antiretroviral agent). Any previous exposure to an HIV integrase inhibitor other than GSK1349572 will be exclusionary • No evidence of viral resistance to any antiretroviral drug indicative of primary transmitted resistance at screening • Able to understand and comply with protocol requirements • Able to provide written informed consent prior to screening • French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category • Note: Subjects starting abacavir as part of the NRTI backbone must have been screened and be negative for the HLA-B*5701 allele	**Exclusion criteria:** • Any pre-existing or serious mental or physical disorder which could compromise ability to comply with the protocol or compromise subject safety • Women who are pregnant or breastfeeding; • An active AIDS-defining condition at the screening visit • Previous participation in an experimental drug and/or vaccine trial(s) within 30 days or 5 half-lives • History of clinically relevant pancreatitis or hepatitis within the previous 6 months, including HBsAg positive result. Asymptomatic HCV infection will not be exclusionary, however subject who will require HCV therapy during the trial should be excluded. Any subject with a history of liver cirrhosis with or without hepatitis viral co-infection will be excluded • Any condition which could interfere with the absorption, distribution, metabolism or excretion of the drug • Any acute or Grade 4 laboratory abnormality at screening • History of upper gastrointestinal bleed and/or subjects with active peptic ulcer disease • Estimated creatinine clearance <50 mL/min • Alanine aminotransferase (ALT) greater than or equal to 5 times ULN • Alanine aminotransferase (ALT) greater than or equal to 3xULN and bilirubin greater than or equal to 1.5xULN (with >35% direct bilirubin) • Lipase greater than or equal to 3xULN; • Hemoglobin < 100 g/L(10 g/dL)

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<tr><td></td><td></td><td>

History of allergy to the study drugs or their components or drugs of their class
Treatment with radiation therapy, cytotoxic chemotherapeutic agents, any agents with activity against HIV-1 or immunomodulators within 28 days prior to screening
Treatment with an HIV-1 immunotherapeutic vaccine within 90 days prior to screening
History of protocol-defined cardiac diseases
Personal or family history of prolonged QT syndrome
Any clinically significant finding, as specified in the protocol, on electrocardiograph (ECG);
Significant blood loss in excess of 500 mL within a 56 day period prior to screening visit;
Immunization within 30 days prior to first dose of investigational product;
French subjects: The subject has participated in any study using an investigational drug during the previous 60 days or 5 half-lives, or twice the duration of the biological effect of the experimental drug or vaccine - whichever is longer, prior to screening for the study or the subject will participate simultaneously in another clinical study.

</td></tr>
<tr><td>Intervention</td><td colspan="2">Intervention: once daily DTG 10mg (N=53) or 25mg (N=51) or 50 mg (N=51) or EFV 600mg (N=50) and at the investigators' discretion, patients received an NRTI backbone of coformulated TDF/FTC or ABC/3TC.</td></tr>
<tr><td>Baseline characteristics</td><td colspan="2">
<table>
<tr><th>Characteristic</th><th>DTG 10mg (N=53)</th><th>DTG 25mg (N=51)</th><th>DTG 50mg (N=51)</th><th>EFV 600mg (N=50</th></tr>
<tr><td>Age, years, mean (SD)</td><td>34.2 (9.25)</td><td>37.0 (9.79)</td><td>37.0 (8.89)</td><td>40.7 (11.19)</td></tr>
<tr><td>Female sex, n (%)</td><td>11 (20.8)</td><td>5 (9.8)</td><td>6 (11.8)</td><td>6 (12.0)</td></tr>
<tr><td>Male sex, n (%)</td><td>42 (79.8)</td><td>46 (90.2)</td><td>45 (88.2)</td><td>44 (88.0)</td></tr>
<tr><td>Viral load, HIV RNA log_{10} c/mL, median (IQR)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>CD4 cell count, cells/µL, median (IQR)</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
</table>
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Primary and secondary endpoints	**Primary endpoint**: Number of participants with HIV-1 RNA <50 copies/milliliter (c/mL) at week 16 **Secondary endpoints**: • Viral change over the Initial 2 weeks of treatment • Number of participants with plasma HIV-1 RNA <50 c/mL • Number of participants with plasma HIV-1 RNA <400 c/mL • Incidence of treatment-emergent genotypic and phenotypic resistance to DTG and other antiretroviral therapies used in the study • Number of participants with any adverse event (AE) and any serious adverse events (SAE) • Change from baseline in CD4 cell count
Method of analysis	Plasma samples were collected for quantitative HIV-1 RNA analysis at Week 16. The analysis was performed using the time to loss of virological response (TLOVR) dataset. In the TLOVR dataset, participant responses at a specified threshold of HIV-1 RNA (<50 copies/mL) are determined by using the Food and Drug Administration's TLOVR algorithm. Using the TLOVR algorithm, participants are considered to have failed on therapy if they never achieved confirmed RNA levels below the threshold, if they had confirmed rebound of RNA above the threshold, if they made a non-permitted change in background regimen, or if they permanently discontinued investigational product for any reason. Data are reported per the Week 16 report. In later cuts of the data, the Week 16 values may have changed (because of the nature of the TLOVR algorithm). ITT-E Population included all randomized participants who received at least one dose of study medication
Subgroup analyses	NA

SPRING-2

Trial name	SPRING-2
NCT number	NCT01227824
Objective	To assess the efficacy and safety of DTG versus RAL, in combination with two widely recommended NRTI backbones, as first-line treatment for antiretroviral-naivee adults with HIV-1.
Publications – title, author, journal, year	• Once-daily dolutegravir versus raltegravir in antiretroviral-naivee adults with HIV-1 infection: 48-week results from the randomised, double-blind, non-inferiority SPRING-2 study, Raffi et al., Lancet, 2013 [18] • Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naivee adults with HIV-1 infection (SPRING-2 study): 96-week results from a randomised, double-blind, non-inferiority trial, Raffi et al., Lancet Infect Dis, 2013 [23] • A Trial Comparing GSK1349572 50mg Once Daily to Raltegravir 400mg Twice Daily (SPRING-2), ClinicalTrials.gov, accessed June 2018 [24] • Assessment report – Triumeq, European Medicines Agency, 26 June 2014 [16]

Study type and design	Randomised, multi-centre, double-blind, Phase 3 study. Enrolled patients were randomly assigned 1:1 via a central procedure using phone and web interface. The trial was double-blind and double-dummy until Week 96. No crossover was allowed. Patients, care providers and the sponsor were masked to treatment assignment until Week 48, after which the sponsor staff were unblinded.	
Follow-up time	96 weeks Median follow-up of 1267 days	
Population (inclusion and exclusion criteria)	**Inclusion criteria:** • Screening plasma HIV-1 RNA ≥1000 c/mL • Antiretroviral-naïve (≤10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection) • Ability to understand and sign a written informed consent form • Willingness to use approved methods of contraception to avoid pregnancy (women of child bearing potential only) • Age equal to or greater than 18 years	**Exclusion criteria:** • Women who are pregnant or breastfeeding • Active CDC Category C disease • Moderate to severe hepatic impairment • Anticipated need for HCV therapy during the study • Allergy or intolerance to the study drugs or their components or drugs of their class • Malignancy within the past 5 years • Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of screening • Treatment with radiation therapy, cytotoxic chemotherapeutic agents or any immunomodulator within 28 days of screening • Exposure to an agent with documented activity against HIV-1 in vitro or an experimental vaccine or drug within 28 days of first dose of study medication • Primary viral resistance in the screening result • Verified Grade 4 laboratory abnormality • ALT >5 xULN • ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin) • Estimated creatinine clearance <50 mL/min • Recent history (≤3 months) of upper or lower gastrointestinal bleed
Intervention	**Intervention**: DTG 50 mg once daily (N=411). At the investigators' discretion, patients received an NRTI backbone of coformulated TDF/FTC (DTG+TDF/FTC; N=242) or ABC/3TC (DTG+ABC/3TC; N=169). Patients received placebo tablets matching the alternative study drug. **Comparator**: RAL 400 mg twice daily (N=411). At the investigators' discretion, patients received an NRTI backbone of coformulated TDF/FTC (RAL+TDF/FTC); N=247) or ABC/3TC (RAL+ABC/3TC; N=164). Patients received placebo tablets	

<table>
<tr><td></td><td>matching the alternative study drug.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Characteristic</th><th>DTG (N=411)</th><th>RAL (N=411)</th></tr>
<tr><td>Age, years, median (range)</td><td>37 (18–68)</td><td>35 (18–75)</td></tr>
<tr><td>Female sex, n (%)</td><td>63 (15.3)</td><td>56 (13.6)</td></tr>
<tr><td>White race, n (%)</td><td>346 (84)</td><td>352 (86)</td></tr>
<tr><td>BMI, kg/m^2</td><td>NR</td><td>NR</td></tr>
<tr><td>Viral load, HIV RNA log_{10} c/mL, median (IQR)</td><td>4.52 (4.08–5.06)</td><td>4.58 (4.12–5.07)</td></tr>
<tr><td>CD4 cell count, cells/µL, median (IQR)</td><td>359 (276–470)</td><td>362 (267–469)</td></tr>
<tr><td colspan="3">CDC category, n (%)</td></tr>
<tr><td>A: Asymptomatic or lymphadenopathy or acute HIV</td><td>359 (87)</td><td>347 (84)</td></tr>
<tr><td>B: Symptomatic, not AIDS</td><td>43 (10)</td><td>55 (13)</td></tr>
<tr><td>C: AIDS</td><td>9 (2)</td><td>9 (2)</td></tr>
<tr><td colspan="3">HIV risk factors</td></tr>
<tr><td>Homosexual contact</td><td>NR</td><td>NR</td></tr>
<tr><td>Heterosexual contact</td><td>NR</td><td>NR</td></tr>
<tr><td>Injectable drug use</td><td>NR</td><td>NR</td></tr>
<tr><td>Transfusion</td><td>NR</td><td>NR</td></tr>
<tr><td>Haemophilia-associated injections</td><td>NR</td><td>NR</td></tr>
<tr><td>Occupational exposure</td><td>NR</td><td>NR</td></tr>
<tr><td>Vertical/perinatal transmission</td><td>NR</td><td>NR</td></tr>
<tr><td>Other</td><td>NR</td><td>NR</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Primary endpoint: Proportion of participants with HIV RNA of less than 50 c/mL at week 48, as determined with the use of the Snapshot algorithm from the FDA. Patients whose last HIV-1 RNA result was less than 50 c/mL in the analysis window (i.e. 48 weeks, plus or minus 6 weeks) were counted as responders. Patients whose HIV-1 RNA was not suppressed or who withdrew or did not have data at the analysis timepoint were counted as non-responders. The protocol allowed one switch in backbone NRTI for management of toxic effects; patients who switched NRTI after week 4 were regarded as non-responders according to the snapshot algorithm.
Secondary endpoints:
• Change from baseline in CD4 cell count
• Incidence and severity of adverse events</td></tr>
</table>

	• Changes in laboratory parameters • Genotypic or phenotypic evidence of resistance • DTG pharmacokinetics, pharmacokinetic and pharma codynamic relations • Health outcomes, assessed using the EQ-5D
Method of analysis	Efficacy and safety analyses were based on the intent-to-treat exposed or safety populations, which consisted of all patients randomly assigned to treatment groups who received at least one dose of study drug.
Subgroup analyses	Data for the backbone-specific subgroups are presented for the primary endpoint of virologic response. These analyses were prespecified; randomisation was stratified by backbone choice (and by baseline HIV RNA). The backbone was investigator-selected and therefore the analyses are subject to selection bias. In addition, the backbone was not blinded so the results may be subject to performance bias or detection bias. The study was not fully powered for subgroup analyses.

Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immune deficiency syndrome; ALT, alanine aminotransferase; ART, antirteroviral therapy; ATV, atazanavir; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CrCl, creatinine clearance; DTG, dolutegravir; EQ-5D, EuroQol 5-level instrument; FDA, Food and Drug Administration; FDC, fixed-dose combination; FTC, emtricitabine; HDL, high-density lipoprotein; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IP, investigational product; IQR, interquartile range; ITT-E, intention-to-treat exposed; LDL, low-density lipoprotein; NA, not applicable; NC, North Carolina; NR, not reported; RNA, ribonucleic acid; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; US, United States; USA, United States of America.

5 Clinical questions

5.1 Clinical efficacy outcomes

5.1.1 Presentation of relevant studies

This SLR found 9 publications of which 8 presented clinical efficacy data [2-4, 6-26] and one presented patient reported outcomes (PRO) [5]. Two of those 8 were phase II dose finding studies. SPRING-1 a phase II study evaluating 3 different dosis of DTG (5, 25 and 50mg) compared to 600mg of EFV in combination with either TDF/FTC or ABC/3TC, at the discretion of the investigator [21-22]. The other phase II study compared 75mg of biktarvy to 50mg of DTG in combination with coformultaed descovy (TAF/FTC) as a backbone [2-3]. These phase II studies will be excluded from the comparative anaylsis since difference in drug dosis used between phase II and phase III program makes comparision difficult.

The other 6 studies were all phase 3, randomised, active-controlled studies where no crossover was permitted, all presented relevant clinical efficacy data and all used a virologic response of <50 c/mL, according to the FDA snapshot algorithm [26], at Week 48 as their primary endpoint. The FLAMINGO study was open-label whilst the other 5 studies were double-blind. Only the SINGLE study, which compared DTG+ABC/3TC to EFV/TDF/FTC, presented data to Week 144 (open label post week 96), with FLAMINGO and SPRING-2 reporting data to 96 weeks and the remaining studies reporting to 48 weeks only.

Two studies compared B/F/TAF head-to-head to DTG-based regimens; GS-US-380-1489 [4] compared B/F/TAF to DTG/ABC/3TC and GS-US-380-1490 [7] compared B/F/TAF to DTG + FTC/TAF. The other 4 included studies compared DTG-based regimens to alternative regimens. In ARIA [9] and SINGLE [17-18] DTG was given in combination with ABC/3TC, whereas in FLAMINGO [12-13] and SPRING-2 [23-24] DTG was given in combination with either TDF/FTC or ABC/3TC, at the discretion of the investigator.

In terms of the patient characteristics GS-US-380-1489, GS-US-380-1490, FLAMINGO, SINGLE and SPRING-2 were similar; the populations were predominantly of white race and male sex with a mean or median age in the mid-30s. Whereas, in the ARIA study the population was completely female with a lower proportion of enrolled participants identifying as being of white race. Disease characteristics were similar for all 6 studies with respect to mean or median baseline viral load and CD4 cell counts. There was some variation in baseline CD4 cell counts with the B/F/TAF studies enrolling patients with a higher average baseline CD4 cell count than the other 4 studies, likely reflective of changes in clinical practice since the phase 3 studies for DTG began. Guidelines now recommend starting treatment irrespective of the CD4 cell count.

Since head-to-head studies between bictegravir and dolutegravir do exist and a cross-study comparison is not appreciated, only those providing direct evidence (GS-US-380-1489 and GS-US-380-1490) [4,7] in naïve population are included in the comparative analyses. Additionally only study GS-US-380-1489 investigated PROs in a double-blinded manner and data was published separately [5].

5.1.2 Results per study

GS-US-380-1489

Trial name: GS-US-380-1489 [4,6]											
NCT number: NCT02607930											
Outcome	Timepoint	Study arm	N	n (%)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
					Difference	95% CI	P value	Hazard/Odds/ Risk ratio	95% CI	P value	
Virologic response (HIV RNA <50 c/mL [FDA Snapshot analysis])	Week 48	B/F/TAF	314	290 (92.4)	-0.6	-4.8 ; 3.6	0.78	RR=0.99	0.95 ; 1.04	0.75	FDA snapshot algorithm, difference (95.002%) based on Mantel-Haenszel proportions adjusted by baseline HIV-1 RNA (≤100,000 vs >100,000 c/mL) and region (USA vs ex-USA). P value based on the Cochran-Mantel-Haenszel test, stratified by baseline HIV-
	Week 48	DTG/ABC/3TC	315	293 (93.0)							

											1 RNA (≤100,000 vs >100,000 c/mL) and region (USA vs ex-USA). Relative difference based on non-stratified method
Virologic failure (HIV RNA >50 c/ml), per protocol	Week 48	B/F/TAF	289	2 (0.7)	-1.36	-3.24 ; 0.53	0.16	RR=0.34	0.069 ; 1.66	0.18	Absolute and relative difference based on non-stratified method
	Week 48	DTG/ABC/3TC	293	6 (2.0)							
Resistance	Week 48	B/F/TAF	1	0 (0)	0.00	-65.5 ; 65.5	1.00	NA	NA	NA	Resistance analysis of the five participants with protocol-defined criteria for resistance testing.
	Week 48	DTG/ABC/3TC	4	0 (0)							

Abbreviations: 3TC, lamivudine; ABC, abacavir; AIDS, acquired immune deficiency syndrome; ATV, atazanavir; BIC, bictegravir; CI, confidence interval; DTG, dolutegravir; DRV, darunavir; FDA, Food and Drug Administration; FTC, emtricitabine; HIV, human immunodeficiency virus; NCT, National Clinical Trial; NR, not reported; NRTI, nucleoside reverse transcriptase inhibtor; PI, protease inhibitor; RNA, ribonucleic acid; TAF, tenofovir alafenamide; USA, United States of America.

Statistical method: The calculations of absolute and relative differences for binary endpoints were based on the number of patients and the observed number of events per treatment group. Absolute differences were always calculated as B/F/TAF minus comparator whereas relative differences were calculated as B/F/TAF divided by comparator, i.e. the relative risk was used as relative effect measure. Confidence intervals and p-values for the absolute and relative differences were calculated using the normal approximation without a continuity correction.

GS-US-380-1490

Trial name: GS-US-380-1490 [7-8]											
NCT number: NCT02607956											
Outcome	Timepoint	Study arm	N	n (%)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
					Difference	95% CI	P value	Hazard/Odds/ Risk ratio	95% CI	P value	
Virologic response (HIV RNA <50 c/mL [FDA Snapshot analysis])	Week 48	B/F/TAF	320	286 (89.4)	-3.5	-7.9 ; 1.0	0.12	RR=0.96	0.92 ; 1.01	0.11	FDA snapshot algorithm, difference based on Mantel-Haenszel proportions adjusted by baseline HIV-1 RNA (≤100,000 vs >100,000 c/mL) and region (USA vs ex-USA). P value based on the Cochran-Mantel-Haenszel test, stratified by baseline HIV-1 RNA (≤100,000 vs >100,000 c/mL) and region (USA vs ex-USA). Relative difference based on non-stratified method
	Week 48	DTG+TAF/FTC	325	302 (92.9)							
Virologic failure (HIV RNA >50 c/ml), per protocol	Week 48	B/F/TAF	282	3 (1.1)	0.73	-0.64 ; 2.09	0.30	RR=3.16	0.33 ; 30.2	0.32	Per protocol. Absolute and relative difference based on non-stratified method
		DTG+TAF/FTC	297	1 (0.3)							
Resistance	Week 48	B/F/TAF	7	0 (0)	0.00	-27.8 ; 27.8	1.00	NA	NA	NA	Resistance analysis of the 12 participants with protocol-defined criteria for resistance testing.
		DTG+TAF/FTC	5	0 (0)							

Abbreviations: 3TC, lamivudine; AIDS, acquired immune deficiency syndrome; CI, confidence interval; DTG, dolutegravir; FDA, Food and Drug Administration; FTC, emtricitabine; HIV, human immunodeficiency virus; NCT, National Clinical Trial; NR, not reported; RNA, ribonucleic acid; TAF, tenofovir alafenamide; USA, United States of America.

Statistical method: The calculations of absolute and relative differences for binary endpoints were based on the number of patients and the observed number of events per treatment group. Absolute differences were always calculated as B/F/TAF minus comparator whereas relative differences were calculated as B/F/TAF divided by comparator, i.e. the relative risk was used as relative effect measure. Confidence intervals and p-values for the absolute and relative differences were calculated using the normal approximation without a continuity correction.

5.1.3 Efficacy comparative analyses

This SLR found two studies (GS-US-380-1489 and GS-US-380-1490) which provide relevant direct head-to-head evidence in naïve patient population. Since head-to-head studies between bictegravir and dolutegravir do exist and a cross-study comparison is not appreciated, only those providing direct evidence (GS-US-380-1489, GS-US-380-1490) are included in the comparative analyses.

GS-US-380-1489 [4,6]

In this double blinded, randomized, active-controlled head to-head comparison study 611 naïve patients were randomly assigned to receive B/F/TAF (n=316) or DTG/ABC/3TC (n=315), of whom 314 and 315 patients, respectively, received at least one dose of study drug.

The primary endpoint of the study was the proportion of patients with plasma HIV-1 RNA <50 copies/mL at weel 48, with a non-inferiority margin of 12% based on the FDA snapshot algorithm [26]. The efficacy of B/F/TAF was high, and non-inferior to that of DTG/ABC/3TC, with no differences between treatment groups and/or in efficacy among subgroups. Viral suppression by per-protocol analysis was 99% in both treatment groups, more specifically the proportion of participants with HIV-1 RNA less than 50 copies per mL was 99·3% [n=287 of 289] in the B/F/TAF group vs 98·6% [n=289 of 293] in the DTG/ABC/3TC group; difference 0·7%, 95·002% CI –1·4 to 2·8; p=0·43.

There were 19 discontinuations in the B/F/TAF group (1 pregnancy, 3 investigator discretion, 1 non-compliance, 1 protocol violation, 4 patients decision, 9 lost to follow up) and 16 in the DTG/ABC/3TC group (4 AE, 1 non-compliance, 5 patients decision, 6 lost to follow up) respectively. None of those discontinuations was due to lack of efficacy and there were no treatment-emergent resistance developed to the components of either regimen.

GS-US-380-1490 [7-8]

In this double blinded, randomized, active-controlled head to-head comparison study 657 naive patients were randomly assigned to receive B/F/TAF (n=327) or DTG + FTC/TAF (n=330), of whom 320 and 325 patients, respectively, received at least one dose of study drug.

The BIC regimen was non-inferior to the DTG regimen for the primary outcome. A treatment response difference that was not significant. Rates of virological failure were similar and low (<1%) in both groups. The numerically lower response rate for the BIC group was primarily driven by a higher percentage of participants with early discontinuations than in the DTG group (11 vs 3) due to other reasons (eg, lost to follow-up or withdrawn consent) with their final HIV-1 RNA greater than 50 copies per mL. There were 6 participants who received the BIC regimen but never returned for virological testing after their baseline visit. Excluding these study participants in a post-hoc analysis as well as an additional participant who did not provide a post-baseline HIV-1 RNA due to death at day 28, the difference between the two groups was reduced (91·4% vs 92·9%; difference –1·5%, 95% CI −5·8 to 2·8, p=0·48).

Viral suppression by per-protocol analysis was 99% in both treatment groups. In fact the proportion of participants with HIV-1 RNA of less than 50 copies per mL for the per-protocol analysis was 279 (99%) of 282 participants in the BIC group and 296 (99·7%) of 297 in the DTG group (difference –0·7%, 95% CI –2·6 to 1·2, p=0·33).

There were 28 discontinuations in the bictegravir regimen (2 pregnancy, 8 lost to follow up, 4 investigator discretion, 2 protocol violation, 7 patients decision, 5 AE) and 20 in the dolutegravir regimen (1 AE, 2 non-compliance, 7 patients decision, 5 lost to follow up, 2 died, 2 pregnancy, 1 protocol violation). None of

these discontinuations was due to lack of efficacy, and no emergent drug resistance was found in the small number of study participants who met criteria for virological failure and were tested for genotypic and phenotypic resistance.

GS-US-380-1489 and GS-US-380-1490: Efficacy pooled data analysis

	B/F/TAF 380-1489-1490 (N=634)	DTG/ABC/3TC 380-1489 (N=315)	DTG+FTC/TAF 380-1490 (N=325)
HIV RNA<50copies/ml	576 (90.9%)	293 (93.0%)	302 (92.9%)
B/F/TAF vs. DTG/ABC/3TC			
Difference in percentages (95%CI)	-2.1% (-5.9% to 1.6%)		
p-value	0.26		
B/F/TAF vs. DTG+FTC/TAF			
Difference in percentages (95%CI)	-1.9% (-5.6% to 1.8%)		
p-value	0.32		
HIV RNA >= 50 copies/ml	17 (2.7%)	8 (2.5%)	4 (1.2%)
HIV RNA >= 50 copies/ml in week 48 window	5 (0.8%)	6 (1.9%)	1 (0.3%)
Discontinued study drug due to lack of efficacy	0	0	0
Discontinued study drug due to other Reasons and Last Available HIV RNA >= 50 copies/ml	12 (1.9%)	2 (0.6%)	3 (0.9%)
No Virologic data in Week 48 window	41 (6.5%)	14 (4.4%)	19 (5.8%)
Discontinued study drug due to AE/Death	3 (0.5%)	4 (1.3%)	3 (0.9%)
Discontinued study drug due to other Reasons and Last Available HIV RNA < 50 copies/ml	27 (4.3%)	9 (2.9%)	14 (4.3%)
Missing data during window but on study drug	11 (1.7%)	1 (0.3%)	2 (0.6%)

- P-value for the superiority test comparing percentages of subjects with HIV RNA < 50 copies/ml between treatment groups was from the CMH test stratified by baseline HIV RNA startum (<=100000 vs. > 100000 copies/ml)
- The difference in percentages of subjects with HIV RNA < 50 copies/ml between treatment groups and its 95% CI was calculated based on MH proportion adjusted by baselines HIV RNA startum (<=100000 vs. > 100000 copies/ml)

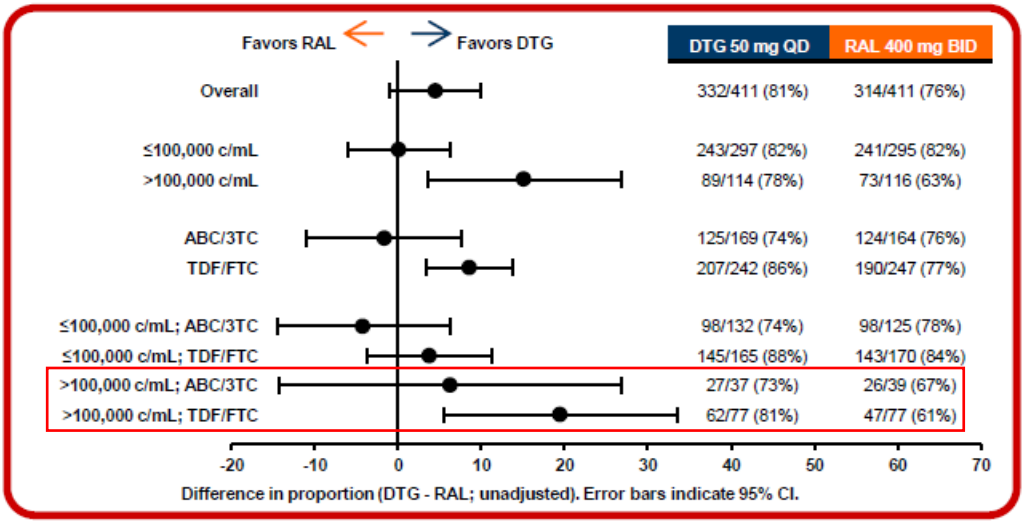
The table above shows pooling of the BIC/FTC/TAF data from studies GS-US-380-1489 and GS-US-380-1490. As comparator arms in the two studies are different, ie. ABC/3TC and FTC/TAF, pooling of the data from comparator arms is not justified. There are no data available directly comparing regimens with an identical third agent combined with either ABC/3TC or FTC/TAF in a randomized, controlled clinical study on treatment-naïve subjects. However, for ABC/3TC and FTC/TDF such data exist, from study A5202 [27] and from SPRING-2 [28] study, the latter in combination with dolutegravir, suggesting differences in clinical efficacy between the two NRTI backbones, as described below.

The AIDS Clinical Trials Group Study A5202 [27] was a phase 3B, randomized, partially blinded study comparing four antiretroviral regimens for the initial treatment of HIV-1 infection. A multicenter, 96-week, non-inferiority study, which enrolled 1857 treatment-naïve subjects to lamivudine/abacavir (3TC/ABC) or emtricitabine/tenofovir-DF (FTC/TDF) with atazanavir/ritonavir (ATV+RTV) or efavirenz (EFV). The study was double-blinded with regard to the NRTIs and randomization was stratified according to the screening HIV-1 RNA level obtained before study entry (≥100,000 vs. <100,000 copies/milliliter).

The primary hypotheses of the study were that for each of the regimens that included ritonavir-boosted ATV and EFV, ABC/3TC was equivalent to FTC/TDF and for each NRTI regimen, ritonavir-boosted ATV was

equivalent to EFV. Regimens were considered equivalent if the two-sided 95% confidence interval for the hazard ratio was between 0.71 and 1.40. The primary efficacy end point was the time from randomization to virologic failure (defined as a confirmed HIV-1 RNA level ≥1000 copies/milliliter at or after 16 weeks and before 24 weeks, or ≥200 copies per milliliter at or after 24 weeks).
The study showed that ABC/3TC backbone had a significantly shorter time to virologic failure than did the FTC/TDF backbone (hazard ratio, 2.33; 99.95% confidence interval [CI], 1.01 to 5.36; 95% CI, 1.46 to 3.72; P<0.001). Those with high screening viral load (VL) (≥ 100,000 c/mL) had a shorter time to virologic failure when assigned ABC/3TC vs. FTC/TDF. The estimated probability of remaining free of virologic failure beyond 48 weeks was 0.84 (95% CI, 0.79 to 0.88) in the 3TC/ABC group and 0.93 (95% CI, 0.90 to 0.96) in the FTC/TDF group. Virologic failures were less frequent in the FTC/TDF group according to the protocol-defined criteria for both early and late virologic failure. In the low HIV RNA stratum, shorter times to virologic failure were not observed (HR = 1.26 and HR = 1.24 for time to virologic failure with ATV+RTV and EFV, respectively).
Higher efficacy of FTC/TDF compared to ABC/3TC was also seen in SPRING-2 [28] where high VL favored DTG in combination with FTC/TDF (86%) compared to DTG+ABC/3TC (74%) in treatment-naïve subjects. Although the study was not designed to evaluate the backbone, an absolute efficacy difference of 12% was seen in favor of FTC/TDF over ABC/3TC (Figure 4).

Figure 4: Raffi F. et al., IAS 2013, Kuala Lumpur. Poster #TULBPE17



With no available data comparing FTC/TAF with 3TC/ABC when combined with an identical third agent, it is not possible to conclude that as FTC/TAF would show similar clinical efficacy like FTC/TDF in overperforming 3TC/ABC, as suggested by data from A5202 and SPRING-2 studies [27-28]. However FTC/TAF showed similar efficacy to FTC/TDF, both combined with cobicistat/elvitegravir, up to 144 weeks in studies GS-US-292-0104 and GS-US-292-0111 on treatment-naïve subjects [29]. It can therefore be suggested that FTC/TAF would not be inferior to FTC/TDF and would then also show better clinical efficacy than ABC/3TC when combined with the same third agent. Therefore pooling of the data from two different comparator arms is not appropriate.

<u>Concluding on efficacy (GS-US-380-1489 and GS-US-380-1490) [4,6,7,8]:</u>

These studies showed that BIC based regimen was non-inferior to DTG based treatment in naïve treatmentpatients. No participants discontinued treatment due to lack of efficacy and drug resistance was not detected neither to bictegravir nor to the backbone. In randomized trials, emergent DTG resistance in

previously untreated patients has not been reported; only two case studies have been reported with combination therapy in clinical practice [30]. The lack of emergent drug resistance in our studies is consistent with the potency of BIC against wild type and integrase-resistant HIV variants and its high *in-vitro* barrier to resistance [31-34] and suggests that treatment with the BIC regimen will also be associated with a low risk of drug resistance in the long term.

5.2 Safety outcomes

5.2.1 Presentation of relevant studies

Two studies compared B/F/TAF head-to-head to DTG-based regimens; GS-US-380-1489 [4, 6] compared B/F/TAF to DTG/ABC/3TC and GS-US-380-1490 [7-8] compared B/F/TAF to DTG + F/TAF. Since head-to-head studies between bictegravir and dolutegravir do exist and a cross-study comparison is not appreciated, only those providing direct evidence (GS-US-380-1489 and GS-US-380-1490) in naïve population are included in the comparative analyses.

In terms of the patient characteristics, GS-US-380-1489 and GS-US-380-1490 were similar; the populations were predominantly of white race and male sex with a mean or median age in the mid-30s. Disease characteristics were similar with respect to mean or median baseline viral load and CD4 cell counts.

5.2.2 Results per study

GS-US-380-1489

Trial name: GS-US-380-1489 [4, 6]											
NCT number: NCT02607930											
Outcome	Timepoint	Study arm	N	n (%)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
					Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
SAE	Week 48	B/F/TAF	314	19 (6.1)	-1.9	- 5.87 ; 2.10	0.35	RR=0.76	0.43 ; 1.36	0.36	Coded with the Medical Dictionary for Regulatory Activities (version 19.1). Relatedness of adverse events to study drugs was indicated by the investigator in a binary manner (yes or no).
	Week 48	DTG/ABC/3TC	315	25 (7.9)							
AE (Grade 3 or 4)	Week 48	B/F/TAF	314	23 (7.3)	-0.3	-4.40 ; 3.82	0.89	RR=0.96	0.55 ; 1.67	0.89	
	Week 48	DTG/ABC/3TC	315	24 (7.6)							
Serious TRAEs	Week 48	B/F/TAF	314	1 (0.3)	0	-0.88 ; 0.88	1.00	RR=1.00	0.06 ; 16.0	1.00	
	Week 48	DTG/ABC/3TC	315	1 (0.3)							
Discontinuation due to adverse events	Week 48	B/F/TAF	314	0 (0)	-1.3	-2.65 ; 0.11	0.07	RR=0.11	0.01; 2.06	0.14	
	Week 48	DTG/ABC/3TC	315	*4 (1.3)							
Any TRAE	Week 48	B/F/TAF	314	82 (26.1)	-14.2	-21.5 ; -6.93	<0.001	RR=0.65	0.51 ; 0.81	<0.001	

	Week 48	DTG/ABC/3TC	315	127 (40.3)							
AE occurring with ≥5% incidence in either group											
Outcome	Timepoint	Study arm	N	n (%)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	Description of methods used for estimation
Nausea	Week 48	B/F/TAF	314	32 (10.2)	-12.7	-18.4 ; -6.95	<0.001	RR=0.45	0.30 ; 0.66	<0.001	Coded with the Medical Dictionary for Regulatory Activities (version 19.1). Relatedness of adverse events to study drugs was indicated by the investigator in a binary manner (yes or no).
	Week 48	DTG/ABC/3TC	315	72 (22.9)							
Headache	Week 48	B/F/TAF	314	36 (11.5)	-2.2	-7.36 ; 2.99	0.41	RR=0.84	0.56 ; 1.27	0.41	
	Week 48	DTG/ABC/3TC	315	43 (13.7)							
Diarrhoea	Week 48	B/F/TAF	314	40 (12.7)	-0.28	-5.51 ; 4.96	0.92	RR=0.98	0.65 ; 1.47	0.92	
	Week 48	DTG/ABC/3TC	315	41 (13.0)							
Fanconi syndrome	Week 48	B/F/TAF	314	0 (0)	0.00	-0.62 ; 0.62	1.00	NA	NA	NA	
	Week 48	DTG/ABC/3TC	315	0 (0)							
Insomnia	Week 48	B/F/TAF	314	14(4.5)	-1.9	-5.42 ; 1.64	0.29	RR=0.70	0.36 ; 1.37	0.30	
	Week 48	DTG/ABC/3TC	315	20 (6.3)							
Assessment of other safety outcomes in relation to the SPC											
Outcome	Timepoint	Study arm	N	Result	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	Description of methods used for estimation
Change from baseline bone mineral density, hip, mean % (SD)	Week 48	B/F/TAF	314	-0.78% (2.22)	Least-squares mean difference 0.238%	-0.151–0.626	0.23	NA	NA	NA	Dexa scan at BL, week 24 and 48 **ANOVA
	Week 48	DTG/ABC/3TC	315	-1.02% (2.31)							
Change from baseline bone	Week 48	B/F/TAF	314	-0.83% (3.19)	Least-squares	-0.766–	0.39	NA	NA	NA	Dexa scan at BL, week 24 and 48

mineral density, lumbar spine, mean % (SD)	Week 48	DTG/ABC/3TC	315	-0.60% (3.10)	mean difference -0.235%	0.297					**ANOVA
eGFR	Week 48	B/F/TAF	314	-10.5 (19.5– 0.2)	NA	NA	0.20	NA	NA	NA	eGFR calculated with the Cockcroft-Gault formula and p values are from two-sided Wilcoxon rank-sum tests.
	Week 48	DTG/ABC/3TC	315	-10.8 (-21.6– -2.4)							
Ischaemic heart disease (IHD)	Week 48	See next table									

*****Chronic pancreatitis and steatorrhoea (n=1), nausea and generalized rash (n=1), depression (n=1), and thrombocytopenia (n=1).

******Difference in percentage changes from baseline between treatment groups and 95% Cis and P values were constructed with ANOVA including treatment groups as fixed effect in the model

Abbreviations: 3TC, lamivudine; ABC, abacavir; AE, adverse event; AIDS, acquired immune deficiency syndrome; CI, confidence interval; DTG, dolutegravir; eGFR, estimated glomerular filtration rate; FTC, emtricitabine; HIV, human immunodeficiency virus; IHD, ischaemic heart disease; NCT, National Clinical Trial; NR, not reported; SD, standard deviation; SPC, Summary of Product Characteristics; TAF, tenofovir alafenamide; TRAE, treatment-related adverse event.

Statistical method: The calculations of absolute and relative differences for binary endpoints were based on the number of patients and the observed number of events per treatment group. Absolute differences were always calculated as B/F/TAF minus comparator whereas relative differences were calculated as B/F/TAF divided by comparator, i.e. the relative risk was used as relative effect measure. Confidence intervals and p-values for the absolute and relative differences were calculated using the normal approximation without a continuity correction.

GS-US-380-1489: Changes from Baseline in Fasting Lipids Laboratory Parameters at Week 48:

Fasting Lipids Assessment	B/F/TAF (n=314)		DTG/ABC/3TC (n=315)		*P value
	n	Median (Q1, Q3)	n	Median (Q1, Q3)	
Total cholesterol (mg/dL)					
Baseline	305	159 (133, 181)	305	162 (138, 186)	
Changes at week 48	282	13 (-3, 31)	283	11 (-6, 28)	0.11
Direct LDL (mg/dL)					
Baseline	305	101 (83, 123)	305	101 (84, 126)	
Changes at week 48	282	7 (-5, 21)	283	4 (-9, 18)	0.069
Triglycerides (mg/dL)					
Baseline	305	93 (67, 132)	305	96 (66, 138)	
Changes at week 48	282	9 (-20, 37)	283	3 (-25, 27)	0.098
HDL (mg/dL)					
Baseline	305	42 (34, 51)	305	42 (35, 51)	
Changes at week 48	282	5 (-2, 11)	283	5 (0, 11)	0.12
Total cholesrol to HDL ratio					
Baseline	305	3.7 (3.0, 4.7)	305	3.7 (3.0, 4.6)	
Changes at week 48	282	-0.1 (-0.5, 0.4)	283	-0.2 (-0.7, 0.2)	0.013

*P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.

Trial name: GS-US-380-1490 [7, 8]											
NCT number: NCT02607956											
Outcome	Timepoint	Study arm	N	n (%)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
					Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
SAE	Week 48	B/F/TAF	320	NR	NR	NR	NR	NR	NR	NR	Coded with the Medical Dictionary for Regulatory Activities (version 19.1). Relatedness of adverse events to study drugs was indicated by the investigator in a binary manner (yes or no).
	Week 48	DTG+TAF/FTC	325	NR							
AE (Grade 3 or 4)	Week 48	B/F/TAF	320	NR	NR	NR	NR	NR	NR	NR	
	Week 48	DTG+TAF/FTC	325	NR							
Serious TRAEs	Week 48	B/F/TAF	320	NR	NR	NR	NR	NR	NR	NR	
	Week 48	DTG+TAF/FTC	325	NR							
Discontinuation due to adverse events	Week 48	B/F/TAF	320	*5 (1.6)	1.25	-0.23 ; 2.74	0.098	RR=5.08	0.60 ; 43.23	0.14	
	Week 48	DTG+TAF/FTC	325	1 (0.3)							
Any TRAEs	Week 48	B/F/TAF	320	57 (17.8)	-7.73	-14.05 ; -1.40	0.017	RR=0.70	0.52 ; 0.94	0.019	
	Week 48	DTG+TAF/FTC	325	83 (25.5)							
AE occurring with ≥5% incidence in either group											
Outcome	Timepoint	Study arm	N	n (%)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	Description of methods used for estimation
Nausea	Week 48	B/F/TAF	320	25 (7.8)	-1.1	-5.38 ; 3.16	0.61	RR=0.88	0.52 ; 1.46	0.61	Coded with the Medical Dictionary for Regulatory Activities (version 19.1).
	Week 48	DTG+TAF/FTC	325	29							

				(8.9)							Relatedness of adverse events to study drugs was indicated by the investigator in a binary manner (yes or no).
Headache	Week 48	B/F/TAF	320	40 (12.5)	0.19	-4.90 ; 5.28	0.94	RR=1.02	0.67 ; 1.53	0.94	
	Week 48	DTG+TAF/FTC	325	40 (12.3)							
Diarrhoea	Week 48	B/F/TAF	320	37 (11.6)	-0.44	-5.41 ; 4.54	0.86	RR=0.96	0.63 ; 1.47	0.86	
	Week 48	DTG+TAF/FTC	325	39 (12.0)							
Fanconi syndrome	Week 48	B/F/TAF	320	NR	NA	NA	NA	NA	NA	NA	
	Week 48	DTG+TAF/FTC	325	NR							
Insomnia	Week 48	B/F/TAF	320	16 (5.0)	0.69	-2.56 ; 3.94	0.68	1.16	0.58 ; 2.34	0.68	
	Week 48	DTG+TAF/FTC	325	14 (4.3)							
Assessment of other safety outcomes in relation to the SPC											
Change from baseline bone mineral density, hip	Week 48	B/F/TAF	320	ND	NA	NA	NA	NA	NA	NA	ND
	Week 48	DTG+TAF/FTC	325	ND							
Change from baseline bone mineral density, lumbar spine	Week 48	B/F/TAF	320	ND	NA	NA	NA	NA	NA	NA	ND
	Week 48	DTG+TAF/FTC	325	ND							
Change from baseline eGFR, median (IQR)	Week 48	B/F/TAF	320	-7.3 (-17.3–0.1)	NA	NA	0.0181	NR	NR	NR	eGFR calculated with the Cockcroft-Gault formula and p values are from two-sided Wilcoxon rank-sum tests.
	Week 48	DTG+TAF/FTC	325	-10.8 (-20.0–-1.7)							

Ischaemic heart disease (IHD)	See next table

*cardiac arrest [n=1], paranoia [n=1], chest pain [n=1], abdominal distension [n=1], and sleep disorder, dyspepsia, tension headache, depressed mood, and insomnia [n=1]
Abbreviations: AE, adverse event; AIDS, acquired immune deficiency syndrome; BIC, bictegravir; CI, confidence interval; DTG, dolutegravir; eGFR, estimated glomerular filtration rate; FTC, emtricitabine; HIV, human immunodeficiency virus; IHD, ischaemic heart disease; IQR, interquartile range; NCT, National Clinical Trial; NR, not reported; SPC, Summary of Product Characteristics; TAF, tenofovir alafenamide; TRAE, treatment-related adverse event.

Statistical method: The calculations of absolute and relative differences for binary endpoints were based on the number of patients and the observed number of events per treatment group. Absolute differences were always calculated as B/F/TAF minus comparator whereas relative differences were calculated as B/F/TAF divided by comparator, i.e. the relative risk was used as relative effect measure. Confidence intervals and p-values for the absolute and relative differences were calculated using the normal approximation without a continuity correction.

GS-US-380-1490: Changes from Baseline in Fasting Lipids Laboratory Parameters at Week 48:

	B/F/TAF (n=320)		DTG/ABC/3TC (n=325)		
Fasting Lipids Assessment	n	Median (Q1, Q3)	n	Median (Q1, Q3)	*P value
Total cholesterol (mg/dL)					
Baseline	314	156 (136, 182)	321	161 (138, 186)	0.30
Changes at week 48	278	12 (-3, 30)	295	15 (1, 31)	0.14
Direct LDL (mg/dL)					
Baseline	314	98 (81, 120)	321	99 (82, 124)	0.46
Changes at week 48	278	9 (-6, 25)	295	12(-3, 25)	0.21
Triglycerides (mg/dL)					
Baseline	314	97 (72, 134)	321	95 (70, 131)	0.40
Changes at week 48	278	3 (-21, 31)	295	7 (-14, 35)	0.23
HDL (mg/dL)					
Baseline	314	43 (35, 52)	321	43 (35, 52)	0.97
Changes at week 48	278	5 (0, 11)	295	5 (-1, 12)	0.68
Total cholesrol to HDL ratio					
Baseline	314	3.7 (3.0, 4.5)	321	3.7 (3.0, 4.5)	0.85
Changes at week 48	278	-0.1 (-0.5, 0.3)	295	-0.1 (-0.6, 0.4)	0.7

*P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.

5.2.3 Safety comparative analyses

The treatment regimens were well tolerated and with most adverse events reported as mild or moderate in severity.

In study GS-US-380-1489 [4] there were less participants in the B/F/TAF group with drug-related adverse events than did those in the DTG/ABC/3TC group (82 [26%] vs 127 [40%] participants, respectively). The difference between groups was driven mainly by drug-related nausea (5% [n=17] vs 17% [n=55]; p<0·0001). Also in study GS-US-380-1490 [7] participants in the bictegravir group had a lower incidence of drug-related adverse events than did those in the dolutegravir group (57 [18%] of 320 vs 83 [26%] of 325, p=0·022). In this study no drug-related adverse events of grade 2 or higher were reported in >2% of participants in either group.

Discontinuations due to adverse effects ascribed to study medications occurred rarely in both groups and none occurred in more than one participant, indicating a lack of a pattern to these events. In study GS-US-380-1489 four (1%) participants in the DTG/3TC/ABC group discontinued due to an AE; nausea and generalized rash (n=1), thrombocytopenia (n=1), chronic pancreatitis and steatorrhoea (n=1), and depression (n=1), all of which were deemed by the investigator to be related to study drugs. While in study GS-US-380-1490 AEs led to five participants discontinuing study medication in the bicgetgravir group; (cardiac arrest [n=1], paranoia [n=1], chest pain [n=1], abdominal distension [n=1], and sleep disorder, dyspepsia, tension headache, depressed mood, and insomnia [n=1]); all except for the events of cardiac arrest and paranoia were considered by the investigators to be related to study drugs.

Bone safety

B/F/TAF demonstrated a bone safety profile comparable with that of DTG/ABC/3TC, a regimen that is not associated with bone toxicity. In ART-naïve subjects (GS-US-380-1489), mean (SD) percentage changes from baseline in hip and spine BMD were comparable between the B/F/TAF and DTG/ABC/3TC treatment groups.

Renal safety

B/F/TAF demonstrated a renal safety profile comparable with that of DTG/ABC/3TC, a regimen that is not associated with renal toxicity. No subject had proximal tubulopathy (including Fanconi Syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE. Across the Phase 3 studies, changes from baseline in serum creatinine and $eGFR_{CG}$ were consistent with the known inhibitory effect of BIC or DTG on renal tubular secretion via OCT2 and/or MATE1. These changes were not clinically relevant and are not reflective of changes in actual glomerular filtration rate. Changes in serum creatinine and $eGFR_{CG}$ were observed by Week 4 and remained stable thereafter through Week 48.

Hepatic safety:

No clinically relevant median changes from baseline were observed in alkaline phosphatase, ALT, AST, or total bilirubin for the B/F/TAF or comparator group in any of the Phase 3 studies.

Graded total bilirubin increases occurred in a higher percentage of subjects treated with B/F/TAF than the comparator in Studies GS-US-380-1489, GS-US-380-1490, however, the increases were primarily Grade 1 or Grade 2 in severity and were not associated with hepatic AEs or other liver-related laboratory abnormalities.

Laboratory findings

B/F/TAF demonstrated a clinical laboratory safety profile similar to that of comparator regimens. There were no clinically relevant changes from baseline in the B/F/TAF group or differences between the B/F/TAF and comparator groups in median values for hematology or clinical chemistry parameters (including metabolic parameters), and median values were generally within reference ranges.

In study GS-US-380-1489 changes from baseline in fasting lipid measures were generally similar between groups at week 48. There was a small (–0·1), statistically significant (p=0·0130) difference in the total cholesterol to HDL ratio between groups. However, the proportion of patients initiating lipid-modifying drugs during the study did not differ significantly between the B/F/TAF group and the DTG/ABC/3TC group (2·5% [n=8 of 314] vs 2·9% [n=9 of 315]; p=1·00). Also in study GS-US-380-1490 changes from baseline in fasting lipid parameters were similar between groups at week 48. There were no differences between groups in initiation of lipid-modifying agents during the study (five [2%] of 320 in the bictegravir group vs six [2%] of 325 in the doltegravir group; p=1·00).

Concluding on safety (GS-US-380-1489; GS-US-380-1490) [4, 7]:

Based on safety data provided it can be concluded that no new risks or safety issues have been identified for the B/F/TAF. Furthermore, significantly less treatment related AEs has been reported to bictegravir compared to dolutegravir. Our results suggest that the fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide is an efficacious and well tolerated regimen for the treatment of HIV-1 infected individuals.

Long-term tolerability of a drug is important since HIV is a chronic infection. Pooling the data to perform a meta-anaylsis can not be justified since we belive that a difference between the two backbone (FTC/TAF, ABC/3TC) torleratbity profil do exist. Data from the SINGLE trial showed that 71% of subjects maintained viral suppression below 50 copies/ml at 144 weeks data window [47]. Whereas, in the 104/111 trial and at 144 weeks 84% of subjects on Genvoya maintained viral suppression blow 50 copies/ml [45]. A cross study comparision is not appreciated but one could speculate that the difference in efficacy could be due to different tolerability profiles of the regimens. Therefore pooling of the data from two different comparator arms is not appropriate.

5.3 Quality of life outcomes

5.3.1 Presentation of relevant studies

Patient wellbeing (e.g., PROs) has become an important differentiator between regimens since the efficacy of triple-therapy ARV regimens remain consistently high. Only 3 of the included studies presented the quality-of-life outcomes of interest to the Danish Medicines Council (DMC) GS-US-380-1489; FLAMINGO and SINGLE. However, neither FLAMINGO nor SINGLE provided direct head-to-head comparison between B/F/TAF and dolutegravir plus 2 NRTIs and since cross-study comparison is not appreciated, only those providing direct evidence (GS-US-380-1489) in naïve population are included in the comparative analyses.

GS-US-380-1489 in naïve patients represent the first prospective randomized double-blind study to compare patient-reported symptoms among HIV-1 adults randomized to receive B/F/TAF versus DTG/ABC/3TC. Study GS-US-380-1489 PROs results were published separtley in a peer-reviewed journal [5]. The trial (GS-US-380-1489) was double blind, active controlled and compared biktarvy to triumeq head to head [4].

5.3.1 Methods

For study GS-US-380-1489, post-baseline study visits occurred at weeks 4, 8, 12, 24, 36, and 48, with PRO measures administered at baseline and weeks 4, 12, and 48. Participants and investigators were masked to treatment allocation. In terms of the patient characteristics, GS-US-380-1489; the populations were predominantly of white race and male sex with a mean or median age in the mid-30s. Disease characteristics were also similar for both groups with respect to mean or median baseline viral load and CD4 cell counts.

The dependent variable in this study was the HIV-Symptom Index (HIV-SI). The HIV-SI is a validated PRO instrument that assesses the burden of 20 common symptoms associated with HIV treatment or disease [48]. Respondents are asked about their experience with each of 20 symptoms during the past 4 weeks using a 5-point, Likert-type scale. Response options and scores are as follows: (0) “I don’t have this symptom;” (1) “I have this symptom and it doesn’t bother me;” (2) “I have this symptom and it bothers me a little;” (3) “I have this symptom and it bothers me;” (4) “I have this symptom and it bothers me a lot.”

Consistent with Edelman and colleagues [49], symptoms were dichotomized into not bothersome (scores of 0 or 1) or bothersome (scores of 2, 3 and 4). The overall bothersome symptom count at baseline was generated by counting the number of individual symptoms scored as bothersome and used as a covariate in regression analyses and longitudinal modeling.

Other PRO instruments used to describe health related quality of life (HRQL) included the Short Form (SF)-36 [50]. For our analyses, we further transformed the physical component summary (PCS) and mental component summary (MCS) scores into norm-based scoring, with a mean of 50 and a standard deviation of 10 using the QualityMetric Health Outcomes™ Scoring Software 4.5 (QualityMetric Incorporated [now part of OPTUM], Lincoln, RI, USA). The PCS and MCS from SF-36 were used as covariates in regression and longitudinal analyses of the HIV-SI.

If multiple responses were provided for an item on the HIV-SI, the most severe (i.e., largest value) of the responses was used. Baseline demographic and clinical characteristics were summarized using descriptive statistics. To determine between-treatment comparisons, we used the Fisher exact test for categorical data or a 2-sided Wilcoxon rank sum test for continuous data.

The change from baseline in SF-36 PCS/MCS scores were summarized using descriptive statistics, and a 2-sided Wilcoxon rank sum test was used for between-treatment comparisons. The prevalence (i.e., number and percentage of participants) of reported poor sleep quality on the PSQI was also summarized, and the Fisher exact test was used for betweentreatment comparison.

Unadjusted and adjusted analyses at weeks 4, 12, and 48 were performed to evaluate the relationship between treatment assignment and the probability of experiencing an HIV-SI symptom, with and without additional covariates (adjusted and unadjusted, respectively). Specifically, HIV-SI symptoms were modeled as binary outcomes using a logistic regression. Descriptive variables were evaluated for multicollinearity and models were fitted/tested with independent variables of treatment and a subset of clinical and demographic covariates (selected from a larger list of potential demographic and clinical variables). The subset of clinical and demographic covariates was selected in two steps:

- First, for each symptom/time point, stepwise model selection was used to identify statistically significant covariates from all potential covariates (i.e., all these BL demographic and clinical characteristics, BL HIV-1 RNA, and BL C4 cell counts)

- Second, all the sixty models (i.e., 20 symptoms × 3 visits) were reviewed and a single set of covariates were selected across all models to ensure easy interpretation andsimplification of the model.

Longitudinal modeling was performed using generalized mixed-effects models to show symptom patterns over each of the four study visits using data from the HIV-SI.

5.3.2 Results per study

At baseline in treatment-naive adults (Study 380-1489), median [IQR] SF-36 PCS and MCS scores were comparable between the B/F/TAF and ABC/DTG/3TC groups (57.4 [52.6–60.0] vs 56.6 [52.2–59.3], p = 0.18 and 49.0 [37.7–55.2] vs 49.5 [40.0–56.3], p = 0.40, respectively). Changes from baseline at week 48 in PCS and MCS scores were also similar between groups; median (IQR) change from baseline in PCS was 0.1 (− 3.3 to 3.1) versus 0.2 (− 2.6 to 2.8), p = 0.85 and in MCS was 2.3 (− 1.6 to 9.0) versus 2.1 (− 4.0 to 7.0), p = 0.090.

GS-US-380-1489

Trial name: GS-US-380-1489 [4-6]										
NCT number: NCT02607930										
Outcome	Study arm	N	Result (change from BL) median IQR	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
				Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value	
Change from baseline in SF-36 PCS	B/F/TAF	314	0.1 (-3.3-3.1)	NA	NA	0.85	NA	NA	NA	Absolute and relative difference based on non-stratified method
	DTG/ABC/3TC	315	0.2 (-2.6-2.8)							
Change from baseline in SF-36 MCS	B/F/TAF	314	2.3 (-1.6-9.0)	NA	NA	0.09	NA	NA	NA	
	DTG/ABC/3TC	315	2.1 (-4.0-7.0)							

Abbreviations: 3TC, lamivudine; ABC, abacavir; BIC, bictegravir; CI, confidence interval; DTG, dolutegravir; HIV, human immunodeficiency virus; NCT, National Clinical Trial; NR, not reported; SF-36, 36-item Short Form Health Survey; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Statistical method: The calculations of absolute and relative differences for binary endpoints were based on the number of patients and the observed number of events per treatment group. Absolute differences were always calculated as B/F/TAF minus comparator whereas relative differences were calculated as B/F/TAF divided by comparator, i.e. the relative risk was used as relative effect measure. Confidence intervals and p-values for the absolute and relative differences were calculated using the normal approximation without a continuity correction.

The association between treatment and each bothersome symptom from the HIV-SI was examined by logistic regression models and longitudinal analyses. The adjusted logistic regression models showed that B/F/TAF was associated with a lower risk of experiencing bothersome symptoms at two

or more time points (Table 7). A complete table of the unadjusted and adjusted logistic regression models appears as Table ESM1 in the supplied material.

Table 7: Unadjusted and Adjusted Associations between Treatment and Bothersome Symptoms at Weeks 4, 12 and 48 in Study GS-US-380-1489 (Treatment-Naïve)

Symptom Description	Week 4						Week 12						Week 48					
	Unadjusted			adjusted			Unadjusted			adjusted			Unadjusted			adjusted		
	OR	95%, CI	P	OR	95%, CI	p-value	OR	95%, CI	p-value	OR	95%, CI	p-value	OR	95%, CI	p-value	OR	95%, CI	p-value
Fatigue/loss of energy	0.68	0.49-0.94	0.018	0.58	0.40-0.84	0.004[a,f,g]	0.70	0.51-0.98	0.036	0.62	0.43-0.89	0.010[a,f,g]	0.69	0.49-0.96	0.030	0.57	0.39-0.85	0.005[a,b,f,g]
Dizzy/lightheadedness	0.69	0.47-1.02	0.066	0.59	0.39-0.91	0.016[a]	0.83	0.54-1.27	0.38	0.74	0.46-1.17	0.20[a,g]	0.54	0.35-0.84	0.006	0.47	0.29-0.77	0.003[a,f,g]
Nausea/vomiting	0.51	0.34-0.77	0.001	0.47	0.30-0.73	<0.001[b]	0.44	0.26-0.74	0.002	0.39	0.23-0.68	<0.001[g]	0.75	0.44-1.26	0.27	0.70	0.40-1.23	0.21[a,b,f]
Difficulty sleeping	0.88	0.63-1.22	0.45	0.79	(0.54 -1.17	0.24[a,e,f]	0.66	0.47-0.93	0.017	0.58	0.40-0.85	0.005[a,c,d,f]	0.73	0.52-1.03	0.075	0.64	0.44-0.94	0.022[a,b,g]
Headaches	0.89	0.61-1.31	0.55	0.86	0.57-1.29	0.47[a,d]	0.86	0.58-1.28	0.45	0.80	0.52-1.24	0.32[a,b,c]	0.50	0.33-0.78	0.002	0.46	0.29-0.73	0.001[a]
Loss of appetite	0.78	0.50-1.22	0.27	0.67	0.39-1.14	0.14[a,b,f]	0.53	0.33-0.84	0.007	0.43	0.25-0.72	0.002[a,b,f]	0.72	0.43-1.21	0.22	0.61	0.33-1.10	0.10[a,b,f]
Bloating/pain/gas in stomach	1.00	0.69-1.44	0.98	0.95	0.63-1.42	0.81[a,b,f]	0.90	0.61-1.33	0.60	0.86	0.57-1.30	0.48[a]	0.67	0.45-1.00	0.048	0.61	0.40-0.93	0.022[a,f]
Weight loss/wasting	1.02	0.60-1.75	0.93	0.92	0.51-1.67	0.79[a,b,f]	0.61	0.35-1.06	0.079	0.53	0.29-0.97	0.039[a]	1.02	0.61-1.69	0.94	0.95	0.55-1.66	0.87[a,f]

Adjusted logistic regression model includes treatment as the independent variable and the bothersome HIVSI item as the dependent variable, adjusted for Baseline HIVSI count, age, sex, Baseline VACS Index, serious mental illness, Baseline SF-36 PCS, and Baseline SF-36 MCS.
P-value is for treatment effect; **bolding** indicates significant treatment effect in one or more of the models.
The following covariates were statistically significant (p<0.05) in the model: [a]Baseline HIVSI count; [b]Age; [c]Sex; [d]Baseline VACS Index; [e]Serious mental illness; [f]Baseline SF-36 PCS; [g]Baseline SF-36 MCS.
An odds ratio (OR) < 1 represents less bothersome symptom for B/F/TAF

The prevalence of bothersome symptoms over time in treatment naïve adults, revealed a statistically significant difference in the prevalence of three symptoms, fatigue/loss of energy, nausea/vomiting, and loss of appetite, between the B/F/TAF and DTG/ABC/3TC groups over time, all favoring the B/F/TAF group. Three additional symptoms also showed that the effect over time is dependent on treatment group. These were headaches,

bloating/pain/gas in stomach, and changes in body composition, each with lower prevalence over 48 weeks for B/F/TAF. No symptom favored the DTG/ABC/3TC group (Figure 5, Table 8).

Descriptive analyses showed that differences between B/F/TAF and DTG/ABC/3TC appeared as early as week 4 and were generally maintained through 48 weeks. The greatest differences between the two treatment groups were seen in participant reports of nausea/vomiting, difficulty sleeping, fatigue/loss of energy, and dizzy/light-headedness in treatment naïve participants.

Figure 5: Prevalence of Bothersome Symptoms Over Time by Treatment Group in Study GS- 380-1489 (Treatment-Naïve) that had at least two significant findings.

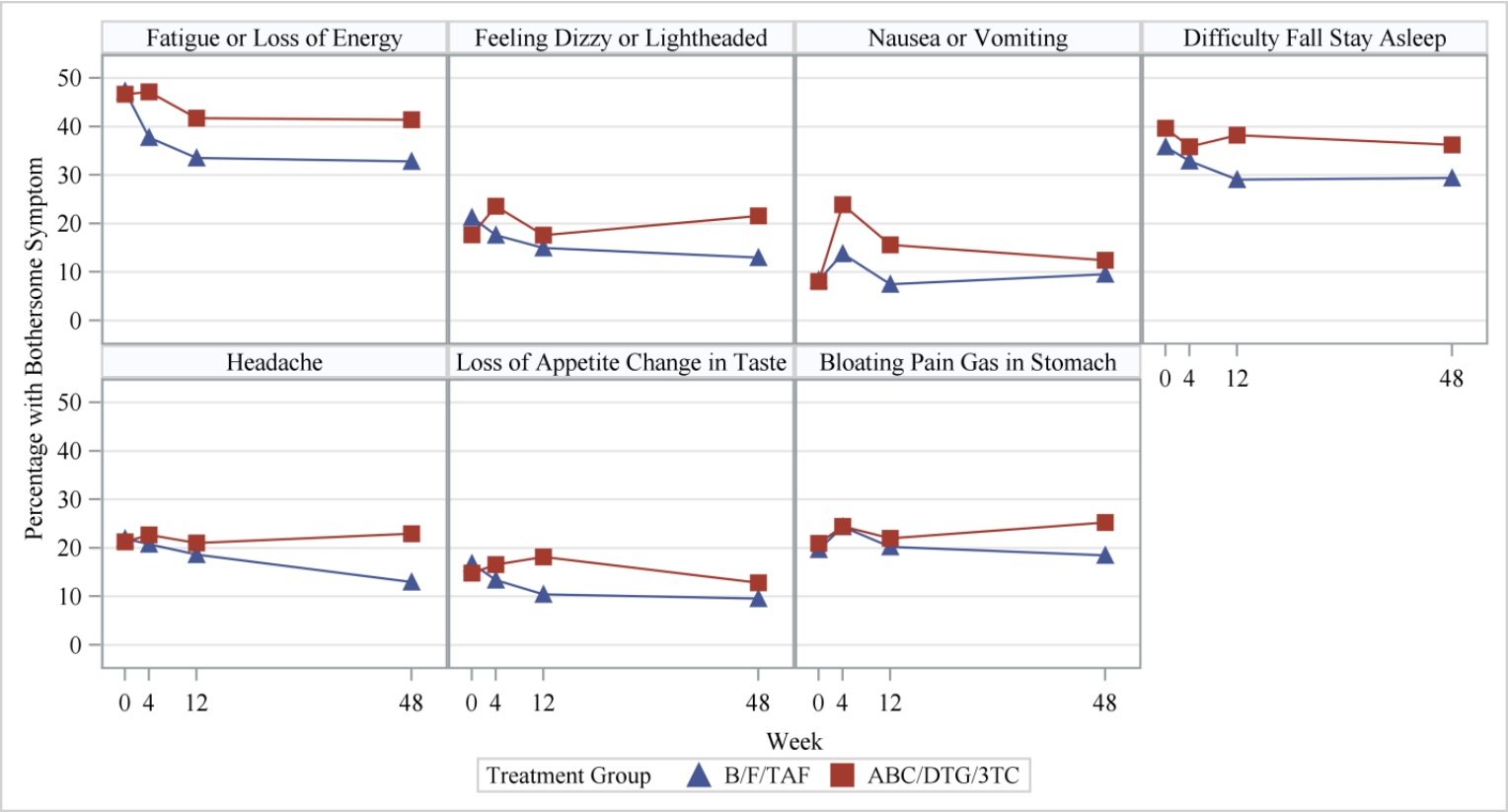


Table 8: Frequency of bothersome symptoms by treatment and study visit

Individuals reporting symptom, %	Baseline	Week 4	Week 12	Week 48	P-value

	B/F/TAF (n = 311)	DTG/ABC/3TC (n = 313)	B/F/TAF (n = 313)	DTG/ABC/3TC (n = 310)	B/F/TAF (n = 307)	DTG/ABC/3TC (n = 309)	B/F/TAF (n = 293)	DTG/ABC/3TC (n = 298)	
Fatigue/loss of energy	47.3	46.6	**37.7**	**47.1**	**33.6**	**41.7**	**32.8**	**41.4**	
Dizzy/lightheadedness	21.3	17.7	17.6	23.5	15.0	17.6	**13.0**	**21.5**	
Nausea/vomiting	8.4	8.0	**13.7**	**23.9**	**7.5**	**15.6**	9.6	12.4	
Difficulty sleeping	35.8	39.6	32.9	35.8	**29.1**	**38.2**	29.4	36.2	<0.05
Headaches	21.9	21.2	20.8	22.7	18.6	21.0	**13.0**	**22.9**	
Loss of appetite	16.8	14.8	13.4	16.6	**10.5**	**18.1**	9.6	12.8	
Bloating/pain/gas in stomach	19.7	21.0	24.4	24.4	20.3	22.0	**18.5**	**25.3**	
Weight loss/wasting	**18.3**	**11.3**	9.6	9.4	7.2	11.4	11.6	11.4	

n is the number of participants with response for at least one symptom
***Bold** characters* are for significantly different percentages between treatment groups ($p < 0.05$), *p* value is calculated from the unadjusted logistic regression model

5.3.3 PRO comparative analyses

The results indicate that B/F/TAF was associated with fewer patient-reported bothersome symptoms over 48 weeks, including nausea and some neuropsychiatric symptoms. Descriptive analyses showed that differences between B/F/TAF and ABC/DTG/3TC appeared as early as week 4 and were generally maintained through 48 weeks.

In treatmentnaïve participants, the greatest differences between the two treatment groups were seen in participant reports of nausea/vomiting, difficulty sleeping, fatigue/loss of energy, and dizzy/lightheadedness. The use of PRO tools within these studies provides insight into patient-reported symptoms that may be underreported by patients during standard screening for adverse drug events.[51] Others have suggested increasing the use of PRO tools in clinical research in order to further differentiate the benefit of various regimens [52-54].

Additionally, the use of longitudinal modeling allows for a greater understanding of the prevalence of HIV symptoms over time. The double-blind design of both studies eliminated the potential bias of symptom reporting had these studies been open label. As the efficacy of well tolerated antiretroviral FDC products in clinical trials reaches above 90%, it is important to demonstrate the comparative impact of the different FDC options available on symptoms and the degree that they are perceived by the patient as being bothersome. Tolerability and acceptance of long-term therapy impacts a patient's adherence to and persistence with that therapy, and adherence to anti-retroviral treatments has been shown to improved outcomes and lower health care cost.

There are limitations to this analysis that should be considered. While the results of the two studies are generalizable to a broad patient population they may not be generalizable to patients who are not white males as the majority of the study participants were male and white. Further, unlike investigator-reported symptoms, those reported by study participants are not graded using a standard grading scheme. Therefore, the severity of the participant-reported symptom may not be clear. However, the Likert scale provides a sense of the degree to which a symptom is considered bothersome and, arguably, any symptom potentially related to a chronic treatment that is perceived to be bothersome to any extent is undesirable. Lastly, generalizability of study findings must be done with caution as the current study populations were relatively healthy with few co-morbidities; Overall, these studies demonstrated that B/F/TAF was associated with fewer bothersome symptoms, especially nausea and vomiting, as well as sleep difficulties, over close to a year of follow-up than ABC/DTG/3TC in both treatment-naïve. Patient-reported symptoms may be an important consideration when selecting among highly efficacious options for the treatment of HIV infection and should continue to be studied in clinical trials.

Concluding on PROs:

Results suggest that patient-reported wellbeing may be better with B/F/TAF compared to DTG/ABC/3TC. B/F/TAF was associated with a significantly lower prevalence of multiple bothersome symptoms across gastrointestinal disorders, neuropsychiatric events, and sleep.

The added clinical value of Biktarvy

The added clinical value of the fixed dose combination of Biktarvy (B/F/TAF) compared to the combination of Triumeq (DTG/ABC/3TC) are as follows:

- Both DTG and ABC are associated with hypersensitivity reactions. Initiation of treatment with DTG/ABC/3TC must be delayed pending HLA B*5701 testing. Coformulated B/F/TAF does not

require HLA B*5701 might lend itself to rapid or same-day initiation of treatment in the clinical setting.

- Coformulated B/F/TAF can be given to individuals with an eGFR of 30 mL/min or more, whereas use of DTG/ABC/3TC is limited to those with an eGFR of more than 50 mL/min.
- PRO in naive patients show less bothersome symptoms associated with Biktarvy compared to Triumeq [22].
- Triumeq contains ABC and some, but not all, studies have shown an association between ABC use and an increased risk of myocardial infarction, although a pathophysiological underlying mechanism has not been defined [29-35].
- Biktarvy contains TAF:
    - TAF is active against hepatitis B virus and is approved for treatment of hepatitis B as a single drug (VEMLIDY). HIV treatment guidelines recommend TAF or TDF as components of regimens for treatment of people coinfected with HIV and hepatitis B virus [36]. While B/F/TAF is suitable for a rapid initiation even without prior knowledge of the patient's HBV status, initiating DTG/ABC/3TC is not recommended until HBV coinfection has been ruled out.
    - TAF has shown significant improvements in clinical categories of osteopenia and osteoporosis [37-39].
    - TAF has shown significant decrease in renal biomarkers in patients with renal impairment – 144 weeks data – study 112 [40].
- Biktarvy is the smallest integrase-containing STR which make it easier to swallow (Biktarvy 721mg vs Triumeq 1750mg)

Biktarvy® (50/200/25mg)
Film-coated tablets (721mg), approximately 16 x 8 mm

Triumeq® (600/300/50mg)
Film-coated tablets (1750mg), approximately 22 x 11 mm

5.4 Quality assessment

Study	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis use an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
GS-US-380-1489 [2, 3]	**Yes.** Participants were randomised 1:1, via a computer-generated allocation sequence (block size of four). Randomisation was stratified by plasma HIV-1 RNA (≤100,000 c/mL, >100,000 to ≤400,000 c/mL) and CD4 count (<50 cells/µL, 50-199 cells/µL or ≥200 cells/µL)	**Yes.** Randomisation list was generated using validated, centralised software	**Yes.** The trial was double-blind until Week 144. Study investigators determined eligibility, obtained a participant number, and received automated treatment assignment on the basis of a randomisation sequence	**Yes.** The overall groups were well-balanced; randomisation was stratified by plasma HIV-1 RNA and CD4 count	**Yes.** A higher proportion of patients randomised to DTG/ABC/3TC discontinued the study compared to B/F/TAF due to adverse events but more patients in the B/F/TAF arm discontinued for other reasons compared to the DTG/ABC/3TC arm	**Yes.** Full study results have not been posted to ClinicalTrials.gov yet so there may be further results	**No.** The primary endpoint used the full analysis set, however this is appropriate as it is a non-inferiority trial
GS-US-380-1490 [4, 5]	**Yes.** Participants were randomised 1:1, via a computer-generated allocation sequence (block size of four). Randomisation was stratified by plasma HIV-1 RNA (≤100,000 c/mL, >100,000 to ≤400,000 c/mL or >400,000 c/mL) and CD4 count (<50 cells/µL, 50-199 cells/µL or ≥200 cells/µL)	**Yes.** Randomisation list was generated using validated, centralised software	**Yes.** The trial was double-blind until Week 144. Study investigators determined eligibility, obtained a participant number, and received automated treatment assignment on the basis of a randomisation sequence	**Yes.** The overall groups were well-balanced; randomisation was stratified by plasma HIV-1 RNA and CD4 count	**Yes.** A higher proportion of patients in the B/F/TAF arm discontinued for other reasons compared to the DTG/ABC/3TC arm	**No.** Extensive results presented on ClinicalTrials.gov	**No.** The primary endpoint used the full analysis set, however this is appropriate as it is a non-inferiority trial
ARIA [6-8]	**Yes.** Randomisation and identifier code assignment were allocated centrally with a validated computerised system. Randomisation was 1:1, stratified by plasma HIV-1 RNA (≤ or >100,000 c/mL) and CD4	**Yes.** Randomisation list was generated using validated, centralised software	**No.** Open label so possible bias, but not a switch study so less likely to influence reporting of AEs	**Yes.** The overall groups were well-balanced; randomisation was stratified by plasma HIV-1 RNA and CD4 count	**No.** NA	**No.** Extensive results presented on ClinicalTrials.gov	**Yes.** Missing = failure; for the CFB data, missing data = patient was omitted from the analysis; Intent-to-treat exposed (ITT-E) population, comprising all randomised subjects who received at least 1

Study	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis use an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
	count (≤ or >350 cells/mm3)						dose of study medication, was used for assessing most outcomes. Other outcomes used a "safety population"
FLAMINGO [9, 10, 12, 13]	**Yes.** Randomisation was conducted via central interface. Selection of NRTI backbone was done pre-randomisation	**Yes.** Randomisation list was generated using validated software by study statistician	**No.** Open-label design may introduce a number of biases (e.g. performance and ascertainment bias)	**Yes.** The overall groups were well-balanced; randomisation was stratified by baseline HIV-1 RNA (≥100,000 and <100,000 copies per millilitre) and NRTI backbone	**Yes.** A higher proportion of patients randomised to DRV/r discontinued the study compared to DTG (greatest difference in discontinuations due to adverse events and withdrawal of consent at Week 96); discontinuation by backbone was not presented in the paper or supplementary materials	**Yes.** Various safety outcomes and laboratory values at Week 96 are discussed, but "data not shown"	**No.** Primary analysis used modified ITT-exposure or modified safety populations, excluding one patient at one study site in Russia that was closed early after the sponsor became aware of issues of non-compliance to good clinical practice in another ViiV Healthcare-sponsored study
SINGLE [14-16]	**Yes.** Randomisation was performed in block sizes of six, with the use of a central procedure. The study statistician generated the randomisation schedule with validated randomisation software	**Yes.** Care providers enrolled participants and used an automated phone system to retrieve container numbers from the randomisation system as well as a randomisation number from the randomisation schedule	**Yes.** The trial was double-blind and double-dummy until Week 96, after which the trial became open-label. The sponsor central study team remained blinded until the last subject's week 48 visit for the primary analysis. Participants, sponsor study site staff, and care providers were to remain blinded until each subject's week 96 visit	**Yes.** Demographic and disease characteristics at baseline were well balanced between the treatment groups	**Yes.** The authors stated: "More participants in the EFV–TDF–FTC group than in the DTG–ABC–3TC group withdrew from the trial prematurely (84 and 51 participants, respectively), most commonly owing to adverse events." The study used the FDA Snapshot Analysis	**No.** All outcomes mentioned in the methods were reported	**Yes.** Efficacy and safety analyses were performed in the ITT population and safety population, respectively

Study	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis use an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
SPRING-2 [13, 18-20]	**Yes.** Central procedure using phone and web interface	**Yes.** Randomisation list was generated using validated software by study statistician	**Yes.** NA	**Yes.** Baseline demographics were similar between treatment groups; randomisation was stratified by baseline HIV-1 RNA (≥100,000 and <100,000 copies per millilitre) and NRTI backbone	**No.** NA	**Yes.** Outcomes (such as lipid changes from baseline and EQ-5D) were discussed but 'data not shown'	**No.** Primary analysis used modified ITT exposed (included all patients randomly assigned to treatment groups who received at least one dose of study drug)

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7 Appendices

Appendix 1 – Search Strategies

Search strategies are shown below for MEDLINE, including MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and Versions (Table 2), The Cochrane Library (Table 3), the EMA website (Table 4) and ClinicalTrials.gov (Table 5).

TABLE 2. SEARCH TERMS FOR MEDLINE, WITH THE ADDITION OF TERMS FOR PILOT/PHASE I/PHASE II STUDIES (SEARCHED VIA OVID SP ON THE 6TH SEPTEMBER 2018)

Term group	#	Searches	Results
Disease area	1	exp hiv infections/	-
	2	exp hiv/	-
	3	(human immunodeficiency virus or hiv).tw.	-
	4	exp acquired immunodeficiency syndrome/	-
	5	(acquired adj (immunodeficiency or immune deficiency) adj (syndrome or disease)).tw.	-
	6	Aids.tw.	-
	7	or/1-6	412703
Study design	8	exp randomized controlled trials as topic/	-
	9	exp randomized controlled trial/	-
	10	exp random allocation/	-
	11	exp double blind method/	-
	12	exp single blind method/	-
	13	exp clinical trial/	-
	14	exp clinical trial, phase III/	-
	15	exp clinical trial, phase IV/	-
	16	clinical trial, phase i.pt.	
	17	clinical trial, phase ii.pt.	
	18	clinical trial, phase iii.pt.	-
	19	clinical trial, phase iv.pt.	-
	20	controlled clinical trial.pt.	-
	21	randomized controlled trial.pt.	-
	22	multicenter study.pt.	-
	23	clinical trial.pt.	-
	24	exp Clinical Trials as topic/	-
	25	clinical trials, phase i as topic/	
	26	clinical trials, phase ii as topic/	
	27	(clinical adj trial$).tw.	-
	28	exp cross-over studies/ or (crossover adj (trial$ or stud$)).tw.	-
	29	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	-
	30	exp placebos/	-
	31	placebo$.tw.	-
	32	(allocat$ adj2 random$).tw.	-
	33	Randomi?ed controlled trial$.tw.	-
	34	Rct.tw.	-
	35	((single arm or single-arm or open-label or non-blinded or pilot or feasibility) adj3 (study or studies or trial*)).tw.	-
	36	or/8-35	1619187
Interventions and comparators	37	exp tenofovir/ or (tenofovir or taf).tw.	-
	38	exp emtricitabine/ or (emtricitabine or emtriva$ or coviracil or	-

Term group	#	Searches	Results
		ftc).tw.	
	39	37 and 38	-
	40	Descovy$.tw.	-
	41	39 or 40	-
	42	(bictegravir or "GS-9883" or "GS9883" or bic).tw.	-
	43	41 and 42	-
	44	(abacavir or ziagen$ or filabac or zepril or abc).tw.	-
	45	exp lamivudine/ or (lamivudine or epivir$ or heptodin$ or heptovir$ or inhavir$ or ladiwin$ or lamidac$ or lamivir$ or zeffix$ or zefix$ or 3tc).tw.	-
	46	44 and 45	-
	47	Kivexa$.tw.	-
	48	46 or 47	-
	49	exp tenofovir/ or (tenofovir or tdf or viread$).tw.	-
	50	38 and 49	-
	51	exp emtricitabine, tenofovir disoproxil fumarate drug combination/ or Truvada$.tw.	-
	52	50 or 51	-
	53	(dolutegravir or tivicay$ or dtg).tw.	-
	54	48 and 53	-
	55	52 and 53	-
	56	41 and 53	-
	57	(biktarvy$ or bictarvy$ or triumeq$).tw.	-
Treatments combined	58	43 or 54 or 55 or 56 or 57	157
Exclusion terms	59	exp animals/ not exp humans/	-
	60	(comment or editorial or "case reports").pt.	-
	61	(case stud$ or case report$).ti.	-
	62	historical article/ or Case study/	-
	63	or/59-62	-
Totals	64	7 and 36 and 58	-
	65	64 not 63	**64**

TABLE 3. SEARCH TERMS FOR THE COCHRANE LIBRARY (SEARCHED VIA WILEY ONLINE ON THE 29TH MAY 2018)

Term group	#	Search terms	Results
HIV	1	[mh hiv]	3059
	2	[mh "hiv infections"]	9942
	3	("human immunodeficiency virus" or hiv):ti,ab,kw	17274
	4	[mh "acquired immunodeficiency syndrome"]	1282
	5	(acquired next (immunodeficiency or "immune deficiency") next (syndrome or disease)):ti,ab,kw	2037
	6	Aids:ti,ab,kw	7156
	7	{or#1-#6}	20744
Intervention and comparators	8	[mh emtricitabine] or (emtricitabine or emtriva* or coviracil or ftc):ti,ab,kw	1277
	9	[mh tenofovir] or (tenofovir or taf):ti,ab,kw	1940

	10	#8 and #9	1098
	11	(descovy*):ti,ab,kw	1
	12	#10 or #11	1098
	13	(bictegravir or "GS-9883" or GS9883 or bic):ti,ab,kw	107
	14	#12 and #13	9
	15	(abacavir or ziagen* or filabac or zepril or abc):ti,ab,kw	1618
	16	[mh lamivudine] or (lamivudine or epivir* or heptodin* or heptovir* or inhavir* or ladiwin* or lamidac* or lamivir* or zeffix* or zefix* or 3tc):ti,ab,kw	2410
	17	#15 and #16	443
	18	(kivexa*):ti,ab,kw	15
	19	#17 or #18	445
	20	[mh tenofovir] or (tenofovir or viread* or tdf):ti,ab,kw	2032
	21	#8 and #16	394
	22	[mh "emtricitabine, tenofovir disoproxil fumarate drug combination"] or (Truvada*):ti,ab,kw	48
	23	#21 or #22	437
	24	(dolutegravir or tivicay* or dtg):ti,ab,kw	173
	25	#19 and #24	50
	26	#23 and #24	40
	27	#12 and #24	49
	28	#14 or {or #25-#27}	70
	29	(bictarvy* or biktarvy* triumeq*):ti,ab,kw	0
	30	#28 or #29	70
Combined	31	#7 and #30	67
Total	32	#31 in Trials	64

EMA Website

Under the “Human medicines” page, the keyword search option was used, with the “active substance or common name” option selected. The terms below were used sequentially:

TABLE 4. EMA WEBSITE SEARCH TERMS

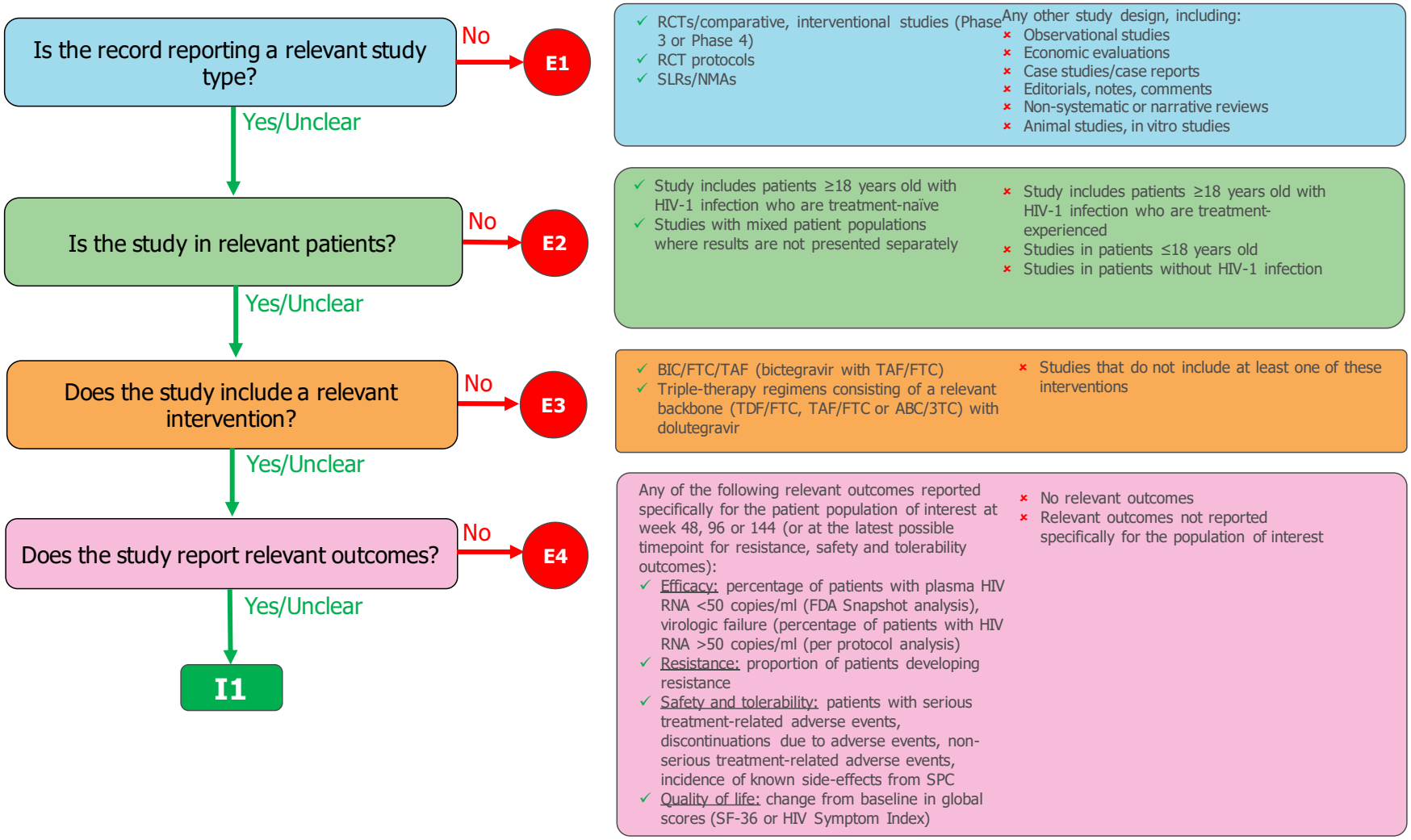
Term group	Search terms	Results
Intervention	Bictegravir	0
	GS-9883	0
	GS9883	0
	Bic	0
	Dolutegravir	3
	DTG	0
	Tivicay	0

TABLE 5. CLINICALTRIALS.GOV SEARCH TERMS

Term group	Search terms
Condition/Disease	HIV OR AIDS OR human immunodeficiency virus OR acquired immunodeficiency syndrome
Intervention/Treatment	bictegravir OR GS-9883 OR GS9883 OR bic OR dolutegravir OR dtg OR tivicay
Status	Active, not recruiting, Completed Studies
Study Type	Interventional Studies
Study Results	Studies with Results
Study Phase	Phase 3, Phase 4
Hits	**14 trials**

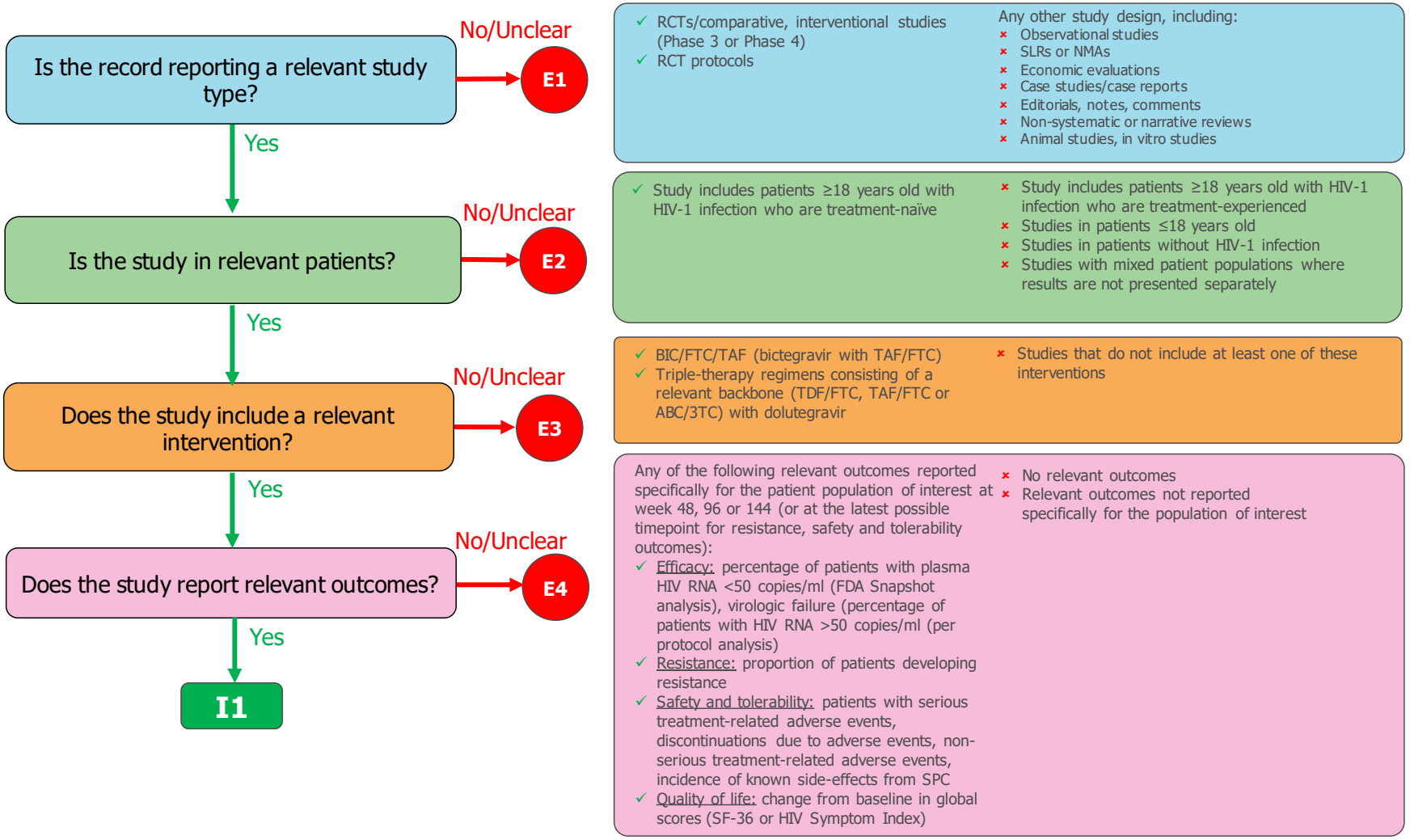
Appendix 2 – Eligibility Flowcharts

FIGURE 2. FLOWCHART FOR THE ABSTRACT SIFT (SIFT 1)



Footnote: I# (where '#' denotes a number) indicates an inclusion category, while E# (where '#' denotes a number) indicates an exclusion category.

FIGURE 3. FLOWCHART FOR THE FULL-TEXT SIFT (SIFT 2)



Footnote: I# (where '#' denotes a number) indicates an inclusion category, while E# (where '#' denotes a number) indicates an exclusion category.

Appendix 3 – Included Studies

These details are presented in the main report.

Appendix 4 – Excluded Studies

TABLE 6. STUDIES EXCLUDED AFTER FULL-TEXT REVIEW

#	Reference	Reason for exclusion
1	Granier C, Cuffe R, Martin-Carpenter L, et al. Consistency of dolutegravir treatment difference in HIV+ treatment naivees at week 96. Topics in antiviral medicine. Volume 23, 2015:231.	Not a relevant study type
2	Guirant-Corpi L, Olivares N, Aguirre A, et al. Cost minimization analysis of rilpivirine/emtricitabine/tenofovir in treatment naivee HIV+ patients with adverse events when treated with standard therapy. Value in health. Conference: ISPOR 22nd annual international meeting. United states. Volume 20, 2017:A78-a79.	Not a relevant study type
3	J ML, Raffi F, Moyle G, et al. An Indirect Comparison of Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate and Abacavir/Lamivudine + Dolutegravir in Initial Therapy.[Erratum appears in PLoS One. 2016;11(7):e0159286; PMID: 27391807]. PLoS ONE [Electronic Resource] 2016;11:e0155406.	Not a relevant study type
4	Jiang J, Xu X, Guo W, et al. Dolutegravir(DTG, S/GSK1349572) combined with other ARTs is superior to RAL- or EFV-based regimens for treatment of HIV-1 infection: a meta-analysis of randomized controlled trials. AIDS Research & Therapy [Electronic Resource] 2016;13:30.	Not a relevant study type=
5	Molina J-M, Clotet B, Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ ritonavir in treatment-naivee HIV-1-positive individuals: 96 week results from FLAMINGO. Journal of the international AIDS society. Volume 17, 2014:6-7.	Not a relevant study type
6	Okoli C, Murungi A, Paice A, et al. Safety and efficacy of dolutegravir in treatment naivee patients, 50 years and over: subgroup analysis of 48-week results from SPRING-2, SINGLE, FLAMINGO and ARIA. HIV medicine. Conference: 23rd annual conference of the British HIV association, BHIVA 2017. United kingdom. Volume 18, 2017:19.	Not a relevant study type
7	Patel DA, Snedecor SJ, Tang WY, et al. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naivee HIV-1-infected patients: a systematic review and network meta-analysis. PLoS ONE [Electronic Resource] 2014;9:e105653.	Not a relevant study type
8	Pialoux G, Marcelin A, Cawston H, et al. Cost-effectiveness of dolutegravir/abacavir/lamivudine in HIV-1 treatment-Naivee (TN) patients in France. Expert review of pharmacoeconomics & outcomes research, 2017:1-9.	Not a relevant study type
9	Raffi F, Rachlis A, Stellbrink H-J, et al. Once-daily dolutegravir (DTG; S/GSK1349572) is non-inferior to raltegravir (RAL) in antiretroviral-naivee adults: 48 week results from SPRING-2 (ING113086). Journal of the international AIDS society. Volume 15, 2012:55.	Not a relevant study type
10	Rogatto F, Bouee S, Jeanbat V, et al. An indirect comparison of efficacy and safety of elvitegravir/cobicistat/emtricitabine/tenofovir and dolutegravir + abacavir/lamivudine. Journal of the International AIDS Society 2014;17:19779.	Not a relevant study type
11	Rutherford GW, Horvath H. Dolutegravir Plus Two Nucleoside Reverse Transcriptase Inhibitors versus Efavirenz Plus Two Nucleoside Reverse Transcriptase Inhibitors As Initial Antiretroviral Therapy for People with HIV: A Systematic Review. PLoS ONE [Electronic Resource] 2016;11:e0162775.	Not a relevant study type
12	Sax P, DeJesus E, Ward D, et al. Randomised trial of bictegravir or dolutegravir with FTC/TAF for initial HIV therapy. HIV medicine. Conference: 23rd annual conference of the british HIV association, BHIVA 2017. United kingdom. Volume 18, 2017:17.	Not a relevant study type
13	Tebas P, Quercia R, Paice A, et al. SINGLE W144: greater changes in bone turnover markers in antiretroviral therapy-naivee individuals initiating efavirenz/ emtricitabine/tenofovir disoproxil fumarate compared with dolutegravir plus abacavir/lamivudine. HIV medicine. Volume 16, 2015:12.	Not a relevant study type
14	Walmsley S, Berenguer J, Khuong-Josses M-A, et al. Dolutegravir Regimen Statistically Superior To Tenofovir/Emtricitabine/Efavirenz: 96-Wk Data. Topics in antiviral medicine., 2014:261-262.	Not a relevant study type
15	Yazdanpanah Y, Khuong-Josses M-A, Hocqueloux L, et al. 48 week bone marker changes with Dolutegravir (DTG) plus Abacavir/ Lamivudine (ABC/3TC) vs. Tenofovir/Emtricitabine/Efavirenz (EFV/TDF/ FTC): the SINGLE trial. BMC infectious diseases. Conference: international symposium HIV and emerging infectious diseases 2014. France. Volume 14, 2014.	Not a relevant study type
16	Blanco J, Alejos B, Moreno S. Impact of dolutegravir and efavirenz on immune recovery markers: results from a randomized clinical trial. Clinical microbiology and infection. Volume (no pagination), 2018.	No relevant outcomes reported

17	Raffi F, Rachlis A, Brinson C, et al. Dolutegravir efficacy at 48 weeks in key subgroups of treatment-naivee HIV-infected individuals in three randomized trials. AIDS (London, England). Volume 29, 2015:167-174.	No relevant outcomes reported

Protokol for vurdering af den kliniske merværdi af bictegravir/emtricitabine/ tenofovir alafenamid til behandling af voksne med hiv-1-infektion

Handelsnavn	Biktarvy
Generisk navn	Bictegravir/emtricitabine/tenofovir alafenamid
Firma	Gilead
ATC-kode	J05AR20
Virkningsmekanisme	Kombinationspræparat af tre antiretrovirale midler: hiv-integrasehæmmer (bictegravir), nukleosid-revers transkriptasehæmmer (emtricitabine) og nukleotid-revers transkriptasehæmmer (tenofovir alafenamid)
Administration/dosis	50 mg/200 mg/25 mg bictegravir/emtricitabine/tenofovir alafenamid kombinationstablet én gang dagligt
Forventet EMA-indikation	*"Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus 1 (HIV 1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir"*
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	18. maj 2018 18. maj 2018 19076 1.0

Indhold

Forkortelser

ACTG:	*AIDS Clinical Trials Group*
AIDS:	*Aquired immunodeficiency syndrome*
CI:	Konfidensinterval
DHK:	Det Danske HIV kohorte Studie
EMA:	*European Medicines Agency*
GRADE:	*Grading of Recommendations Assessment, Development and Evaluation System* (System til vurdering af evidens)
HIV:	Human immundefektvirus
HR:	*Hazard Ratio*
ITT:	*Intention-to-treat*
NRTIs:	Nukleosid- og nukleotid-revers-transkriptasehæmmere
OR:	*Odds Ratio*
RR:	Relativ Risiko

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af bictegravir/emtricitabine/tenofovir alafenamid som mulig standardbehandling af patienter med hiv-1-infektion. I protokollen angives en definition af populationer, komparator og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende bictegravir/emtricitabine/tenofovir alafenamid modtaget den 26. februar 2018.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af bictegravir/emtricitabine/tenofovir alafenamid sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol skal besvares med en sammenlignende analyse mellem bictegravir/emtricitabine/tenofovir alafenamid og den specificerede komparator af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

2 Baggrund

Hiv-infektion er en kronisk infektion med human immundefektvirus (hiv), som primært overføres seksuelt og via blod. Hiv angriber immunforsvaret ved at inficere CD4-positive T-hjælperlymfocytter (kaldet CD4-celler), som er en type af hvide blodlegemer og en del af immunforsvaret. Behandles infektionen ikke, vil virus forårsage, at CD4-cellerne ødelægges, og mængden af CD-4 celler vil falde. En aftagende mængde af CD4-celler vil medføre en tiltagende svækkelse af immunforsvaret, som vil resultere i, at den inficerede person udvikler *aquired immunodeficiency syndrome* (aids) og slutteligt dør [1].

Hiv er særlig prævalent blandt mænd, som har sex med mænd, personer med blødersygdom, stofmisbrugere og personer fra Afrika syd for Sahara [2].

Der findes to typer af hiv, type 1 og 2. Hiv-2 er mest udbredt i Vestafrika, mens type 1 forekommer i hele verden. Den langt overvejende del af den danske patientpopulation har hiv-1-infektion. Der lever kun få personer med hiv-2 infektion i Danmark. Incidensen af nydiagnosticerede hiv-patienter i Danmark har i mange år ligget stabilt mellem 200 og 300 [3,4]. I 2016 fik 182 personer i Danmark diagnosen hiv. Herudover blev der anmeldt 62 personer, som allerede var diagnosticeret i udlandet [3].

Det estimeres, at der ved udgangen af 2016 levede omkring 6.200 mennesker med hiv i Danmark [3]. Ifølge data fra Det Danske HIV kohorte Studie (DHK) var i alt 5.502 af de hiv-inficerede personer på dette tidspunkt under antiretroviral behandling [2].

2.1 Nuværende behandling

Patienter med hiv-1-infektion behandles i dag med kombinationsbehandlinger bestående af tre antiretrovirale midler. Målet med behandlingen er at hæmme virusreplikation og herved forhindre, at sygdommen udvikles. Effektiv behandling muliggør, at immunsystemets funktion genoprettes/bevares, hvilket nedsætter risikoen for at udvikle aids betydeligt og dermed nedsætter risikoen for, at patienten dør. En vellykket behandling vil desuden også eliminere hiv-smitte [1,4].

De antiretrovirale lægemidler virker på de proteiner, som hiv-partiklen indeholder, og som er nødvendig for hiv-partiklens syntese og fortsatte evne til at inficere nye CD4-celler. De mest hyppigt anvendte antiretrovirale midler kan inddeles i fire forskellige grupper efter virkningsmekanisme:

Nukleosid- og nukleotid-revers-transkriptasehæmmere (NRTIs) er nukleotid-/nukleosidanaloger, som hæmmer hiv revers-transkriptase, en hiv-specifik RNA-afhængig DNA-polymerase, som omsætter det virale RNA til DNA, hvorved det kan inkorporeres i værtscellen. Idet nukleotid-/nukleosidanalogerne indsættes af DNA-polymerasen, inhiberes DNA-syntesen. Gruppen inkluderer lægemidlerne lamivudin, abacavir, tenofovir disoproxil, tenofovir alafenamid og emtricitabine [5].

Non-nukleosid-revers-transkriptasehæmmere nedsætter lige som NRTIs også aktiviteten af hiv revers-transkriptase, men virker ved direkte binding til enzymet. Gruppen inkluderer efavirens, rilpivirin, nevirapin og etravirin [5].

Integrasehæmmere inhiberer aktiviteten af den hiv-kodede integrase og hæmmer herved integration af hiv DNA i værtens DNA. Gruppen inkluderer dolutegravir, raltegravir, elvitegravir. Elvitegravir gives i kombination med boosteren cobicistat, som øger eksponeringen for og derved virkningen af CYP3A-substrater som elvitegravir [6]. Det nye lægemiddel, bictegravir, er også en integrasehæmmer.

Proteasehæmmere inhiberer den hiv-specifikke protease, hvilket resulterer i, at nydannede hiv-partikler forbliver umodne og ikkeinfektiøse. Gruppen inkluderer atazanavir og darunavir [6]. Proteasehæmmerne gives med en af de to boostere ritonavir og cobicistat [4].

Behandlingsnaive patienter behandles som standard med en kombinationsbehandling af to nukleosid-revers-transkriptasehæmmere og et tredje stof, som enten er én non-nukleosid-revers-transkriptasehæmmer, proteasehæmmer eller integrasehæmmer [4,7]. Behandlingen skiftes, såfremt der optræder resistensudvikling, bivirkninger, betydelige interaktioner eller adhærensproblemer. Der tages ved valg af et alternativt regime hensyn til patientens medicinhistorie og resistensudvikling, som kan være meget kompleks [4,7]. Der tages også hensyn til nemhed for patienten ved medicinindtaget. Op til 50 % af patienterne skifter medicin inden for det første år.

Fordi valg af behandling er afhængig af flere faktorer, og behandlingen skiftes for flere patienter, er der ikke et enkelt behandlingsregime, der kan betragtes som standardbehandling. Behandling med bictegravir vil være relevant hos patienter, som skal behandles med en integrasehæmmer.

2.2 Bictegravir/emtricitabine/tenofovir alafenamid

Bictegravir/emtricitabin/tenofovir alafenamid har EMA-indikationen behandling af voksne patienter med hiv-1-infektion uden nuværende eller tidligere tegn på resistens over for integrasehæmmere, emtricitabine eller tenofovir.

Bictegravir/emtricitabin/tenofovir alafenamid er en kombinationstablet bestående af tre antiretrovirale midler: Det nye lægemiddel bictegravir som er en 2.-generations integrasehæmmer og de i forvejen godkendte og markedsførte nukleos(t)id-revers-transkriptasehæmmere emtricitabin og tenofovir alafenamid.

Bictegravir/emtricitabin/tenofovir alafenamid er tilgængelig som filmovertrukne tabletter indeholdende 50 mg bictegravir, 200 mg emtricitabin og 25 mg tenofovir alafenamid. Der gives en kombinationstablet oralt én gang dagligt.

3 Kliniske spørgsmål

De kliniske spørgsmål indeholder specifikation af patientgruppen, interventionen, alternativet/-erne til interventionen og effektmål.

3.1 Klinisk spørgsmål 1

Hvad er den kliniske merværdi af bictegravir/emtricitabine/tenofovir alafenamid til behandlingsnaive patienter med hiv-1-infektion sammenlignet med dolutegravir og to NRTIs?

Population

Behandlingsnaive patienter med hiv-1-infektion.

Den godkendte indikation omfatter også patienter, som skal skifte behandling, der ikke er resistente overfor integrasehæmmere, emtricitabine eller tenofovir. Fagudvalget vurderer, at sammenligningen med komparator for behandlingsnaive kan ekstrapoleres til denne patientgruppe.

Intervention

Bictegravir/emtricitabine/tenofovir alafenamid som beskrevet i pkt. 2.2.

Komparator

Dolutegravir sammen med to NRTIs

Effektmål

Tabel 1 summerer de valgte effektmål.

3.2 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.
For alle effektmål ønskes både absolutte og relative værdier, jævnfør ansøgningsskemaet. For de relative værdier vurderes den kliniske relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Effektmål	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Viral suppression	Kritisk	Alvorlige symptomer	Andel af patienter der opnår plasma hiv RNA < 50 kopier/ml iht. til FDAs snapshot analyse efter 48 uger	5 procentpoint
Viral svigt	Kritisk	Alvorlige symptomer	Andel af patienter, der har hiv RNA > 50 kopier/ml ved uge 48 (i per protokolanalyse)	3 procentpoint

Resistens-udvikling	Kritisk	Alvorlige symptomer	Andel af patienter der udvikler resistens.	2 procentpoint
Bivirkninger	Kritisk	Alvorlige bivirkninger	Andel af patienter med alvorlige bivirkninger af studiemedicinen	2 procentpoint
	Vigtigt	Alvorlige bivirkninger	Andel af patienter med behandlingsophør pga. uønskede hændelser ved 48 uger.	5 procentpoint
	Vigtigt	Ikkealvorlige bivirkninger	Andel af patienter med ikke alvorlige bivirkninger af studiemedicinen	10 procentpoint
	Vigtig	Ikkealvorlige bivirkninger og symptomer	Kvalitativ vurdering af kendte bivirkninger som beskrevet i produktresuméerne, herunder hvor der er betydelige forskelle i forekomst.	-
Livskvalitet	Vigtig	Helbredsrelateret livskvalitet	Forskelle i ændring fra baseline i global scores på SF-36 eller forskel på Hiv Symptom Index score efter 48 uger, hvis det førstnævnte ikke er tilgængelige.	0,5 SD point på SF-36 2 generende symptomer på Hiv index score

Tabel 1. Oversigt over valgte effektmål. For hver effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de fire kategorier (overlevelse, alvorlige symptomer og bivirkninger, helbredsrelaterede livskvalitet og ikkealvorlige symptomer og bivirkninger).

For opgørelse af bivirkninger og resistens udvikling ønskes længst mulig opfølgningstid. For de resterende effektmål ønskes data fra 48 ugers opfølgning. Hvis data er tilgængelige fra 96 eller 144 uger ønskes disse også præsenteret. De mindste klinisk relevante forskelle for bictegravir/emtricitabine/tenofovir alafenamide er fastsat ud fra en forventet opfølgningstid på 48 uger.

3.2.1 Beskrivelse af effektmål

Kritiske effektmål

Antiretroviral virkning (hiv-RNA)

Ved tidlig behandling med moderne effektive antiretrovirale behandlingsregimer forventes det ikke, at en patient med hiv-infektion oplever alvorlige kliniske symptomer inden for tidsrammen af et klinisk forsøg. Derfor er surrogatmålet hiv-RNA blevet den gyldne standard for at måle den antiretrovirale virkning af et behandlingsregime. Mængden af hiv-RNA i plasma er et mål for viral replikation. Suppression af hiv-RNA er et etableret surrogatmål for forbedring af kliniske endepunkter [8–10]. Både FDA og EMA anbefaler at benytte andelen af patienter, der opnår og fortsat har viral suppression, til at måle effekten af

antiretrovirale behandlingsregimer [8,9]. EMA og FDA anbefaler, at viral suppression måles ved at benytte den lavest målbare grænse for hiv-RNA. FDA har udviklet en snapshotalgoritme til at opgøre effekten af antiretrovirale midler. Den antiretrovirale virkning vil i denne rapport vurderes på to måder, dels ved FDA-snapshotalgoritmens mål for "viral suppression", defineret som hiv-RNA < 50 kopier/ml ved uge 48 og dels ved algoritmens "virale svigt", defineret som hiv-RNA ≥ 50 ved uge 48.

FDA's snapshot algoritme af "viral suppression", defineret som hiv-RNA < 50 kopier/ml ved uge 48

FDA snapshotalgoritmens mål for andelen af patienter, der opnår hiv-RNA < 50 kopier/ml ved uge 48, giver et samlet estimat af behandlingens performance. Grænsen ved 50 kopier/ml afspejler den mest almindelige detektionsgrænse ved laboratorieundersøgelser. Udover patienter der har en hiv-RNA ≥ 50 kopier/ml, kan patienter heller ikke registreres som havende hiv-RNA < 50 kopier/ml, hvis de har skiftet behandling eller ikke har fået målt hiv-RNA inden for det rette tidsrum, uanset deres hiv-RNA-niveau. De antiretrovirale regimer er i dag meget effektive til at supprimere virus-RNA, og over 90 % af patienterne i kliniske studier responderer på behandlingen i forhold til FDA's snapshotalgoritme. Derfor kan stor forbedring ikke forventes. Taget dette i betragtning vurderer fagudvalget, at en forskel på 5 procentpoint i andelen af patienter, der opnår plasma hiv RNA < 50 kopier/ml i henhold til FDA's snapshotanalyse efter 48 uger, er klinisk relevant.

"Viral svigt", defineret som hiv-RNA ≥ 50 kopier/ml ved uge 48

Patienter med hiv-RNA ≥ 50 kopier/ml plasma indgår i FDA's snapshotanalyse og angiver andelen af patienter, hvor den antiretrovirale behandling ikke har supprimeret virusmængden ved 48 uger. Fagudvalget vurderer dette som værende af kritisk betydning for vurderingen. Effektmålet ønskes opgjort som andelen af patienter, der har hiv-RNA ≥ 50 kopier/ml ved uge 48. Da opgørelsen for viral suppression i henhold til FDA's snapshotanalyse tager højde for skift af behandling og behandlingsophør pga. bivirkninger, ønsker fagudvalget at se opgørelse af viral svigt for den patientgruppe, der faktisk modtager behandling, og fagudvalget ønsker derfor at se resultater for per protokol-populationen. For patienter, der behandles med komparator, vurderer fagudvalget, at kun ganske få patienter vil opleve viral svigt. Fagudvalget forventer derfor ikke at kunne opnå stor forbedring på denne parameter og vil ikke tillade en større ændring i negativ retning. I relation hertil er den mindste klinisk relevante forskel af fagudvalget sat til 3 procentpoint.

Resistens

Hiv-virus kan hurtig mutere og derved udvikle resistens mod de antiretrovirale midler, der bruges i behandlingen. Opstår resistens, skal patienten skiftes til et andet antiviralt regime. Jo flere regimer en patient bliver resistent overfor, des svære er det at opnå antiviral effekt. Udvikling af resistens vil altså påvirke patientens mulighed for fremtidig behandling. Fagudvalget vurderer derfor, at effektmålet resistens er kritisk for vurderingen. Resistens måles ved en genotypisk og fænotypisk test af viral integrase, protease og revers transkriptase hos patienter, der oplever viral svigt. Effektmålet ønskes opgjort som andelen af patienter, der har udviklet resistens ved 48 uger. Den mindste klinisk relevante forskel mellem grupperne er fastsat af fagudvalget til 2 procentpoint. Der er ikke set udvikling af resistens overfor komparatoren dolutegravir i kliniske studier af behandlingsnaive patienter, derfor forventes det ikke, at bictegravir vil kunne præstere bedre på denne parameter. Fagudvalget vil ikke tillade en forværring ved en ny behandling og selv små forskelle, uanset retningen af forskellen, vil være relevante.

Alvorlige bivirkninger (serious adverse reactions, SAR)

Alvorlige bivirkninger måles ved andelen af patienter, som oplever en eller flere alvorlige bivirkninger. En

alvorlig bivirkning (serious adverse reaction, SAR) er en alvorlig uønsket hændelse (SAE), der er blevet vurderet at være relateret til lægemidlet. Bivirkningen skal opfylde en eller flere af følgende alvorlighedskriterier: resulterer i død, er livstruende, medfører hospitalsindlæggelse eller forlængelse af aktuelt hospitalsophold, resulterer i vedvarende eller betydelig invaliditet eller uarbejdsdygtighed, eller, ved administration til gravide, medfører anomali eller misdannelse hos barnet. Da behandlingen er livslang, accepteres kun en lille forskel i forekomsten af alvorlige bivirkninger, og den mindste klinisk relevante forskel mellem grupperne er fastsat af fagudvalget til 2 procentpoint.

Kliniske endepunkter/dødelighed
Målet med antiretroviral behandling er at nedsætte hiv-mængden i kroppen, hvilket efterfølgende giver øget CD4-celletal, som igen medfører nedsat risiko for aids og død. Mortalitet anses altid for at være et kritisk effektmål om end ikke til at være effektiv til at måle effektforskellige hiv-kombinationsregimer. Dødeligheden blandt patienter med hiv-infektion, som starter moderne kombinationsbehandling i vestlige lande, er så lav, at det ikke kan forventes at finde forskelle i kliniske afprøvningsstudier. Fagudvalget forventer derfor ikke at modtage data for dette effektmål.

Vigtige effektmål

Andel af patienter der oplever bivirkninger, som vurderes at være relateret til studiemedicinen
Da behandlingen er livslang, ønsker fagudvalget en opgørelse over, hvor mange patienter der får ikkealvorlige bivirkninger. En bivirkning er en uønsket hændelse, som er vurderet at være relateret til lægemidlet. Da de fleste bivirkninger i denne kategori er milde eller moderate, accepterer fagudvalget en vis grad af bivirkninger. Nogle patienter har desuden bivirkninger i en overgang, hvorefter de fortager sig. Fagudvalget vurderer på denne baggrund, at den mindste klinisk relevant forskel er 10 procentpoint.

Andel af patienter som ophørte med behandling pga. uønskede hændelser
I FDA's snapshotanalyse indgår også, hvor stor en andel af patienterne der ophørte behandling med studiemedicinen pga. uønskede hændelser. Forskellen på andelen af patienter der stopper behandling pga. en uønsket hændelse i et direkte sammenlignende studie kan være med til at nuancere billedet af bivirkninger, da denne opgørelse er uafhængig af vurderingen af, om hændelsen er relateret til lægemidlet. Fagudvalget vurderer, at en forskel på 5 procentpoint mellem grupperne er klinisk relevant.

Specifikke bivirkninger
Da behandlingen er livslang, er det vigtigt, at bivirkningsprofilen for de enkelte lægemidler belyses. Fagudvalget ønsker at EMAs produktresumé inddrages til at belyse, hvilke specifikke bivirkninger der optræder hyppigere i den ene behandlingsgruppe. Fagudvalget vil benytte dette til at vurdere alvorlighed, håndterbarhed og tyngde af bivirkningerne.

Dertil ønsker fagudvalget en sammenligning af lipidprofil, herunder plasmaværdier for total kolesterol, triacylglycerider, LDL og HDL og ændringer i knoglemineraltæthed (BMD) mellem intervention og komparator.

Livskvalitet
Livskvalitet kan have stor betydning for den enkelte patient og er derfor et patientnært effektmål. Særligt i denne patientpopulation, hvor behandlingen forventes at være livslang, er det vigtigt, at patienternes livskvalitet belyses, og effektmålet er derfor "vigtigt". Fagudvalget ønsker, at livskvaliteten for patienterne

først og fremmest bliver opgjort ved brug af et værktøj, der er udviklet til at måle livskvalitet. Derfor ønsker fagudvalget, at effektmålet livskvalitet måles med den globale score af det generiske instrument SF-36. Hvis livskvalitet ikke er opgjort ved SF-36, ønskes der resultater for Hiv Symptom Index. Fagudvalget bemærker, at Hiv Symptom Index til en vis grad er et surrogat for livskvalitet, da værktøjet primært fokuserer på selvrapporterede bivirkninger.

SF-36

SF-36 er et generisk instrument til at måle livskvalitet, som bygger på 36 spørgsmål. Spørgeskemaet er delt i 8 helbredsrelaterede domæner: Skalaerne omfatter helbredsområderne fysisk funktion, fysisk betingede begrænsninger, psykisk betingede begrænsninger, social funktion, fysisk smerte, psykisk helbred, energi samt alment helbred. Scoren måles på en skala fra 0-100, hvor højere score repræsenterer bedre livskvalitet [11]. SF-36 er valideret til brug hos patienter med hiv-infektion [12,13]. Livskvalitet skal opgøres på den globale score af SF-36, hvor forskellen på ændring fra baseline skal angives. For helbredsrelateret livskvalitet kan 0,5 SD af baselineværdier være en klinisk relevant forskel, og fagudvalget har derfor valgt at anvende 0,5 SD som den mindste klinisk relevante forskel [14].

Hiv Symptom Index

Hiv Symptom Index er udviklet til at sætte større fokus på tilstedeværelsen af hiv- eller behandlingsrelaterede symptomer hos hiv-inficerede patienter. Målet hermed er at forbedre fokus på og behandling af symptomer, som er associeret med adhærens og livskvalitet [15]. Hiv Symptom Index er udviklet og valideret af AIDS Clinical Trials Group (ACTG) [15]. Hiv Symptom Index er et spørgeskema med 20 punkter, der beskriver tilstedeværelsen og byrden af symptomer, der opstår hos voksne med hiv-infektion. Hvert punkt scores ved hjælp af en fempunkts ordinær skala, der spænder fra 'Jeg har ikke dette symptom' til 'Jeg har dette symptom, og det generer mig meget'. Ved den samlede scoring summeres antallet af symptomer, der er til stede, og antallet, der betragtes som generende. Fagudvalget bemærker, at denne index score til en vis grad afspejler bivirkningsprofilen, som allerede er belyst ved flere andre effektmål. Fagudvalget ønsker effektmålet opgjort som det gennemsnitlige antal generende symptomer, da fagudvalget finder dette er den mest relaterbare måde at opgøre livskvalitet, og dette er gjort i flere studier[16–18]. Generende symptomer er symptomer som patienten har scoret med 3 eller 4 i spørgeskemaet. De studier der har benyttet spørgeskemaet, er meget heterogene. Fagudvalget forventer at en ændring på 2 generende symptomer vil have betydning for livskvaliteten af den enkelte patient, hvilket også stemmer overens med at 0,5 SD for generende symptomer ved baseline er 2-3 i to publicerede studier [17,18]. Den mindste klinisk relevante forskel er derfor 2 generende symptomer målt ved gennemsnitlige antal mellem de to grupper efter 48 uger.

Mindre vigtige effektmål

Immunologisk respons bestemt ved CD4-celletal

Suppression af virusreplikation muliggør genopretning/bevarelse af patientens immunforsvar, hvilket medfører en betydelig nedsat risiko for aids og nedsat risiko for død. Patientens immunstatus kan måles ved patientens CD4-celletal. Fagudvalget vurderer, at immunstatus er et meningsfuldt effektmål, dog forventes det ikke, at CD4-tallet vil have klinisk betydning, når patienterne har relativt høje CD4-tal (median > 400 celler/µl) ved baseline, hvilket vil være tilfældet hos de fleste studiepopulationer. Desuden forventer fagudvalget, at CD4-celletallet vil stige sammenligneligt hos patienter, som opnår viral suppression, hvilket er medtaget som effektmål. Fagudvalget finder derfor, at effektmålet er mindre vigtigt.

4 Litteratursøgning

Databaser for søgningen

Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library).

Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgetermer

Søgningen skal inkludere det generiske navn og handelsnavnet for både det aktuelle lægemiddel og dets komparator(er), som kombineres med termer for indikationen. I skemaet nedenfor er angivet, hvilket lægemiddel og indikation der skal søges på. Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der er angivet i tabellen herunder

For lægemidlet og komparator skal der søges på termer for både det generiske navn, handelsnavnet og alternative stavemåder og eventuelle "MeSH/supplementary Concepts". Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes. For indikationen skal der søges på termer for indikationen, alternative stavemåder og eventuelle "MeSH". Også for indikationen skal både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning anvendes.

Lægemiddel	*Blokkene til venstre og højre kombineres med **AND***	**Indikation**
• bictegravir • biktarvy • GS-9883 • GS9883 *Der skal som minimum søges på ovennævnte termer. Der skal søges på det generiske navn, handelsnavn og alternative stavemåder og eventuelle MeSH/Supplementary Concepts, som kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive lægemidlet korrekt, f.eks. ved coformuleringer.*		• HIV • Human Immunodeficiency Virus • HIV infection *Der skal som minimum søges på ovenstående termer for indikationen. Dette inkluderer alternative stavemåder og eventuelle MeSH, som kombineres med **OR**. AND kan bruges, hvor flere termer skal forekomme samtidigt for at beskrive indikationen korrekt.*

De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

Kriterier for udvælgelse af litteratur

Inklusions- og eksklusionskriterier skal opstilles ud fra PICO-beskrivelserne (dvs., at de medtagene artikler eksempelvis skal omhandle patienter med hiv-infektion, en intervention hvor bictegravir er kombineret med emtricitabine og tenofovir alafenamid og komparator indeholder dolutegravir og to NRTIs). Studier ekskluderes på baggrund af de PICO-beskrivelser, der er angivet under det kliniske spørgsmål. Studierne skal rapportere mindst et af de kritiske eller vigtige effektmål.

Hvis der findes randomiserede kontrollerede studier, som kan besvare det kliniske spørgsmål, inkluderes data fra disse. Hvis der ikke findes randomiserede kontrollerede studier, kan data fra ukontrollerede kliniske studier inddrages. Data kan også ekstraheres fra EMAs EPAR, selvom denne ikke identificeres i litteratursøgningen.

Der ekskluderes først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Vurderingen af klinisk merværdi baseres på data fra publicerede fuldtekstartikler og data fra EMA's EPAR – Public assessment report. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data og data fra f.eks. abstracts kan fremsendes og vil indgå i vurderingen, såfremt Medicinrådet finder, at de er nødvendige for at sikre en fair sammenligning. Data skal i så fald stamme fra de forsøg, hovedpublikationerne rapporterer fra, og ansøger skal acceptere, at Medicinrådet offentliggør dem i ansøgningsskemaet og i rapporten vedr. klinisk merværdi.

5 Databehandling/analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Alt relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser specielt ift. præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (eksempelvis viral suppression, viral svigt, resistensudvikling, alvorlige bivirkninger, ikkealvorlige bivirkninger, behandlingsophør pga. uønskede hændelser), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risiko reduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end et sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

6 Andre overvejelser

Fagudvalget bemærker, at ved valg af behandling til den enkelte patient er det vigtigt at tage faktorer, der påvirker nemhed for patienten i betragtning, da dette kan påvirke behandlingscompliance. Nemhed for patienten kan påvirkes af tabletstørrelse, antal af tabletter, doseringshyppighed, om tablet(terne) skal tages med eller uden mad, og om der er interaktioner med andre lægemidler, herunder lægemidler til behandling af opportunistiske infektioner.

Da der er tale om livslang behandling, kan det kræve lang opfølgningstid at få afdækket den fulde bivirkningsprofil inklusive potentielle langtidsbivirkninger eller sjældne, men alvorlige bivirkninger. Fagudvalget vil derfor også tage længden og mængden af klinisk observationstid i betragtning.

Fagudvalget vil tage i betragtning, om der er praktiske forhold, som varierer mellem lægemidlerne, f.eks. behov for HLA-B5701 screening.

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8 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende hiv/aids

Formand	*Indstillet af*
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Olav Ditlevsen Larsen *Overlæge, ph.d.*	Region Syddanmark
Toke Barfoed *Overlæge, lektor*	Region Sjælland
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Marianne Kjettrup-Jensen *Farmaceut*	Dansk Selskab for Sygehusapoteksledelse
Bjarne Ørskov Lindhardt *Ledende overlæge, klinisk lektor*	Udpeget af formanden
Helle Elena Andersen	Danske Patienter
Bent Hansen	Danske Patienter

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