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Clinical evidence review of doravirine for treating HIV-1 in adults

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About this clinical evidence review

Clinical evidence reviews are a summary of the best available evidence for a single technology within a licensed indication, for commissioning by NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

This evidence review considers doravirine for treating human immunodeficiency virus type 1 (HIV-1) infection in adults who are treatment naive or treatment experienced, who have demonstrated no evidence of resistance to the Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) class.

Three studies were selected for inclusion in this review. Evidence for this review comes from non-inferiority trials, 2 double blinded and 1 open label active control. The evidence considers both the single dose formulation and fixed dose combination formulations of doravirine, and considers treatment naive and experienced populations.

Effectiveness

Evidence from the DRIVE-FORWARD and DRIVE-AHEAD studies suggest that doravirine single and combination dose formulations are non-inferior to antiretroviral therapies used in the studies in reducing viral load, specifically HIV-1 RNA to below 50 copies per ml, irrespective of starting baseline load, in a treatment naive population. The studies report that doravirine is as effective as comparator treatments at increasing CD4 cell count and it shows evidence of significantly better lipid control. The studies also show that doravirine avoids virologic resistance. In the DRIVE-AHEAD study there were significantly lower neuropsychiatric adverse events with doravirine.

The DRIVE-SHIFT study largely confirms these findings for the fixed dose combination formulation of doravirine in a treatment experienced adult population with no history of virologic failure who have virological suppression. Doravirine is shown to be non-inferior to comparator treatments in maintaining viral load below 50 copies per ml, has similar results on CD4 count, and shows evidence of significantly better lipid control.

Safety and tolerability

In the treatment naive population both formulations of doravirine are shown to be at least as effective as comparator treatments in their safety and tolerability profile. In the DRIVE-FORWARD study the results, adverse events and rates of protocol

defined virological failure (PDVF) with doravirine are broadly similar to the darunavir comparator. In the DRIVE-AHEAD study there were statistically significantly fewer neuropsychiatric adverse events specifically, and similar adverse event rates generally with doravirine compared to efavirenz/emtricitabine/tenofovir disoproxil fumarate. There were statistically significantly fewer discontinuations due to an adverse event or a drug related adverse event with doravirine compared to efavirenz/emtricitabine/tenofovir disoproxil fumarate. In both the treatment naive and treatment experienced populations where the combination fixed doravirine is investigated, PDVF numbers are higher but the cases of resistance on testing is lower.

Evidence gaps and limitations

While all the studies include UK based patients, it is not clear how large their numbers are, and there is not a large UK focused trial. The fixed dose combination formulation of doravirine contains an NRTI backbone that is different to the ones recommended by the British HIV Association (BHIVA) guidelines. In the DRIVE-AHEAD study where this formulation is used, the NRTI backbone used in the treatment and comparator differs, making it difficult to attribute differences to doravirine alone. In the DRIVE-SHIFT study it is unclear what NRTI backbone was used in the comparator making it less certain that any differences in outcomes are due to doravirine alone.

Table of contents

Abbreviations

Term	Definition
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
BHIVA	British HIV Association
CI	Confidence interval
DOR/3TC/TDF	Doravirine/lamivudine/tenofovir disoproxil fumarate
DSG	Delayed switch group
EFV/FTC/TDF	Efavirenz/emtricitabine/tenofovir disoproxil fumarate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
FTC	Emtricitabine
INI	Integrase inhibitor
ISG	Immediate switch group
IQR	Inter-quartile range
MDT	Multidisciplinary team
NICE	National Institute for Health and Care Excellence
NRTI	Nucleos(t)ide reverse-transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PHE	Public Health England
PI	Protease inhibitor
SD	Standard deviation

Medical definitions

Term	Definition
CD4 cell	A type of white blood cell that kills viruses in the body
NRTI 'backbone'	A class of antiretroviral drug that prevents the replication of HIV DNA to which a third drug is added in antiretroviral therapy. 'NRTI' is used to denote nucleoside reverse transcriptase inhibitors (e.g. lamivudine and emtricitabine) and nucleotide reverse transcriptase inhibitors (e.g. tenofovir).
Viral load	A measure of the number of viral particles in the body, reported as copies per millilitre of blood (copies/ml)
Virological failure	A term used to describe when the viral load in someone with HIV is greater than 200 copies/ml despite the use of antiretroviral therapy.
Virologically suppressed	A term used to describe when the level of HIV in the body is too low to be detected. This is usually when there are less than 50 copies of HIV-1 virus per ml of blood.

1 Introduction

Disease background

1.1 Human immunodeficiency virus (HIV) is a virus that if left untreated causes Acquired Immunodeficiency Syndrome (AIDS). HIV weakens the body's immune system by destroying CD4 positive (CD4+) T cells, a type of white blood cell that is vital in fighting infection. AIDS is the name used to describe a number of potentially life threatening infections and illnesses that occur when the body's immune system has been damaged by HIV. There is currently no cure for HIV but recent developments in antiretroviral therapy (ART) have transformed the outlook for people living with HIV to a manageable long term chronic condition, with a near normal life expectancy. ART prevents damage to the immune system by suppressing the HIV virus which reduces the risk of infection and of progression to AIDs.

Focus of review

1.2 In line with the marketing authorisation the focus of the review is doravirine for the treatment of HIV-1 in adults (aged 18 years and over) without past or present evidence of resistance to the NNRTI class.

Epidemiology and needs assessment

1.3 In England, 85,537 people received treatment for HIV in 2017 and 3,973 people were newly diagnosed with the condition (Country and PHE region HIV data tables, Public Health England, 2018). Over 98% of all people with HIV in the UK in 2017 were on antiretroviral therapy, and 97% of those had a viral load of less than 200 copies per ml (Public Health England, 2018).

1.4 HIV is a lifelong condition and the prevalence of comorbidities, including cardiovascular (CV) disease, chronic kidney disease (CKD), mental health disorders and osteoporosis is higher in people living with HIV, compared with those living without HIV (Bagkeris 2018). HIV services need to continuously evolve to meet the changing needs of people living with HIV

including the management of comorbidities and other complex health conditions.

Product overview

Mode of action

1.5 Doravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). NNRTIs inhibit HIV reverse transcriptase (RT). RT is an enzyme used by the body to generate complementary DNA. NNRTIs interact with HIV RT shutting down its ability to replicate the HIV virus, reducing the amount of HIV in the body (viral load).

1.6 Doravirine is available in 2 different formulations. It is available as a tablet containing 100mg of doravirine alone, to be used in addition to a nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone, as an alternative third agent in the treatment of HIV-1. It is also available as a fixed dose combination tablet containing 100mg of doravirine, 300mg of lamivudine and 300mg of tenofovir disoproxil fumarate equivalent to 245mg of tenofovir disoproxil. The fixed dose combination tablet does not require additional NRTIs to be taken.

Regulatory status

1.7 Doravirine has a marketing authorisation in the UK for treating HIV-1. The fixed dose combination tablet is indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir. The single entity tablet is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class.

Dosing information

1.8 For the single entity tablet, oral film coated tablets containing a 100mg dose of doravirine are taken once daily.

1.9 For the fixed dose combination tablet, oral film coated tablets containing a fixed dose combination of 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil fumarate) are taken once daily.

Treatment pathway and current practice

1.10 Treatment (antiretroviral therapy) is started immediately upon diagnosis of HIV. The overall goal of treatment is HIV-1 viral suppression (maintaining a low viral count). British HIV Association Treatment (BHIVA) guidelines for adults currently recommend the following first-line treatment :

- A nucleoside reverse-transcriptase inhibitor (NRTI) backbone consisting of 2 drugs from the following:
  - Tenofovir disoproxil fumarate and emtricitabine: recommended for individuals who do not show established or significant risk factors for kidney or bone problems. OR
  - Tenofovir alafenamide and emtricitabine: preferred option if the individual has established or significant risk factors for kidney or bone problems. OR
  - Abacavir and lamivudine: alternative option, although an individual should not be given abacavir if they are HLA-B*57:01 positive. AND
- A third drug: of which the preferred options are atazanavir/ritonavir, or darunavir/ritonavir, or raltegravir or elvitegravir/cobicistat or rilpivirine, or dolutegravir. An alternative option is efavirenz.

Current commissioning criteria

1.11 There are existing NHS England commissioning policies for HIV drugs other than doravirine. However, not all HIV drugs commissioned by NHS England have a published policy. There are currently 4 published clinical commissioning policies which could be of relevance to doravirine:

- Antiretroviral therapy is routinely commissioned to provide immediate treatment to all HIV positive people (adults and adolescents) regardless of the degree of damage to the body's immune system or risk of

transmission of HIV to another individual (see Clinical Commissioning Policy: Immediate antiretroviral therapy for treatment of HIV-1 in adults and adolescents).

- Tenofovir alafenamide (TAF) is routinely commissioned in adults with HIV-1 who have definite contraindications for tenofovir disoproxil fumarate (TDF), such as chronic kidney disease and/or osteoporosis, or those with relative contraindications such as approaching thresholds of osteoporosis and renal markers of disease (see Clinical Commissioning Policy: Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents). Patients with proven or suspected resistance to the component drugs in TAF should not be given this medication.
- Elvitegravir/cobicistat/emtricitabine/tenofovir is routinely commissioned in adults with HIV-1 who are unable to take efavirenz, or other first or second line treatments, due to toxicity, intolerance or adherence issues, as agreed in a HIV multidisciplinary team. For exclusion criteria please see Clinical Commissioning Policy: Elvitegravir/cobicistat/emtricitabine/tenofovir for treatment of HIV in adults.
- Dolutegravir is routinely commissioned in patients with HIV-1 who are unable to tolerate the first line therapy of efavirenz, or in those requiring an integrase inhibitor due to treatment failure or resistance. It should be combined with the lowest cost, clinically indicated backbone and at least 2 other anti-viral drugs to which the virus is sensitive. All patients considered for treatment must be discussed in a HIV specialist treatment multidisciplinary team (MDT) setting and the decision recorded. For commissioning exclusion criteria please see Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 infection (all ages).

1.12 The 2013/14 NHS Standard contract for specialised human immunodeficiency virus services (adults) could also be relevant to doravirine.

2 Evidence

Literature search

2.1 A literature search identified 130 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts. Ten references were obtained in full text and assessed for relevance. Inclusion and exclusion criteria were applied to the full text studies and 2 of the studies identified by NICE were included in the clinical evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

2.2 The company submission identified one additional study, an unpublished manuscript on the DRIVE-SHIFT trial, which was submitted for publication during the course of this review. This took the total number of studies included in the evidence review to 3.

Overview of included studies

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
DRIVE-FORWARD Molina et al (2018) Non-inferiority, double-blind RCT	Adults with previously untreated HIV-1 (n=766, 383 in each group)	Intervention: Doravirine + 2 NRTIs[a] Comparator: Ritonavir boosted darunavir + 2 NRTIs[a]	Proportion of patients achieving HIV-1 RNA<50 copies per ml at week 48
DRIVE-AHEAD Orkin et al (2019) Non-inferiority, double-blind RCT	Adults with previously untreated HIV-1 (n=728, 364 in each group)	Intervention: DOR/3TC/TDF Comparator: EFV/FTC/TDF	Proportion of patients achieving HIV-1 RNA<50 copies per ml at week 48
DRIVE-SHIFT Johnson et al (2019) Open label, randomised, active controlled, non-inferiority trial	Adults with HIV-1 with no history of virologic failure who have been virologically suppressed for ≥6 months on a stable regimen consisting of an NRTI backbone and ritonavir- or	Intervention: DOR/3TC/TDF Comparator: Ritonavir- or cobicistat boosted PI (atazanavir, darunavir or lopinavir), or cobicistat boosted INI (elvitegravir), or an NNRTI (efavirenz, nevirapine, or rilpivirine), each in	Proportion of patients maintaining HIV-1 RNA<50 copies per ml at week 48 in the immediate switch group compared to week 24 in the delayed switch group

	cobicistat boosted PI, cobicistat boosted INI, or an NNRTI. (n=670, 447 intervention, 223 comparator)	combination with two NRTIs	

[a] Investigator selected, either tenofovir and emtricitabine or abacavir and lamivudine

Abbreviations: NRTI Nucleos(t)ide reverse-transcriptase inhibitor; NNRTI Non-nucleoside reverse-transcriptase inhibitor; RCT Randomised controlled trial; DOR/3TC/TDF Doravirine/lamivudine/tenofovir disoproxil fumarate; EFV/FTC/TDF Efavirenz/emtricitabine/tenofovir disoproxil fumarate; PI Protease inhibitor; INI Integrase inhibitor

Key outcomes

2.3 The key outcomes for effectiveness and safety identified in the scope are discussed below. Table 2 below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study are in appendices 3 and 4.

Effectiveness

Viral load

2.4 The proportion of patients with HIV-1 RNA less than 50 copies per ml at 48 weeks follow up was the primary outcome in the DRIVE-FORWARD (single entity tablet), DRIVE-AHEAD (fixed dose combination tablet), and DRIVE-SHIFT (fixed dose combination tablet, treatment experienced population) studies. All of these studies were powered on the primary outcome.

2.5 For DRIVE-FORWARD and DRIVE-AHEAD, assuming a true response rate of 80%, a sample size of 340 participants in each treatment group had 90% power to detect non-inferiority at a one-sided α of 0.025. Non-inferiority was established if the lower bound of the 95% confidence interval (CI) for the treatment difference (doravirine minus darunavir for DRIVE-FORWARD, doravirine/lamivudine/tenofovir disoproxil fumarate

minus efavirenz/emtricitabine/tenofovir disoproxil fumarate for DRIVE-AHEAD) was greater than -10%.

2.6 For the DRIVE-SHIFT study, assuming a true response rate of 85% for both treatment groups, a sample size of 440 participants in the doravirine/lamivudine/tenofovir disoproxil fumarate as a fixed dose combination tablet (DOR/3TC/TDF) immediate switch group (ISG) and 220 in the baseline regimen delayed switch group (DSG), the study had 80% power to demonstrate the primary hypothesis that switching to DOR/3TC/TDF through 48 weeks is non-inferior to continuing the baseline regimen through 24 weeks at a one-sided α of 0.025, if the lower bound of the two sided 95% CI was greater than -8%.

Single entity tablet in treatment naive population

2.7 The number of participants with a viral load less than 50 copies/ml at week 48 in DRIVE-FORWARD in the group that received doravirine with emtricitabine/tenofovir disoproxil fumarate or doravirine with abacavir sulfate/lamivudine was 84% (321/383) compared to 80% (306/383) in the group that received darunavir and ritonavir with emtricitabine/tenofovir disoproxil fumarate or darunavir and ritonavir with abacavir sulfate/lamivudine (difference of 3.9%, 95% CI -1.6 to 9.4, p value not reported), indicating non-inferiority of doravirine to darunavir. These results included all patients who received treatment. Further analyses were conducted on smaller populations which excluded varying numbers of treatment discontinues from the analysed population, see Table 7 for further details. These produced similar results and also indicated non-inferiority.

2.8 The DRIVE-FORWARD study also found that doravirine was non-inferior to darunavir and ritonavir in the number of participants with a viral load of less than 40 copies/ml at 48 weeks (83.3% [319/383] with doravirine, 79.1% [303/383] with darunavir and ritonavir, difference of 4.2%, 95% CI -1.4 to 9.7) and the number of participants with a viral load of less than 200 copies/ml (85.6% [328/383] with doravirine, 82.5% [316/383] with

darunavir and ritonavir, difference of 3.1%, 95% CI -2.1 to 8.4). Results were similar for other population specifications, see Table 7 for further details.

2.9 These results for the primary outcome were broken down by subgroups in DRIVE-FORWARD, based on baseline, and other treatment, characteristics. This showed that while there was generally a treatment difference in favour of doravirine, there were no significant differences between the treatment and comparator based on the starting level of HIV-1 RNA (over 100,000 copies per ml, or equal to and less than 100,000 copies per ml), what NRTI backbone individuals were given (tenofovir and emtricitabine or abacavir and lamivudine), and starting CD4+ T cell count (over 200 cells per mm^3, or less than and equal to 200 cells per mm^3).

Fixed dose combination tablet in treatment naive population

2.10 The number of participants with a viral load less than 50 copies/ml at week 48 in the DRIVE-AHEAD study was non-inferior in the group that received the fixed dose combination tablet of doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) compared to the group that received efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) (84.3% [307/364] compared to 80.8% [294/364], difference of 3.5%, 95% CI -2.0 to 9.0, p value not reported).

2.11 Similar results were reported for individuals achieving HIV-1 RNA<40 copies/ml at week 48, 305 (83.8%) for DOR/3TC/TDF compared to 290 (79.7%) for EFV/FTC/TDF (difference 4.1%, 95% CI, -1.5 to 9.7), and HIV-1 RNA<200 copies/ml, 313 (86%) DOR/3TC/TDF compared to 301 (82.7%) EFV/FTC/TDF (difference not reported).

2.12 These results for the primary outcome were broken down by subgroups in DRIVE-AHEAD, based on baseline, and other treatment, characteristics. This showed that there were no significant differences in the number of participants with a viral load less than 50 copies/ml by baseline HIV-RNA (>100,000, ≤100,000, >500,000,or ≤50,000 copies per ml) or baseline

CD4+ T cell count (≤50, <50 and ≤ 200, and >200 cells per mm^3). Further there were no significant differences in the primary outcome measure between the intervention and control by ethnicity, continent, viral subtype (B or Non-B), and hepatitis B (HBV) or hepatitis C (HBC) co-infection (positive or negative). There was however a significant difference in favour of efavirenz in individuals 31 years of age and under, and in favour of doravirine in those aged over 31.

Fixed dose combination tablet in treatment experienced population

2.13 The DRIVE-SHIFT study enrolled individuals with HIV-1 and who were virologically suppressed for 6 months or more with no history of virological failure, on a PI, INI, or NNRTI (see Table 1 for treatment details) as a 3rd agent. Individuals were randomly assigned to switch to doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) on day 1 of the study (immediate switch group, ISG) or to continue on their baseline regimen until week 24 and then switch to DOR/3TC/TDF (delayed switch group, DSG). At week 24, 419 (93.7%) of participants in the DOR/3TC/TDF ISG and 211 (94.6%) in the baseline regimen DSG had HIV-1 RNA<50 copies/ml (difference -0.9%, 95% CI -4.7 to 3.0). At 48 weeks, the primary outcome measurement point, 406 (90.8%) in the DOR/3TC/TDF ISG had HIV-1 RNA<50 copies/ml, demonstrating that DOR/3TC/TDF at week 48 is non-inferior to existing antiretroviral therapy at week 24 (difference -3.8%, 95% CI -7.9 to 0.3).

2.14 After week 24, 209 individuals in the baseline regimen DSG switched to DOR/3TC/TDF. At week 48, 198 (94.7%) of these individuals had HIV-1 RNA<50 copies/ml.

2.15 The proportion of individuals with HIV-1<50 copies/ml was examined by subgroups defined by baseline demographic (age, gender, ethnicity, and region) and clinical (CD4 T-cell count, ART regimen, duration of prior regimen, history of NNRTI mutations, HBV or HCV co-infection) characteristics. In all instances there were no statistically significant differences in favour of either treatment, baseline regimen or

DOR/3TC/TDF indicating non-inferiority of doravirine to existing antiretroviral therapy.

2.16 The proportion of individuals with HIV-1 RNA≥ 50 copies per ml also indicated non-inferiority. The number of participants with ≥50 copies per ml was 1.8% in the baseline regimen and DOR/3TC/TDF groups at week 24 and 1.6% in the DOR/3TC/TDF ISG at week 48

2.17 After week 24, 209 individuals in the DSG switched to DOR/3TC/TDF. At week 48, 198 (94.7%) had HIV-1<50 copies/ml, 6 (2.9%) had HIV-1 RNA≥ 50 copies per ml, and 5 (2.4%) had no virological data.

CD4+ T cell count

Single entity tablet in treatment naive population

2.18 The average change in the number of CD4 cells from the beginning of treatment (baseline) to 48 weeks follow up in DRIVE-FORWARD was 193 cells per microlitre (µl) in the doravirine group compared to 186 per µl in the darunavir group (mean difference 7.1 per µl, 95% CI -20.8 to 35).

Fixed dose combination tablet in treatment naive population

2.19 The average change in the number of CD4 cells from the beginning of treatment (baseline) to 48 weeks follow up reported in DRIVE-AHEAD was an increase of 198 per µl for doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) and of 188 per µl for efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) (mean difference 10.1 per µl, 95% CI -16.1 to 36.3). The difference in the increase between the groups was from baseline not statistically significant.

Fixed dose combination tablet in treatment experienced population

2.20 In DRIVE-SHIFT, the mean change in the number of CD4 cells from baseline at week 24 was 5 cells/mm^3 in the doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) immediate switch group (ISG),

18 cells/mm^3 in the baseline regimen delayed switch group (DSG), and at 48 weeks, 14 cells/mm^3 in the DOR/3TC/TDF ISG.

Safety and tolerability

Viral resistance

2.21 Protocol defined virological failure (PDVF) defined as non-response (confirmed HIV-1 RNA of 200 copies or more per ml at week 24 or 36, or confirmed HIV-1 RNA of 50 copies or more per ml at week 48), or rebound (confirmed HIV-1 RNA of 50 copies or more per ml after initial response of HIV-1 RNA less than 50 copies per ml at any time during the study), was reported as an exploratory outcome in DRIVE-FORWARD, DRIVE-AHEAD, and DRIVE-SHIFT studies. In all cases a confirmation of PDVF required 2 consecutive measures of HIV-1 RNA≥ 50 copies/ml at least 1 week apart.

Single entity tablet in treatment naive population

2.22 In the DRIVE-FORWARD study 19 (5%) individuals in the doravirine group compared to 24 (6%) in the darunavir group had a protocol defined virological failure (PDVF) at 48 weeks. The majority of these were due to virological rebound after an initial response: 17/19 (89%) in the doravirine group and 19/24 (79%) in the darunavir group. Of the 43 individuals who had PDVF, 15 (7 in the doravirine and 8 in the darunavir group), underwent resistance testing. No genetic mutations associated with resistance to doravirine were identified and no phenotypic resistance to doravirine was observed. In the darunavir group, polymorphic mutations in the viral protease gene, but with no decrease in phenotypic susceptibility to darunavir, was observed in 3 individuals. No primary genotypic resistance mutations or phenotypic resistance to any of the NRTI backbone treatments were identified in either group.

2.23 Forty (10%) participants in the doravirine group and 53 (14%) participants in the darunavir group discontinued treatment for reasons other than PDVF. Of the 2 people in the doravirine group that had resistance testing, 1 developed a resistance to doravirine and emtricitabine (discontinued

due to non-compliance) and the other was phenotypically resistant to doravirine (discontinued due to a rash). 3 people in the darunavir group had resistance testing and no resistance to darunavir was reported.

Fixed dose combination tablet in treatment naive population

2.24 In the DRIVE-AHEAD study 22 participants (6.0%) in the doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) group and 14 (3.8%) in the efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) group met the criteria for protocol defined virological failure (PDVF). The majority (16/22 and 10/14, respectively) were due to viral rebound. 13 individuals in the DOR/3TC/TDF group, and 10 in the EFV/FTC/TDF of these had a successful genotype test. The figures for phenotypic testing were 13 and 9 respectively. 7 in the DOR/3TC/TDF group had developed a genotypic resistance to doravirine, 9 in the EFV/FTC/TDF a genotypic resistance to efavirenz. 6 individuals developed a phenotypic resistance to doravirine and 8 to efavirenz. 5 of the individuals tested in the DOR/3TC/TDF group showed evidence of genotypic resistance, and 5 of phenotypic resistance to an NRTI. 5 of the individuals tested in the EFV/FTC/TDF group showed evidence of genotypic resistance, and 4 of phenotypic resistance to an NRTI. It is not clear if the same individuals were tested for phenotypic and genotypic resistance. The statistical significance of the difference between the groups was not reported.

2.25 35 individuals in the DOR/3TC/TDF group and 50 in the EFV/FTC/TDF group discontinued the study for reasons other than PDVF. Of these 9 had a successful genotype test, and 9 a successful phenotype test in the DOR/3TC/TDF group. For the EFV/FTC/TDF group the corresponding numbers were 13 and 12 respectively. In those tested no individuals in the DOR/3TC/TDF group showed evidence of genotypic or phenotypic resistance to doravirine, or an NRTI. In the EFV/FTC/TDF group genotypic resistance, and phenotypic resistance to efavirenz, was found in 3 individuals.

Fixed dose combination tablet in treatment experienced population

2.26 In the DRIVE-SHIFT study, 6 participants in the doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) immediate switch group (ISG), 1 in the baseline regimen delayed switch group (DSG), and 1 in the DSG after switching to DOR/3TC/TDF had a protocol defined virological failure (PDVF). None of these individuals had RT mutations that confer resistance to other NRTIs, but are considered susceptible to doravirine treatment at baseline. 2 in the DOR/3TC/TDF ISG and 1 in the baseline regimen DSG had samples suitable for resistance testing. None in the DOR/3TC/TDF ISG showed genotypic or phenotypic resistance to DOR, 3TC or TDF. The single DSG participant showed genotypic and phenotypic resistance to 3TC and FTC at week 12, conferred through RT M184M/I.

2.27 Viral resistance testing was undertaken in 1 participant in the DOR/3TC/TDF ISG, and 2 in the baseline regimen DSG who had discontinued early without PDVF. None of these were found to have a genotypic or phenotypic resistance to any of the study drugs.

Adverse events

Single entity tablet in treatment naive population

2.28 The DRIVE-FORWARD study reports all cause and treatment related adverse events and serious adverse events. 80% of individuals who received doravirine reported an all causes adverse event, 31% had a treatment related adverse event. 19 (5%) had an all causes serious adverse event, and 1 (<1%) had a serious adverse event which was treatment related. 6 (2%) of patients had to discontinue treatment due to an adverse event, 4 (1%) due to a treatment related adverse event. The figures were broadly similar in the darunavir group, 78% had an adverse event of any cause, 32% had a treatment related adverse event, 6% had a serious adverse event all cause, and 1 (<1%) had a treatment related serious adverse event. 12 (3%) patients discontinued treatment due to an adverse event all causes, 8 (2%) due to a treatment related adverse

event. The most common adverse events in both arms were diarrhoea, nausea and headache. With the exception of the higher incidence of diarrhoea in the darunavir group, there were no clinically relevant differences in the incidence of treatment related adverse events between the two groups.

Fixed dose combination tablet in treatment naive population

2.29 The primary safety outcome measure in the DRIVE-AHEAD study was the proportion of participants with dizziness, sleep disorders/disturbances, and altered sensorium. By week 48 these all occurred in statistically significantly fewer participants in the doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) group compared to the efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) group (dizziness 8.8% compared to 37.1%, $p \leq 0.001$; sleep disorders/disturbances 12.1% compared to 25.2%, $p \leq 0.001$; and altered sensorium 4.4% compared to 8.2%, $p < 0.05$).

2.30 In the DRIVE-AHEAD study there were statistically significantly fewer people with any adverse events, drug related adverse events, discontinuations due to adverse events and discontinuations due to drug related adverse events by week 48 in the DOR/3TC/TDF group compared to the EFV/FTC/TDF group ($p \leq 0.05$). There were numerically fewer serious, and serious drug related adverse events in the DOR/3TC/TDF group, but the difference between the groups was not statistically significant.

2.31 In the DRIVE-AHEAD study, the most common adverse event affecting both groups was diarrhoea (11% DOR/3TC/TDF, 13% EFV/FTC/TDF), and headache (13% DOR/3TC/TDF, 12% EFV/FTC/TDF). Outside of neuropsychiatric events there were statistically significantly fewer people with skin/subcutaneous tissue disorders in the DOR/3TC/TDF group compared to the EFV/FTC/TDF group ($p < 0.05$). There were no categories or individual adverse events that were reported in statistically significantly

fewer people in the EFV/FTC/TDF group compared to the DOR/3TC/TDF group.

Fixed dose combination tablet in treatment experienced population

2.32 In the DRIVE-SHIFT study by week 24, 308 (68.9%) in the doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) immediate switch group (ISG), and 117 (52.5%) in the baseline regimen delayed switch group (DSG) had any adverse event, 19.5% and 2.2% respectively a drug related adverse event, and 2.9% and 3.6% a serious adverse event. 11 (2.5%) in the DOR/3TC/TDF ISG discontinued due to an adverse event, 1 (0.4%) in the baseline regimen DSG. 7 (1.6%) in the DOR/3TC/TDF ISG discontinued due to a drug related adverse event, none in the baseline regimen. There were no deaths in either group. After switching at week 24 to DOR/3TC/TDF, the DSG by week 48 had 126 (60.3%) any, 29 (13.9%) drug related, and 4 (1.9%) serious adverse events. There were 4 discontinuations due to any adverse event, and 4 due to a drug related adverse event, there were no deaths.

Blood lipids

Single entity tablet in treatment naive population

2.33 At 48 weeks in the DRIVE-FORWARD study there was a statistically significantly greater reduction from baseline ($p<0.0001$) in LDL cholesterol and non-HDL cholesterol in the doravirine group compared to the darunavir group (mean change in LDL-cholesterol -4.5 mg per decilitre (-4.5mg/dl), in the doravirine group, 9.9 mg/dl in the darunavir group [mean difference -14.6 mg/dl, 95% CI -18.2 to -11.1; $p<0.0001$]; mean change in non-HDL cholesterol, -5.3 mg/dl in the doravirine group, 13.8 mg/dl in the darunavir group [mean difference -19.3 mg/dl, 95% CI -23.3 to -15.4; $p<0.0001$]).

2.34 Total cholesterol and triglyceride concentrations decreased slightly in the doravirine group (-1.4 and -3.1 mg/dl respectively) but increased in the darunavir group (17.9 and 22 mg/dl respectively). The mean change in

HDL cholesterol was similar between the 2 groups, 3.9 mg/dl doravirine, and 4.2 mg/dl darunavir. P values were not reported.

Fixed dose combination tablet in treatment naive population

2.35 At 48 weeks in the DRIVE-AHEAD study, there was a statistically significantly greater reduction from baseline ($p<0.0001$) in LDL cholesterol and non-HDL cholesterol in the doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) group compared to the efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/3TC/TDF) group (mean change in LDL-cholesterol -1.6 mg/dl in the DOR/3TC/TDF group and 8.7 mg/dl in the EFV/FTC/TDF group, mean change in non-HDL-cholesterol -3.8 mg/dl in the DOR/3TC/TDF group and 13.3 mg/dl in the EFV/FTC/TDF group).

2.36 At 48 weeks in the DRIVE-AHEAD study, total cholesterol and triglyceride concentrations fell in the DOR/3TC/TDF group (-2.0 and -12.4 mg/dl respectively) but increased in the EFV/FTC/TDF group (21.8 and 22.0 mg/dl respectively). Mean levels of HDL-C increased in both groups, by 1.9 mg/dl for the DOR/3TC/TDF group and 8.5 mg/dl for the EFV/FTC/TDF group. P values were not reported.

Fixed dose combination tablet in treatment experienced population

2.37 In the DRIVE-SHIFT study at week 24, there was a statistically significant difference ($p<0.0001$) in the mean change in LDL-C and non-HDL-C between the doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) immediate switch group (ISG) and baseline regimen delayed switch group (DSG), in participants whose baseline regimen included a ritonavir boosted protease inhibitor. LDL-C -16.5 mg/dl DOR/3TC/TDF ISG, -1.9 mg/dl baseline regimen DSG, difference -14.7 mg/dl, 95% CI -18.9 to -10.4; Non-HDL-C, -24.7 DOR/3TC/TDF ISG, -1.3 mg/dl baseline regimen DSG, difference -23.0 mg/dl, 95% CI -28.0 to -18.1. There were negative mean differences between the ISG and DSG for cholesterol, triglycerides, and HDL-C of -25.8, -42.9, and -3.0, respectively. In all instances while

specific p values were not reported, the 95% CI were all within a negative range, showing a p value<0.05.

Evidence gaps and limitations

2.38 The evidence base is limited to 3 reasonably large company sponsored trials, with very similar methodologies. None of the studies directly compare doravirine to an integrase inhibitor.

2.39 While all the studies include UK based patients, the exact number of participants from the UK is not known. It is likely to be a relatively small part of the overall multi-national trial population recruited from over 20 countries.

2.40 The fixed dose combination formulation of doravirine contains an NRTI backbone that is different to the ones recommended in the BHIVA guidance. In the DRIVE-AHEAD study where this formulation is used, the NRTI backbone used in the treatment and comparator differs, making it difficult to attribute differences to doravirine alone. In the DRIVE-SHIFT study it is unclear what NRTI backbone was used in the comparator arm making it less certain that any differences in outcomes are due to doravirine alone.

Table 2 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Viral load<50 copies per ml at 48 weeks follow up	DRIVE-FORWARD	9/10	Directly applicable	A	Viral load is a measure of how much of the HIV virus there is in the blood, measured by the amount of HIV genetic material (RNA) present in the body. The measurement is given as the number of copies of the virus per millilitre of blood (copies/ml). If there are high levels of HIV in the blood, the risk of the person with HIV becoming ill from other infections and developing AIDS increases. The aim of antiretroviral therapy is to reduce viral load to less than 50 copies/ml to lower the risk of the person with HIV acquiring other infections. In addition, when viral load is less than 50 copies/ml, the risk of HIV being passed on to another person is extremely low, even during unprotected sexual intercourse. The DRIVE studies reported that the number of participants who had a viral load of less than 50 copies/ml at week 48 was statistically significantly non-inferior in the groups that received doravirine compared with the groups who received other ART (DRIVE-FORWARD 84% vs. 80%, treatment difference 3.9%, 95% CI -1.6 to 9.4; DRIVE-AHEAD 84% vs. 81%, treatment difference 3.5%, 95% CI -2.0 to 9.0; DRIVE-SHIFT 91% at week 48 with doravirine vs. 95% at week 24 with existing ART, treatment difference -3.8%, 95% CI -7.9 to 0.3). The results remained statistically significantly non-inferior for subgroups based on baseline characteristics, with the exception of age in the DRIVE-AHEAD study. The evidence suggests that doravirine is as effective as existing antiretroviral therapies in maintaining a viral load of less than 50 copies/ml. The results should be treated with some caution as the studies were powered on the primary outcome, a viral load<50 copies per ml. The fixed dose combination doravirine formulation contains an NRTI backbone combination that is different to the ones recommended in the BHIVA
	DRIVE-AHEAD	8/10	Directly applicable		
	DRIVE-SHIFT	7/10	Directly applicable		

					guidelines. In the DRIVE-FORWARD study the NRTI backbone differed between the intervention and control making it less certain that the outcome was as a result of doravirine, in the DRIVE-SHIFT study the NRTI backbone was not specified. The trials are all multi-national and multi-centre containing an undisclosed number of UK based patients, who are likely to amount to a small component of the overall study population.
CD4 cell count	DRIVE-FORWARD	9/10	Directly applicable	A	CD4 cells are white blood cells that fight infections in the body. The higher the number of CD4 cells in the body, the more capable the body is of fighting infection. A CD4 cell count of over 500 indicates that the body is able to effectively fight most infections. A CD4 cell count of below 200 indicates that the body is at high risk of developing serious illnesses. The HIV-1 virus kills CD4 cells, increasing the risk of the person with HIV developing serious illnesses. The DRIVE studies reported that there was no statistically significant difference in change in CD4 cell count with doravirine compared to existing ART (DRIVE-FORWARD increase of 193 cells/µl vs. increase of 186 cells/µl, mean difference 7.1 cells/µl, 95% CI -20.8 to 35; DRIVE-AHEAD increase of 198 cells/µl vs. increase of 188 cells/µl, mean difference 10.1 cells/µl, 95% CI -16.1 to 36.3; DRIVE-SHIFT increase of 14 cells/µl with doravirine at week 48 vs. increase of 18 cells/µl with existing ART at week 24, mean difference not reported). The evidence suggests that doravirine is as effective as existing antiretroviral treatments in promoting CD4 cells. The results should be treated with some caution due to the reasons given previously.
	DRIVE-AHEAD	8/10	Directly applicable		
	DRIVE-SHIFT	7/10	Directly applicable		
Viral resistance	DRIVE-FORWARD	9/10	Directly applicable	A	Viral resistance refers to when a virus is no longer affected by a drug that used to be effective against it. It means that a virus will continue to multiply despite the presence of a drug that would usually kill it. Viral resistance is caused by a mutation in a virus gene. Frequent mutations occur in the HIV-1 virus because it replicates very quickly and does not correct any mutations
	DRIVE-AHEAD	8/10	Directly applicable		
	DRIVE-SHIFT	7/10	Directly applicable		

					that occur when it replicates. The frequent mutations in the HIV-1 virus increases the risk of it becoming resistant to drugs. The DRIVE studies used protocol defined virologic failure (PDVF) as their measure of viral resistance. The number of participants with PDVF was similar in the groups that received doravirine and the groups that received existing ART (DRIVE-FORWARD 5% vs. 6%, p value not reported; DRIVE-AHEAD 6% vs. 4%, p value not reported; DRIVE-SHIFT 1% vs. <1%, p value not reported). There were 2 (1%) reported cases of resistance to doravirine in the DRIVE-FORWARD study, with no reported cases of resistance to existing ART. However, in the DRIVE-AHEAD study fewer people developed resistance to doravirine (7 [2%] people with genotypic resistance and 6 [2%] people with phenotypic resistance) compared to existing NNRTIs (12 [3%] people with genotypic resistance and 11 [3%] people with phenotypic resistance). There were no reported cases of resistance to doravirine or other NNRTIs in the DRIVE-SHIFT study. The statistical significance of the differences in viral resistance between the groups was not reported. The results suggest that doravirine is as effective as existing antiretroviral treatments in avoiding viral resistance to treatment. The results should be treated with caution for the reasons given previously.
Blood lipids	DRIVE-FORWARD	9/10	Directly applicable	A	Blood lipids are fats in the blood, such as fatty acids and cholesterol. The presence of elevated or abnormal levels of lipids or lipoproteins in the blood (hyperlipidaemia) increases the risk of developing heart disease, gall bladder disease and pancreatitis. HIV infection and some HIV medications can increase the risk of hyperlipidaemia. In the DRIVE studies there was a statistically significantly greater decrease in LDL cholesterol (p<0.0001 in all studies), HDL cholesterol (p values not reported), and non-HDL cholesterol (p<0.0001 in all studies) from baseline with doravirine compared to existing ART. There was also a reduction in cholesterol and triglycerides from baseline with doravirine compared to existing ART, but the statistical significance of this was not reported. The
	DRIVE-AHEAD	8/10	Directly applicable		
	DRIVE-SHIFT	7/10	Directly applicable		

					results for change in total cholesterol/HDL cholesterol ratio from baseline were mixed, with 1 study reporting a statistically non-significant difference between doravirine and existing ART and another study reporting a smaller reduction with doravirine compared to existing ART, but without reporting the statistical significance. The evidence suggests a statistically significant reduction in lipid levels with doravirine compared to existing antiretroviral treatments. The results should be treated with some caution for the reasons given previously.
Adverse events	DRIVE-FORWARD	9/10	Directly applicable	A	Adverse events are unintentional and undesirable signs and symptoms reported during a study. They may be related to drugs being used in the study or they may be caused by other factors, such as natural progression of an existing condition. They can be mild or serious. If an event is thought to be related to the drugs being used in a study, it is known as a drug-related adverse event. In DRIVE-FORWARD, all cause adverse events were reported in 80% of the participants in the doravirine group and 78% of participants in the comparator group. The adverse events were treatment related in 31% and 32% of the participants respectively, and less than 1% of participants in each group had a serious treatment related adverse event. Around 1% of participants in the doravirine group and 2% of participants in the comparator group discontinued treatment because of treatment related adverse events. In DRIVE-AHEAD, all cause adverse events were reported in 83% of the participants in the doravirine group and 91% of participants in the comparator group (treatment difference statistically significant, p value not reported). The adverse events were treatment related in 31% and 63% of the participants respectively (treatment difference statistically significant, p value not reported), and around 1% of participants in each group had a serious treatment related adverse event (treatment difference not statistically significant, p value not reported). Two percent of participants in the doravirine group and 6% of participants in the comparator group
	DRIVE-AHEAD	8/10	Directly applicable		
	DRIVE-SHIFT	7/10	Directly applicable		

					discontinued treatment because of treatment related adverse events (treatment difference statistically significant, p value not reported). In DRIVE-SHIFT, all cause adverse events were reported in 69% of the participants in the doravirine group at 48 weeks and 53% of participants in the comparator group at 24 weeks. The adverse events were treatment related in 20% and 2% of the participants respectively, and less than 1% of participants in each group had a serious treatment related adverse event. Around 2% of participants in the doravirine group and none of the participants in the comparator group discontinued treatment because of treatment related adverse events. The results suggest that in the treatment naive population doravirine formulations are at least as effective at avoiding adverse events as existing antiretroviral treatments. The results are less clear for the treatment experienced group with a higher overall number of adverse events and a noticeably higher number of drug related adverse events. The results should be treated with some caution for the reasons given previously.

3 Related NICE guidance and NHS England clinical policies

NICE has not issued any guidance on the treatment of the HIV-1 virus, but has produced the following related guidance.

- HIV testing: encouraging uptake (2017) NICE quality standard 157
- HIV testing: increasing uptake among people who may have undiagnosed HIV (2016) NICE guideline 60
- Pre-exposure prophylaxis of HIV in adults at high risk: Truvada (emtricitabine/tenofovir disoproxil) (2016) NICE evidence summary 78
- Deep dermal injection of non-absorbable gel polymer for HIV-related lipoatrophy (2013) NICE interventional procedures guidance 439

There are related commissioning policies from NHS England

- Immediate antiretroviral therapy for treatment of HIV-1 in adults and adolescents. March 2018. NHS England Reference: 170028P
- Use of cobicistat as a booster in treatment of HIV infection (all ages). Updated September 2018. NHS England Reference F03/P/b.
- Dolutegravir for treatment of HIV-1 infection (all ages). Updated August 2018. NHS England Reference B06/P/a.
- Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents. Updated February 2017. NHS England Reference: 16043/P
- Elvitegravir/cobicistat/emtricitabine/tenofovir for treatment of HIV in adults. July 2015. NHS England Reference F03/P/a

4 References

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Feng M, Sachs NA, Xu M, et al. (2016) Doravirine Suppresses Common Nonnucleoside Reverse Transcriptase Inhibitor-Associated Mutants at Clinically Relevant Concentrations. Antimicrobial Agents and Chemotherapy;60(4):2241-7.

Gatell J M; Hagins D P; Thompson M, et al. (2014). Forty-eight-week efficacy and safety and early CNS tolerability of doravirine (MK-1439), a novel NNRTI, with TDF/FTC in ART-naive HIV-positive patients

Gatell J M; Raffi F; Plettenberg A, et al. (2015) Efficacy and safety of doravirine 100 mg QD vs. efavirenz 600 mg QD with TDF/FTC in ART-naive HIV-infected patients: week 24 results. Journal of the international AIDS society, vol 18 pp 36-37

Gatell J M; Raffi F; Plettenberg A, et al. (2016). Doravirine 100mg QD vs efavirenz TDF/FTC in ART-naive HIV patients: Week 48 results [CROI Abstract 470]. In Special Issue: Abstracts From the 2016 Conference on Retroviruses and Opportunistic Infections. Top Antivir Med; 24(e-1):391

Johnson M, Kumar P, Molina, JM et al. (2019) Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. JAIDS: Journal of Acquired Immune Deficiency Syndromes, published ahead of print in April 2019, accessed on 14th May 2019 https://journals.lww.com/jaids/Abstract/publishahead/Switching_to_Doravirine_Lamivudine_Tenofovir.96395.aspx

Molina JM, Squires K, Sax, P et al. (2018) Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. The Lancet HIV, volume 5, issue 5, pages e211-e220

Morales-Ramirez J O; Gatell J M; Hagins D P, et al. (2014). Safety and antiviral effect of MK-1439, a novel NNRTI (FTC/TDF) in art-naive HIV-infected patients. Topics in Antiviral Medicine; vol 22 PT E-1 pp46-47

Orkin C, Squires K, Molina JM, et al. (2019) Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus–1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clinical Infectious Diseases, volume 68, issue 4, pages 535-544

Public Health England (2018). United Kingdom National HIV Surveillance Data Tables

Schürmann D; Sobotha C; Gilmartin J, et al. (2016). A randomized, double-blind, placebo-controlled, short-term monotherapy study of doravirine in treatment-naive HIV-infected individuals. AIDS. 30(1):57–63, JAN

Waters L, Ahmed N, Angus B et al. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update).

This clinical evidence review has been written by NICE, following the process set out in the standard operating procedure.

Appendix 1 Search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
Platform: Ovid
Version: 1946 to November 06, 2018
Search date: 07/11/18
Number of results retrieved: 40
Search strategy:

1 doravirine.ti,ab. (38)
2 pifeltro.ti,ab. (0)
3 mk-1439.ti,ab. (11)
4 913P6LK81M.ti,ab. (0)
5 delstrigo.ti,ab. (0)
6 J05AR.ti,ab. (0)
7 "DOR/3TC/TDF".ti,ab. (1)
8 or/1-7 (43)
9 (HIV or HIV-1 or "human immunodeficiency virus").ti,ab. (305196)
10 HIV-1/ (74498)
11 (antiretroviral or anti-retroviral or "viral load").ti,ab. (72613)
12 NNRTI.ti,ab. (2343)
13 or/9-12 (322917)
14 8 and 13 (41)
15 limit 14 to english language (40)
16 Animals/ not (Animals/ and Humans/) (4479417)
17 15 not 16 (40)

Database: Embase
Platform: Ovid
Version: 1974 to 2018 November 06
Search date: 07/11/18
Number of results retrieved: 74
Search strategy:

1 doravirine.ti,ab. (50)
2 doravirine/ (76)
3 pifeltro.ti,ab. (0)
4 mk-1439.ti,ab. (16)
5 913P6LK81M.ti,ab. (0)
6 delstrigo.ti,ab. (0)
7 J05AR.ti,ab. (3)
8 "DOR/3TC/TDF".ti,ab. (2)
9 or/1-8 (85)
10 (HIV or HIV-1 or "human immunodeficiency virus").ti,ab. (377372)
11 exp Human immunodeficiency virus 1/ (74581)
12 (antiretroviral or anti-retroviral or "viral load").ti,ab. (98144)
13 NNRTI.ti,ab. (3741)
14 or/10-13 (406524)
15 9 and 14 (80)
16 limit 15 to english language (79)
17 nonhuman/ not (human/ and nonhuman/) (4251748)
18 16 not 17 (74)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL;
Platform: Wiley
Version:
CDSR – Issue 11 of 12, November 2018
CENTRAL – Issue 10 of 12, October 2018
Search date: 07/11/18
Number of results retrieved: CDSR 0; CENTRAL 16.
Search strategy:

#1	doravirine:ti,ab	21
#2	pifeltro:ti,ab	0
#3	mk-1439:ti,ab	7
#4	913P6LK81M:ti,ab	0
#5	delstrigo:ti,ab	0
#6	J05AR:ti,ab	0
#7	(DOR NEXT 3TC NEXT TDF):ti,ab	1
#8	{or #1-#7}	22
#9	(HIV or HIV-1 or "human immunodeficiency virus"):ti,ab	18606
#10	MeSH descriptor: [HIV-1] this term only	2546
#11	(antiretroviral or anti-retroviral or "viral load"):ti,ab	8033
#12	NNRTI:ti,ab	409
#13	{or #9-#12}	19994
#14	#8 and #13	22
#15	"clinicaltrials.gov".so	170418
#16	#14 not #15	16

Database: DARE; HTA database; NHS EED via Centre for Reviews and Dissemination website
DARE – (legacy database, last updated March 2015)
HTA
NHS EED (legacy database, last updated March 2015)
Search date: 07/11/18
Number of results retrieved: DARE – ; HTA – ; NHS EED – .
Search strategy:
1 (doravirine or mk-1439) OR (pifeltro) OR (913P6LK81M) 0
2 (delstrigo) OR (J05AR) OR ("DOR/3TC/TDF") 0

No results for doravirine terms so did not continue strategy further

Appendix 2 Study selection

The search strategy presented in appendix 1 yielded 130 studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

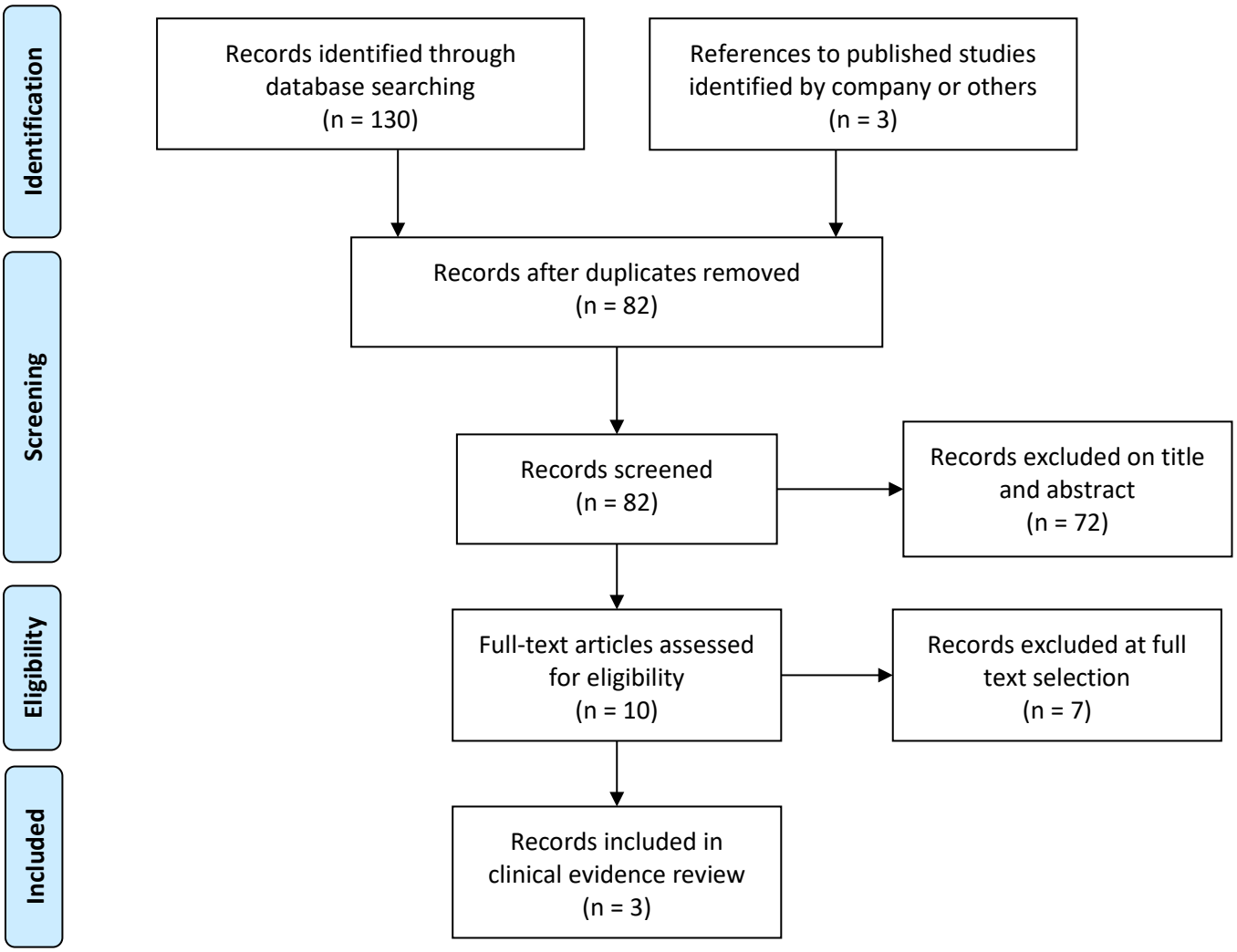
Sifting criteria	Inclusion	Exclusion
Population	Adults with HIV-1	Non-humans
Intervention	Doravirine in a single dose tablet regimen containing the NRTI backbone in the single tablet. Doravirine in a single dose tablet containing doravirine alone, designed to be taken in combination with the NRTI backbone	
Comparator	Any other antiretroviral therapy	
Outcomes	**Efficacy** • Percentage of patients with an undetectable HIV-1 viral load (<50 copies/ml) post naïve initiation and/or switch • Change in CD4 cell count from baseline • Change in HIV-1 RNA count from baseline • Liver enzyme levels • Blood lipid levels **Adverse events** • Incidence and severity of adverse events • Discontinuations due to adverse events • Overall adverse events **Other** • Medication adherence • Treatment-emergent resistance • The following outcomes are included as standard and will be considered where evidence allows: survival; progression free survival; health related quality of life (including mobility; self-care; usual activities; anxiety/depression); replacement of more toxic treatment; dependency on care giver/supporting independence; safety (including adverse effects); and delivery of the medicine.	

Other		Abstracts Non-English language Duplicates Opinion pieces, commentaries, epidemiological studies, burden of disease studies

Table 3 Studies excluded at full text

Study reference	Reason for exclusion
Colombier M A; Molina J M. (2018) Doravirine: A review. Current Opinion in HIV and AIDS; 13 (4): 308-314	Review document containing no new evidence.
Feng M, Sachs NA, Xu M, et al. (2016) Doravirine Suppresses Common Nonnucleoside Reverse Transcriptase Inhibitor-Associated Mutants at Clinically Relevant Concentrations. Antimicrobial Agents and Chemotherapy. 60(4):2241-7.	Non-human, pharmacological study with outcomes outside of scope
Gatell J M; Hagins D P; Thompson M, et al. (2014). Forty-eight-week efficacy and safety and early CNS tolerability of doravirine (MK-1439), a novel NNRTI, with TDF/FTC in ART-naive HIV-positive patients	Conference presentation/abstract
Gatell J M; Raffi F; Plettenberg A, et al. (2016). Doravirine 100mg QD vs efavirenz TDF/FTC in ART-naive HIV patients: Week 48 results [CROI Abstract 470]. In Special Issue: Abstracts From the 2016 Conference on Retroviruses and Opportunistic Infections. Top Antivir Med; 24(e-1):391	Conference presentation/abstract
Gatell J M; Raffi F; Plettenberg A, et al. (2015) Efficacy and safety of doravirine 100 mg QD vs. efavirenz 600 mg QD with TDF/FTC in ART-naive HIV-infected patients: week 24 results. Journal of the international AIDS society, vol 18 pp 36-37	Conference presentation/abstract
Morales-Ramirez J O; Gatell J M; Hagins D P, et al. (2014). Safety and antiviral effect of MK-1439, a novel NNRTI (FTC/TDF) in art-naive HIV-infected patients. Topics in Antiviral Medicine; vol 22 PT E-1: 46-47	Conference presentation/abstract
Schürmann D; Sobotha C; Gilmartin J, et al. (2016). A randomized, double-blind, placebo-controlled, short-term monotherapy study of doravirine in treatment-naive HIV-infected individuals. AIDS. 30(1):57–63, JAN	Placebo comparator

Figure 1 Flow chart of included studies



Appendix 3 Evidence tables

Table 4 Molina et al. 2018

Study reference	Molina JM, Squires K, Sax, P et al. (2018) Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. The Lancet HIV, volume 5, issue 5, pages e211-e220
Unique identifier	NCT02275780
Study type (and NSF-LTC study code)	Randomised, double blind, phase 3, non-inferiority trial (P1)
Aim of the study	To assess the safety and efficacy of fixed dose doravirine when used as a third agent versus ritonavir boosted darunavir in treatment naïve HIV-1.
Study dates	1 December 2014 to 20 October 2015
Setting	125 clinical centres in 15 countries (Argentina, Australia, Austria, Canada, Chile, Denmark, France, Germany, Italy, Romania, Russian Federation, South Africa, Spain, UK, USA)
Number of participants	786 received treatment and were included in the full analysis set
Population	Adults (aged 18 and over) naïve to antiretroviral therapy with plasma HIV-1 RNA of at least 1000 copies per ml at screening Baseline demographics and clinical characteristics Male: Doravirine 83%, Darunavir 85% Female: Doravirine 17%, Darunavir 15% Ethnicity: White: Doravirine 73%, Darunavir 73% Ethnicity: Black: Doravirine 22%, Darunavir 23% Ethnicity: Asian: Doravirine 2%, Darunavir 2% Ethnicity: Other: Doravirine 3%, Darunavir 2% Median age in years (IQR): Doravirine 33 (27-41), Darunavir 34 (27-53) Median CD4 count, cells per µl (IQR): Doravirine 410 (299-550), Darunavir 393 (257-547) Median HIV-1 RNA log_{10} copies per ml (IQR): Doravirine 4.4 (4.0-4.9), Darunavir 4.4 (4.0 to 4.8) Patients were randomly assigned to treatment. Statistical significance of any differences in baseline characteristics was not reported
Inclusion criteria	Adults (aged≥18 years) with HIV-1 infection naive to antiretroviral therapy. Plasma HIV-1 RNA of at least 1000 copies per ml at screening. Alkaline phosphatase concentrations three times the upper limit of normal or less. Aminotransferase concentrations five times the upper limit of normal or less.

	A creatinine clearance rate of 50 ml/min or higher at the time of screening. No documented or known resistance to any of the study regimen components.
Exclusion criteria	History or evidence of any condition, therapy, laboratory abnormality or circumstance that might confound results or interfere with participation in the study. Use of recreational or illicit drugs or a recent history of alcohol or drug dependency. Treatment for a viral infection other than HIV-1, with an agent that is active against HIV-1. Documented or known resistance to any study drug. Participation in a study with an investigational compound or device within 30 days prior to informed consent. Use of systemic immunosuppressive therapy or immune modulators within 30 days prior to informed consent or is anticipated to need them during the study. Requires or is anticipated to require any of the prohibited medications noted in the protocol. Significant hypersensitivity or other contraindication to any of the components of the study drugs. Current (active) diagnosis of acute hepatitis due to any cause. Pregnant, breastfeeding, or expecting to conceive during the study. Expecting to donate eggs or sperm during the study. Have an immediate family member who is investigational site or sponsor staff with direct involvement in the trial.
Intervention(s)	• Emtricitabine 200mg/tenofovir disoproxil fumarate 300mg and doravirine 100mg • Abacavir sulfate 600mg/lamivudine 300mg and doravirine 100mg
Comparator(s)	• Emtricitabine 200mg/tenofovir disoproxil fumarate 300mg and darunavir 800mg and ritonavir 100mg • Abacavir sulfate 600mg/lamivudine 300mg and darunavir 800mg and ritonavir 100mg
Length of follow-up	48 weeks
Outcomes	Primary outcome: • Proportion of patients achieving HIV-1 RNA<50 copies per ml at week 48
	Secondary and exploratory outcomes: • HIV-1 RNA<40 copies per ml • Change from baseline in CD4 T-cell count • HIV-1 RNA<200 copies per ml • Time to loss of virological response • Protocol defined virological failure • The development of viral resistance to the study medications

	Safety outcomes: • Change from baseline in LDL-cholesterol and non-HDL-cholesterol • Incidence of adverse events • Time to discontinuation because of adverse events • Predefined limits of change in laboratory parameters
Source of funding	Company funded (Merck, Sharp and Dohme Corp)

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Research design is clearly stated and appropriate
3. Are the methods clearly described?	2/2	Clearly described and appropriate
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	The data was adequate and interpreted appropriately. The study was sufficiently populated for its power calculations to establish non-inferiority on the primary outcome.
5. Are the results generalisable?	1/2	This is a multi-centre trial involving 125 centres in 15 countries, including 8 from the UK. The findings are very likely generalizable to UK clinical practice. Nonetheless, results are not reported by country, and there is a slight under-representation of females overall for a UK setting.
Total	9/10	
Applicability *	Directly applicable	The intervention and indication are directly relevant to the decision problem.

* Note - Direct studies focus on people with the indication and characteristics of interest.

Table 5 Orkin et al. 2019

Study reference	Orkin C, Squires K, Molina JM, et al. (2019) Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus–1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clinical Infectious Diseases, volume 68, issue 4, pages 535-544
Unique identifier	NCT02403674
Study type (and NSF-LTC study code)	Randomised, double blind, phase 3, non-inferiority trial (P1)
Aim of the study	To demonstrate the non-inferior efficacy of DOR/3TC/TDF to EFV/FTC/TDF
Study dates	48 week cut off point 20 March 2017
Setting	126 sites in 24 countries (Australia, Belgium, Canada, Chile, Colombia, Denmark, Germany, Guatemala, Honduras, Israel, Mexico, Netherlands, New Zealand, Peru, Portugal, Puerto Rico, Russia, South Africa, Spain, Switzerland, Taiwan, Thailand, UK, and USA)
Number of participants	728 treated (364 per treatment arm)
Population	Adults (aged 18 and over) naive to antiretroviral therapy with plasma HIV-1 RNA of at least 1000 copies per ml within 45 days before study treatment Baseline demographics and clinical characteristics DOR/3TC/TDF: Median age, years (range) 32 (18-70); Male 84%; Ethnicity: White 49%; Ethnicity: Black or African American 18%; Ethnicity: Asian 16%; Ethnicity: Other 17%; Median CD4 count, cells/mm^3 (range) 414 (19-1399); Median HIV-1 RNA, log10 copies/ml (range) 4.4 (2.4-6.1) EFV/FTC/TDF: Median age, years (range) 30 (18-69); Male 85%; Ethnicity: White 47%; Ethnicity: Black or African American 19%; Ethnicity: Asian 18%; Ethnicity: Other 17%; Median CD4 count, cells/mm^3 (range) 388 (19-1452); Median HIV-1 RNA, log10 copies/ml (range) 4.5 (2.6-6.4) Patients were randomly assigned to treatment. Statistical significance of any differences in baseline characteristics was not reported
Inclusion criteria	Men and women 18 years of age or older with plasma HIV-1 RNA of ≥1000 copies/ml (within 45 days before study treatment) who were naive to antiretroviral therapy
Exclusion criteria	Documented or known resistance to any study drug. Treatment for a viral infection other than HIV-1 (such as hepatitis B) with an agent that is active against HIV-1. Significant hypersensitivity or other contraindication to any of the components of the study drugs.

	Current (active) diagnosis of acute hepatitis due to any cause. Evidence of decompensated liver disease; or liver cirrhosis and a Child-Pugh Class C score or Pugh-Turcotte (CPT) score>9. Pregnancy, breastfeeding, or expecting to conceive. Use of recreational or illicit drugs, or recent history of drug or alcohol abuse or dependence.
Intervention(s)	Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
Comparator(s)	Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
Length of follow-up	48 weeks
Outcomes	Primary outcome: • HIV-1 RNA<50 copies per ml
	Secondary and exploratory outcomes: • HIV-1 RNA<40 copies per ml • HIV-1 RNA<200 copies per ml • Change from baseline in CD4 T-cell count • Protocol defined virological failure
	Safety outcomes: • Proportion of participants with neuropsychiatric adverse events in 3 categories which represented most commonly reported in the phase 2b study (dizziness, sleep disorders/disturbances, and altered sensorium) • Incidence of any adverse event and drug related adverse events • Change from baseline in fasting lipids (LDL-cholesterol and non-HDL-cholesterol)
Source of funding	Company funded (Merck, Sharp and Dohme Corp)

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	The research question and aims are clearly stated
2. Is the research design appropriate for the aims and objectives of the research?	2/2	The research design is robust and appropriate
3. Are the methods clearly described?	2/2	Clear and appropriate
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Data adequate and interpreted appropriately. However the possible impact of differences in the NRTI backbone between treatment and control are not considered.
5. Are the results generalisable?	1/2	This is a large multi-national study with a UK component. While the results are likely generalizable to the UK, the results are not broken down by country, and there is an under-representation of females. The combination of NRTI backbone drugs used in the doravirine fixed dose combination drug differs from the ones recommended by BHIVA.
Total	8/10	
Applicability *	Directly applicable	Directly applicable

* Note - Direct studies focus on people with the indication and characteristics of interest.

Table 6 Johnson et al. 2019

Study reference	Johnson M, Kumar P, Molina, JM et al. (2019) Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. JAIDS: Journal of Acquired Immune Deficiency Syndromes, published ahead of print in April 2019, accessed on 14th May 2019 https://journals.lww.com/jaids/Abstract/publishahead/Switching_to_Doravirine_Lamivudine_Tenofovir.96395.aspx
Unique identifier	NCT02397096
Study type (and NSF-LTC study code)	Randomised, open label, active controlled, non-inferiority trial (P1)
Aim of the study	To demonstrate the non-inferior efficacy of DOR/3TC/TDF to a baseline regimen consisting of an NRTI backbone and 3rd agent PI, INI, or NNRTI in a treatment experienced population with no experience of virological failure
Study dates	Individuals screened, and randomised to treatment, between 17 June 2015 and 10 February 2017
Setting	122 centres in Europe, North America, Latin America, and Asia. 9 of which were in the UK.
Number of participants	670 treated (447 DOR/3TC/TDF immediate switch group [ISG], and 223 baseline regimen delayed switch group [DSG])
Population	Adults with HIV-1 with no history of virologic failure, who were virologically supressed for 6 months or more on a ritonavir or cobicistat PI or NNRTI in addition to an NRTI backbone. Baseline demographics and clinical characteristics ISG / DSG Median age in years (range) 43 (21 to 71) / 42 (22 to 71) Male 372 (83.2%) / 194 (87%) Ethnicity: White 77% / 75.3% Ethnicity: Black or African American 12.5% / 15.2% Ethnicity: Asian 3.8% / 3.6% Ethnicity: Other 6.7% / 5.8% Median CD4 count, cell/m^3 (range) 633 (82 to 1928) / 625 (140 to 1687) Prior antiretroviral regimen: Boosted PI: Darunavir 37.1% / 36.8% Boosted PI: Atazanavir 21.5% / 19.3% Boosted PI: Lopinavir 12.1% / 13.9% Cobicistat boosted elvitegravir 5.6% / 5.4% NNRTI: Efavirenz 17.4% / 16.1% NNRTI: Nevirapine 3.8% / 5.4% NNRTI: Rilpivirine 2.5% / 3.1% The baseline demographics and clinical characteristics were 'balanced' between the groups (p value not reported).

Inclusion criteria	HIV-1 RNA<40 copies per ml at screening Calculated creatinine clearance ≥50 ml/min Pre-treatment HIV-1 genotyping was required for participants receiving a boosted PI or boosted elvitegravir
Exclusion criteria	Resistance to doravirine, 3TC, or TDF Acute hepatitis, decompensated liver disease, liver cirrhosis, and use of systemic immunosuppressive therapy or immune modulators within 30 days before study treatment Individuals receiving lipid-lowering agents who were not on a stable dose at enrolment
Intervention(s)	Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg (DOR/3TC/TDF)
Comparator(s)	A ritonavir or cobicistat boosted PI (atazanavir, darunavir, or lopinavir), or cobicistat boosted elvitegravir, or an NNRTI (efavirenz, nevirapine, or rilpivirine), each in combination with 2 NRTIs (unspecified)
Length of follow-up	48 weeks, the delayed switch group switched to the intervention at week 24
Outcomes	Primary outcome: • HIV-1 RNA<50 copies per ml at week 48 in the immediate switch group, compared to week 24 in the delayed switch group
	Secondary outcomes: • HIV-1 RNA≥50 copies per ml • Change from baseline in CD4 T-cell count • Protocol defined virological failure (PDVF)
	Safety outcomes: • Incidence of any adverse event and drug related adverse events • Change from baseline in fasting lipids (LDL-cholesterol and non-HDL-cholesterol)
Source of funding	Company funded (Merck, Sharp and Dohme Corp)

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	The research question and aims are clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The study design means that it is possible for time differentials to influence the results.
3. Are the methods clearly described?	2/2	The methods are clearly described
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Due to uncertainties created by the study design and by possible differences in NRTI backbones there are uncertainties around the conclusions.
5. Are the results generalisable?	1/2	The study uses the fixed dose combination formulation of doravirine. It is unclear what NRTI backbone is used in the comparator arm, and if it differs between treatment and control arms
Total	7/10	
Applicability *	Directly applicable	

* Note - Direct studies focus on people with the indication and characteristics of interest.

Appendix 4 Results tables

Table 7 Molina et al. 2018

	Doravirine (n=383) ∂	Darunavir and ritonavir (n=383) ∂	Difference (95% CI), p value if reported
N=766∂			
Primary outcome: Proportion of patients with HIV-1 RNA<50 copies/ml (48 weeks) Ω			
Snapshot approach*∂	321 (84%)	306 (80%)	3.9% (-1.6 to 9.4), NR
Sensitivity analysis: snapshot approach #*	316/353 (89.5%)	298/341 (87.4%)	2.1% (-2.7 to 6.9), NR
Supportive analysis: observed failure approach^∂	321/364 (88.2%)	306/355 (86.2%)	1.9% (-3.1 to 6.8), NR
Results were analysed by baseline HIV-1 RNA (≤10,000 and >10,000), NRTI component (TDF/FTC and ABC/3TC), and CD4+ T cell count (≤200 and >200) using the observed failure approach, and results were consistent with the overall effect, showing no difference			
Secondary outcomes (48 weeks)- FAS population∂			
HIV-1 RNA<40 copies per ml Ω			
Snapshot approach*	319 (83.3%)	303 (79.1%)	4.2% (-1.4 to 9.7), NR
Observed failure approach^	319/364 (87.6%)	303/355 (85.4%)	2.2% (-2.9 to 7.2), NR
Average change in the number of CD4 cells from baseline^ t	193 per µl	186 per µl	Mean difference 7.1 per µl (-20.8 to 35), NR
HIV-1 RNA<200 copies per ml	328 (85.6%)	316 (82.5%)	3.1% (-2.1 to 8.4), NR
Observed failure approach^ Ω	328/364 (90.1%)	316/355 (89%)	1.1% (-3.5 to 5.6), NR
Protocol defined virological failure (PDVF)	19 (5%)	24 (6%)	
PDVF breakdown: Non response	2 (<1%)	5 (1%)	Note: The figure of 6 successful phenotype tests for doravirine is taken from the supplementary appendix. A figure of 7 is quoted in the published paper
Viral rebound	17 (4%)	19 (5%)	
Successful genotype test performed	7 (2%)	8 (2%)	
Primary NNRTI resistance	0	0	
Primary NRTI resistance	0	0	
Primary PI resistance	0	0[e]	
Successful phenotype test performed	6 (2%)	8 (2%)	
Any phenotype drug resistance	0	0	
Discontinued for reasons other than PDVF	40 (10%)	53 (14%)	
Discontinues non PDVF breakdown: Successful genotype test performed	2 (1%)	2 (1%)	

Primary NNRTI resistance Primary NRTI resistance Primary PI resistance Successful phenotype test performed Any phenotype drug resistance	 1 (<1%) 1 (<1%) 1 (<1%) 2 (1%) 2 (1%)	 0 0 0 3 (1%) 0	
Safety outcomes (48 weeks)			
Mean change in LDL-cholesterol from baseline	-4.5 mg/dl (SD 20.6)	9.9 mg/dl (SD 20.6)	Mean difference -14.6 mg/dl (-18.2 to -11.1), p<0.0001
Mean change in non-HDL – cholesterol from baseline	-5.3 mg/dl	13.8 mg/dl	Mean difference -19.3 mg/dl (-23.3 to -15.4), p<0.0001
Mean change in cholesterol from baseline	-1.4 mg/dl	17.9 mg/dl	Not reported
Mean change in triglycerides from baseline	-3.1 mg/dl	22 mg/dl	Not reported
Mean change in HDL-cholesterol	3.9 mg/dl	4.2 mg/dl	Not reported
Most common[Δ] laboratory abnormalities [c]			
Fasting LDL≥190mg/dl (Grade 3)	1/332 (<1%)	9/320 (3%)	-2.5% (-5.0 to -0.8) [Π]
Fasting glucose>250 to 500 mg/dl (Grade 3)	4/335 (1%)	1/327 (<1%)	0.9% (-0.6 to 2.8) [Π]
Creatinine (mg/dl)>1.8 to <3.5 x ULN or 1.5 to <2 x baseline (Grade 3)	5/380 (1%)	10/378 (3%)	-1.3% (-3.6 to 0.7) [Π]
Asparte Aminotransferase (IU/L): 5 to <10 x ULN (Grade 3)	2/380 (1%)	6/378 (2%)	-1.1% (-3 to 0.5) [Π]
Alanine Aminotransferase (IU/L): 5 to <10 x ULN (Grade 3)	4/369 (1%)	6/375 (2%)	-0.5% (-2.5 to 1.3) [Π]
Lipase (IU/L) 3 to <5 x ULN (Grade 3) ≥5 x ULN (Grade 4)	 6/380 (2%) 4/380 (1%)	 6/378 (2%) 3/378 (1%)	[Π] -0% (-2 to 2) 0.3% (-1.4 to 2)
Creatine Kinase (IU/L) 10 to <20 x ULN (Grade 3) ≥20 x ULN (Grade 4)	 7/380 (2%) 6/380 (2%)	 7/378 (2%) 7/378 (2%)	[Π] -0% (-2.2 to 2.1) -0.3% (-2.4 to 1.8)

Adverse events[¥]	Doravirine (FAS)		Darunavir and ritonavir (FAS)	
	All cause	Treatment related	All cause	Treatment related
Any adverse event	307 (80%)	117 (31%)	300 (78%)	123 (32%)
Serious adverse event	19 (5%)	1 (<1%)	23 (6%)	1 (<1%)
Discontinued due to adverse event [a]	6 (2%)	4 (1%)	12 (3%)	8 (2%)
Most common adverse events**:**				
Upper abdominal pain	19 (5%)	9 (2%)	10 (3%)	2 (1%)
Diarrhoea	54 (14%)	21 (5%)	86 (22%)	49 (13%)

Nausea	41 (11%)	25 (7%)	46 (12%)	29 (8%)
Fatigue	31 (8%)	18 (5%)	20 (5%)	8 (2%)
Nasopharyngitis	30 (8%)	0	39 (10%)	0
Upper respiratory infection	36 (9%)	0	23 (6%)	0
Back pain	21 (5%)	0	8 (2%)	0
Dizziness	19 (5%)	11 (3%)	15 (4%)	7 (2%)
Headache	53 (14%)	23 (6%)	41 (11%)	10 (3%)
Cough	19 (5%)	1 (<1%)	6 (2%)	0
Events of clinical interest				
Rash[b]	28 (7%)	8 (2%)	32 (8%)	12 (3%)
Neuropsychiatric [+]	44 (11%)	22 (6%)	50 (13%)	19 (5%)
ULN Upper limit of normal range, IU/L International units per litre, CI Confidence interval, NR Not reported, SD Standard deviation				

[∂] Full analysis set (FAS) population included all randomised patients who received at least one dose of a study drug, 766 individuals (383 per treatment arm). Different approaches to deal with missing data altered the population size, but where the FDA snapshot approach was used these figures were unaltered. Results are based on this population size unless stated otherwise.

*The primary analysis used the FDA snapshot approach whereby all missing data is treated as treatment failure, including early discontinuation of the study therapy.

[#] Per protocol population consists of all participants included in the FAS population with none of the following reasons for exclusion: discontinuation for reasons not related to treatment; major protocol deviations that could affect efficacy; noncompliance with study medication; and GCP noncompliance.

^ Observed failure approach, only participants who had missing data due to discontinuation of treatment due to poor efficacy were considered to have treatment failure thereafter

[a] Figures for the doravirine group include 1 individual who died and 1 who discontinued treatment after week 48

[b] 2 people in the doravirine group and 1 in darunavir

[c] Participants counted once per test in the highest grade reported. Only those with a worsened grade from baseline were included

[Δ] occurring in at least 4 participants in either treatment group

+ Includes disturbances in attention, dizziness, somnolence, abnormal dreams, confusion, depressed mood, depression, insomnia, major depression, nightmares and psychotic disorder

[Π] 95% CIs were calculated using the Miettinen and Nurminen method

[Ω] 95% CIs for treatment difference calculated using stratum adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum

[e] Polymorphic mutations in the viral protease gene were identified in 3 individuals in the darunavir group but none were associated with decreased phenotypic susceptibility to darunavir

[t] 95% CI for mean difference calculated using t-distribution

[y] One individual in the doravirine group died of unknown causes, considered unrelated to treatment, at 7 months

Table 8 Orkin et al. 2019

	DOR/3TC/TDF (n=364) ∂	EFV/FTC/TDF (n=364) ∂	Difference (95% CI), p value if reported
N=728∂			
Primary outcome: Proportion of patients with HIV-1 RNA<50 copies/ml (48 weeks) Ω			
Snapshot approach*∂	307 (84.3%)	294 (80.8%)	3.5% (-2.0 to 9.0), NR
Similar results showing non-inferiority (no difference) were found across starting HIV-1 RNA and CD4 count, and other baseline characteristics, prognostic and diagnostic factors except age.			
Secondary and exploratory virological outcomes (48 weeks)- FAS population∂			
HIV-1 RNA<50 copies per ml			
Observed failure approach^	307/346 (88.7%)	294/331 (88.8%)	NR
HIV-1 RNA<40 copies per ml			
Snapshot approach*	305 (83.8%)	290 (79.7%)	4.1% (-1.5 to 9.7)
HIV-1 RNA<200 copies per ml			
Snapshot approach*	313 (86%)	301 (82.7%)	NR
Average change in the number of CD4 cells from baseline^ t	198 per µl	188 per µl	Mean difference 10.1 per µl (-16.1 to 36.3), NR
Protocol defined virological failure (PDVF)	22 (6%)	14 (3.8%)	
PDVF breakdown:			
Viral rebound	16	10	
Genotype test performed	13 (3.4%)	10 (2.5%)	
Genotypic NNRTI resistance	7 (1.9%)	9 (2.5%)	
Genotypic NRTI resistance	5 (1.4%)	5 (1.4%)	
Phenotype test performed	13 (3.4%)	9 (2.5%)	
Phenotypic NNRTI resistance	6 (1.6%)	8 (2.2%)	
Phenotypic NRTI resistance	5 (2%)	8 (2%)	
Discontinued for reasons other than PDVF	35 (9.6%)	50 (13.7%)	
Discontinues non PDVF breakdown:			
Genotype test performed	9 (2.5%)	13 (3.4%)	
Genotypic NNRTI resistance	0	3 (0.8%)	
Genotypic NRTI resistance	0	0	
Phenotype test performed	9 (2.5%)	12 (3.3%)	
Phenotypic NNRTI resistance	0	3 (0.8%)	
Phenotypic NRTI resistance	0	0	
Safety outcomes (48 weeks)			
Primary outcome measure - Neuropsychiatric adverse events:			
Dizziness	8.8%	37.1%	p≤0.001
Sleep disorders/disturbances	12.1%	25.2%	p≤0.001

Altered sensorium Secondary categories: Depression and suicide/ self-injury Psychosis and psychotic disorders	4.4% 4.1% 0.3%	8.2% 6.6% 1.1%	p=0.033 p value NR p value NR
Mean change in LDL-cholesterol from baseline	-1.6 mg/dl	8.7 mg/dl	Mean difference, p<0.0001
Mean change in non-HDL – cholesterol from baseline	-3.8 mg/dl	13.3 mg/dl	Mean difference, p<0.0001
Mean change in cholesterol from baseline	-2.0 mg/dl	21.8 mg/dl	Not reported
Mean change in triglycerides from baseline	-12.4 mg/dl	22.0 mg/dl	Not reported
Mean change in HDL-cholesterol	1.9 mg/dl	8.5 mg/dl	Not reported
Mean change in total cholesterol/HDL-cholesterol ratio	-0.23	-0.18	Difference -0.07 (-0.21 to 0.07), p value not reported
Most common[Δ] laboratory abnormalities [c]			
Fasting LDL≥190mg/dl (Grade 3)	1/332 (0.3%)	5/309 (1.6%)	-1.3% (-3.5 to 0.2) [Π]
Fasting Triglycerides>500 to 1000 mg/dl (Grade 3)	2/336 (0.6%)	8/318 (2.5%)	-1.9% (-4.4 to 0) [Π]
Creatinine (mg/dl)>1.8 to <3.5 x ULN or increase of 1.5 to <2 x baseline (Grade 3)	7/363 (1.9%)	3/359 (0.8%)	1.1% (-0.7 to 3.2) [Π]
Aspartate Aminotransferase (IU/L): 5 to <10 x ULN (Grade 3)	1/363 (0.3%)	5/359 (1.4%)	-1.1% (3 to 0.3) [Π]
Alanine Aminotransferase (IU/L): 5 to <10 x ULN (Grade 3)	2/363 (0.6%)	5/359 (1.4%)	-0.8% (-2.7 to 0.8) [Π]
Lipase (IU/L) 3 to <5 x ULN (Grade 3)	 3/363 (0.8%)	 5/359 (1.4%)	[Π] -0.6% (-2.5 to 1.2)
Creatine Kinase (IU/L) 10 to <20 x ULN (Grade 3) ≥ 20 x ULN (Grade 4)	 6/363 (1.7%) 2/363 (0.6%)	 7/359 (1.9%) 4/359 (1.1%)	[Π] -0.3% (-2.5 to 1.9) -0.6% (-2.3 to 1.0)
Adverse events (FAS)	DOR/3TC/TDF	EFV/FTC/TDF	Treatment difference
Deaths[b]	1 (<1%)	3 (1%)	-0.5 (-2.2 to 0.8)
Any adverse event	301 (83%)	330 (91%)	-8.0 (-13.0 to -3.1)
Drug related adverse event	113 (31%)	229 (63%)	-31.9 (-38.6 to -24.8)
Serious adverse event	13 (4%)	21 (6%)	-2.2 (-5.5 to 0.9)
Drug related serious adverse event	1 (<1%)	4 (1%)	-0.8 (-2.5 to 0.5)
Discontinued due to adverse event	11 (3%)	24 (7%)	-3.6 (-6.9 to -0.5)
Discontinued due to drug related adverse event	8 (2%)	21 (6%)	-3.6(-6.7 to -0.8)
Neuropsychiatric adverse event	86 (24%)	207 (57%)	-33.2 (-39.8 to -26.4)
Most common adverse events (incidence ≥ 5% in either treatment group)**:**			
Gastrointestinal disorders	120 (33%)	136 (37%)	-4.4 (-11.3 to 2.5)
Diarrhoea	39 (11%)	49 (13%)	-2.7 (-7.6 to 2.0)

Nausea	28 (8%)	39 (11%)	-3.0 (-7.3 to 1.2)
Vomiting	15 (4%)	27 (7%)	-3.3 (-6.9 to 0.1)
General disorders	56 (15%)	53 (15%)	0.8 (-4.4 to 6.1)
Fatigue	21 (6%)	22 (6%)	-0.3 (-3.8 to 3.3)
Infections and infestations	183 (50%)	174 (48%)	2.5 (-4.8 to 9.7)
Nasopharyngitis	39 (11%)	31 (9%)	2.2 (-2.1 to 6.6)
Pharyngitis	20 (5%)	15 (4%)	1.4 (-1.8 to 4.7)
Upper respiratory tract infection	33 (9%)	23 (6%)	2.7 (-1.2 to 6.8)
Nervous system disorders	95 (26%)	177 (49%)	-22.5 (-29.3 to -15.6)
Dizziness	32 (9%)	135 (37%)	-28.3 (-34.0 to -22.5)
Headache	47 (13%)	45 (12%)	0.5 (-4.3 to 5.4)
Somnolence	12 (3%)	27 (7%)	-4.1 (-7.6 to -0.9)
Psychiatric disorders	62 (17%)	122 (34%)	-16.5 (-22.7 to -10.2)
Abnormal dreams	17 (5%)	42 (12%)	-6.9 (-11.0 to -3.0)
Insomnia	19 (5%)	32 (9%)	-3.6 (-7.4 to 0.1)
Skin/subcutaneous tissue disorders	61 (17%)	95 (26%)	-9.3 (-15.3 to -3.4)
Rash	17 (5%)	44 (21%)	-7.4 (-11.6 to -3.5)
The most common reasons for discontinuation were rashes (10 EFV/FTC/TDF, 0 DOR/3TC/TDF) and CNS-related events (9 EFV/FTC/TDF, 4 DOR/3TC/TDF). The most common drug-related adverse events for DOR/3TC/TDF and EFV/FTC/TDF were dizziness (7% vs 32%, respectively), abnormal dreams (5% vs 9%), nausea (5% vs 7%), and rash (2% vs 9%)			
ULN Upper limit of normal range, IU/L International units per litre, CI Confidence interval, NR Not reported, CNS Central nervous system			

[∂] Full analysis set (FAS) population included all randomised patients who received at least one dose of a study drug, 728 individuals (364 per treatment arm). Different approaches to deal with missing data altered the population size, but where the FDA snapshot approach was used these figures were unaltered. Results are based on this population size unless stated otherwise.

*The primary analysis used the FDA snapshot approach whereby all missing data is treated as treatment failure, including early discontinuation of the study therapy.

^ Observed failure approach, only participants who had missing data due to discontinuation of treatment due to poor efficacy were considered to have treatment failure thereafter

[b] None considered related to study therapy

[c] Participants counted once per test in the highest grade reported. Only those with a worsened grade from baseline were included

[Δ] occurring in at least 4 participants in either treatment group

[Π] 95% CIs were calculated using the Miettinen and Nurminen method

[Ω] 95% CIs for treatment difference calculated using stratum adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum

[t] 95% CI for mean difference calculated using t-distribution

Table 9 Johnson et al. 2019

	DOR/3TC/TDF ISG (n=447)	Baseline regimen DSG (n=223)	Difference (95% CI), p value if reported
N=670			
Primary outcome: Proportion of patients with HIV-1 RNA<50 copies/ml (48 weeks) Ω			
Snapshot approach*: Week 24	419 (93.7%)	211 (94.6%)	-0.9 % (-4.7 to 3.0), NR
Snapshot approach: Week 48	406 (90.8%)	week 24 result, 94.6%	-3.8% (-7.9 to 0.3), NR
Similar results showing non-inferiority (no difference) were also found when the results for the primary outcome were stratified/subgrouped by baseline prognostic and demographic factors.			
Secondary and exploratory virological outcomes (48 weeks)- Snapshot approach∂			
HIV-1 RNA≥50 copies per ml:			
Snapshot approach - Week 24	1.8%	1.8%	NR
Snapshot approach - Week 48	1.6%	Week 24 result, 1.8%	-0.2 (-2.5 to 2.1), p value NR^
Average change in the number of CD4 cells from baseline:^ t			NR
Week 24	5 cells/mm^3	18 cell/mm^3	
Week 48	14 cells/mm^3		
Protocol defined virological failure (PDVF)	6	1 (+1 in DSG after switching to DOR/3TC/TDF)	NR
PDVF breakdown:			NR
Genotype test performed	2	1	
Genotypic NNRTI resistance	0	0	
Genotypic NRTI resistance	0	1	
Genotypic INI resistance	N/A	0	
Phenotype test performed	2	1	
Phenotypic NNRTI resistance	0	0	
Phenotypic NRTI resistance	0	1	
Phenotypic INI resistance	N/A	0	
Discontinued for reasons other than PDVF	NR	NR	
Discontinues non PDVF breakdown:			
Genotype test performed	1	2	
Genotypic NNRTI resistance	0	0	
Genotypic NRTI resistance	0	0	
Genotypic INI resistance	N/A	0	

Phenotype test performed Phenotypic NNRTI resistance Phenotypic NRTI resistance Genotypic INI resistance	1 0 0 N/A	2 0 0 0	
Safety outcomes (24 weeks)			
	ISG (n=266)[+]	DSG (n=133)[+]	
Mean change in LDL-cholesterol from baseline	-16.5 mg/dl	-1.9 mg/dl	Mean difference -14.7, 95% CI -18.9 to -10.4, p<0.0001
Mean change in non-HDL – cholesterol from baseline	-24.7 mg/dl	-1.3 mg/dl	Mean difference -23.0, 95% CI -28.0 to -18.1, p<0.0001
Mean change in cholesterol from baseline	-26.2 mg/dl	0.5 mg/dl	Mean difference -25.8, 95% CI -30.9 to -20.7, p value NR
Mean change in triglycerides from baseline	-43.2 mg/dl	0.9 mg/dl	Mean difference -42.9, 95% CI -59.1 to -26.7, p value NR
Mean change in HDL-cholesterol	-1.5 mg/dl	1.8 mg/dl	Mean difference -3.0, 95% CI -4.8 to -1.2, p value NR
Mean change in total cholesterol/HDL-cholesterol ratio	-0.44	-0.57	NR
Most common[Δ] laboratory abnormalities [c]	ISG Week 0-24	DSG Week 0-24	DSG Week 24-48
Fasting LDL≥190mg/dl (Grade 3)	0/372	3/184 (1.6%)	0/176
Fasting Triglycerides>500 to 1000 mg/dl (Grade 3)	1/391 (0.3%)	2/197 (1%)	1/184 (0.5%)
Total cholesterol (Grade 3)	0/391	2/197 (1%)	0/184
Glucose (Grade 3)	1/395 (0.3%)	2/197 (1%)	0/184
Alanine Aminotransferase (IU/L): Grade 4	0/444	0/221	2/208 (1%)
Lipase (IU/L) 3 to <5 x ULN (Grade 3)	4/444	0/221 (1.4%)	2/208 (1%)
Total bilirubin (mg/dl), grade 3	0/444	5/221 (2.3%)	0/208
Creatine Kinase (IU/L) 10 to <20 x ULN (Grade 3)	3/444 (0.7%)	3/221 (1.4%)	0/208
Adverse events	ISG Week 0-24 n=447	DSG Week 0-24 n=223	DSG Week 24-48 n=209
Deaths	0	0	0
Any adverse event	308 (68.9%)	117 (52.5%)	126 (60.3%)
Drug related adverse event[a]	87 (19.5%)	5 (2.2%)	29 (13.9%)
Serious adverse event	13 (2.9%)	8 (3.6%)	4 (1.9%)

Drug related serious adverse event	2 (0.4%) [b]	0	1 (0.5%)
Discontinued due to adverse event	11 (2.5%)	1 (0.4%)	4 (1.9%)[c]
Discontinued due to drug related adverse event	7 (1.6%)	0	4 (1.9%)
Most common adverse events (incidence ≥ 5% in any group)**:**			
Nasopharyngitis	33 (7.4%)	12 (5.4%)	9 (4.3%)
Headache	29 (6.5%)	5 (2.2%)	14 (6.7%)
Most common drug related adverse events (incidence ≥ 2% in any group)[a]**:**			
Headache	7 (1.6%)	1 (0.4%)	5 (2.4%)
ULN Upper limit of normal range, IU/L International units per litre, CI Confidence interval, NR Not reported, ISG Immediate switch group, DSG Delayed switch group			

*The primary analysis used the FDA snapshot approach whereby all missing data is treated as treatment failure, including early discontinuation of the study therapy.

Ω 95% CIs for treatment difference calculated using stratum adjusted Mantel-Haenszel

^ For this endpoint, a margin of 4 percentage points was used to assess the non-inferiority of a switch to DOR/3TC/TDF through 48 weeks compared to continuation of the baseline regimen through 24 weeks

+ These results for lipid levels only included participants receiving a ritonavir boosted PI regimen at study entry

[a] Determined by the investigator to be related to the study therapy

[b] During weeks 24 -48 2% of individuals in the ISG had a serious adverse event. Based on interpretation of text in the paper it appears that 4 of these had a serious adverse event considered related to DOR/3TC/TDF, producing 5 in total when added to the 1 in the DSG. 2 of these were resolved with no change in therapy, and the study drug was discontinued in the remaining cases.

[c] During weeks 24-48, 0.9% of patients in the ISG discontinued treatment due to an adverse event.

Appendix 5 Grading of the evidence base

Each study is assigned one of the following codes:

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	Criteria
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.