NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JULY 2021

Daprodustat for anaemia associated with chronic kidney disease

NIHRIO ID	8058	**NICE ID**	10584
Developer/Company	GlaxoSmithKline UK Ltd	**UKPS ID**	650657

Licensing and market availability plans	Currently in phase II and III clinical trials.

SUMMARY

Daprodustat is in clinical development for people with anaemia associated with chronic kidney disease (CKD). Anaemia is the term used to describe a decrease in normal levels of red blood cells and is assessed by the level of haemoglobin, the protein that transports oxygen throughout the body. Anaemia commonly occurs in patients with kidney dysfunction because the kidneys no longer produce sufficient amounts of a hormone which stimulates red blood cell production. Patients with CKD or kidney failure often experience varying degrees of anaemia as their disease progresses. This limits oxygen delivery to tissues, contributing to symptoms such as weakness and fatigue.

Daprodustat is a novel oral medicinal product that blocks an enzyme called prolyl hydroxylase, leading to the promotion of the production of red blood cells. For many patients with CKD, treating anaemia comes with risks associated with cardiovascular safety and injectable administration. If approved, daprodustat may offer a potential alternative oral treatment option that could address some of these risks.

PROPOSED INDICATION

Treatment of patients, on dialysis or non-dialysis, with anaemia associated with CKD.[1-6]

TECHNOLOGY

DESCRIPTION

Daprodustat (Duvroq; GSK-1278863) is a prolyl hydroxylase inhibitor that acts by inhibiting hypoxia-inducible factor (HIF)-prolyl hydroxylases. HIF, a heterodimeric nuclear factor, is a crucial intermediate form for protection mechanisms against hypoxia. Its stability is drastically reduced by the oxygen dependent enzymatic hydroxylation of proline residues by prolyl hydroxylases. Hence these prolyl hydroxylase (PH) inhibitors selectively stimulate HIF-2 and HIF-1 mediated erythropoiesis for the treatment of anaemia. The alpha subunit of HIF-1 is a target for prolyl hydroxylation by HIF prolyl-hydroxylase, which makes HIF-1 a target for degradation by an E3 ubiquitin ligase, leading to quick degradation by the proteasome.[7-9]

Daprodustat is in clinical development for the treatment of anaemia associated with chronic kidney disease (CKD). In the phase III clinical trial (NCT03409107, NCT03400033), daprodustat will be given by oral administration as 9 millimeter (mm) or 7 mm film-coated tablets once daily or three times weekly.[4,5]

INNOVATION AND/OR ADVANTAGES

Daprodustat is a novel HIF-PH inhibitor.[10,11] HIF-PH inhibitors are a new class of drug that trigger the body's adaptations to hypoxia (i.e. oxygen deprivation) and encourages the bone marrow to make more red blood cells and so reduce anaemia, thereby benefitting patients.[12] PH inhibition promotes the production of red blood cells that carry oxygen to where it is needed, similar to the effects that occur in the body at high altitude.[11,12] For many patients with CKD, treating anaemia with current erythropoietin-stimulating agents (ESAs) comes with risks of death and serious cardiovascular events.[11] Daprodustat may offer a potential alternative oral treatment option that could address these risks; and the cold storage requirements of injectible ESAs/recombinant human erythropoietin.[11,12]

In a phase IIA randomised clinical trial both CKD stage 3/4/5 and CKD stage 5D populations showed a dose-dependent increase in erythropoietin (EPO) concentrations and consequent increases in reticulocytes and haemoglobin (Hb) levels. The percentage of daprodustat participants with a Hb level increase >1.0g/dL (CKD stage 3/4/5) were 63% to 91%. The percentage of daprodustat participants with a Hb level increase >0.5g/dL were 71% to 89%. A dose-dependent decrease in hepcidin levels and increase in total and unsaturated iron binding were observed in all daprodustat-treated patients.[13]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Daprodustat does not currently have Marketing Authorisation in the EU/UK for any indication.

The most frequent adverse events (incidence ≥10%) with daprodustat during 52 weeks therapy were nasopharyngitis, diarrhoea, shunt stenosis, contusion and vomiting.[6]

Daprodustat is also in phase II clinical development for patients undergoing elective descending thoracic aorta/thoracoabdominal aortic aneurysm repair (surgical procedures) and peripheral vascular disease.[14]

PATIENT GROUP

DISEASE BACKGROUND

Anaemia associated with CKD is a condition in which the body has fewer red blood cells than normal. Healthy kidneys produce a hormone called erythropoietin (EPO). EPO prompts the bone marrow to make red blood cells. A diseased or damaged kidney does not make enough EPO. As a result, the bone marrow makes fewer red blood cells, causing anaemia. Red blood cells carry oxygen to tissues and organs throughout the body and enable them to use energy from food. With anaemia, red blood cells carry less oxygen to tissues and organs - particularly the heart and brain - and those tissues and organs may not function as well as they should.[15]

Anaemia commonly occurs in people with CKD - the permanent, partial loss of kidney function. Anaemia might begin to develop in the early stages of CKD, when someone has 20 to 50 percent of normal kidney function. Anaemia tends to worsen as CKD progresses. Most people who have total loss of kidney function, or kidney failure, have anaemia. Other common causes of anaemia in people with CKD include blood loss from haemodialysis and low levels of the some nutrients found in food like iron, vitamin B12 and folic acid.[15]

The signs and symptoms of anaemia in someone with CKD may include weakness, fatigue, or feeling tired, headaches, problems with concentration, paleness, dizziness, difficulty breathing or shortness of breath and chest pain.[15]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK, stage 3-5 CKD, an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m2, has been widely used in prevalence estimates.[16] For CKD stage 3-5, the HSE 2016 report estimated prevalence of 4% in men and 6% in women, aged ⩾16 years.[17] By applying the HSE prevalence to the mid-year 2020 population of England, as recorded by the Office for National Statistics (ONS), there are an estimated total of 896,687 men and 1,396,844 women in England with stage 3-5 CKD.[18]

Prevalence data for anaemia in CKD patients not on dialysis for England has not been identified. However, a recently published cross-sectional survey in clinical settings across five European countries, including the UK, suggested that about 61% of those patients were anaemic, and when compared with patients without anaemia they tended to be older and more likely to be male. Anaemia treatment was prescribed in 35% of the patients.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Patient treatment is coordinated by one or more desginated contact who is responsible for anaemia management. This is through monitoring and management, providing information and support for the patient, family and any carers, and working between primary and secondary care. Patient education programs are offered to cover the following:[20]

- Practical information regarding CKD with anaemia management
- Information such as symptoms, causes, associated medications and treatment phases
- Professional support, including community services and continuity of care
- Lifestyle (including diet and exercise)
- Adaptation to chronic disease

Erythropoietin-stimulating agent (ESA) therapy is recommended for people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function. ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency.[20,21]

Iron therapy is indicated for people with anaemia of CKD who are iron deficient and who are or are not receiving ESA therapy.[20,21]

CURRENT TREATMENT OPTIONS

In England, NICE guidelines recommend the initiation of ESA and iron supplementation in people with CKD and anaemia. NICE establishes that, in people treated with iron, the serum ferritin levels should not rise above 800 micrograms/litre.[20]

There are a number of different ESA treatments available such as epoetin alfa and darbepoetin alfa, NICE recommends to discuss the choice of ESA with the person with anaemia of CKD when initiating treatment and at subsequent review, taking into consideration the patient's dialysis status, the route of administration and the local availability of ESAs.[20]

There is no evidence to distinguish between ESAs in terms of efficacy.[20] Intravenous or subcutaneous forms of administrations may be recommended depending on the CKD stage and whether the patients are receiving hemofiltration or hemodiafiltration therapy and treatment setting, efficacy considerations, and the class of ESA used.[22]

PLACE OF TECHNOLOGY

If licenced, daprodustat will offer an oral treatment option for patients, on dialysis or non-dialysis, with anaemia associated with CKD.

CLINICAL TRIAL INFORMATION

Trial	**ASCEND-ND; NCT02876835; 2016-000542-65;** A Phase 3 Randomized, Open-label (Sponsor-blind), Active-controlled, Parallel-group, Multi-center, Event Driven Study in Non-dialysis Subjects With Anemia Associated With Chronic Kidney Disease to Evaluate the Safety and Efficacy of Daprodustat Compared to Darbepoetin Alfa **Phase III –** Completed **Location(s):** 16 EU countries, UK, United States, Canada and other countries **Actual study completion date:** April 2021
Trial design	Randomised, open label, active-controlled parallel assignment.
Population	N= 3,872; aged 18 to 99 years old; non-dialysis subjects with anaemia associated with CKD
Intervention(s)	• Oral daprodustat once daily • Oral placebo tablets will be taken from Week -4 up to randomisation (Day 1) • Participants will receive supplemental iron therapy if ferritin is <=100 ng/mL or TSAT is <=20%
Comparator(s)	Darbepoetin alfa administered subcutaneously (SC).
Outcome(s)	Primary Outcome Measures : • Time to the first occurrence of adjudicated major adverse cardiovascular event (MACE) (composite of all-cause mortality, non-fatal myocardial infarction (MI) and non-fatal stroke) [Time Frame: Randomization (Day 1) to end of study (event-driven, up to 4.1 years)] • Mean change in hemoglobin (Hgb) between baseline and efficacy period (EP) See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**ASCEND-D; NCT02879305; 2016-000541-31;** A Phase 3 Randomized, Open-label (Sponsor-blind), Active-controlled, Parallel-group, Multi-center, Event Driven Study in Dialysis Subjects With Anemia Associated With Chronic Kidney Disease to Evaluate the Safety and Efficacy of Daprodustat Compared to Recombinant Human Erythropoietin, Following a Switch From Erythropoietin-stimulating Agents

	Phase III – Completed **Location(s):** 17 EU countries, UK, United States, Canada and other countries **Actual study completion date:** November 2020
Trial design	Randomised, open label, active-controlled parallel assignment.
Population	N= 2,964; aged 18 to 99 years old; dialysis subjects with anaemia associated with CKD.
Intervention(s)	• Oral daprodustat once daily. • Oral placebo tablets will be taken from Week -4 up to randomisation (Day 1) • Participants will receive supplemental iron therapy if ferritin is <=100 ng/mL or TSAT is <=20%
Comparator(s)	• Darbepoeitin alfa administered subcutaneously (SC) in patients on peritoneal dialysis • Participants on haemodialysis (HD) will be administered epoetin alfa intravenously (IV)
Outcome(s)	Primary Outcome Measures: • Time to the first occurrence of adjudicated major adverse cardiovascular event (MACE) (composite of all-cause mortality, non-fatal myocardial infarction [MI] and non-fatal stroke) [Time Frame: Randomization (Day 1) to end of study (event-driven, up to 3.3 years)] • Mean change in hemoglobin (Hgb) between Baseline and efficacy period (EP) (mean over Weeks 28-52 See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**ASCEND-NHQ; NCT03409107; 2017-002270-39;** A 28-week, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multi-center, Study in Recombinant Human Erythropoietin (rhEPO) naïve Non-dialysis Participants With Anemia Associated With Chronic Kidney Disease to Evaluate the Efficacy, Safety and Effects on Quality of Life of Daprodustat Compared to Placebo **Phase III –** Completed **Location(s):** 5 EU countries, UK, United States, Canada and other countries

	Actual study completion date: October 2020
Trial design	Randomised, double-blind, parallel assignment.
Population	N= 614; aged 18 years and older; non-dialysis participants with anaemia associated with CKD.
Intervention(s)	• Oral daprodustat once daily • Iron therapy will be administered if ferritin is <50 Nano gram per milliliter and/or TSAT is <15 percent
Comparator(s)	Matched placebo, alongside equivalent iron therapy.
Outcome(s)	Primary Outcome Measure: • Mean change from Baseline in Hgb up to evaluation period (EP) [Time Frame: Baseline and up to Week 28] The EP is from Week 24 to Week 28. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**ASCEND-ID; NCT03029208; 2016-000507-86;** A 52-week Open-label (Sponsor-blind), Randomized, Active-controlled, Parallel-group, Multi-center Study to Evaluate the Efficacy and Safety of Daprodustat Compared to Recombinant Human Erythropoietin in Subjects With Anemia Associated With Chronic Kidney Disease Who Are Initiating Dialysis **Phase III –** Completed **Location(s):** 4 EU countries, UK, United States, Canada and other countries **Actual study completion date:** September 2020
Trial design	Randomised, open-label, active-controlled parallel assignment.
Population	N= 312; aged 18 to 99 years old; all sexes; subjects with anaemia associated CKD who are initiating dialysis CKD and CKD-associated anaemia; undergoing dialysis
Intervention(s)	• Oral daprodustat once daily. • Iron therapy will be administered if ferritin is <=100 ng/mL and/or TSAT is <=20%
Comparator(s)	Darbepoetin alfa administered SC or IV.
Outcome(s)	Primary Outcome Measure:

	Mean change from Baseline in hemoglobin (Hgb) during evaluation period (EP) [Time Frame: Randomization (Day 1) to Week 52] The Baseline Hgb will be the value obtained on Day 1. The EP is defined as the period from the end of the stabilization period (Week 28) to Week 52. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**ASCEND-TD; NCT03400033; 2017-004372-56;** A Phase 3 Randomized, Double-blind, Active-controlled, Parallel-group, Multi-center Study in Hemodialysis Participants With Anemia of Chronic Kidney Disease to Evaluate the Efficacy, Safety and Pharmacokinetics of Three-times Weekly Dosing of Daprodustat Compared to Recombinant Human Erythropoietin, Following a Switch From Recombinant Human Erythropoietin or Its Analogs **Phase III –** Completed **Location(s):** 4 EU countries, UK, United States, Canada and other countries **Actual study completion date:** June 2020
Trial design	Randomised, quadruple masked, active-controlled, parallel assignment.
Population	N= 407; ages 18 to 99 years old; haemodialysis patients with anaemia of CKD.
Intervention(s)	• Oral daprodustat tablet administered three-times weekly • 0.9% IV sodium chloride saline for the 52 weeks treatment period
Comparator(s)	• IV Epoetin alfa • Matched placebo tablets
Outcome(s)	Primary Outcome Measure: • Mean change in Hemoglobin (Hgb) between Baseline and over Evaluation period [EP] (Weeks 28 to 52) [Time Frame: Baseline and up to Week 52] Blood samples will be collected from subjects for Hgb measurements See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**ASCEND: Fe; NCT03457701;** A Repeat Dose, Open Label, Two Period, Randomized, Cross Over Study to Compare the Effect of Daprodustat to Recombinant, Human Erythropoietin (rhEPO) on Oral Iron Absorption in Adult Participants With Anemia Associated With Chronic Kidney Disease Who Are Not on Dialysis **Phase II –** Recruiting **Location(s):** United States **Primary competion date:** October 2021
Trial design	Randomised, open label
Population	N= 12; aged 18 years and older; non-dialysis participants with anaemia associated with CKD
Intervention(s)	Oral daprodustat once daily. See trial record for further details.
Comparator(s)	No comparator.
Outcome(s)	Primary Outcome Measure: Percentage of iron absorbed [Time Frame: Up to Day 57] Venous blood samples will be collected for measurement of erythrocyte isotopic iron content to compare the efficacy of daprodustat to rhEPO (i.e., epoetin alfa or darbepoetin alfa) on iron absorption on Days 29, 43 and 57. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of daprodustat is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Roxadustat for treating anaemia in people with chronic kidney disease (ID 1483). Expected March 2022
- NICE guideline. Chronic kidney disease: managing anaemia (NG8). June 2015
- NICE clinical guideline. Chronic kidney disease in adults: assessment and management (CG182). July 2014
- NICE quality standard. Chronic kidney disease in adults (QS5). March 2011

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Services for Haemoglobinopathy care (All Ages). B08/S/a.

OTHER GUIDANCE

- The Renal Association. Clinical Practice Guideline Anaemia of Chronic Kidney Disease. Updated February 2020.[23]
- Kidney Disease Improving Global Outcomes (KDIGO). KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. August 2012.[22]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. *Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Non-Dialysis (ASCEND-ND). Trial ID: NCT02876835*. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT02876835 [Accessed 19 Jul 2021].

2 Clinicaltrials.gov. *Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Dialysis (ASCEND-D). Trial ID: NCT02879305*. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT02879305 [Accessed 19 Jul 2021].

3 Clinicaltrials.gov. *Anemia Studies in Chronic Kidney Disease (CKD): Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor (PHI) Daprodustat in Non-Dialysis Subjects Evaluating Hemoglobin (Hgb) and Quality of Life (ASCEND-NHQ). Trial ID: NCT03409107*. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT03409107 [Accessed 22 Jun 2021].

4 Clinicaltrials.gov. *Anemia Studies in Chronic Kidney Disease (CKD): Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor (PHI) Daprodustat-in Incident Dialysis (ASCEND-ID). Trial ID: NCT03029208*. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT03029208 [Accessed 22 Jun 2021].

5 Clinicaltrials.gov. *Anemia Studies in Chronic Kidney Disease (CKD): Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor (PHI) Daprodustat-Three-times Weekly Dosing in Dialysis (ASCEND-TD). Trial ID: NCT03400033*. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT03400033 [Accessed 22 Jun 2021].

6 Clinicaltrials.gov. *Anemia Studies in CKD: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor (PHI) Daprodustat- Iron (ASCEND: Fe). Trial ID: NCT03457701*. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03457701 [Accessed 19 Jul 2021].

7 Nangaku M, Izuhara Y, Takizawa S, Yamashita T, Fujii-Kuriyama Y, Ohneda O, et al. A Novel Class of Prolyl Hydroxylase Inhibitors Induces Angiogenesis and Exerts Organ Protection Against Ischemia. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2007;27(12):2548-54. Available from: https://doi.org/doi:10.1161/ATVBAHA.107.148551.

8 Fong GH, Takeda K. Role and regulation of prolyl hydroxylase domain proteins. *Cell Death & Differentiation*. 2008 2008/04/01;15(4):635-41. Available from: https://doi.org/10.1038/cdd.2008.10.

9 Sanghani NS, Haase VH. Hypoxia-Inducible Factor Activators in Renal Anemia: Current Clinical Experience. *Advances in chronic kidney disease*. 2019;26(4):253-66. Available from: https://doi.org/10.1053/j.ackd.2019.04.004.
10 Dhillon S. Daprodustat: First Approval. *Drugs*. 2020;80(14):1491-7. Available from: https://doi.org/10.1007/s40265-020-01384-y.
11 Becker KA, Jones JJ. An Emerging Treatment Alternative for Anemia in Chronic Kidney Disease Patients: A Review of Daprodustat. *Advances in therapy*. 2018;35(1):5-11. Available from: https://doi.org/10.1007/s12325-017-0655-z.
12 GlaxoSmithKline. *GSK receives first regulatory approval for Duvroq (daprodustat) in Japan for patients with anaemia due to chronic kidney disease.* 2020. Available from: https://www.gsk.com/en-gb/media/press-releases/gsk-receives-first-regulatory-approval-for-duvroq-daprodustat-in-japan-for-patients-with-anaemia-due-to-chronic-kidney-disease/ [Accessed 23 Jun 2021].
13 Brigandi RA, Johnson B, Oei C, Westerman M, Olbina G, de Zoysa J, et al. A Novel Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor (GSK1278863) for Anemia in CKD: A 28-Day, Phase 2A Randomized Trial. *Am J Kidney Dis*. 2016 Jun;67(6):861-71. Available from: https://doi.org/10.1053/j.ajkd.2015.11.021.
14 Clinicaltrials.gov. *Phase II and phase III clinical trials for daprodustat.* Available from: https://clinicaltrials.gov/ct2/results?term=daprodustat&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 23 Jun 2021].
15 NIH National Institute of Diabetes and Digestive and Kidney Diseases. *Anemia in Chronic Kidney Disease.* Available from: https://www.niddk.nih.gov/health-information/kidney-disease/anemia [Accessed 22 Jun 2021].
16 National Institute for Health and Care Excellence (NICE). *Chronic Kidney Disease Update Scope.* 2012. Available from: https://www.nice.org.uk/guidance/cg182/documents/chronic-kidney-disease-update-final-scope2 [Accessed 22 Jun 2021].
17 NHS Digital. *Health Survey for England, 2016.* 2016. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/health-survey-for-england-2016 [Accessed 19 Jul 2021].
18 Office for National Statistics (ONS). *Mid-Year Population Estimates, UK, June 2020.* 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland [Accessed 19 Jul 2021].
19 Covic A, Jackson J, Hadfield A, Pike J, Siriopol D. Real-World Impact of Cardiovascular Disease and Anemia on Quality of Life and Productivity in Patients with Non-Dialysis-Dependent Chronic Kidney Disease. *Advances in therapy*. 2017 Jul;34(7):1662-72. Available from: https://doi.org/10.1007/s12325-017-0566-z.
20 National Institute for Health and Care Excellence (NICE). *Managing anaemia in people with chronic kidney disease* Available from: http://pathways.nice.org.uk/pathways/anaemia-management-in-people-with-chronic-kidney-disease [Accessed 23 Jun 2021].
21 Padhi S, Glen J, Pordes BAJ, Thomas ME. Management of anaemia in chronic kidney disease: summary of updated NICE guidance. *BMJ : British Medical Journal*. 2015;350:h2258. Available from: https://doi.org/10.1136/bmj.h2258.
22 Kidney Disease Improving Global Outcomes (KDIGO). *KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease.* 2012. Available from: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf [Accessed 23 Jun 2021].
23 The Renal Association. *Clinical Practice Guideline Anaemia of Chronic Kidney Disease.* Available from: https://renal.org/sites/renal.org/files/Updated-130220-Anaemia-of-Chronic-Kidney-Disease-1-1.pdf [Accessed 23 Jun 2021].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.