Exploring the use of monoclonal antibodies and antiviral therapies for early treatment of COVID-19 outpatients in real-world setting: a nationwide study from the United Kingdom and Italy

BioDrugs

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Conflicts of interest
Gianluca Trifirò has served in the last three years on advisory boards/seminars funded by SANOFI, Eli Lilly, AstraZeneca, AbbVie, Servier, Mylan, Gilead, Amgen; he was the scientific director of a Master program on pharmacovigilance, pharmacoepidemiology and real-world evidence which has received non-conditional grant from various pharmaceutical companies; he coordinated a pharmacoepidemiology team at the University of Messina until Oct 2020, which has received funding for conducting observational studies from various pharmaceutical companies (Boehringer Ingelheim, Daichii Sankyo, PTC Pharmaceuticals). He is also scientific coordinator of the academic spin-off "INSPIRE srl" which has received funding for conducting observational studies from contract research organizations (RTI Health Solutions, Pharmo Institute N.V.). All the above-mentioned activities are not related to the topic of the manuscript. Mariam Molokhia has received grants previously from the International Serious Adverse Events Consortium, SAEC (not related to the topic of the manuscript). The other authors have no conflict of interest to disclose.

Supplementary table 1. Monoclonal antibodies and antivirals for the early treatment of COVID-19 outpatients: date of marketing authorization and approval for use in outpatients, and eventual withdrawal, following evaluation by European Medicines Agencies (EMA), Italian Medicines Agency and Medicines (AIFA), Healthcare products Regulatory Agency (MHRA) and Food and Drug Administration (FDA), and indication of use approved by the EMA and MHRA.

		EMA	AIFA		MHRA		FDA
		Date of authorization/ withdrawal	**Date of authorization/ withdrawal**	**Indication of use**	**Date of authorization/ withdrawal**	**Indication of use**	**Date of authorization/ withdrawal**
Monoclonal antibodies	**Bamlanivimab**	-	09/03/2021 Revoked: 08/05/2021	-	-	Treatment of adults and adolescents (≥12 y.o.; ≥40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	09/11/2020 Revoked: 15/04/2021
	Sotrovimab	17/12/22021	04/08/2021	Treatment of adults and adolescents (≥12 y.o.; ≥40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	01/12/2021	Treatment of adults and adolescents (≥12 y.o.; ≥40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	26/05/2021 Withdrawn: 05/04/2022
	Regdanvimab	12/11/2021	25/11/2021	Treatment of adults with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	-	-	-
	Casirivimab/ imdevimab	12/11/2021	22/03/2021	Treatment of adults and adolescents (≥12 y.o.; ≥40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	19/08/2021	Treatment of adults and adolescents (≥12 y.o.; ≥40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	21/11/2020 restricted 24/01/2022
	Bamlanivimab/ etesevimab	11/03/2021 Withdrawn from rolling review: 29/10/2021	17/03/2021	Treatment of adults and adolescents (≥12 y.o.; ≥40 kg) with COVID-19 who do not require oxygen supplementation	-	-	09/02/2021 restricted 24/01/2022

				and who are at increased risk of progressing to severe COVID-19			
	Tixagevimab/ cilgavimab	15/09/2022	03/08/2022	Treatment of adults and adolescents (≥12 y.o.; ≥40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	-	-	-
Antivirals	**Nirmatrelvir/ ritonavir**	28/01/2022	03/02/2022	Treatment of adults with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	31/12/2021	Treatment of adults with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	22/12/2021
	Molnupiravir	23/11/2021	28/12/2021	Treatment of adults with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	04/11/2021	Treatment of adults with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	23/12/2021
	Remdesivir	03/07/2020 **Approval for use in outpatients:** 21/12/2021	08/10/2020 **Approval for use in outpatients:** 28/12/2021	Treatment of adults and adolescents (≥12 y.o.; ≥40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	EAMS: 26/05/2020	Treatment of adults and adolescents (≥12 y.o.; ≥40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	EUA: 01/05/2020 Approval: 22/10/2020 **Approval for use in outpatients:** 21/01/2022

Abbreviations: AIFA= Italian Medicines Agency, EAMS= Early Access to Medicines Scheme, EMA= European Medicines Agencies, EUA= Emergency Use Authorization, MHRA= Medicines and Healthcare products Regulatory Agency, FDA= Food and Drug Administration, y.o.= years old. *****Same indication of use for AIFA.

Supplementary table 2. Prescription and administration of monoclonal antibodies and antiviral therapies for early treatment of COVID-19 outpatients.

		Prescription	Administration
Monoclonal antibodies	**Casirivimab/ imdevimab**	These drugs must be prescribed by specialists and are dispensed in hospitals.	Casirivimab/imdevimab 600mg/600 mg administered as a single intravenous infusion or by subcutaneous injection. Its use is limited to hospital/healthcare facilities.
	Sotrovimab		Sotrovimab 500 mg administered as a single intravenous infusion. Its use is limited to hospital/healthcare facilities.
	Tixagevimab/ cilgavimab		Tixagevimab/cilgavimab300mg/300mg administered as two separate sequential intramuscular injections. Its use is limited to hospital/healthcare facilities.
	Bamlaniviamb/ Etesevimab		Bamlanivimab/ etesevimab 700mg/1,400mg administered as a single intravenous infusion. Its use is limited to hospital/healthcare facilities.
Antivirals	**Remdesivir**		3-day administration: - Day 1: remdesivir 200 mg administered as a single loading dose by intravenous infusion - Day 2 and 3: remdesivir 100 mg (once a day) administered as a single intravenous infusion. Its use is limited to hospital/healthcare facilities.
	Molnupiravir		Daily for 5 days (at home): Molnupiravir 800 mg taken orally every 12 hours.
	Nirmatrelvir/ Ritonavir*		Daily for 5 days (at home): Nirmatrelvir/ ritonavir 300mg/100mg all taken together orally every 12 hours.

*Nirmatrelvir/ritonavir can also be prescribed by general practitioners and dispensed at the pharmacy in Italy.