Supplementary appendix

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Text S1 – Methods

The EAP is underway in Health Region 1, Lobaye district of CAR, located in the south-west of the country bordering the Republic of Congo and the Democratic Republic of the Congo. Mbaïki hospital – the district primary and referral health care facility with good access to the capital city Bangui – was selected as the main treatment centre at which tecovirimat would be administered for the EAP. Communication and travel within this highly rural, sparsely populated, and densely forested region is challenging, which has implications both for case finding and referral. While cases are reported also from other parts of CAR, the security situation in the country is such that the Lobaye district was the only practicable option.

A suspected case is defined as a subject presenting with clinical signs and symptoms indicative of monkeypox, such as fever and characteristic rash. We set in place an intensified active surveillance system: suspected cases are identified through referrals from community health workers, other health facilities and community leaders, and through contact tracing in villages of the district by the EAP team. Following the identification of a suspected case, blood and lesion samples are taken from the subject and blood samples are also taken from close contacts (regardless of the presence of clinical signs and symptoms) and transferred to the Institut Pasteur de Bangui reference laboratory for case confirmation. Eligible patients are those who received laboratory confirmation of monkeypox infection and weighed ≥13 kg. Patients receiving repaglinide are ineligible due to risk of interactions with tecovirimat.

Following consent, adult patients receive 600 mg of tecovirimat (3 x 200 mg capsules) twice daily for 14 days. Dosing for paediatric patients is based on weight: children weighing 13kg to <25kg receive 200 mg of tecovirimat (1 capsule) twice daily for 14 days; children weighing 25kg to <40 kg receive 400 mg of tecovirimat (2 capsules) twice daily for 14 days; and children weighing ≥40 kg receive 600 mg of tecovirimat (three capsules) of tecovirimat twice daily for 14 days. Patients are to stay in hospital for the duration of treatment, with follow-up visits planned on days 15 and 28.

Data on clinical signs and symptoms, including lesion burden, are recorded daily during treatment and at each follow-up visit.

Blood or lesions samples on pus or crusts are scheduled on days 1, 4, 8 and 14 during treatment, and then at day 28, to assess viral presence of MPXV using the G2R-G real-time PCR assay and the Congo Basin clade of the virus using the C3L real-time PCR assay. In this cohort, multiple samples were taken from some patients at some study visits. Patients with positive PCR on day 14 had an additional sample on day 21. Monkeypox disease is confirmed by detecting viral DNA on blood samples and/or lesion swabs.

As tecovirimat is administered via an EAP, outcome measures and endpoints were not predefined. Patient outcomes are monitored by evaluating the total number and location of lesions, temperature, degree of incapacity, presence of adverse events, patient survival, and virus DNA levels throughout treatment and follow-up.

Serious Adverse Events are monitored from consent until the patient's final study visit. Causality is assessed independently by the study clinician responsible for treating the patient and a medical monitor appointed by the Sponsor. If the study clinician and medical monitor return conflicting assessments, the causality assessment determining the strongest relationship to tecovirimat takes precedence. Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to the responsible ethics committees.

The EAP was approved by the Ministry of Health, Central African Republic, and obtained ethical clearance by the national ethics committee ("Comité Ethique et Scientifique, Université de Bangui Faculté des Sciences de la Santé") and Oxford Tropical Research Ethics Committee (OxTREC) at the University of Oxford.

The EAP is registered on the ISRCTN registry (reference: ISRCTN43307947).

Statistical analysis

A descriptive analysis of the demographics, signs and symptoms, and patient outcome of the enrolled patients who were treated with tecovirimat is presented. Signs and symptoms are reported as the number and proportion of patients for whom each sign or symptom was recorded at admission (baseline) and at any time post-baseline. A denominator is provided for each variable to indicate the number of patients for whom data were available.

Lesion presence is summarised as the number and proportion of patients for whom lesions are reported overall and by location at admission and any time post-baseline. At point of data collection, lesions were categorised as either active lesions, scabs or scars and are summarised here as either the presence of active lesions or the presence of lesions of any type. Lesion burden is summarised on a categorical scale: None; 1-5 lesions; 6-25 lesions; 26-100 lesions; >100 lesions. The median time to no active lesions is also reported.

The number and proportion of patients testing positive on PCR for MPXV, G2R-G and the Congo Basin clade, is reported for all study timepoints overall and per sample type tested (blood, active lesion and crust). The mean, standard deviation and range of reported CT values are also presented where more than one sample is available at any given timepoint.

A summary of serious adverse events (SAEs), including number of SAEs per patient and severity, is also provided.

The analysis was conducted by JB.

Table S2 – Case Report Form

RECRUITMENT	
Patient ID number	Site : [___][___] – Patient : [___][___][___]
Date of hospitalisation for suspected monkeypox	[_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]
Name of site at which the patient was identified	☐ MBAIKI ☐ LOKO ☐ ZOUMEA ☐ MONGOUMBA
ELIGIBILITY CRITERIA	
Weight ≥13 kg	☐ YES ☐NO
Does the patient take repaglinide?	☐ YES ☐ NO If yes, the patient must be excluded from the study
Does the patient have confirmation by PCR of monkeypox infection?	☐ YES ☐ NO Date sample taken [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]
Has the patient (or their parent or representative) consented to be treated with tecovirimat?	☐ YES ☐ NO
Date of consent	[_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]
Name of the person who consented the patient	

1. DEMOGRAPHIC DATA

Sex at birth	☐Male ☐ Female
Age	[___][___] years OR [___][___]months
Weight	[_____][___] (kg)

2. COMORBIDITIES

Heart failure	☐YES ☐NO ☐Not known	**Diuretics**	☐YES ☐NO ☐Not known
COPD/ Asthma	☐YES ☐NO ☐Not known	**Nasal steroids**	☐YES ☐NO ☐Not known
Diabetes	☐YES ☐NO ☐Not known	**Oral hypoglycaemic agents** **Insulin**	☐YES ☐NO ☐Not known ☐YES ☐NO ☐Not known
Chronic renal failure	☐YES ☐NO ☐Not known	**Dialysis**	☐YES ☐NO ☐Not known
HIV	☐YES ☐NO ☐Not known	**Antiretroviral treatment**	☐YES ☐NO ☐Not known
Malnutrition	☐YES ☐NO		

	☐Not known		

3. SIGNS AND SYMPTOMS FORM (TO BE COMPLETED AT ADMISSION)

Date of evaluation : [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_] **Date of symptom onset :** [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_] **Date of infection (if known)** [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_] Not known ☐						
Fever	☐YES ☐NO ☐Not known Number of days [_D_][_D_]					
Skin rash (lesions)	☐YES ☐NO Number of days [_D_][_D_]					
Lesion characteristics	Distribution of lesions	**Site**	**Number of each type of lesion at each site**			
			New lesion	**Crusts**	**Scars**	**Other**
		☐ Palms of hands				
		☐ Soles of feet				
		☐ Face				
		☐ Back				
		☐ Thighs				
		☐ Legs				
		☐ Arms				
		☐ Forearms				
		☐ Abdomen				
		☐ Chest				
		☐ Genitals				
		☐ Mouth				
		☐ Nose				
		☐ Other, Specify :_____				
	Pain at lesion site	☐YES ☐NO If yes, pain score : [__][__]				
	Please describe any other lesion complications :	_____ _____ _____				
Keratitis	☐YES ☐NO ☐Not known Number of days [_D_][_D_]					
Cough	☐YES ☐NO ☐Not known Number of days [_D_][_D_]					
Clear sputum :	☐YES ☐NO ☐Not known Number of days [_D_][_D_]					
Upper respiratory symptoms (sore throat, runny nose)	☐YES ☐NO ☐Not known Number of days [_D_][_D_] If yes, please specify _____					
Lower respiratory symptoms (productive cough, wheezing, respiratory distress)	☐YES ☐NO ☐Not known Number of days [_D_][_D_] If yes, please specify _____					
Breathlessness	☐YES ☐NO ☐Not known Number of days [_D_][_D_]					

Lymphadenopathy	☐YES ☐NO ☐Not known Number of days [_D_][_D_]	
Site of lymphadenopathy	Axillary	☐YES ☐NO Left☐ Right☐
	Cervical	☐YES ☐NO Left☐ Right☐
	Inguinal	☐YES ☐NO Left☐ Right☐
	Other	☐YES ☐NO Site_____ Left☐ Right☐
Vomiting	☐YES ☐NO ☐Not known Number of days [_D_][_D_]	
Diarrhoea	☐YES ☐NO ☐Not known Number of days [_D_][_D_]	
Headache	☐YES ☐NO ☐Not known Number of days [_D_][_D_]	
Muscle pain	☐YES ☐NO ☐Not known Number of days [_D_][_D_]	
Joint pain	☐YES ☐NO ☐Not known Number of days [_D_][_D_]	
Seizure	☐YES ☐NO ☐Not known Number of days [_D_][_D_]	
Level of consciousness	☐ Alert ☐ Confused ☐ Vocal ☐ Pain ☐ Unconscious	
Level of capacity	**Patient is able to feed himself/herself**	☐YES ☐NO ☐Not known
	Patient is able to drink	☐YES ☐NO ☐Not known
	Patient is able to walk	☐YES ☐NO ☐Not known

Vital signs	
Respiratory rate	[___][___]/min
Pulse	[___][___]/min
Blood pressure	Systolic [___][___]/mmHg Diastolic [___][___]/mmHg
Temperature	[___][___].[___] C
Oxygen saturation	[___][___]% ☐ Dans l'atmosphère ☐ On oxygen treatment [___][___]L/min

4. PRÉLÈVEMENT D'ÉCHANTILLONS POUR LE LABORATOIRE À L'ADMISSION

Blood	☐YES ☐NO Date [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]	PCR	☐Positive ☐Negative
Lesion swab	☐YES ☐NO Date [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]	PCR	☐Positive ☐Negative
Malaria RDT	☐YES ☐NO Date [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]	☐Positive ☐Negative	
HIV RDT	☐YES ☐NO Date [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]	☐Positive ☐Negative	
HIV test (confirmation at IPB)	☐YES ☐NO Date [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]	☐Positive ☐Negative	

Female patients of childbearing potential: Pregnancy test	☐YES ☐NO Date [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]	☐Positive ☐Negative **Si positive** [___][___] weeks

5. SIGNS AND SYMPTOMS FORM (EVERY DAY OF TREATMENT, D15, D21 (IF APPLICABLE) AND D28)

Date of evaluation : [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]						
Fever	☐YES ☐NO ☐Not known					
Skin rash (lesions)	☐YES ☐NO					
Lesion characteristics	Distribution of lesions	**Site**	**Number of each type of lesion at each site**			
			New lesion	**Crusts**	**Scars**	**Other**
		☐ Palms of hands				
		☐ Soles of feet				
		☐ Face				
		☐ Back				
		☐ Thighs				
		☐ Legs				
		☐ Arms				
		☐ Forearms				
		☐ Abdomen				
		☐ Chest				
		☐ Genitals				
		☐ Mouth				
		☐ Nose				
		☐ Other, Specify :_____				
	Pain at lesion site	☐YES ☐NO If yes, pain score : [__][__]				
	Please describe any other lesion complications :	_____ _____ _____				
Keratitis	☐YES ☐NO ☐Not known					
Cough	☐YES ☐NO ☐Not known					
Clear sputum :	☐YES ☐NO ☐Not known					
Upper respiratory symptoms (sore throat, runny nose)	☐YES ☐NO ☐Not known If yes, please specify _____					
Lower respiratory symptoms (productive cough, wheezing, respiratory distress)	☐YES ☐NO ☐Not known If yes, please specify _____					
Breathlessness	☐YES ☐NO ☐Not known					

Lymphadenopathy	☐YES ☐NO ☐Not known	
Site of lymphadenopathy	Axillary	☐YES ☐NO Left☐ Right☐
	Cervical	☐YES ☐NO Left☐ Right☐
	Inguinal	☐YES ☐NO Left☐ Right☐
	Other	☐YES ☐NO Site_____ Left☐ Right☐
Vomiting	☐YES ☐NO ☐Not known	
Diarrhoea	☐YES ☐NO ☐Not known	
Headache	☐YES ☐NO ☐Not known	
Muscle pain	☐YES ☐NO ☐Not known	
Joint pain	☐YES ☐NO ☐Not known	
Seizure	☐YES ☐NO ☐Not known	
Level of consciousness	☐ Alert ☐ Confused ☐ Vocal ☐ Pain ☐ Unconscious	
Level of capacity	**Patient is able to feed himself/herself**	☐YES ☐NO ☐Not known
	Patient is able to drink	☐YES ☐NO ☐Not known
	Patient is able to walk	☐YES ☐NO ☐Not known

Vital signs	
Respiratory rate	[___][___]/min
Pulse	[___][___]/min
Blood pressure	Systolic [___][___]/mmHg Diastolic [___][___]/mmHg
Temperature	[___][___].[___] C
Oxygen saturation	[___][___]% ☐ Dans l'atmosphère ☐ On oxygen treatment [___][___]L/min

6. TREATMENT FORM (TO BE COMPLETED ON EVERY DAY OF TREATMENT)

DAILY TREATMENT **Date of evaluation :** [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]		
Morning dose of tecovirimat	☐YES ☐NO ☐Not known	Dose ____mg Time [_H_][_H_]/[_M_][_M_]
	If the dose was forgotton, modified or refused, please state the reason: _____	
Evening dose of tecovirimat	☐YES ☐NO ☐Not known	Dose ____mg Time [_H_][_H_]/[_M_][_M_]
	If the dose was forgotton, modified or refused, please state the reason: _____	
Paracetamol	☐YES ☐NO ☐Not known	
NSAID	☐YES ☐NO ☐Not known	
Intravenous solutions	☐YES ☐NO ☐Not known	

7. LABORATORY RESULTS (TO BE COMPLETED AT D4, D8, D14 AND D28)

RÉSULTATS DE LABORATOIRE		
Prélèvement jour [_D_]	☐OUI ☐NON	PCR Result : ☐Positif ☐Négatif

8. EFFICACY EVALUATION (TO BE COMPLETED AT D15)

Date of evaluation : [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]

☐ Recovery without sequelae

☐ Recovery with sequelae

Sequelae : _____

☐ Death

Date of death : [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]

Cause of death : _____

☐ Early withdrawal

☐ Loss to follow-up

Reason for loss to follow-up : _____

If the patient withdrew from the study Date : [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]	Adverse event	☐YES ☐NO Reason : _____ (add further details on the AE form)
	Patient decision	☐YES ☐NO Reason : _____
	Clinician decision	☐YES ☐NO Reason : _____
	Other	☐YES ☐NO Reason : _____

Did the patient complete treatment with tecovirimat for 14 days as per the protocol? ☐YES ☐NO

If YES, start date : [_J_][_J_]/[_M_][_M_]/[_A_][_A_] **End date :** [_J_][_J_]/[_M_][_M_]/[_A_][_A_]

If NO, start date : [_J_][_J_]/[_M_][_M_]/[_A_][_A_] **End date :** [_J_][_J_]/[_M_][_M_]/[_A_][_A_]

If NO, reason : _____

9. EFFICACY EVALUATION (TO BE COMPLETED AT D21 (IF APPLICABLE) AND D28)

Date of evaluation : [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]

☐ Recovery without sequelae

☐ Recovery with sequelae

Sequelae : _____

☐ Death

Date of death : [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]

Cause of death : _____

☐ Early withdrawal

☐ Loss to follow-up

Reason for loss to follow-up : _____

If the patient withdrew from the study Date : [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]	Adverse event	☐YES ☐NO Reason : _____ (add further details on the SAE form, if applicable)
	Patient decision	☐YES ☐NO Reason : _____
	Clinician decision	☐YES ☐NO Reason : _____
	Other	☐YES ☐NO Reason : _____

10. PREGNANCY FOLLOW-UP

Has the mother consented to pregnancy follow-up ?	☐YES ☐NO
Date of pregnancy test :	[_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]
Date of last menstruation :	[_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]
Expected delivery date :	[_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]
Pregnancy outcome :	☐ Baby is in good health ☐ Congenital malformations requiring admission to the neonatal unit ☐ Abortion (by choice) ☐ Abortion (for medical reasons) ☐ Miscarriage ☐ Stillbirth ☐ Neonatal death ☐ Maternal death
Date of outcome	[_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]

11. DECLARATION OF APPROVAL BY THE INVESTIGATOR

I have examined this CRF and confirm that, to the best of my knowledge, it accurately reflects the information obtained for this participant. All entries have been made either by me or by a person under my supervision who has been assigned according to the Delegation Log.
NAME : _____ **Signature :** _____ **Date :** [_D_][_D_]/[_M_][_M_]/[_Y_][_Y_]

Table S3 - Patients' demographic information and characteristics at baseline, and post-baseline and outcomes

	Baseline	**Post-baseline[a]**
Demographic characteristics		
Male : female	4 : 10	--
Age (years): median (range)	23 (4 - 38)	--
Comorbidities		--
Malaria: n/N (%) patients	11/13 (85%)	--
HIV: n/N (%) patients tested	1/3 (7%)	--
General characteristics		
Time (days) from symptom onset to treatment start: median (range)	21 (5-45)	--
Signs and symptoms	**n/N (%) patients**	**n/N (%) patients**
Fever (temperature >38·0 °C)	9/14 (64%)	12/14 (86%)
Lesions:	14/14 (100%)	14/14 (100%)
New lesions:	10/14 (71%)	11/14 (79%)
Number of lesions (total): median (range)	302 (54-7586)	351 (0-8170)
Location of lesions:		
Hands	14/14 (100%)	14/14 (100%)
Feet	14/14 (100%)	14/14 (100%)
Face	14/14 (100%)	14/14 (100%)
Back	14/14 (100%)	14/14 (100%)
Thighs	14/14 (100%)	14/14 (100%)
Legs	14/14 (100%)	14/14 (100%)
Arms	14/14 (100%)	14/14 (100%)
Forearms	14/14 (100%)	14/14 (100%)
Abdomen	14/14 (100%)	14/14 (100%)
Chest	14/14 (100%)	14/14 (100%)
Genitals	11/14 (79%)	12/14 (86%)
Mouth	10/14 (71%)	10/14 (71%)
Nose	11/14 (79%)	12/14 (86%)
Other	13/14 (93%)	14/14 (100%)
Lesion pain	11/14 (79%)	11/14 (79%)
Lesion pain score: median (range)	7 (5-9)	5 (1-10)
Lymphadenopathy	14/14 (100%)	14/14 (100%)
Keratitis	2/14 (14%)	2/14 (14%)
Cough	5/14 (36%)	6/14 (43%)
Clear sputum	3/13 (23%)	3/14 (21%)
Upper respiratory symptoms	11/14 (79%)	11/14 (79%)
Lower respiratory symptoms	4/14 (29%)	5/14 (36%)
Breathlessness	0/13 (0%)	1/14 (7%)
Vomiting	0/14 (0%)	1/14 (7%)
Diarrhoea	0/14 (0%)	0/14 (0%)
Headache	14/14 (100%)	14/14 (100%)
Back pain	11/14 (79%)	13/14 (93%)
Muscle pain	14/14 (100%)	14/14 (100%)
Seizure	0/14 (0%)	1/14 (7%)
Patient is able to eat independently	13/14 (93%)	13/14 (93%)
Patient is able to drink independently	14/14 (100%)	13/14 (93%)
Patient is able to walk independently	13/14 (93%)	13/14 (93%)
Outcome	**Post-baseline n/N (%) patients**	
Completed full course of treatment	14/14 (100%)	
Patient outcome		

PCR positive at day 4	7/14 (50%)
Blood	6/7 (86%)
Active lesion	2/7 (29%)
Lesion crust	1/7 (14%)
PCR positive at day 8	1/10 (10%)
Blood	1/1 (100%)
Active lesion	0/1 (0%)
Lesion crust	0/1 (0%)
PCR positive at day 14	1/8 (12%)
Blood	1/1 (100%)
Active lesion	1/1 (100%)
Lesion crust	1/1 (100%)
PCR positive at day 21	1/2 (50%)
Blood	1/1 (100%)
Active lesion	0/1 (0%)
Lesion crust	1/1 (100%)
PCR positive at final visit	1/13 (8%)
Blood	1/1 (100%)
Active lesion	1/1 (100%)
Lesion crust	0/1 (0%)
Time (days) to no new lesions: median (range)	5 (0-28)
Recovered without sequelae at D28	4/13 (31%)
Recovered with sequelae at D28	9/13 (69%)
Death	1/14 (7%)
Serious Adverse Events	
Patients with at least one serious adverse event	2/14 (14%)
Severity:	
Mild	0
Moderate	0
Severe	0
Life-threatening	1/2 (50%)
Fatal	1/2 (50%)
System:	
Blood and lymphatic system	1/2 (50%)
Other	1/2 (50%)

[a] Post-baseline includes any timepoint following baseline, including days on which patients are receiving treatment

Figure S4 – Number of days to no active lesions and average number of active lesions per day

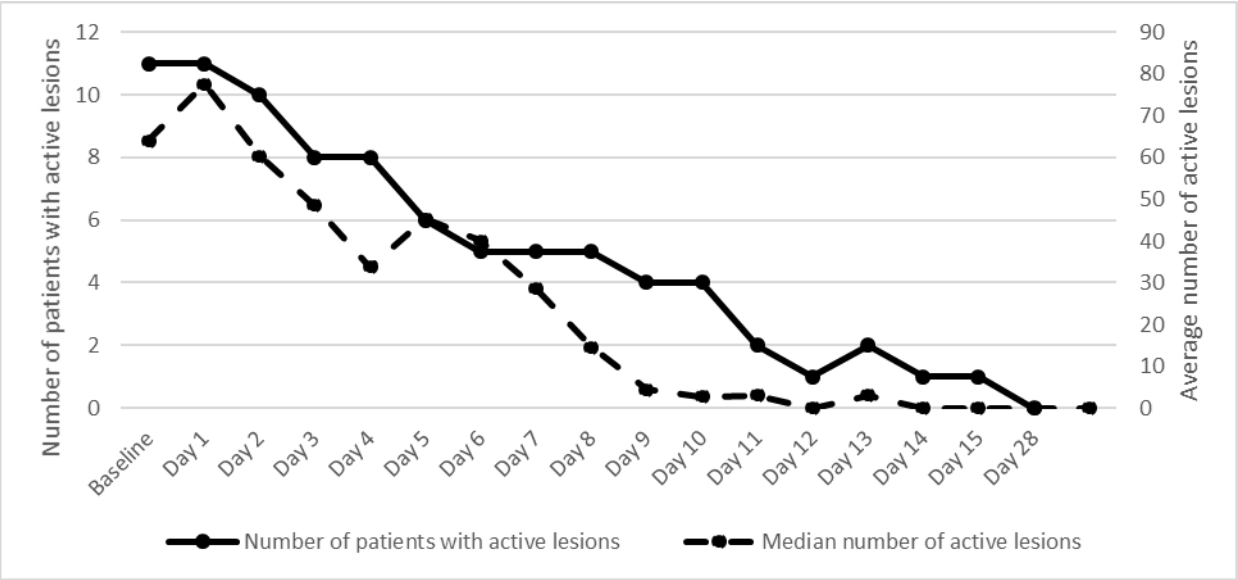

Table S5 - Confirmed cases and case fatality ratio in CAR between 2010 and September 2022 – overall case fatality 10.4%

Year	Month	Confirmed cases	Deaths
2010	June	1	0
2012	April	2	0
2015	December	1	1
2015	December	3	3
2016	January	1	0
2016	August	3	2
2017	January	5	0
2017	April	1	0
2018	February	9	0
2018	June	3	0
2018	August	1	0
2018	September	1	0
2018	September	1	0
2018	September	6	0
2018	October	1	0
2018	October	1	0
2018	November	3	0
2018	December	3	1
2019	January	1	0
2019	February	1	0
2019	August	1	0
2019	August	4	1
2019	September	1	1
2019	September	2	0
2019	September	1	0
2019	September	1	0
2019	October	3	0
2020	November	2	0
2020	November	2	0
2020	November	1	0
2020	December	3	0
2021	February	1	0
2021	August	3	0
2021	September	4	0
2021	September	2	1
2021	September	1	0
2021	October	2	0
2021	November	13	1
2021	November	1	0
2021	December	1	0

2022	January	1	0
2022	February	1	0
2022	February	1	0
2022	March	1	0
2022	July	1	0
2022	July	1	0
2022	August	1	0
2022	August	1	0
2022	September	1	0
Total		106	11