Efficacy & Safety of SOF/DCV in COVID-19

By

Mostafa Yakoot, Basem Eysa, Andrew Hill,
Essam Gouda, Sherine Helmy, Mohamed Hassany,
et al

Study Rationale

- Results from three open-label studies in Iran showed improved survival and clinical recovery for patients treated with sofosbuvir/daclatasvir versus control treatment. However the sample size was only 176 patients and one trial was not randomized.
- In vitro studies suggest that daclatsvir might show antiviral activity against SARS-COV-2 at the standard 60mg once daily dose; sofosbuvir is unlikely to be active at the standard dose, btut might enhance the activity of daclatasvir

Study Design & Setting

- This is a parallel 2-arm randomized, open-label, active-controlled clinical study, conducted in an inpatient setting in an isolation hospital in Cairo.

Inclusion criteria:

1. Subjects or their legal representatives have signed the ICF.
2. Subjects are aged ≥ 18 and ≤ 75;
3. Laboratory-confirmed COVID19 (by PCR assay);
4. Symptomatic COVID19 with clinical severity at baseline as follows: (Mild, Moderate or Severe):

Inclusion Criteria

1. **Mild**：mild clinical symptoms with no picture of pneumonia in CT, but positive 2019-nCoV2 in throat/nasal swabs.
2. **Moderate**：fever, respiratory symptoms, pneumonia visible in CT.
3. **Severe (NOT Critical)**: meeting any of the following criteria:

(a) Respiratory distress, RR≥30 times/min;

(b) Finger oxygen saturation ≤93% in rest state;

(c) PaO2/FiO2 ≤400mmHg and > 200mmHg under.

Exclusion Criteria

(1) Pneumonia due to other etiology.

(2 Critically severe COVID19 cases Requiring invasive ventilation at screening;

(3) Patients who have severe concomitant illness that affects survival.

(4) Pregnant or lactating females.

(5) Hypersensitivity or contraindication to any of the drugs used in the study.

(6) Patients with cirrhosis or abnormal liver enzyme > 3 times the UL of normal

(7) Renal dysfunction [eGFR] <30 mL/min/1.73m2

Patients were randomized into 2 arms:

- **ARM 1** ***(Experimental (n=44)):*** who received the standard of care (SOC) therapy (as per the Egyptian MOH protocol) together with a daily dose of one Gratisovir (Sofosbuvir) 400 mg tablet combined with one Daktavera (Daclatasvir) 60 mg tablet (both are generics by Pharco), on Day 1 through 10.

- **ARM 2** ***(Control (n=45)):*** who received only the standard of care therapy according to the MOH protocol (this included Hydroxychloroquine, Azithromycin, Vitamin C, Zinc supplement, acetaminophen and cough mixtures as needed. Treatment escalation with anticoagulants, parenteral antibiotics, O2 therapy escalated up to ICU admission & mechanical ventilation whenever a case is deteriorated.

Primary endpoints

- **Proportion of clinical recovery (composite) within 21 days, normalization of fever (≤37.2 °C oral), respiratory rate (≤24/minute on room air), and oxygen saturation (≥94% on room air), sustained for at least 24 hours.**

- Time to clinical recovery (composite) from initiation of study treatment until resolution of symptoms sustained for at least 24 hours [Time frame: 21 days].

- Mean change in Clinical status using ordinal scale [Day 3 through Day 21]:
  1) Death; 2) Hospitalized, on invasive ventilation or ECMO; 3) Hospitalized, on non-invasive ventilation or high flow oxygen; 4) Hospitalized with oxygen supplement;
  5) Hospitalized, not requiring oxygen but need medical care;
  6) Hospitalized, not requiring supplemental oxygen or ongoing medical care;
  7) Not hospitalized, limitation on activities and/or requiring home oxygen;
  8) Not hospitalized with normal activity.

Statistical plan

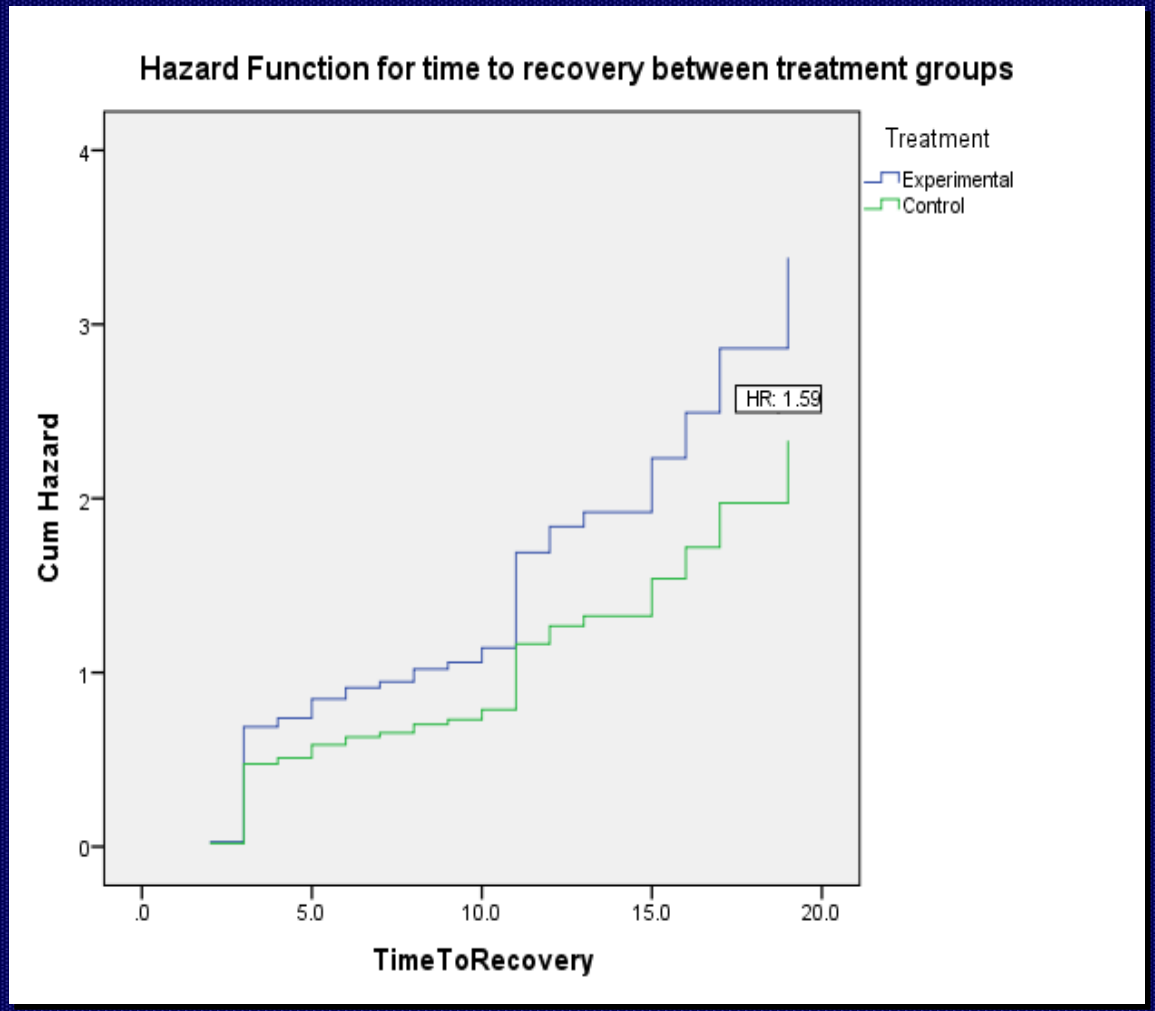
- Group sample sizes of 44 in group one and 44 in group two achieve 81% power to detect a difference between the group proportions of 0.24. The test statistic used is z test for proportions with boot strapping. The significance level of the test was targeted at 0.05.
- A Kaplan –Meier curve was used to report the probability of progression over time (time to events: time to clinical recovery); to be compared between groups using a Cox proportional hazards model with adjustment for baseline disease severity indicators.

Baseline characteristics	EXPERIMENTAL (n=44)	CONTROL (n=45)	
Baseline demographics			
Age, median (IQR)	48 (34-59)	50 (31-60)	
Male, n (%)	18 (41%)	20 (45%)	
Severity of disease at baseline, n (%)			
Mild	6 (14%)	6 (13%)	
Moderate	30 (68%)	31 (69%)	
Severe	8 (18%)	8 (18%)	
Comorbidities, n (%)			
Asthma	0 (0%)	1 (3%)	
Diabetes	9 (22%)	8 (21%)	
Chronic kidney disease	0 (0%)	2 (4%)	
Hypertension	11 (25%)	12 (27%)	
Heart disease	2 (4%)	6 (13%)	
Smoking	12 (29%)	7 (18%)	
Vital signs at baseline, median (IQR)			
O_2 saturation (%)	96 (94-97)	96 (94-98)	
Temperature (°C)	37 (36.8-37.8)	37 (36.9-37.2)	
Respiratory rate (Breaths/min)	19 (18-24)	20 (18-25)	
Pulse (Beats/min)	91 (82-100)	90 (85-98)	
Laboratory findings on admission, median (IQR)			
Lymphocytes	1.9 (1.3-2.4)	2.1 (1.3-2.6)	
D-Dimer (mg/L)	0.46 (0.31-0.59)	0.56 (0.33-1.05)	
C-Reactive protein (mg/dL)	12.2 (4.8-36.4)	23.4 (4.0-70.1)	

Baseline characteristics were balanced between groups

RESULTS

- The proportion of cumulative clinical recovery in the experimental group at day 21 was numerically greater than the control group (91%; CI: 78.8-96.4%) versus (77.8%; 63.7-87.5%); RR:1.17 (CI: 0.97-1.4)).
- The Hazard Ratio (HR) for time to clinical recovery adjusted for baseline severity estimated by Cox-regression was statistically significant: HR: 1.59 (CI: 1.001-2.5)

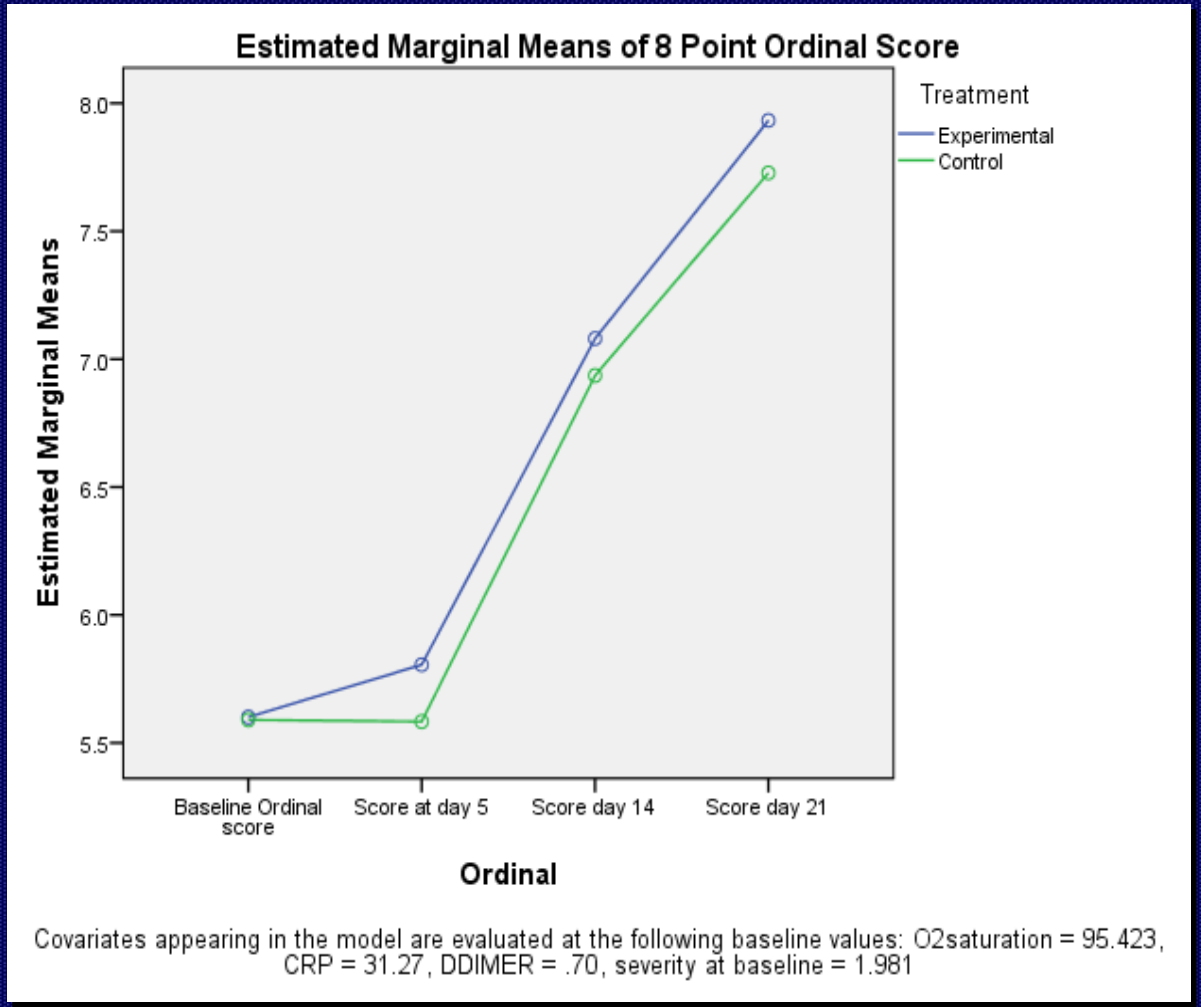


RESULTS

- The experimental group also showed trends to greater numerical improvement in all studied clinical efficacy endpoints including: the 8 points ordinal scale score, the severity of lung lesions score (by CT scan) and “to less than half” the case fatality rate (4.5% versus 11.1%).
- All these effects, though did not reach statistical significance at the study sample size, but being all concordant with the significant HR, they support the study concept.

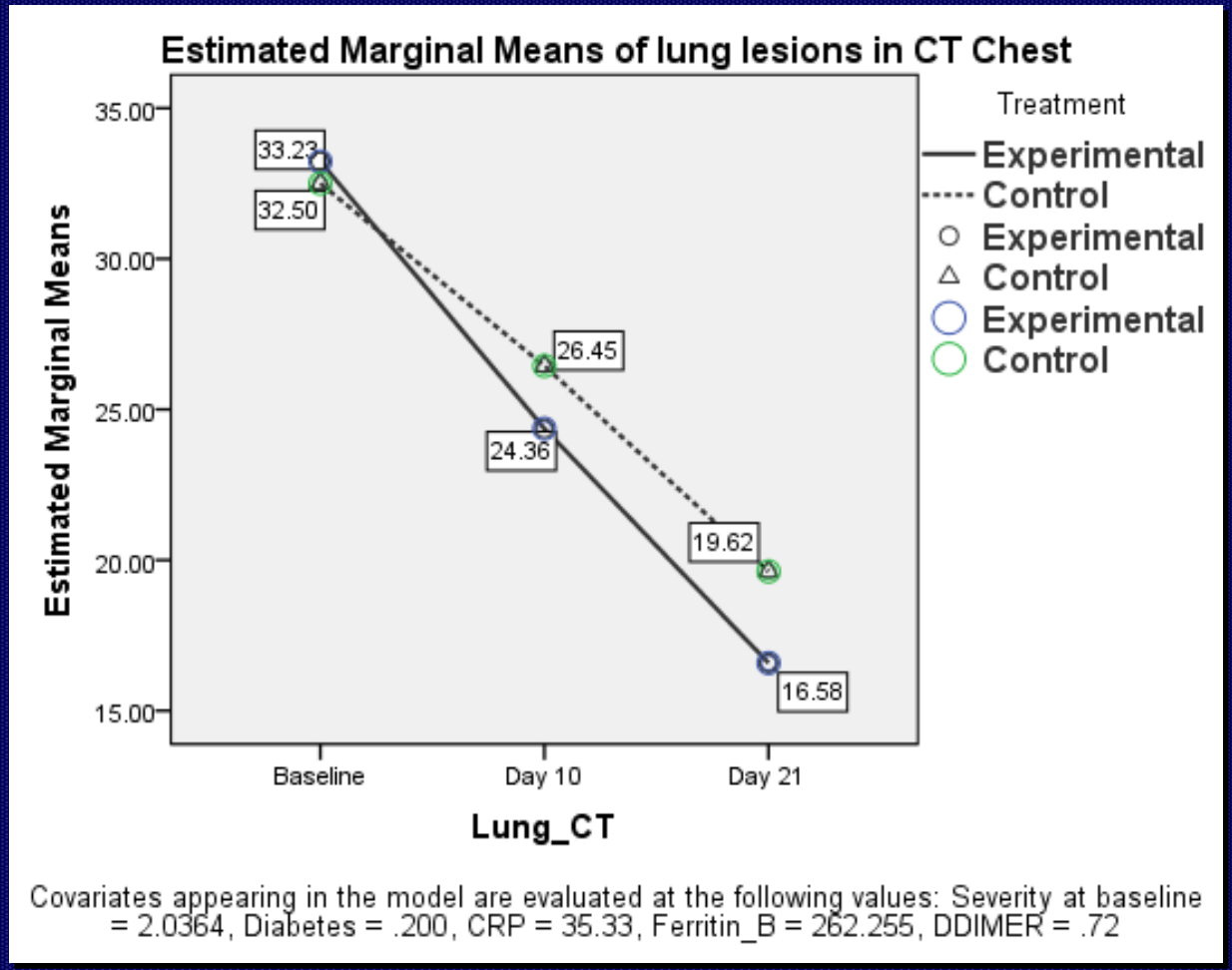
RESULTS

- The 8 point ordinal scale showed concordant higher numerical mean scores in the experimental group than the control group, with adjustment for baseline severity indicators but this did not reach statistical significance in ITT analysis.



RESULTS

- Experimental group showed tendency to better improvement in lung lesions with more steeply reduction in the mean severity scores (numerically); though the difference was not statistically significant at the study sample size.



RESULTS

- The incidence of sustained viral negativity confirmed at day 21 (end of follow up) showed no statistically significant difference between groups in ITT analysis by 2 sided Exact test with boot strapping.

Virus negativity (ITT) sustained to day 21

PCR Negative (ITT)	Experimental	Control	Sig.
Count	28	27	0.61
% within treatment	63.6%	60%	

RESULTS

- **2** patients in the experimental group (4.5%; CI: 1.13 - 15.1%) & 5 in the control group (11.1%; CI: 4.8 - 23.5%) suffered severe deterioration necessitating admission to ICU and invasive mechanical ventilation. All died in the ICU.
- No serious AEs reported, only comparable mild non-serious events in both groups.

Case fatality per treatment group stratified by baseline severity

Baseline severity	Deaths	Treatment		Total
		Experimental	Control	
Mild	Frequency (k/n)	0/6	0/6	0/12
	% within Treatment	0%	0%	0%
Moderate	Frequency (k/n)	1/30	3/31	4/61
	% within Treatment	3.3%	9.7%	6.6%
Severe	Frequency (k/n)	1/8	2/8	3/16
	% within Treatment	12.5%	25%	18.8%
Total severities	Frequency (k/n)	2/44	5/45	7/89
	% within Treatment	4.5%	11.1%	7.9%

DISCUSSION

- The highly variable natural course of COVID-19, with a considerable proportion of spontaneous recovery & low incidence of unpredictable fatality could make the results of observational studies to evaluate treatment difficult to interpret.
- Even in large sized RCTs, it was practically difficult to detect statistically significant reduction in mortality beyond the standard of care (low fatality ~ small effect size)
- That is why we designed this study “though small hypothesis generating” as a randomized controlled trial.

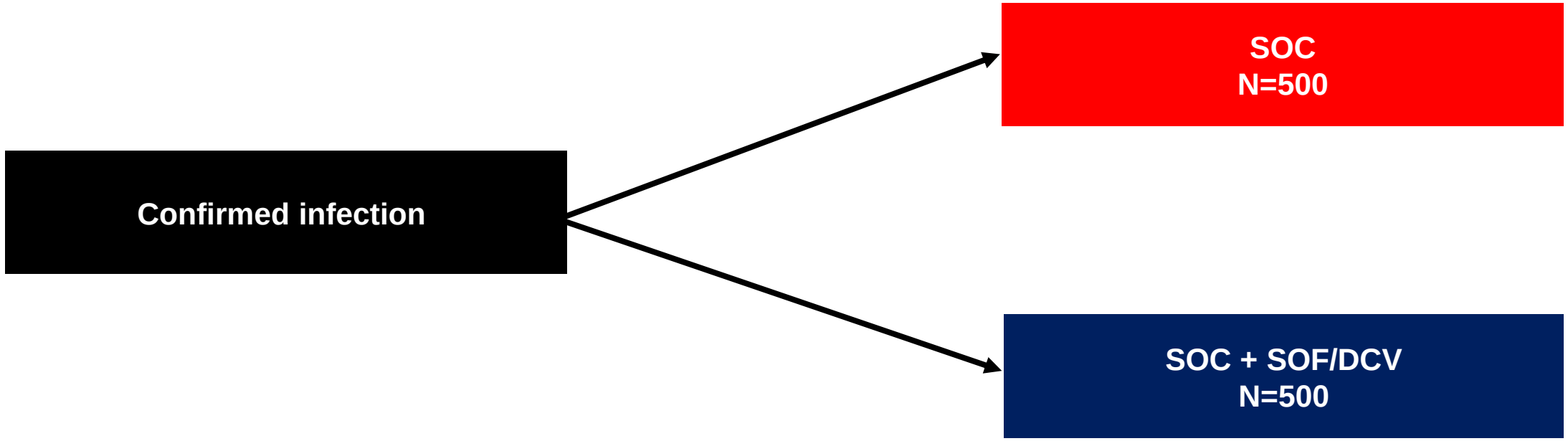
CONCLUSIONS

- Although our sample size was not large to have enough power to detect tiny effect size, yet the HR adjusted for baseline severity by the Cox-regression was statistically significant: HR: 1.6 (95% CI: 1.001-2.5).
- This signifies that, at any time during the study, the clinical recovery in the experimental group has about 1.6 times greater probability than the control group.
- This together with the concordant tendency to better mean scores of the 8 points ordinal scale, greater improvement in lung lesion scores, lower case fatality rate in the experimental group (<half), though did not reach statistical significance, but could add support to the potential benefits of SOF/DCV in the treatment of COVID-19.

Iranian DISCOVER trial of SOF/DCV: n=1000, FULLY RECRUITED

Inclusion criteria: COVID-19 symptoms, oxygen saturation <95%, CT involvement

Primary endpoint: Clinical recovery and hospital discharge



Double-blind, placebo controlled

Trial started in July 2020

Results expected on 5th November 2020