Supplementary Materials

Table S1. In-hospital use of concomitant medications.

	MP (n=337)	DM (n=340)	p-value*
Anticoagulants, No. (%)			
LMWH prophylactic dose†	271 (80.4)	266 (78.2)	0.36
LMWH therapeutic dose‡	88 (26.1)	74 (21.8)	0.38
UFH prophylactic dose§	1 (0.3)	2 (0.6)	0.85
UFH therapeutic dose‖	1 (0.3)	1 (0.3)	0.98
Warfarin¶	2 (0.6)	4 (1.2)	0.56
DOAC**	13 (3.9)	12 (3.5)	0.87
Other treatments, No. (%)			
Tocilizumab	30 (8.9)	24 (7.1)	0.38
Remdesivir	75 (22.3)	66 (19.4)	0.36
Baricitinib	14 (4.2)	17 (5.0)	0.60
Anakinra	2 (0.6)	3 (0.9)	0.67
Casirivimab + Imdevimab	9 (2.7)	12 (3.5)	0.52
Sarilumab	0 (0.0)	2 (0.6)	0.16
Monoclonal antibodies	0 (0.0)	1 (0.3)	0.32

Abbreviations: LMWH, low molecular weight heparin; UFH, unfractionated heparin; DOAC, direct oral anticoagulants.

* P value of the Fisher exact test for dichotomous variables, unpaired Student t test or Wilcoxon; rank-sum test for numerical variables, as appropriate.

† Missing data: 5 MP, 9 DM.

‡ Missing data: 9 MP, 10 DM.

§ Missing data: 12 MP, 11 DM.

‖ Missing data: 13 MP, 12 DM.

¶ Missing data: 9 MP, 10 DM.

** Missing data: 10 MP, 9 DM.

Table S2. Stratification of MV-free days at 28 days according to the severity of respiratory impairment at randomisation.

Stratification variable	Intention-to-treat analysis			Per-protocol analysis		
	MP	DM	p-value*	MP	DM	p-value*
	Median (IQR)			*Median (IQR)*		
None	23.0 (14.0)	24.0 (16.0)	0.49	24.0 (10.0)	26.0 (8.0)	0.09
PaO_2:$FiO_2 \geq 200$ mmHg	28.0 (7.0)	28.0 (6.0)	0.96	28.0 (6.0)	28.0 (5.0)	0.93
PaO_2:$FiO_2 < 200$ mmHg	19.0 (25.0)	19.5 (26.0)	0.70	21.0 (10.0)	22.0 (13.0)	0.39
Low-flow oxygen	28.0 (6.0)	28.0 (5.0)	0.80	28.0 (4.0)	28.0 (3.0)	0.78
HFNC	22.0 (11.0)	21.5 (28.0)	0.40	22.5 (10.0)	24.0 (14.0)	0.98
NIV	16.5 (23.0)	19.0 (23.0)	0.41	20.0 (14.0)	21.0 (9.0)	0.19

Abbreviations: IQR, interquartile range; PaO_2:FiO_2, ratio of partial pressure of arterial oxygen (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2); HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

* P-value of the Wilcoxon rank-sum test.

Table S3. Odds of ICU referral according to the severity of respiratory impairment at randomisation.

Stratification variable	Intention-to-treat analysis				Per-protocol analysis			
	MP	DM	OR	p-value*	MP	DM	OR	p-value*
	no. of events/total no. (%)		(95% CI)		*no. of events/total no. (%)*		(95% CI)	
None	41/337 (12.2)	45/340 (13.2)	0.91 (0.58-1.43)	0.68	7/279 (2.1)	19/286 (5.6)	0.36 (0.15-0.87)	0.02
PaO_2:$FiO_2 \geq 200$ mmHg	11/150 (7.3)	12/174 (6.9)	1.07 (0.46-2.50)	0.88	2/123 (1.6)	5/156 (3.2)	0.50 (0.10-2.62)	0.41
PaO_2:$FiO_2 < 200$ mmHg	29/184 (15.8)	32/163 (19.6)	0.77 (0.44-1.33)	0.34	5/154 (3.2)	13/128 (10.2)	0.30 (0.10-0.86)	0.03
Low-flow oxygen	9/142 (6.3)	12/174 (6.9)	0.91 (0.37-2.23)	0.84	2/122 (1.6)	5/157 (3.2)	0.51 (0.97-2.66)	0.42
HFNC	6/74 (8.1)	8/45 (17.8)	0.41 (0.13-1.26)	0.12	2/66 (3.0)	5/38 (13.16)	0.21 (0.04-1.12)	0.07
NIV	26/120 (21.7)	25/118 (21.2)	1.03 (0.55-1.91)	0.93	3/90 (3.3)	9/89 (10.1)	0.31 (0.08-1.17)	0.08

Abbreviations: PaO_2:FiO_2, ratio of partial pressure of arterial oxygen (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2); HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

* Odds-ratio of event among MP group vs DM group, estimated using logistic regression model.

Table S4. Stratification of the number of hospitalization days among survivors, according to the severity of respiratory impairment at randomisation.

Stratification variable	Intention-to-treat analysis			Per-protocol analysis		
	MP	DM	p-value*	MP	DM	p-value*
	Median (IQR)			*Median (IQR)*		
None	15.0 (11.0)	14.0 (11.0)	0.005	15.0 (10.0)	13.0 (10.0)	0.001
PaO_2:$FiO_2 \geq 200$ mmHg	14.0 (10.0)	12.0 (9.0)	0.006	14.0 (10.0)	12.0 (9.0)	0.009
PaO_2:$FiO_2 < 200$ mmHg	17.0 (13.0)	16.0 (14.0)	0.55	18.0 (11.0)	15.5 (13.0)	0.21
Low-flow oxygen	14.0 (10.0)	12.0 (9.0)	0.003	14.0 (9.0)	12.0 (8.0)	0.001
HFNC	17.0 (12.0)	12.0 (14.0)	0.09	17.0 (11.0)	12.0 (12.0)	0.06
NIV	18.0 (11.0)	18.0 (12.0)	0.78	17.0 (9.0)	17.0 (8.0)	0.96

Abbreviations: IQR, interquartile range; PaO_2:FiO_2, ratio of partial pressure of arterial oxygen (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2); HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

* P-value of the Wilcoxon rank-sum test.

Table S5. Score of the WHO clinical progression scale at days 3, 7 and 14, median (IQR)

	MP (n=325)	DM (n=326)	p-value*
Day 3	6 (1)	6 (1)	0.19
Day 7	6 (1)	6 (1)	0.05
Day 14	5 (5)	4 (5)	0.09

*P-value of the Mann-Whitney test

Table S6. Description of the WHO clinical progression scale by score at days 3, 7 and 14, No. (%)

	Day 3		Day 7		Day 14	
	MP (n=325)	DM (n=326)	MP (n=300)	DM (n=303)	MP (n=298)	DM (n=305)
< 4	0 (0.0)	2 (0.6)	10 (3.3)	23 (7.6)	93 (31.2)	131 (43.0)
4	6 (1.9)	13 (4.0)	16 (5.3)	33 (10.9)	46 (15.4)	36 (11.8)
5	88 (27.1)	94 (28.8)	105 (35.0)	95 (31.4)	83 (27.9)	56 (18.4)
6	225 (69.2)	210 (64.4)	149 (49.7)	127 (41.9)	44 (14.8)	42 (13.8)
7	3 (0.9)	1 (0.3)	4 (1.3)	6 (2.0)	5 (1.7)	5 (1.6)
8	1 (0.3)	2 (0.6)	5 (1.7)	3 (1.0)	4 (1.3)	3 (1.0)
9	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)
10	2 (0.6)	2 (0.6)	11 (3.7)	15 (5.0)	22 (7.4)	31 (10.2)

Legend to the WHO clinical progression scale:
< 4 = non hospitalized
4 = hospitalized, no oxygen therapy
5 = hospitalized, oxygen by mask or nasal prongs
6 = hospitalized, oxygen by NIV or high flow
7 = intubation and mechanical ventilation, $PaO_2:FiO_2 \geq 150$
8 = mechanical ventilation, $PaO_2:FiO_2 < 150$ or vasopressors
9 = mechanical ventilation, $PaO_2:FiO_2 < 150$ and vasopressors, dialysis or ECMO

Table S7. Adverse events related to the study treatment, No. (%)

	MP (n=337)	DM (n=340)	p-value*
Anaphylaxis†	0 (0.0)	0 (0.0)	1.00
Agitation‡	34 (10.1)	30 (8.8)	0.73
Psychosis§	11 (3.3)	5 (1.5)	0.30
Insomnia‖	47 (13.9)	40 (11.8)	0.47
Hyperglycemia¶	113 (33.5)	93 (27.4)	0.15
Any of the above**	147 (43.6)	126 (37.0)	0.08

* P value of the Fisher exact test for dichotomous variables.

† Missing data: 8 MP, 9 DM.

‡ Missing data: 12 MP, 14 DM.

§ Missing data: 14 MP, 13 DM.

‖ Missing data: 19 MP, 13 DM.

¶ Missing data: 20 MP, 16 DM.

** Missing data: 1 MP, 0 DM.

Table S8. In-hospital complications, No. (%)

	MP (n=337)	DM (n=340)	p-value*
Bradycardia†	31 (9.2)	24 (7.1)	0.51
Diarrhea‡	13 (3.9)	16 (4.7)	0.82
Elevation of liver enzymes§	85 (25.2)	89 (26.2)	0.89
Hypokalemia‖	19 (5.6)	17 (5.0)	0.67
Shock requiring vasopressors¶	3 (0.9)	5 (1.5)	0.59
Acute kidney injury**	23 (6.8)	26 (7.6)	0.67
Disseminated intravascular coagulation	15 (4.5)	14 (4.1)	0.83
Acute myocardial infarction††	0 (0.0)	1 (0.3)	0.61
Stroke‡‡	1 (0.3)	0 (0.0)	0.50
Atrial fibrillation§	9 (2.8)	5 (1.5)	0.39
Pulmonary embolism‖‖	21 (6.2)	18 (5.3)	0.73
Bacterial superinfection¶¶	46 (13.6)	49 (14.4)	0.94
Pneumothorax	2 (0.6)	2 (0.6)	0.99
Pneumomediastinum	7 (2.1)	4 (1.2)	0.35
Deep vein thrombosis	1 (0.3)	0 (0.0)	0.32
Bleeding	8 (2.4)	3 (0.9)	0.12
Any of the above	169 (50.1)	158 (46.5)	0.36

* P value of the Fisher exact test for dichotomous variables.
† Missing data: 19 MP, 22 DM.
‡ Missing data: 18 MP, 20 DM.
§ Missing data: 15 MP, 13 DM.
‖ Missing data: 16 MP, 12 DM.
¶ Missing data: 17 MP, 13 DM.
** Missing data: 15 MP, 11 DM.
†† Missing data: 15 MP, 15 DM.
‡‡ Missing data: 15 MP, 13 DM.
§§ Missing data: 16 MP, 12 DM.
‖‖ Missing data: 20 MP, 16 DM.
¶¶ Missing data: 15 MP, 15 DM.

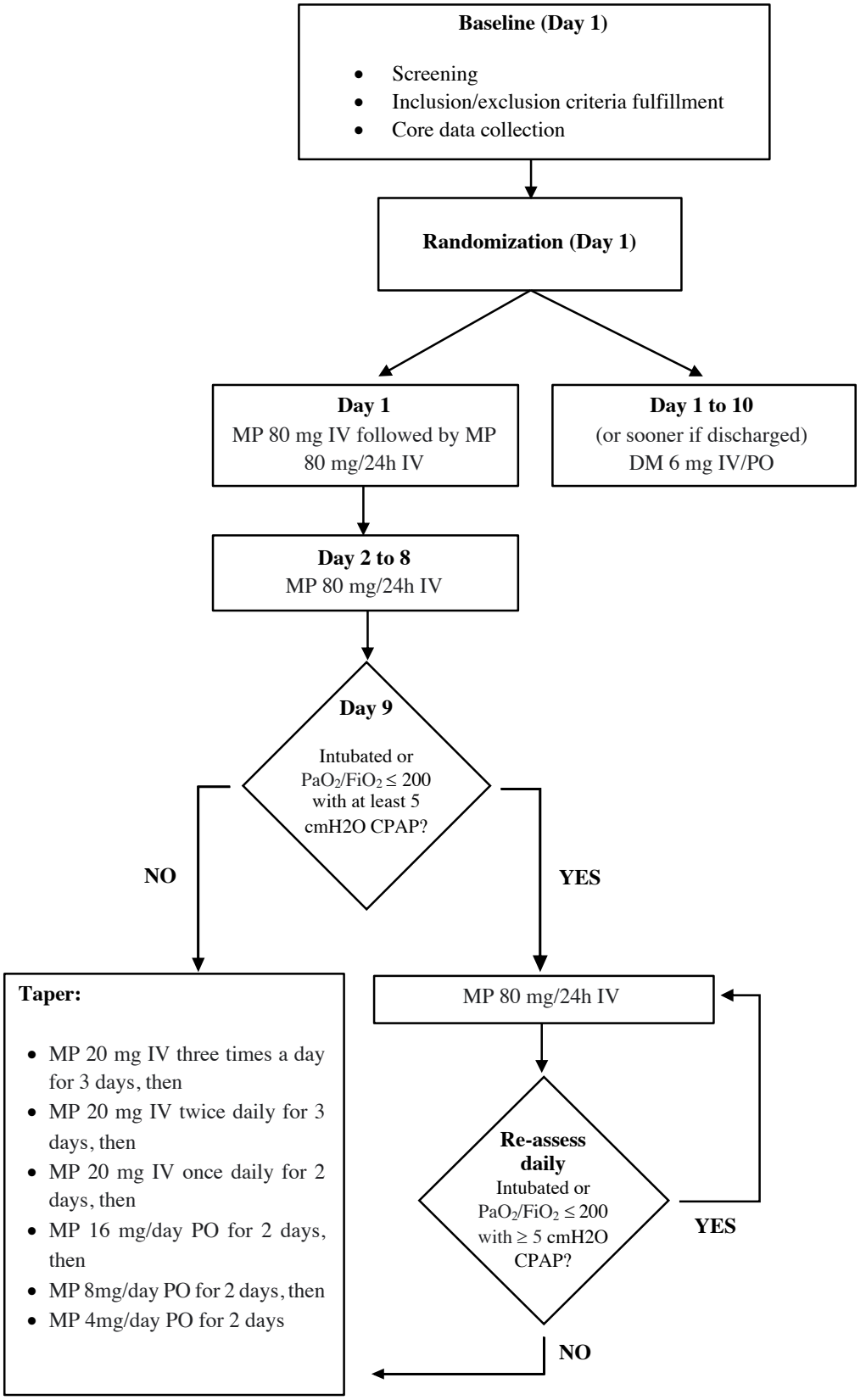
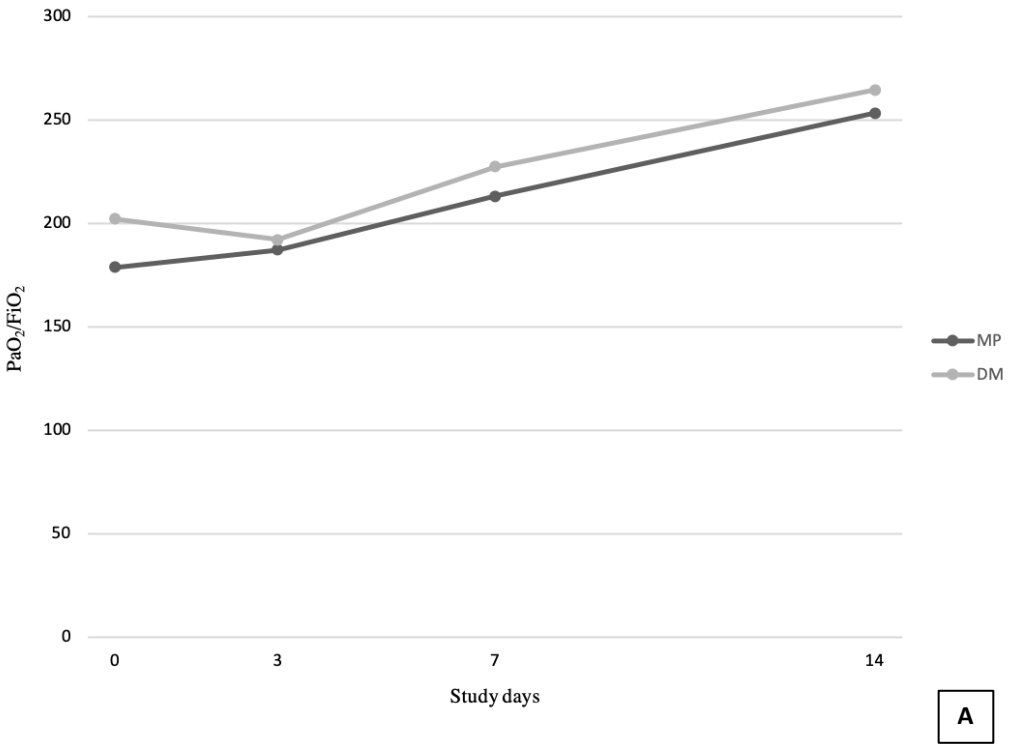


Figure S1. Flow-chart of the treatment schedule in both arms.



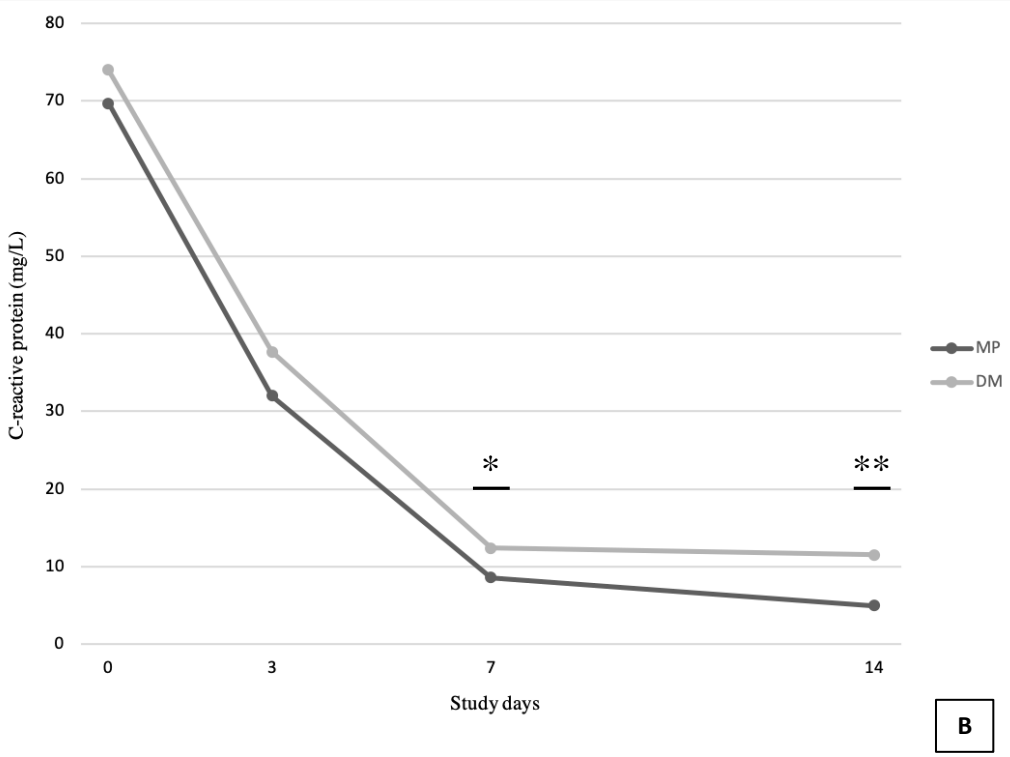


Figure S2. Panel A: time-course of PaO_2:FiO_2 variation. Panel B: time course of C-reactive protein variation, showing significant differences at days 7 (*, $p = 0.006$) and 14 (**, $p = 0.0001$).

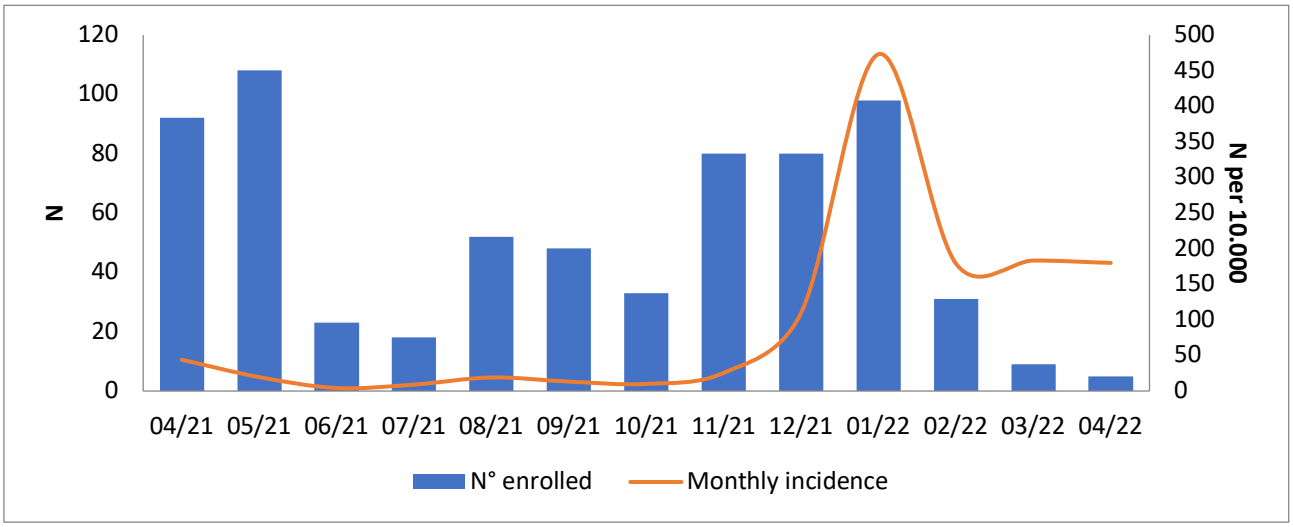


Figure S3. Distribution of the number of enrolled patients per month (blue bars) and incidence of new COVID-19 cases in Italy (orange line).

Supplementary statistical methods

Sequential design procedures

Stopping rules for either futility or efficacy are bound to specific error spending function according to a Fisher's exact test calculated on primary outcome. Preplanned critical values and plots are reported in table S9 and figure S4.

Table S9. Preplanned critical values (Fisher test) for application of early stopping rules.

$$H0: \pi_T - \pi_C = 0$$

Critical values	Stage 1	Stage 2	Stage 3
Reject H0 (Efficacy)	3.421	2.419	1.975
Accept H0 (Futility)	-0.695	1.002	1.975
Information rate	0.333	0.667	1
alpha spent	0.0003	0.0079	0.025

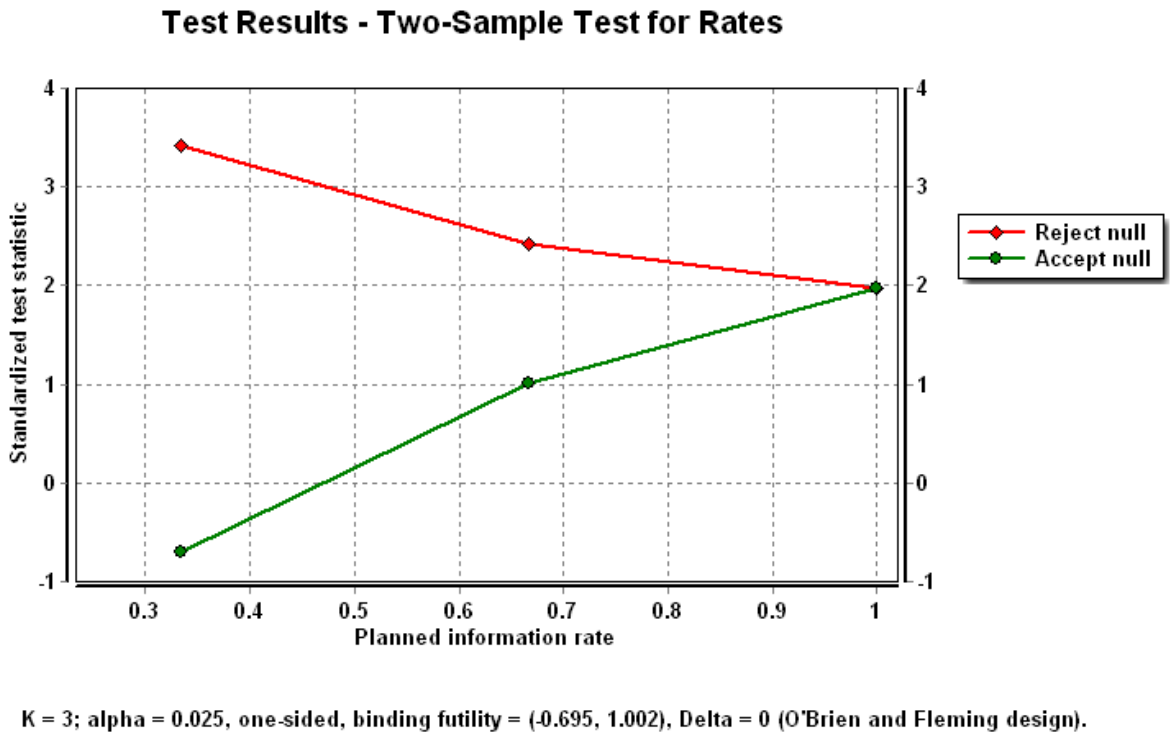


Figure S4. Graphical plot for the application of early stopping rule. Uncertainty area (i.e. H0 is neither accepted nor rejected) lies above the green line and below the red lines.

Sample size

Minimum and maximum sample size will significantly change according to the observed effect within the trial sample (expected average sample size is between 200 and 680 participants. In particular, we expect to enroll 100 participants per arm at the first stage and then between 15 and 175 per arm for each eventual stage if the stopping rules were not met. The actual number of new participants in each

arm will be calculated according to the maximum likelihood estimates on observed efficacy at each interim analysis with an overall conditional power for next stage equal to 90%. This approach allows either to minimize the number of enrolled participants if the experimental hypothesis is too conservative or to have a good power level if the experimental hypothesis is too optimistic. The average sample size with relative power and the overall probability for meeting stopping rules according to different level of efficacy of arm 1 vs. arm 2 are reported in figures S5 and S6.

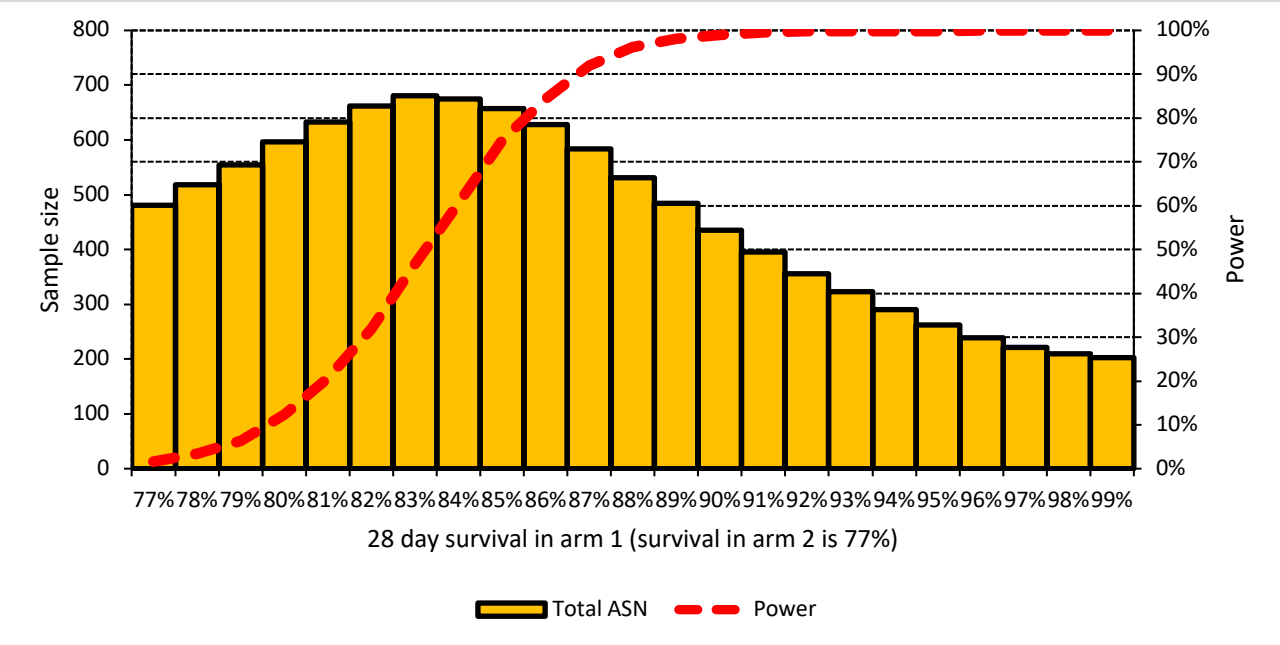


Figure S5. Adaptive sample size and power. The yellow bars represent the number of patients to be enrolled in the trial. Red dotted line shows the study power (i.e. the probability to detect a real difference between arm 1 and arm 2 if arm 1 is superior to arm 2). Simulation has been carried out assuming 1:1 ratio between arms; first analysis is carried out at 200 patients; adaptive sample size between 30-350 and p-value calculated according to Fisher's exact statistics; conditional power for the next analysis 90%; K=3 (i.e. 2 interim analysis and one final analysis).

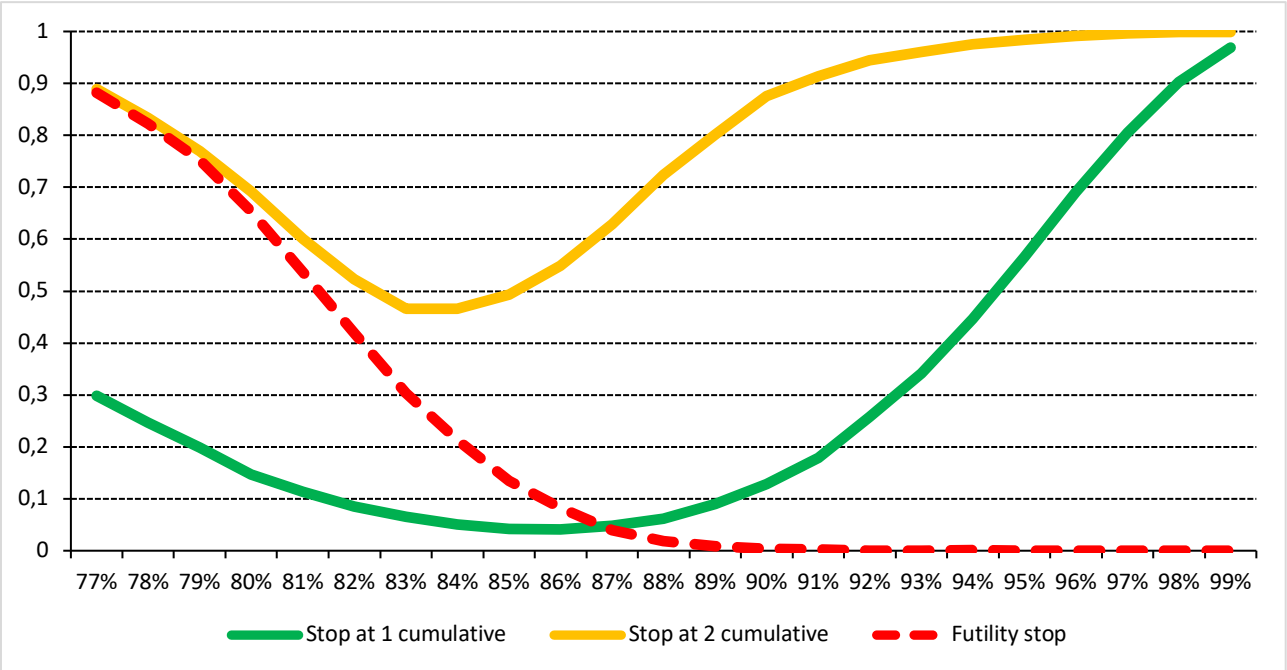


Figure S6. Cumulative probability of trial termination. Continuous lines show the cumulative probability of early termination either at first (green line) or second (yellow line) interim analysis. Early termination at both stages can be driven either by efficacy (i.e. reject H0) or futility (i.e. accept H0). The red dotted line shows the cumulative probability of termination for futility regardless of the stage of analysis (i.e. at first interim, second interim of final analysis).