Supplemental Online Content

Lv J, Wong MG, Hladunewich MA, et al; for the TESTING Study Group. Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy. *JAMA.* Published online May 17, 2022. doi:10.1001/jama.2022.5368

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1 - TESTING Timeline

Date	Name of document / Event	Brief summary of changes / notes
16 June 2011	TESTING Protocol V1.0	▪ Sample size – 1,300
7 December 2011	TESTING Protocol V2.0 Amendment 1	▪ Changes to Steering Committee membership ▪ Inclusion of placebo ▪ Addition of Hong Kong ▪ Administrative clarifications and corrections
8 May 2012 6 August 2012	Recruitment	▪ First participant screened at Peking University First Hospital, China ▪ First participant randomised at Peking University First Hospital, China
3 December 2012	TESTING Protocol V3.0 Amendment 2	▪ Changes to Steering Committee membership ▪ Change to inclusion criteria ▪ Updated CKD-EPI formula ▪ Administrative clarifications and corrections
7 April 2014	TESTING Protocol V4.0 Amendment 3	▪ Removal of the requirement for renal biopsy to be within the last 3 years ▪ Inclusion criteria for eGFR revised from 20 to 90ml/min per 1.73m2 (inclusive) to 20 to 120ml/min per 1.73m2 (inclusive) ▪ Administrative clarifications and corrections
13 May 2015	TESTING Protocol V5.0 Amendment 4	▪ Changes to Steering Committee membership and affiliations ▪ Primary outcome modified from 50% eGFR reduction to 40% decrease in eGFR ▪ Sample size modified to 750 ▪ Updated CKD-EPI formula ▪ Administrative clarifications and corrections

eTable 1 - TESTING Timeline

Date	Name of document / Event	Brief summary of changes / notes
6 November 2015	DSMB Meeting	▪ DSMB meeting immediately followed by a letter recommending that the trial should not continue in its current form
12, 15, 20, 27 November 2015	Steering Committee Meetings	▪ A series of Steering Committee meetings were held to discuss the DSMB letter ▪ 15 Nov 2015 - Decision made to stop recruitment and wean participants off treatment ▪ 20 Nov 2015 - Decision made to develop a low-dose protocol ▪ 27 Nov 2015 - Discussions re low-dose protocol design
16 November 2015	Letter to sites	▪ A letter was sent to all sites informing them of the decision to cease recruitment and wean participants off randomised treatment
25 December 2015	Randomised treatment	▪ All participants weaned off randomised treatment
4 March 2016	SAP – Transitional analysis	▪ The SAP for the transitional analysis of full-dose participants finalised
22 May 2016	Presentation of results	▪ Presentation of the transitional analysis results at ERA/EDTA
12 July 2016	TESTING Protocol V6.0 Amendment 5	▪ Duration of treatment changed from 6-8 months to 6-9 months ▪ Changes to Steering Committee membership ▪ Addition of an Executive Committee which is a subset of the Steering Committee ▪ Additional secondary outcomes to allow comparison between the two cohorts ▪ New section to describe the objectives for low dose cohort ▪ Sample size amended to 500 ▪ Primary outcome target number updated ▪ Adjustment to the treatment regimen for the low dose cohort

eTable 1 - TESTING Timeline

Date	Name of document / Event	Brief summary of changes / notes
		▪ Addition of mandatory prophylactic treatment during the first 3 months after randomisation to reduce the risk of infection ▪ eGFR range for inclusion amended from 20 to 120ml/min per 1.73m2 (inclusive) to 30 to 120ml/min per 1.73m2 (inclusive) ▪ Trial procedures table updated including tracking vital status at all assessments ▪ Addition of screening for latent tuberculosis (India participants only) ▪ Additional text on the role of the DSMC with particular reference to the issues identified in November 2015 ▪ Administrative clarifications and corrections
19 September 2016	TESTING Protocol V7.0 Amendment 6	▪ Clarification on the dose of prophylactic treatment ▪ Inconsistencies amended in the trial procedures table
21 March 2017	Recruitment	▪ First participant randomised to the reduced-dose protocol at Peking University First Hospital, China
9 May 2017	Manuscript submitted to JAMA	▪ Transitional analysis manuscript submitted to JAMA
14 August 2017	Publication	▪ Transitional analysis published in JAMA
31 October 2018	TESTING Protocol V8.0 Amendment 7	▪ Changes to Steering Committee membership ▪ Administrative clarifications and corrections
27 November 2019	Recruitment	▪ Last participant randomised at The First Affiliated Hospital of Zhengzhou University, China
11 June 2021	Follow-up	▪ Last participant, last assessment
20 July 2021	SAP – Final analysis	▪ SAP finalised

eTable 1 - TESTING Timeline

Date	Name of document / Event	Brief summary of changes / notes
25/28 August 2021	Unblinding	▪ Unblinding of results to the Executive and Steering Committees
5 November 2021	Presentation of results	▪ Final results presented at ASN

eTable 2: Inclusion and Exclusion Criteria

Inclusion criteria

1. IgA nephropathy proven on renal biopsy
2. Proteinuria: ⩾ 1.0g/day while receiving maximum tolerated dose of RAS blockade following the recommended treatment guidelines of each country where the trial is conducted
3. eGFR (on most recent test): 20 to 120ml/min per 1.73m2 for participants in the full-dose arm; 30 to 120ml/min per 1.73m2 for participants in the low-dose arm (inclusive)

Exclusion criteria

1. Indication for immunosuppressive therapy with corticosteroids, such as:
   - Minimal change renal disease with IgA deposits;
   - Crescents present in >50% of glomeruli on a renal biopsy within the last 12 months.
2. Contraindication to immunosuppressive therapy with corticosteroids, including
   - Active infection, including HBV infection or clinical evidence of latent or active tuberculosis (nodules, cavities, tuberculoma etc.)
   - Malignancy within the last 5 years, excluding treated non-melanoma skin cancers (i.e. squamous or basal cell carcinoma)
   - Current or planned pregnancy or breastfeeding
   - Women of childbearing age who are not able or willing to use adequate contraception
3. Systemic immunosuppressive therapy in the previous 1 year
4. Malignant /uncontrolled hypertension (>160mmHg systolic or 110mmHg diastolic)
5. Current unstable kidney function for other reasons, e.g. macrohaematuria induced acute kidney injury (past episodes are not a reason for exclusion)
6. Age <14 years old
7. Secondary IgA nephropathy: e.g. due to lupus, liver cirrhosis, IgA vasculitis
8. Patients who are unlikely to comply with the study protocol in the view of the treating physician

eTable 3: Comparison of baseline characteristics between participants randomized to the full-dose and reduced-dose protocols

	Full dose protocol		Reduced dose protocol		
Parameter	**Methylprednisolone (N = 136)**	**Placebo (N = 126)**	**Methylprednisolone (N = 121)**	**Placebo (N = 120)**	**Testing for differences**
Age					0.5596
N	136	126	121	120	
Mean (SD)	38.1 (11.54)	38.1 (10.64)	36.7 (10.74)	36.6 (10.81)	
Median (IQR)	36.5 (29.0; 46.5)	37.0 (28.0; 47.0)	35.0 (28.0; 44.0)	36.0 (28.5; 44.5)	
Sex					0.6274
Female	50 (36.8%)	46 (36.5%)	52 (43.0%)	50 (41.7%)	
Male	86 (63.2%)	80 (63.5%)	69 (57.0%)	70 (58.3%)	
Race/ ethnic origin†					<.0001
Caucasian/European	5 (3.7%)	3 (2.4%)	8 (6.6%)	9 (7.5%)	
Chinese	130 (95.6%)	121 (96.0%)	65 (53.7%)	63 (52.5%)	
South Asian	0 (0.0%)	0 (0.0%)	30 (24.8%)	33 (27.5%)	
South-East Asian	1 (0.7%)	2 (1.6%)	17 (14.0%)	13 (10.8%)	
Japanese	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	
Other Eastern Asian	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	
Mixed	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	
BMI‡					0.0032
N	136	126	120	118	
Mean (SD)	24.37 (4.457)	24.28 (3.746)	25.38 (4.769)	26.11 (4.973)	
Median (IQR)	24.08 (21.39; 26.02)	23.69 (21.64; 26.50)	24.77 (22.27; 27.69)	25.39 (23.14; 28.73)	
Smoking history					0.1547
Non-smoker	102 (75.0%)	95 (75.4%)	97 (80.2%)	101 (84.2%)	
Previous smoker	24 (17.6%)	20 (15.9%)	15 (12.4%)	7 (5.8%)	
Current smoker	10 (7.4%)	11 (8.7%)	9 (7.4%)	12 (10.0%)	
Macrohematuria	27 (19.9%)	24 (19.0%)	15 (12.4%)	14 (11.7%)	0.1550
Hypertension history	71 (52.2%)	52 (41.3%)	57 (47.1%)	61 (50.8%)	0.2989
Tonsillectomy history	1 (0.7%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0.8122
Past systematic corticosteroids therapy	5 (3.7%)	3 (2.4%)	13 (10.7%)	7 (5.8%)	0.0229
Past other immunosuppressant therapy	8 (5.9%)	6 (4.8%)	9 (7.4%)	6 (5.0%)	0.8038
Family history of IgA nephropathy	2 (1.5%)	5 (4.0%)	1 (0.8%)	4 (3.3%)	0.3118
Diabetes Mellitus	1 (0.7%)	3 (2.4%)	6 (5.0%)	7 (5.8%)	0.0923
Coronary Heart Disease	1 (0.7%)	4 (3.2%)	2 (1.7%)	0 (0.0%)	0.1647
Stroke	1 (0.7%)	3 (2.4%)	1 (0.8%)	1 (0.8%)	0.5683
Peptic ulcer	1 (0.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0.6035

	Full dose protocol		Reduced dose protocol		
Parameter	**Methylprednisolone (N = 136)**	**Placebo (N = 126)**	**Methylprednisolone (N = 121)**	**Placebo (N = 120)**	**Testing for differences**
Heart Failure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
eGFR level at screening					0.0086
N	136	126	121	120	
Mean (SD)	59.65 (24.380)	58.46 (22.959)	66.55 (24.405)	66.63 (26.781)	
Median (IQR)	54.76 (40.48; 72.78)	55.97 (42.10; 71.94)	60.84 (47.30; 82.52)	63.49 (42.26; 86.30)	
Baseline eGFR level					0.0082
N	136	126	121	120	
Mean (SD)	58.63 (23.056)	57.74 (23.403)	63.44 (22.072)	66.62 (24.872)	
Median (IQR)	54.10 (42.14; 73.71)	57.43 (39.40; 69.38)	58.67 (44.54; 79.78)	65.24 (44.23; 84.70)	
Urine protein (g/24-hour) at screening					0.3265
N	132	125	121	119	
Mean (SD)	2.604 (1.4902)	2.361 (1.3721)	2.455 (1.5730)	2.752 (2.4537)	
Median (IQR)	2.160 (1.510; 3.090)	2.125 (1.320; 2.920)	2.060 (1.500; 3.040)	1.980 (1.420; 3.128)	
Baseline urine protein (g/24-hour)					0.7075
N	136	126	121	120	
Mean (SD)	2.506 (1.6775)	2.372 (1.2377)	2.382 (1.4090)	2.579 (2.0909)	
Median (IQR)	2.108 (1.475; 3.033)	1.928 (1.490; 2.865)	1.975 (1.390; 2.960)	2.012 (1.496; 3.055)	
Time since renal biopsy (month)					0.0098
N	136	125	121	120	
Mean (SD)	13.21 (33.634)	10.79 (36.482)	15.66 (20.810)	24.24 (38.387)	
Median (IQR)	5.00 (4.00; 8.00)	4.00 (3.00; 8.00)	5.00 (3.00; 18.00)	6.00 (4.00; 27.00)	
Mesangial hypercellularity					0.9029
M0	56 (42.4%)	48 (39.0%)	49 (40.8%)	45 (38.1%)	
M1	76 (57.6%)	75 (61.0%)	71 (59.2%)	73 (61.9%)	
Segmental glomerulosclerosis					0.3521
S0	38 (28.8%)	34 (27.6%)	42 (35.0%)	43 (36.4%)	
S1	94 (71.2%)	89 (72.4%)	78 (65.0%)	75 (63.6%)	
Endocapillary hypercellularity					0.2208
E0	93 (68.4%)	96 (76.2%)	92 (76.0%)	95 (79.2%)	
E1	43 (31.6%)	30 (23.8%)	29 (24.0%)	25 (20.8%)	
Tubular atrophy/interstitial fibrosis					<.0001
T0	51 (38.6%)	43 (35.0%)	72 (60.0%)	75 (63.6%)	
T1	58 (43.9%)	60 (48.8%)	34 (28.3%)	35 (29.7%)	
T2	23 (17.4%)	20 (16.3%)	14 (11.7%)	8 (6.8%)	

SD, standard deviation; Percentages may not total 100 because of rounding; Q denotes quartile
† Race or ethnic group was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
eGFR, estimated glomerular filtration rate

eTable 4: Serious Adverse Events by randomized group overall, and for the full and reduced methylprednisolone dosage regimens						
	Overall combined results		**Full Dose Regimen**		**Reduced Dose Regimen**	
	Methylprednisolone (N = 257)	**Placebo (N = 246)**	**Methylprednisolone (N = 136)**	**Placebo (N = 126)**	**Methylprednisolone (N = 121)**	**Placebo (N = 120)**
Number of SAEs, No.	37	8	30	5	7	3
Number of patients with at least one SAE[a], No.(%)	28 (11)	7 (3)	22 (16)	4 (3)	6 (5)	3 (3)
Hospitalization/Prolongation of hospitalization	25 (10)	7 (3)	19 (14)	4 (3)	6 (5)	3 (3)
Resulted in death	4 (2)	0 (0)	3 (2)	0 (0)	1 (0.8)	0 (0)
Life-threatening	4 (2)	0 (0)	3 (2)	0 (0)	1 (0.8)	0 (0)
Important medical event[b]	2 (0.8)	0 (0)	1 (0)	0 (0)	1 (0.8)	0 (0)
Persistent/Significant disability/Incapacity	1 (0.4)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)
Congenital anomaly/Birth defect[c]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.)	0 (0)
Number of patients reporting the following SAEs of special interest per protocol[d], No.(%)						
Severe infection requiring hospitalization	17(7)	3 (1)	12(9)	1 (0.8)	5 (4)	2 (2)
Pneumocystis jirovecii pneumonia	4(2)	0(0)	4(3)	0(0)	0(0)	0(0)
Pneumonia or respiratory tract infection	3(1)	0(0)	3(2)	0(0)	0	0(0)
Sepsis	2(0.8)	1(0.4)	0(0)	0(0)	2(2)	1(0.8)
Urinary tract infection	2(0.8)	0(0)	1(0.7)	0(0)	1(0.8)	0(0)
Multiple skin infection	1(0.4)	0(0)	0(0)	0(0)	1(0.8)	0(0)
Nocardia infection	1(0.4)	0(0)	1(0.7)	0(0)	0(0)	0(0)
Cryptococcal meningitis	1(0.4)	0(0)	1(0.7)	0(0)	0(0)	0(0)
Tuberculosis with bacterial infection	1(0.4)	0(0)	0(0)	0(0)	1(0.8)	0(0)
Perianal abscess	1(0.4)	0(0)	1(0.7)	0(0)	0(0)	0(0)
Acute febrile illness	0(0)	1(0.4)	0(0)	0(0)	0(0)	1(0.8)
Other infection	1(0.4)	1(0.4)	1(0.7)	1(0.8)	0(0)	0(0)
Gastrointestinal bleeding requiring hospitalization[e]	3 (1)	1 (0.4)	3 (2)	1 (0.8)	0 (0)	0 (0)
Clinically evident fracture or osteonecrosis	3 (1)	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)
New onset diabetes mellitus	2 (0.8)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)

eTable 4: Serious Adverse Events by randomized group overall, and for the full and reduced methylprednisolone dosage regimens						
	Overall combined results		Full Dose Regimen		Reduced Dose Regimen	
	Methylprednisolone (N = 257)	Placebo (N = 246)	Methylprednisolone (N = 136)	Placebo (N = 126)	Methylprednisolone (N = 121)	Placebo (N = 120)

[a] All serious adverse events were reported by site investigators and reviewed by the medical reviewer. The definition of a serious adverse event was derived from the International Conference on Harmonization Guideline for Clinical Safety Data Management and comprised the six listed categories.

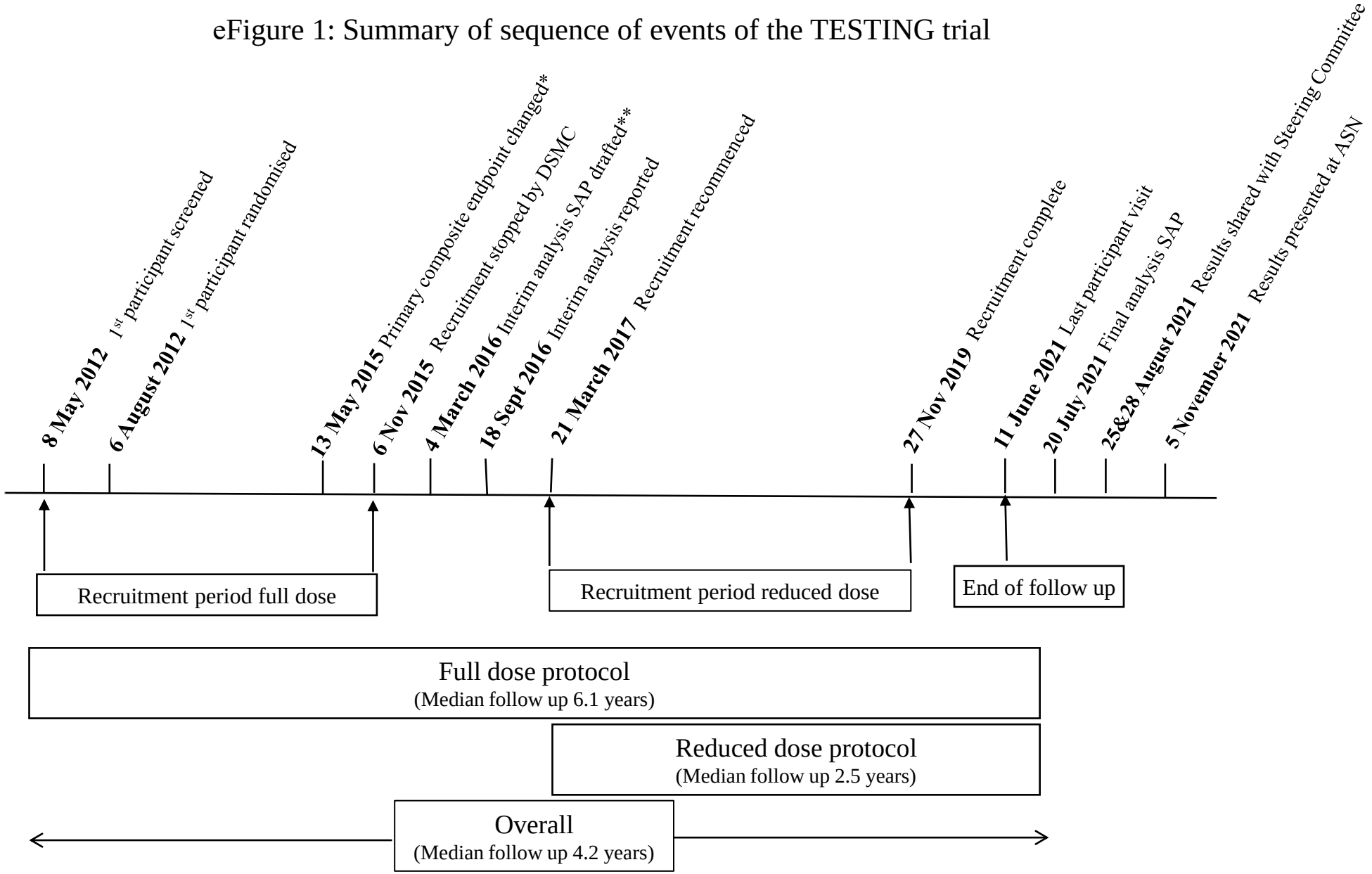
[b] First reported Pneumocystis Carinii Pneumonia and Gram negative sepsis that was reported initially reported as acute tubular necrosis with prolonged hospitalization.

[c] There was no pregnancy reported during the treatment period hence no congenital anomaly or birth defect recorded.

[d] There were no major cardiovascular events reported, defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalisation or death due to cardiovascular disease

[e]One pneumocystis jirovecii pneumonia infection was misclassified as gastrointestinal bleeding in the interim analysis report

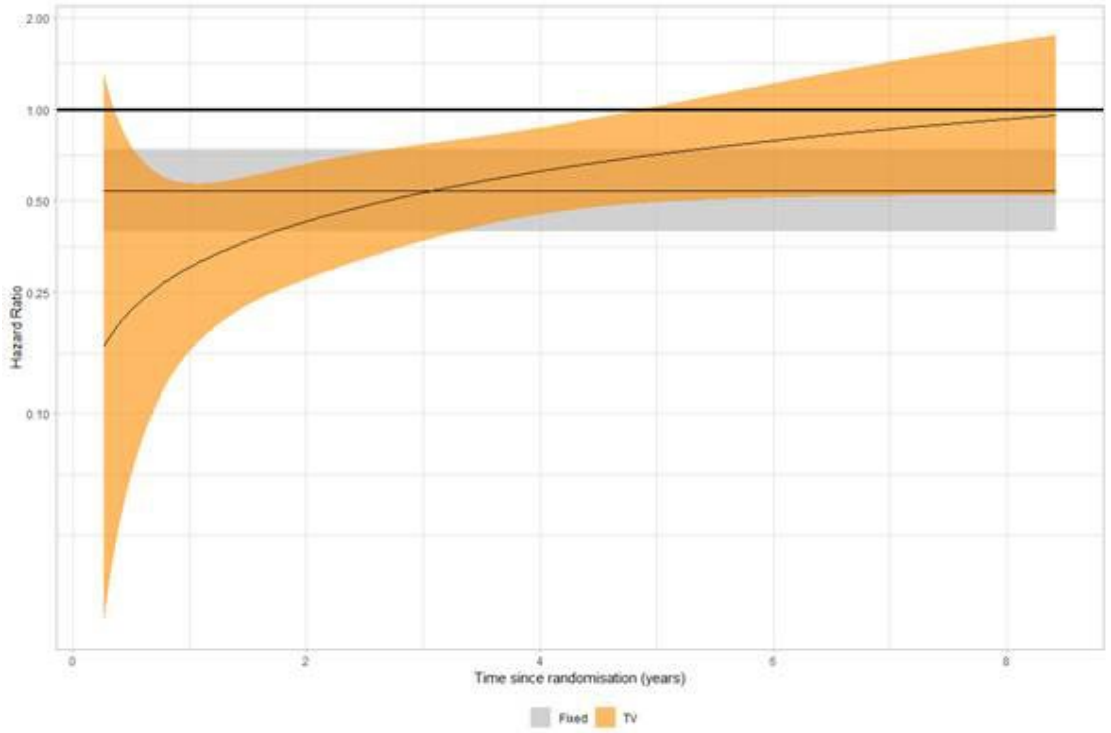
eFigure 1: Summary of sequence of events of the TESTING trial



* Sustained 50% eGFR reduction is replaced with 40% eGFR reduction based on

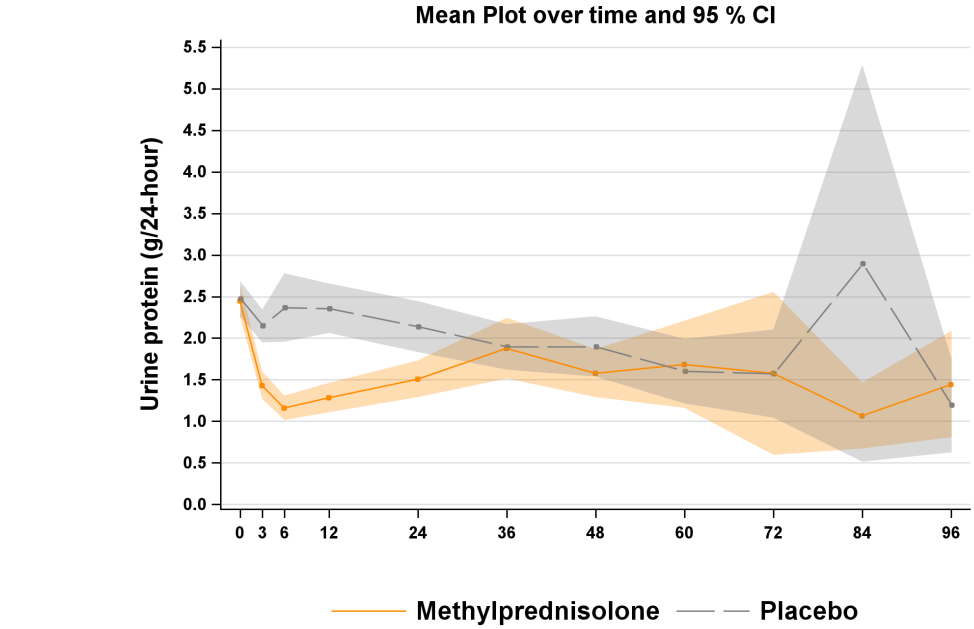
**SAP, statistical analysis plan was finalised by a SAP subcommittee of the Steering Committee, who were blinded to the interim analysis results

DSMC, data safety monitoring committee



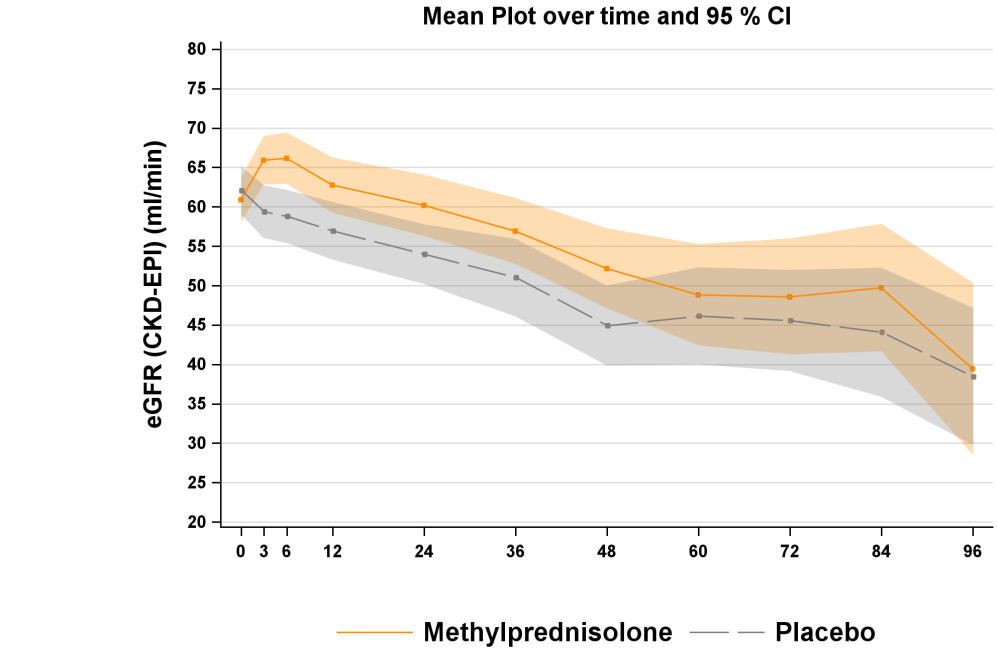
eFigure 2: A post-hoc sensitivity analysis was run using flexible parametric survival models with either constant (grey) or time-varying hazard ratios (orange). The flexible model with constant HR was very similar to the Cox model, with an estimate HR of 0.54 (95% CI 0.39; 0.74). There was some evidence (p=.024) that the time-varying HR was a better fit to the study data than a constant HR, however, both approaches consistently estimated a significant risk reduction with methylprednisolone.

A) Mean 24 hour protein excretion by randomized group over time



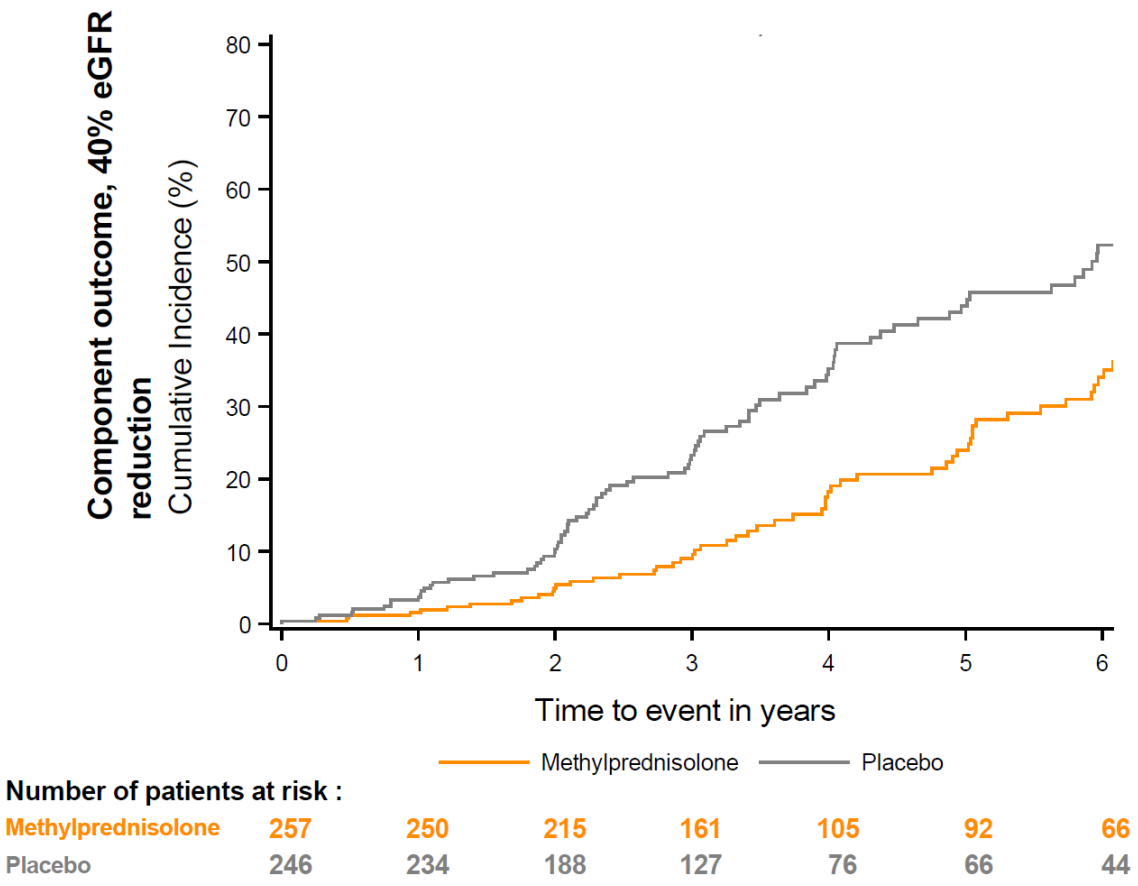
Number of patients :										
Methylprednisolone	257	227	213	178	132	86	54	16	13	11
Placebo	246	217	200	159	98	71	48	14	10	15

B) Mean eGFR over time



Number of patients :										
Methylprednisolone	257	232	218	200	155	104	71	66	45	22
Placebo	246	225	209	185	123	90	59	59	30	24

eFigure 3: Proteinuria and eGFR Reduction by randomized group over time



eFigure 4: Time From Randomization to First Outcome of 40% eGFR Decrease by Treatment Group