Online Supplementary Material 1

Complete exclusion criteria for CLEAR 2

1. An acute gout flare that has not resolved at least 7 days before the Baseline Visit (Day 1)

2. Known hypersensitivity or allergy to allopurinol

3. Any other approved urate-lowering medication indicated for the treatment of gout other than allopurinol (eg, another xanthine oxidase inhibitor [XOI] or uricosuric agent) within 8 weeks of the screening visit

4. Previous administration of pegloticase

5. Previous participation in a clinical study involving lesinurad (RDEA594) or RDEA806 and received active treatment or placebo

6. Pregnant or breastfeeding

7. Consumption of more than 14 drinks of alcohol per week

8. A history or suspicion of drug abuse within the past 5 years

9. A history of myositis/myopathy or rhabdomyolysis

10. Requirement for systemic immunosuppressive or immunomodulatory treatment (eg, azathioprine, 6-mercaptopurine, cyclosporine)

11. Known or suspected human immunodeficiency virus (HIV) infection

12. A positive test for active hepatitis B or hepatitis C infection

13. A history of malignancy within the previous 5 years with the exception of non-melanoma skin cancer that has been treated with no evidence of recurrence, treated cervical dysplasia or treated in situ grade 1 cervical cancer

14. Diagnosis within the last 12 months of: unstable angina, New York Heart Association (NYHA) class III or IV heart failure, myocardial infarction, stroke, or deep venous thrombosis; or currently receiving anticoagulants

15. Uncontrolled hypertension (systolic pressure above 160 mmHg or diastolic pressure above 95 mmHg on repeat measurements on two separate visits during the screening period)

16. An estimated creatinine clearance <30 mL/min calculated by the Cockcroft-Gault formula using ideal body weight

17. A haemoglobin level <10 g/dL (males) or <9 g/dL (females) at any time during the screening period

18. An alanine aminotransferase or aspartate aminotransferase >2.0 x upper limit of normal (ULN) at any time during the screening period

19. A gamma glutamyl transferase level >3 x ULN at any time during the screening period

20. A creatine kinase >2.5 x ULN at any time during the screening period

21. Active peptic ulcer disease requiring treatment

22. A history of xanthinuria, active liver disease or hepatic dysfunction

23. Chronic treatment with more than 325 mg of salicylates per day

24. Treatment with valpromide, progabide, valproic acid, or other known inhibitors of epoxide hydrolase

25. An investigational therapy within 8 weeks or 5 half-lives (whichever is longer) prior to the screening visit

26. Any other medical or psychological condition which, in the opinion of the investigator and/or medical monitor, might create undue risk to the patient or interfere with the patient’s ability to comply with the protocol requirements, or to complete the study

Online Supplementary Material 2

Renal-related TEAEs

Acute prerenal failure

Anuria

Azotaemia

Blood creatinine abnormal

Blood creatinine increased

Blood urea abnormal

Blood urea increased

Blood urea nitrogen/creatinine ratio increased

Creatinine renal clearance abnormal

Creatinine renal clearance decreased

Cystatin C abnormal

Cystatin C increased

Glomerular filtration rate abnormal

Glomerular filtration rate decreased

Hypercreatininaemia

Inulin renal clearance abnormal

Inulin renal clearance decreased

Nephropathy

Nephropathy toxic

Obstructive uropathy

Oliguria

Postrenal failure

Renal cortical necrosis

Renal failure

Renal failure acute

Renal failure chronic

Renal function test abnormal

Renal impairment

Renal injury

Renal papillary necrosis

Renal tubular atrophy

Renal tubular disorder

Renal tubular necrosis

Urate nephropathy

Urea renal clearance decreased

Urine output decreased

Kidney Stone TEAEs

Calculus bladder

Calculus ureteric

Calculus urethral

Calculus urinary

Nephrolithiasis

Renal stone removal

Stag horn calculus

Ureteric calculus removal

Ureterolithotomy

Urinary calculus removal

Urinary stone analysis

Online Supplementary Material 3

Major adverse cardiovascular events (MACE)

All deaths (both CV and non-CV deaths)

Non-fatal myocardial infarction

Non-fatal stroke

Non-major adverse cardiovascular events (non-MACE)

Unstable angina with urgent coronary revascularisation

Cerebral revascularisation (elective and non-elective)

Hospitalised congestive heart failure

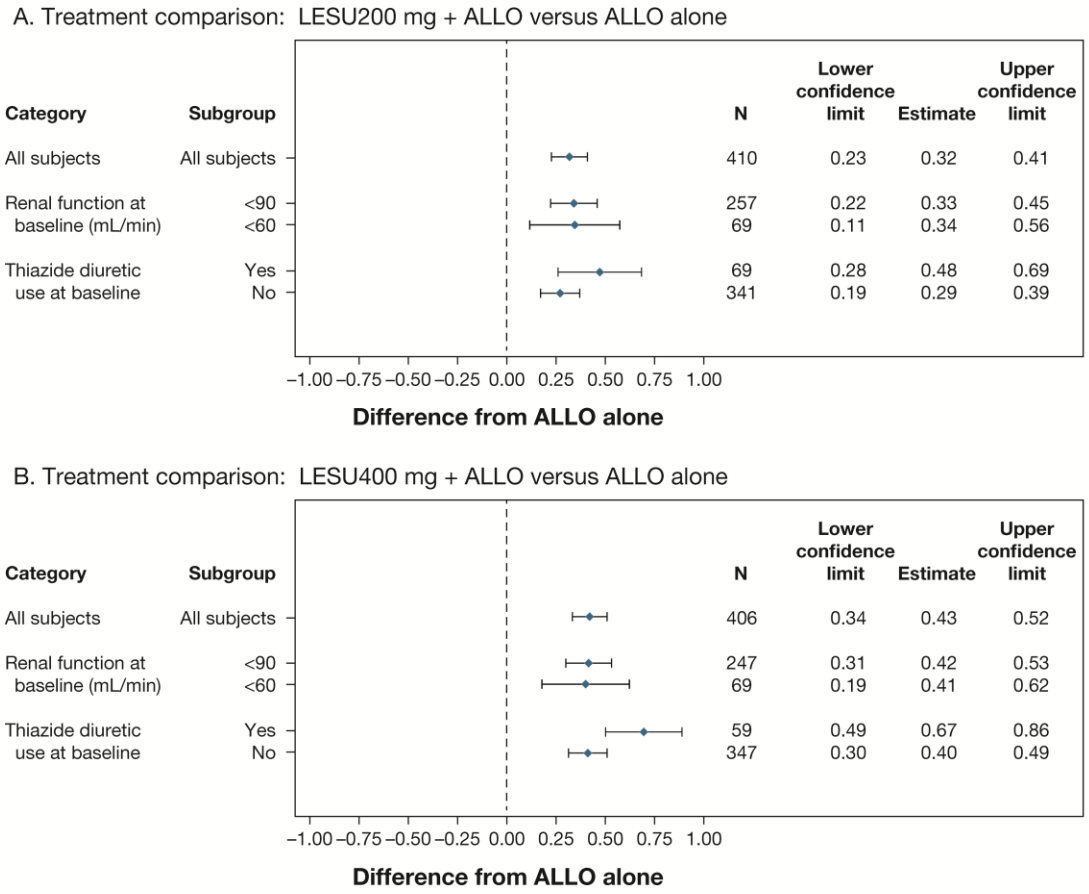
Arrhythmias not associated with ischaemia

Venous and peripheral arterial vascular thrombotic events (eg, pulmonary embolism, deep venous thrombosis, arterial dissection, thrombosis and peripheral arterial ischaemia)

Transient ischaemic attack

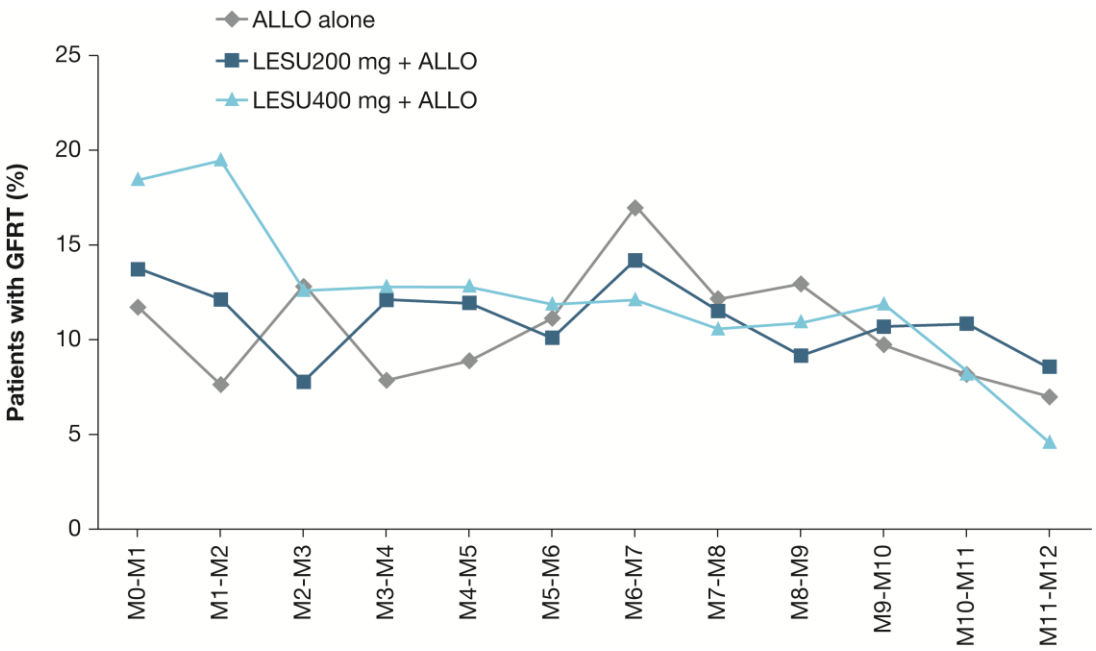
Supplementary Material 4

Supplemental Figure 1. Differences from Allopurinol Alone in Proportion of Patients in Selected Subgroups Achieving Serum Urate Level of <6.0 mg/dL [<357 µmol/L] at Month 6 – Non-responder Imputation (ITT Population).



Allo, allopurinol; LESU, lesinurad.

Supplemental Figure 2. Proportion of Patients With a Gout Flare Requiring Treatment by Month.



Allo, allopurinol; LESU, lesinurad.

Note: Gout flare prophylaxis was discontinued at end of Month 5.

Supplemental Table 1. Incidences and duration of sCr elevation (≥1.5x and ≥2.0x baseline) during study

	ALLO alone (N=206)	**Lesinurad 200 mg + ALLO (N=204)**	**Lesinurad 400 mg + ALLO (N=200)**
sCr elevation ≥1.5x baseline			
Number of patients with elevation	7	12	30
Number of elevations	7	12	39
Number (%) resolutions	4/7 (57.1)	12/12 (100)	32/39 (82.1)
Number (%) resolutions after interruption of study medication	0/7	1/12 (8.3)	5/39 (12.8)
Number (%) resolutions without interruption of study medication	4/7 (57.1)	11/12 (91.7)	27/39 (69.2)
Number (%) unresolved at last visit	3/7 (42.9)	0/12	7/39 (17.9)
Maximum duration (days)			
1-14	2 (28.6)	4 (33.3)	6 (20.0)
>14-28	1 (14.3)	0	6 (20.0)
>28-56	1 (14.3)	6 (50.0)	5 (16.7)
>56-84	1 (14.3)	0	7 (23.3)
>84	2 (28.6)	2 (16.7)	6 (20.0)
sCr elevation ≥2.0x baseline			
Number of patients with elevation	0	4	16
Number of elevations	0	4	19
Number (%) resolutions	0	4/4 (100)	14/19 (73.7)
Number (%) resolutions after interruption of study medication	0	1/4 (25.0)	4/19 (21.1)
Number (%) resolutions without interruption of study medication	0	3/4 (75.0)	10/19 (52.6)
Number (%) unresolved at last visit	0	0/4	5/19 (26.3)
Maximum duration (days)			
1-14	0	3 (75.0)	4 (25.0)
>14-28	0	0	3 (18.8)
>28-56	0	0	4 (25.0)
>56-84	0	0	4 (25.0)
>84	0	1 (25.0)	1 (6.3)

Resolution defined as sCr value ≤1.2x baseline following an elevation.
ALLO, allopurinol; sCr, serum creatinine.

Supplemental Table 2. Incidences (%) of sCr elevation ≥1.5x baseline by categories: gout flare prophylaxis type, sUA level <6.0 mg/dL [<357 µmol/L] by Month 6 and presence of tophi at screening

	ALLO alone	**Lesinurad 200 mg + ALLO**	**Lesinurad 400 mg + ALLO**
Baseline gout flare prophylaxis type			
Colchicine	N=159 5 (3.1)	N=181 11 (6.1)	N=167 24 (14.4)
NSAID	N=51 2 (3.9)	N=23 2 (8.7)	N=36 7 (19.4)
sUA level at Month 6			
<6.0 mg/dL [<357 µmol/L]	N=51 1 (2.0)	N=125 7 (5.6)	N=140 18 (12.9)
≥6.0 mg/dL [≥357 µmol/L]	N=149 6 (4.0)	N=74 5 (6.8)	N=57 12 (21.1)
Presence of tophi at screening			
Yes	N=48 1 (2.1)	N=49 6 (12.2)	N=47 8 (17.0)
No	N=158 6 (3.8)	N=155 6 (3.9)	N=153 22 (14.4)

ALLO, allopurinol; NSAID, non-steroidal anti-inflammatory drug; sUA, serum uric acid.