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ADISINSIGHT REPORT

Lesinurad: First Global Approval

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Abstract Lesinurad (ZURAMPIC®) is an oral urate–anion exchanger transporter 1 (URAT1) inhibitor developed by Ardea Biosciences (a subsidiary of AstraZeneca) for the treatment of hyperuricaemia associated with gout. It reduces serum uric acid (sUA) levels by inhibiting the function of the transporter proteins (URAT1 and organic anion transporter 4) involved in uric acid reabsorption in the kidney. In December 2015, lesinurad was approved in the USA as combination therapy with a xanthine oxidase inhibitor for the treatment of hyperuricaemia associated with gout in patients who have not achieved sUA target levels with a xanthine oxidase inhibitor alone. Lesinurad has also received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use for this indication and is in phase III development as a combination therapy in several other countries. This article summarizes the milestones in the development of lesinurad leading to this first approval for hyperuricaemia associated with gout.

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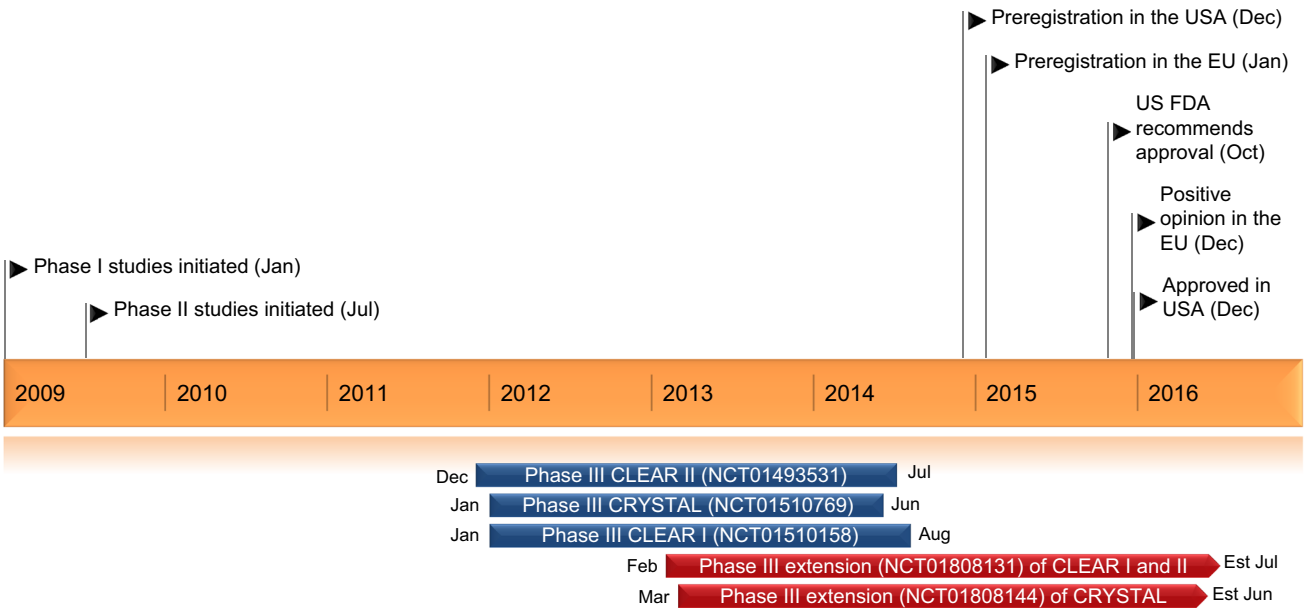
1 Introduction

Hyperuricaemia (i.e. elevated serum urate levels) associated with gout most commonly results from the insufficient renal excretion of uric acid [1, 2]. Urate–anion exchanger transporter 1 (URAT1) has been identified as the major transporter protein associated with the reabsorption of uric acid (from the renal tubule lumen into the epithelial cells of the tubule) [2, 3]. Inhibiting its function blocks the reabsorption of urate, thereby increasing its excretion [3, 4].

Lesinurad (ZURAMPIC®) is an oral URAT1 inhibitor developed by Ardea Biosciences (a subsidiary of AstraZeneca acquired by the company in June 2012) [3, 5]. It was approved in the USA on 22 December 2015 as combination therapy with a xanthine oxidase inhibitor for the treatment of hyperuricaemia associated with gout in patients who have not achieved serum uric acid (sUA) target levels with a xanthine oxidase inhibitor alone [3, 6]. Lesinurad has also received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) for the adjunctive therapy of hyperuricaemia in combination with a xanthine oxidase inhibitor in adults with gout [7].

The recommended (and maximum) dosage of oral lesinurad is 200 mg once daily administered in the morning with food and water [3]. The US prescribing information carries a boxed warning that lesinurad should be used in combination with a xanthine oxidase inhibitor, and one regarding acute renal failure, which occurs more commonly when lesinurad is administered alone [3].

Lesinurad in combination with a xanthine oxidase inhibitor is under phase III development for the treatment of hyperuricaemia associated with gout in several countries, including Australia, Canada, New Zealand, Switzerland and Ukraine. A fixed-dose combination of lesinurad and allopurinol is also under development.



Key development milestones of lesinurad

2 Scientific Summary

2.1 Pharmacodynamics

Lesinurad inhibits the function of URAT1 and organic anion transporter (OAT) 4 (half maximal inhibitory concentrations of 7.3 and 3.7 μmol/L in vitro) [3]. Inhibition of these transporter proteins (responsible for uric acid reabsorption in the kidney) reduces sUA levels [3]. Lesinurad does not interact with glucose transporter 9 (GLUT9) [3], nor does it inhibit OAT1 or OAT3 in vitro [8].

Dose-dependent reductions in sUA levels and increases in urinary uric acid excretion have been observed following single and multiple oral doses of lesinurad [3]. Moreover, tophus area reductions and a lower likelihood of experiencing gout flare requiring therapy correlate positively with the magnitude of sustained reductions in sUA levels, according to a pooled analysis of three phase III studies (CLEAR I and II, and CRYSTAL) [abstract presentation] [9, 10].

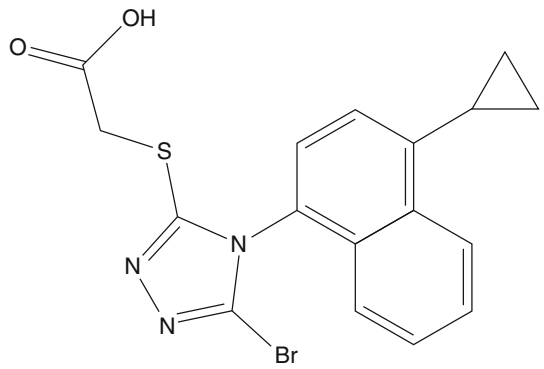
Lesinurad at doses up to 1600 mg did not affect the corrected QT interval of healthy volunteers or patients with gout [3].

2.2 Pharmacokinetics

Oral lesinurad is rapidly absorbed, reaching maximum plasma concentrations (C_{max}) within 1–4 h following the administration a single 200 mg dose (in either the fed or fasted state) [3]. Absolute bioavailability is approximately 100 %. C_{max} and area under the concentration–time curve (AUC) values increased proportionally with single doses of lesinurad 5–1200 mg, with dose proportionality preserved following multiple once-daily dosing. Lesinurad exposure is not affected by food [3].

Lesinurad is highly bound (>98 %) to plasma proteins (mostly albumin); it does not accumulate following multiple doses [3].

Lesinurad undergoes oxidative metabolism predominately via cytochrome P450 (CYP) 2C9 [3]; the metabolites are not known to contribute to lesinurad's uric acid-lowering effects. Lesinurad's elimination half-life was approximately 5 h; its total body clearance was approximately 6 L/h [3].



Chemical structure of lesinurad

Following a single dose of radiolabelled lesinurad, 63 and 32 % of the administered dose was recovered in the urine and faeces within 7 days, with over 60 % of the dose recovered in the urine within 24 h. Unchanged lesinurad in the urine accounts for approximately 30 % of the dose [3].

Compared with healthy volunteers, C_{max} values were generally similar in patients with renal impairment [3]. However, AUC values were elevated by approximately 30, 50–73 and 113 % in patients with mild (estimated CL_{CR} of 60 to <90 mL/min), moderate (estimated CL_{CR} of 30 to <60 mL/min) and severe (estimated CL_{CR} of <30 mL/min) renal impairment, respectively. The pharmacokinetics of lesinurad do not appear to be affected to a clinically significant effect by age, ethnicity, race or sex. No dosage adjustment in required in patients with mild or moderate hepatic impairment [3].

2.2.1 *Potential Drug Interactions*

Lesinurad is an inhibitor of OAT1, OAT3, OATP1B1 and OCT1 in vitro; however, it did not inhibit these transporters in vivo [3]. In vitro, lesinurad had no relevant effect on P-glycoprotein, nor did it appear to be an inhibitor of epoxide hydrolase; however, epoxide hydrolase inhibitors may interfere with the metabolism of lesinurad and thus should not be coadministered with lesinurad [3].

In vitro lesinurad is a substrate for CYP2C9 [3]. Increases in lesinurad exposure have been observed when lesinurad is used concomitantly with CYP2C9 inhibitors, and in CYP2C9 poor metabolizers, with lesinurad exposure decreased (which may reduce lesinurad's therapeutic effect) when the drug is coadministered with moderate CYP2C9 inducers. Lesinurad is a weak CYP3A inducer, but has no relevant effect on any other CYP enzyme for induction or inhibition. Lesinurad reduced the plasma concentrations of CYP3A substrates amlodipine and sildenafil in healthy volunteers participating in interaction studies [3], but demonstrated minimal inhibitory effects on the plasma exposure of atorvastatin, repaglinide and tolbutamide [11]. However, HMG-CoA reductase inhibitors that are sensitive CYP3A substrates may be affected. Thus, the potential reduced efficacy of coadministered drugs that are CYP3A substrates should be considered and their efficacy (e.g. blood pressure and cholesterol levels) monitored [3].

Aspirin >325 mg/day may reduce the efficacy of combination therapy with lesinurad and allopurinol; however, aspirin ≤325 mg/day does not decrease lesinurad's efficacy and can be coadministered [3]. Hormonal contraceptives may not be reliable when lesinurad is coadministered; thus, additional methods of contraception are advised [3].

Features and properties of lesinurad

Alternative names	ZURAMPIC®, RDEA594
Class	Acetic acids, antigouts, cyclopropanes, naphthalenes, small molecules, sulfides, triazoles, uricosurics
Mechanism of action	SLC22A12 protein inhibitors
Route of administration	Oral
Pharmacodynamics	Inhibits the function of URAT1 and OAT4; does not interact with GLUT9, nor does it inhibit OAT1 or OAT3
	Dose-dependently reduces sUA levels and increases urinary uric acid excretion
	Tophus area reductions and a lower likelihood of experiencing gout flare requiring therapy correlate positively with the magnitude of sustained reductions in sUA levels
Pharmacokinetics	C_{max} reached within 1–4 h; total body clearance is ≈6 L/h; elimination half-life is ≈5 h
	Lesinurad C_{max} and exposure is not affected by food
Most frequent adverse events	Headache, influenza and gastrointestinal reflux disease
ATC codes	
WHO ATC code	M04A-B (preparations increasing uric acid excretion)
EphMRA ATC code	M4A (anti-gout preparations)
Chemical name	2-{[5-Bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetic acid

C_{max} maximum concentration, *GLUT* glucose transporter, *OAT* organic anion transporter, *sUA* serum uric acid, *URAT1* urate–anion exchanger transporter 1

2.3 Therapeutic Trials

2.3.1 Monotherapy

The 6-month, randomized, double-blind, placebo-controlled, multinational, phase III LIGHT study (NCT01508702) assessed the efficacy of lesinurad 400 mg once daily as monotherapy in 214 patients [intent-to-treat (ITT) population] with gout and an intolerance or contraindication to xanthine oxidase inhibitor therapy [12]. A significantly greater proportion of patients receiving lesinurad than placebo achieved sUA levels of <6 mg/dL at month 6 (primary endpoint) (29.9 vs. 1.9 %; $p < 0.0001$]. Patients who completed LIGHT were eligible to enrol in an open-label extension study (NCT01650246) in which all patients received lesinurad 400 mg once daily for 6 months. Of the 143 enrolled patients, 119 completed the study prior to early termination by the sponsor and 91 achieved a sUA level of <6 mg/dL at some point [12]. Currently, the US prescribing information carries a boxed warning that lesinurad should be used in combination with a xanthine oxidase inhibitor [3].

2.3.2 In Combination with Allopurinol

A significantly ($p < 0.0001$) greater proportion of patients receiving combination therapy with lesinurad 200 or 400 mg once daily plus allopurinol than placebo plus allopurinol achieved sUA levels of <6 mg/dL by month 6 (primary endpoint) in the phase III CLEAR I (NCT01510158) [54.2 and 59.2 vs. 27.9 %] [13] and CLEAR II (NCT01493531) [55.4 and 66.5 vs. 23.3 %] [14] studies. Moreover, significantly more lesinurad 200 or 400 mg combination therapy recipients than allopurinol recipients achieved sUA levels of <5 mg/dL by month 6 (CLEAR I: 28.9 and 46.3 vs. 10.4 % [13]; CLEAR II: 34.8 and 46.0 vs. 4.9 % [14]). Significant (p values not reported) between-group differences in the proportion of patients achieving sUA levels of <6 and <5 mg/dL were observed at all visits in both studies [13, 14]. No significant differences between the lesinurad 200 or 400 mg combination therapy and allopurinol groups were observed in mean gout flare rate requiring therapy from months 6 to 12, or in the proportion of patients with complete target tophus resolution by month 12 [13, 14].

According to pooled analyses of CLEAR I and II data ($n = 1208$), the sUA-lowering effect of combination therapy with lesinurad and allopurinol does not appear to be altered in patients with renal impairment [15]. Specifically, the proportion of patients achieving a sUA level of <6 mg/dL at months 6 and 12 was significantly ($p < 0.05$) higher with lesinurad 200 or 400 mg combination therapy than allopurinol alone, irrespective of baseline estimated CL_{CR} levels (<60, <90 and ≥90 mL/min) [15]. The estimated effect of lesinurad 200 mg combination therapy on sUA levels in patients receiving thiazide diuretics or low dose aspirin at baseline was also similar to that estimated in the overall population [3].

CLEAR I ($n = 603$; ITT population) [13] and CLEAR II ($n = 610$; ITT population) [14] were randomized, double-blind, multicentre [13] or multinational [14] studies in which adults received either oral lesinurad (200 or 400 mg once daily) plus allopurinol [≥300 mg (≥200 mg in patients with moderate renal impairment)] or placebo plus allopurinol for 12 months.

Lesinurad 200, 400 or 600 mg once daily in combination with allopurinol was more effective than placebo plus allopurinol in achieving clinically relevant and statistically significant reductions in sUA levels in patients ($n = 208$; ITT population) with gout and an inadequate response to allopurinol monotherapy in a 4-week randomized, double-blind, multinational phase II study (NCT01001338) [16]. Significant ($p < 0.0001$) arithmetic mean percentage changes from baseline in sUA levels were observed with lesinurad 200, 400 or 600 mg combination therapy versus allopurinol alone (−16.1, −22.1 and −30.4 vs. +2.6 %). Similar results were observed in patients with CL_{CR} values of ≥90 and <90 mL/min. Significantly ($p < 0.0001$) more lesinurad 200, 400 or 600 mg combination therapy recipients than allopurinol recipients achieved a sUA level of <6 mg/dL at 4 weeks (63.0, 73.8 and 79.2 vs. 25.0 %). Significant between-group differences favouring lesinurad 200, 400 or 600 mg combination therapy were also observed in terms of the proportions of patients achieving sUA levels of <5 and <4 mg/dL (data and statistical analysis not reported). Significantly ($p < 0.05$) higher mean percentage changes from baseline in renal uric acid clearance (43.7, 84.9 and 118.8 vs. 8 %) and the fractional excretion of urinary uric acid (50.7, 110.8 and 129.0 vs. 5.3 %) at 4 weeks were also observed with lesinurad 200, 400 or 600 mg combination therapy versus allopurinol. Allopurinol was administered at the pre-study dose (200–600 mg/day) [16].

In a 44-week blinded extension of the phase II study (NCT01001338) [17], 78 % of lesinurad plus allopurinol recipients and 56 % of placebo plus allopurinol recipients maintained a sUA level of <6 mg/mL, with 59 and 25 % of patients achieving a sUA level of <5 mg/mL. Patients completing the phase II study ($n = 126$) were washed out of their original therapy (but continued to receive allopurinol) before restarting lesinurad or placebo. All lesinurad recipients commenced therapy with the 200 mg dose, with the dose titrated in a stepwise manner (to 400 mg then 600 mg) if the sUA level was not <5 mg/dL. Following dose escalation of lesinurad or placebo, the allopurinol dose could be escalated [17].

2.3.3 In Combination with Febuxostat

In the phase III CRYSTAL study in patients with tophaceous gout (NCT01510769), the proportion of patients achieving a sUA level of <5 mg/dL at month 6 (primary endpoint) was significantly higher with lesinurad 400 mg once daily in combination with febuxostat (76.1 vs. 46.8 %; $p < 0.0001$), but not lesinurad 200 mg once daily in combination with febuxostat (56.6 vs. 46.8 %), than placebo plus febuxostat [18]. At month 12, the proportions of patients achieving a sUA level of <5 mg/dL were 56.6 and 60.6 versus 41.3 % for both lesinurad dosages in combination with febuxostat versus febuxostat alone ($p < 0.05$) [18].

A significantly higher proportion of lesinurad 400 mg combination therapy recipients than febuxostat recipients achieved a sUA level of <6 mg/dL at month 6 (79.8 vs. 63.3 %), but not month 12 (65.1 vs. 58.7 %); the proportion of patients achieving a sUA level of <6 mg/dL following lesinurad 200 mg combination therapy was 67.9 % at month 6 and 59.4 % at month 12 [18]. A sUA level of <4 mg/dL was achieved by 44.3 and 66.1 % of patients in the lesinurad 200 or 400 mg combination therapy groups versus 19.3 % of patients in the febuxostat group at month 6 and by 46.2 and 56.0 versus 16.5 % of patients at month 12 ($p < 0.0001$). A sUA level of <3 mg/dL was achieved in the respective groups by 26.4 and 49.5 versus 1.8 % of patients at month 6 and by 31.1 and 42.2 versus 5.5 % of patients at month 12 ($p < 0.0001$) [18].

A significant ($p < 0.05$) difference in the percentage reduction in tophus area by month 12 was observed with lesinurad 200 or 400 mg combination therapy versus febuxostat (55.8 and 57.9 vs. 31.3 %) [18]. The proportions of patients with the complete resolution of ≥1 tophus by month 12 were 25.5 and 30.3 % in the lesinurad 200 or 400 mg combination therapy groups versus 21.1 % in the febuxostat group [18].

The proportion of patients achieving a sUA level of <5 mg/dL at month 12 was significantly ($p < 0.05$) higher with lesinurad 200 mg combination therapy than febuxostat alone, irrespective of baseline estimated CL_{CR} levels (<90 and ≥90 mL/min) [19]. Moreover, the proportion of patients achieving a sUA level of <5 mg/dL was significantly ($p < 0.05$) higher with lesinurad 400 mg combination therapy versus febuxostat, irrespective of baseline estimated CL_{CR} levels of <60, <90 and ≥90 mL/min at month 6 and <90 and ≥90 mL/min at month 12 [19]. In the subgroup of patients with a sUA level of ≥5 mg/dL following the 3-week febuxostat run-in period ($n = 161$), a significantly ($p < 0.025$) greater proportion of those receiving lesinurad 200 mg or 400 mg combination therapy than those receiving febuxostat achieved a sUA level of <5 mg/dL (44.1 and 70.6 vs. 23.5 %) or <4 mg/dL (28.8 and 56.9 vs. 7.8 %) at month 6 [20].

CRYSTAL was a double-blind, multinational study in which 324 patients (aged 18–85 years) initially received febuxostat 80 mg once daily for 3 weeks before being randomized to receive either oral lesinurad (200 or 400 mg once daily) plus febuxostat or placebo plus febuxostat for 12 months [18]. Mean sUA levels were 8.7 mg/dL at screening and 5.3 mg/dL at randomization (i.e. following the 3-week febuxostat run-in period) [18]. Approximately 50 % of patients achieved sUA levels of <5 mg/dL following the 3-week febuxostat run-in period [20].

Patients completing the 12-month CRYSTAL study could enrol in a 12-month extension study ($n = 196$) (NCT01808144) [21]. Patients originally randomized to receive lesinurad 200 or 400 mg combination therapy (in CRYSTAL) continued to receive their randomized therapy for a further 12 months ($n = 64$ and 65), while those originally randomized to receive febuxostat alone were re-randomized to receive lesinurad 200 or 400 mg combination therapy for 12 months ($n = 33$ and 34). Among patients who continued therapy with lesinurad 200 or 400 mg combination therapy, 59.6 and 66.7 % experienced complete resolution of ≥1 target tophus (primary endpoint) by the end of the extension study, with reductions of 68.3 and 72.4 % in the sum of areas for all target tophi. Gout flares requiring therapy occurred in 32.8 and 13.8 % of patients continuing therapy with lesinurad 200 or 400 mg combination therapy, with few patients experiencing gout flares requiring treatment during the extension study itself. The proportions of patients achieving a sUA level of <5 mg/dL following lesinurad 200 or 400 mg combination therapy for 24 months were 77.1 and 88.5 %. Among patients who commenced therapy with lesinurad 200 or 400 mg combination therapy at the beginning of the extension study, 43.5 and 50.0 % experienced complete resolution of ≥1 target tophus and 79.2 and 71.4 % achieved a sUA level of <5 mg/dL. Rates of gout flares requiring therapy were 37.5 and 38.2 % in the respective groups, with reductions of 64.1 and 44.1 % in the target tophi area [21].

2.4 Adverse Events

Lesinurad as combination therapy with allopurinol was generally well tolerated in patients with gout and an inadequate response to allopurinol monotherapy, particularly at the 200 mg once daily dosage, where its tolerability profile was generally similar to that of placebo plus allopurinol [13, 14]. Combination therapy with lesinurad and febuxostat was also generally well tolerated in patients with tophaceous gout [18].

In a pooled analysis of data from the phase III CLEAR I and II and CRYSTAL studies [3], headache (5.3 % of 511 patients vs. 4.1 % of 516 patients), influenza (5.1 vs. 2.7 %) and gastrointestinal reflux disease (2.7 vs. 0.8 %) were the adverse reactions (other than those considered to be renal adverse reactions) occurring in ≥2 % of patients receiving lesinurad 200 mg once daily plus a xanthine oxidase inhibitor and with a ≥1 % higher incidence in the lesinurad 200 mg once daily plus xanthine oxidase inhibitor group than the placebo plus xanthine oxidase inhibitor group [3]. A generally similar tolerability profile was noted irrespective of median sUA levels [9].

Lesinurad increases the renal excretion of uric acid, which may result in renal events, including transient increases in serum creatinine levels, kidney stones and renal-related adverse events [3]. In pooled data from the three phase III studies, 1.5 to <2-fold and ≥2.0-fold increases from baseline in serum creatinine levels occurred in 3.9 and 1.8 % of lesinurad 200 mg once daily plus xanthine oxidase inhibitor recipients, 10.0 and 6.7 % of 510 lesinurad 400 mg once daily plus xanthine oxidase inhibitor recipients and 2.3 and 0 % of placebo plus xanthine oxidase inhibitor recipients. By study end, resolution of these elevations without treatment interruption had occurred in at least three-quarters of patients. Increases in blood creatinine levels considered to be adverse reactions occurred in 4.3 and 7.8 % of lesinurad 200 or 400 mg once daily plus xanthine oxidase inhibitor recipients versus 2.3% of placebo plus xanthine oxidase inhibitor recipients, with renal failure reported in 1.2, 3.5 and 2.1 % of patients, respectively, and nephrolithiasis in 0.6, 2.5 and 1.7 % of patients, respectively. Increases in blood creatinine levels occurred more frequently in patients receiving lesinurad 200 or 400 mg once daily plus a xanthine oxidase inhibitor than in those receiving placebo plus a xanthine oxidase inhibitor across baseline renal function categories. Renal-related adverse events led to treatment discontinuation in 1.2 % of lesinurad 200 mg once daily plus xanthine oxidase inhibitor recipients, 3.3 % of lesinurad 400 mg once daily plus xanthine oxidase inhibitor recipients and 1.0 % of placebo plus xanthine oxidase inhibitor recipients. Serious renal-related adverse reactions occurred in ≤1.0 % of patients in each treatment group [3].

The numbers of patients with adjudicated major adverse cardiovascular events (MACE; cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) in the three phase III studies were four for lesinurad 200 mg once daily plus xanthine oxidase inhibitor, eight for lesinurad 400 mg once daily plus xanthine oxidase inhibitor and three for placebo plus xanthine oxidase inhibitor [3]. Compared with placebo, the incidence per 100 patient–years was 1.36 for lesinurad 200 mg once daily plus xanthine oxidase inhibitor and 2.71 for lesinurad 400 mg once daily plus xanthine oxidase inhibitor [3]. It is worth noting that a causal relationship between MACE and lesinurad therapy has not been established [3].

In the CRYSTAL extension study, observed adverse events were generally similar to those reported in CRYSTAL [21].

In the phase II combination therapy study, the most common treatment-emergent adverse events (TEAEs) with lesinurad 200, 400 or 600 mg once daily plus allopurinol were gout flare (21.7, 31.0 and 31.3 vs. 20.8% with placebo plus allopurinol), arthralgia (6.5, 2.4 and 4.2 vs. 5.6 %), headache (6.5, 4.8 and 2.1 vs. 1.4 %) and nasopharyngitis (8.7, 0 and 2.1 vs. 1.4 %) [16]. Most TEAEs were mild to moderate in severity; there were no serious adverse events. Gout flare was the most common TEAE considered possibly related to treatment. Treatment discontinuations occurred in <5 % of patients in each treatment group. In the lesinurad 200, 400 or 600 mg once daily plus allopurinol or placebo plus allopurinol groups, the proportions of patients with ≥1.5-fold and ≥2-fold increases from baseline in serum creatinine levels were 0, 12.8, 19.7 and 2.8 %, respectively and 0, 5.1, 9.1 and 1.4 %, respectively [16]. In the extension of this study, lesinurad combination therapy was well tolerated, with a generally similar tolerability profile to that of placebo [17].

In the phase III LIGHT study (which assessed the efficacy of lesinurad 400 mg once daily as monotherapy; see Sect. 2.3.1), ≥1.5-fold increases from baseline in serum creatinine levels, renal failure, increases in blood creatinine levels and nephrolithiasis occurred in 24.3, 9.3, 8.4 and 0.9 % of patients receiving lesinurad 400 mg once daily, but in no patients receiving placebo [3]. The rates of discontinuation were 32.7 % with lesinurad 400 mg once daily versus 15.9 % with placebo [12]. Adverse events reported in the extension study were generally similar to those observed in LIGHT [12].

Key clinical trials of lesinurad (Ardea Biosciences)

Drugs(s)	Indication	Phase	Status	Location(s)	Identifier
Lesinurad/allopurinol fixed-dose combination vs. lesinurad + allopurinol	Healthy volunteers	I	Recruiting	USA	NCT02581553, RDEA594-501
Lesinurad, lesinurad + allopurinol, lesinurad + oxypurinol	Gout	II	Completed	Belgium	Eudract 2009-014762-26, RDEA594-204
Lesinurad vs. placebo	Gout	II	Completed	Multinational	NCT00955981, RDEA594-202
Lesinurad + allopurinol vs. placebo	Gout	II	Active, not recruiting	Multinational	NCT01001338, RDEA594-203
Lesinurad vs. placebo	Gout	III	Completed	Multinational	NCT01508702, RDEA594-303, 2011-003756-39, LIGHT
Lesinurad	Gout	III	Completed	Multinational	NCT01650246, RDEA594-305
Lesinurad + allopurinol vs. allopurinol	Gout	III	Completed	USA	NCT01510158, RDEA594-301, CLEAR I
Lesinurad + allopurinol vs. allopurinol	Gout	III	Completed	Multinational	NCT01493531, RDEA594-302, 2011-003767-29, CLEAR II
Lesinurad + febuxostat vs. febuxostat	Gout	III	Completed	Multinational	NCT01510769, RDEA594-304, 2011-003768-55, CRYSTAL
Lesinurad + allopurinol	Gout	III	Active, not recruiting	Multinational	NCT01808131, RDEA594-306, 2012-004389
Lesinurad + febuxostat	Gout	III	Active, not recruiting	Multinational	NCT01808144, RDEA594-307, 2012-004390-54

2.5 Ongoing Clinical Trials

There are several ongoing studies of lesinurad as combination therapy with a xanthine oxidase inhibitor for the treatment of hyperuricaemia associated with gout, including a phase III extension (NCT01808131) of the CLEAR I and II studies and a phase III extension (NCT01808144) of the CRYSTAL study. A phase II study and its extension (NCT01001338) are also still underway. A phase I study assessing the relative bioavailability of the lesinurad/allopurinol fixed dose combination is also ongoing.

3 Current Status

Lesinurad received its first global approval on 22 December 2015 in the USA for use in combination with a xanthine oxidase inhibitor for the treatment of hyperuricaemia associated with gout in patients who have not achieved target sUA levels with a xanthine oxidase inhibitor alone [3, 6].

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