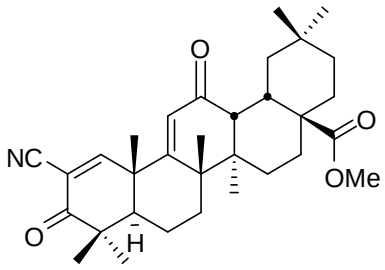
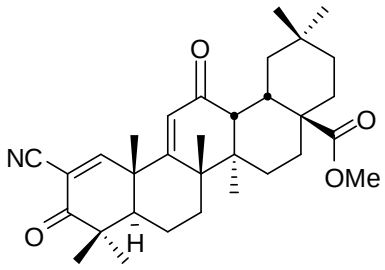
## SUMMARY

In one aspect, the present invention refers to the use of a compound as shown by the following formula:




,

or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating or preventing Alport syndrome in a human patient. In another aspect, the present invention refers to the use of a compound as shown by the following formula:




,

or a pharmaceutically acceptable salt thereof in the preparation of a medicament for improving kidney function of a human patient who has been diagnosed with Alport syndrome. In one example, there are disclosed methods of treating or preventing Alport syndrome in a patients in need thereof, and/or improving the kidney function of patients who has been diagnosed with Alport syndrome. Such methods are described in the sections below, including for example the claims section, which is incorporated herein by reference.

In some examples, the compound is bardoxolone methyl (CDDO-Me or RTA 402). And in some of these examples, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ. In non-limiting examples, the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 1A or FIG. 1B. In other variations, at least a portion of the CDDO-Me is present as a polymorphic form, wherein the polymorphic form is an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a $T_g$. In some variations, the compound is an amorphous form. In some variations, the compound is a glassy solid form of CDDO-Me, having an X-ray powder diffraction pattern with a halo peak at about 13.5 °2θ, as shown in FIG. 1C, and a $T_g$. In some variations, the $T_g$ value falls within a range of about 120 °C to about 135 °C. In some variations, the $T_g$ value is from about 125 °C to about 130 °C.

correlation to eGFR increases and to numerically reduce renal SAEs and ESRD events. These data demonstrate that the increases in eGFR observed in seven CKD studies of bardoxolone methyl treatment reflect true increases in GFR and support the use of eGFR as a reliable marker of renal function (Table 23).

**Table 23: Cross-Study Comparison of Increases in eGFR, Inulin Clearance, Creatinine Clearance with Bardoxolone Methyl Treatment**

| Study | Phase/Country | Patient Population | Mean Placebo-corrected ΔeGFR (mL/min/1.73m$^2$)[1] |
|---|---|---|---|
| 402-C-0801 (Stratum 1) | 2a/US | Diabetic nephropathy | 6.7 ($p < 0.001$)[2] |
| 402-C-0801 (Stratum 2) | 2b/US | Diabetic nephropathy | 7.2 ($p < 0.001$)[2][3] |
| 402-C-0804 (BEAM) | 2/US | CKD/Diabetes | 8.6 ($p < 0.001$ *vs*. PBO) |
| 402-C-0902 | 2/US | CKD/Diabetes | 6.5 ($p < 0.001$)[2] |
| 402-C-0903 (BEACON) | 3/Global | CKD/Diabetes | 6.4 ($p < 0.001$ *vs*. PBO)[c] |
| 402-C-1102 | 1/US | CKD/Diabetes | 9.0 ($p < 0.05$)[2] |
| RTA402-005 (TSUBAKI) | 2/Japan | CKD/Diabetes | 6.6 (inulin GFR) ($p = 0.008$ *vs*. PBO) |
| 402-C-0501 | 1/US | Cancer | 18.2 ($p < 0.0001$)[2] |
| 402-C-0702 | 1/2/US | Cancer | 32.2 ($p = 0.001$)[2] |
| 402-C-1302 (LARIAT) | 2/US | Pulmonary hypertension | 14.7 ($p < 0.001$ *vs*. PBO) |

[1] Unless noted, data are differences between mean eGFR changes from baseline for bardoxolone methyl versus placebo groups and p-values calculated comparing the difference in means between bardoxolone methyl and placebo groups.

[2] Data are mean eGFR changes from baseline for bardoxolone methyl patients and p-values are calculated from two-sided paired *t*-tests comparing eGFR change to 0.

[3] Study also demonstrated a significant increase in creatinine clearance.

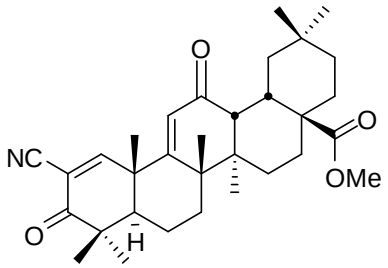
### B. Bardoxolone Methyl Produces a Retained eGFR Increase After Withdrawal of Drug

After one year of treatment with bardoxolone methyl, a residual eGFR increase from baseline is observed after cessation of treatment for four weeks, while an eGFR decline from baseline is observed in placebo patients. Sub-therapeutic concentrations of drug are achieved within approximately 10 days after drug withdrawal. In studies 402-C-0804 and 402-C-0903, approximately 20% to 25% of the on-treatment eGFR increase (or 1 to 4 mL/min/1.73 m$^2$ improvement relative to baseline) was maintained in bardoxolone methyl-treated patients after withdrawal of drug. The increases above baseline were statistically significant in both studies. Placebo-treated patients in these studies lost approximately 1 mL/min/1.73 m$^2$ over the course of a year, and in study 402-C-0903, this loss from baseline was statistically significant.

The sustained increase in eGFR through one year of treatment and the presence of a sustained eGFR improvement after withdrawal of drug suggest that the maladaptive structural

## CLAIMS

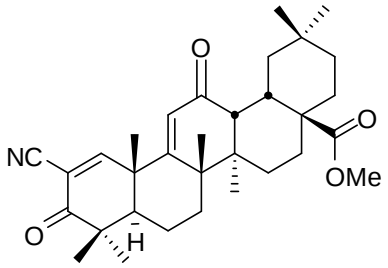
1. Use of a compound as shown by the following formula:




,

or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating or preventing Alport syndrome in a human patient.

2. Use of a compound as shown by the following formula:




,

or a pharmaceutically acceptable salt thereof in the preparation of a medicament for improving kidney function of a human patient who has been diagnosed with Alport syndrome.

3. The use of claim 2, further defined as for treating chronic kidney disease in a patient who has been diagnosed with Alport syndrome.

4. The use of any one of claims 1 to 3, wherein the patient does not have cardiovascular disease.

5. The use of any one of claims 1 to 4, wherein the cardiovascular disease is left-sided myocardial disease, atherosclerosis, restenosis, thrombosis, or pulmonary hypertension.

6. The use of any one of claims 1 to 5, wherein the patient does not have Stage 4 or higher chronic kidney disease.

7. The use of any one of claims 1 to 5, wherein the patient does not have an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 $m^2$.

8. The use of any one of claims 1 to 5, wherein the patient does not have an elevated albumin/creatinine ratio (ACR) is greater than 2000 mg/g.

9. The use of any one of claims 1 to 8, wherein the patient does not have diabetes.

10. The use of any one of claims 1 to 8, wherein the patient does not have a complication associated with diabetes.

11. The use of any one of claims 1 to 10, wherein the patient does not have insulin resistance.

12. The use of any one of claims 1 to 11, wherein the patient does not have fatty liver disease.

13. The use of any one of claims 1 to 12, wherein the patient does not have hepatic impairment.

14. The use of any one of claims 1 to 13, wherein the patient is not overweight.

15. The use of any one of claims 1 to 14, wherein the patient does not have cancer.

16. The use of any one of claims 1 to 15, wherein the patient does not have chronic obstructive pulmonary disease (COPD).

17. The use of any one of claims 1 to 16, wherein the patient is not a smoker.

18. The use of any one of claims 1 and 4 to 17, wherein the patient has impaired renal function.

19. The use of any one of claims 1 to 18, wherein the patient has elevated levels of at least one biomarker associated with renal disease, which is selected from serum creatinine, cystatin C and uric acid.

20. The use of any one of claims 1 to 19, wherein the Alport syndrome is X-linked, autosomal recessive, or autosomal dominant.

21. The use of any one of claims 1 to 20, wherein the patient has a deletion or nonsense mutation of *COL4A5*, a splicing mutation of *COL4A5*, a missense mutation of *COL4A5*, a mutation in *COL4A3*, or a mutation in *COL4A4*.

22. The use of any one of claims 1 to 21, wherein the patient exhibits microhematuria.

23. The use of any one of claims 1 to 22, wherein the patient further exhibits microalbuminuria.

24. The use of any one of claims 1 to 23, wherein the patient further exhibits proteinuria.

25. The use of any one of claims 1 to 24, wherein the patient is less than 75 years old.

26. The use of any one of claims 1 to 25, wherein the patient does not have the following characteristics:

(A) a cardiovascular disease;

(B) an elevated baseline B-type natriuretic peptide (BNP) level;

(C) an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 $m^2$; and

(D) an elevated albumin/creatinine ratio (ACR) > 2000 mg/g.

27. The use of any one of claims 1 to 26, wherein at least a portion of the compound is present as a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ.

28. The use of claim 27, wherein the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 1A or FIG. 1B.

29. The use of any one of claims 1 to 26, wherein at least a portion of the compound is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a transition glass temperature ($T_g$).

30. The use of claim 29, wherein the $T_g$ value is in the range of about 120°C to about 135°C.

31. The use of claim 30, wherein the $T_g$ value is in the range of about 125 C to about 130°C.

32. The use of any one of claims 1 to 31, wherein the compound is used in an amount from about 0.1 mg to about 300 mg of the compound or a pharmaceutically acceptable salt thereof per day.

33. The use of any one of claims 1 to 32, wherein the medicament is to be administered orally, intraarterially or intravenously.

34. The use of any one of claims 1 to 33, wherein the medicament is formulated as a hard or soft capsule or a tablet.

35. The use of any one of claims 1 to 33, wherein the medicament is formulated as a solid dispersion comprising (i) the compound and (ii) an excipient.

36. The use of claim 35, wherein the excipient is a methacrylic acid – ethyl acrylate copolymer.

37. The use of any one of claims 1 to 36, which is characterized in that the medicament is to be used in combination with a second drug.

38. The use of claim 37, wherein the second drug is an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or an aldosterone antagonist.

39. The use of claim 38, wherein the angiotensin-converting enzyme inhibitor is Ramipril, enalapril, Lisinopril, benazepril, fosinopril, quinapril, cilazapril, or trandolapril.

40. The use of claim 38, wherein the angiotensin receptor blocker is losartan, candesartan, irbesartan, telmisartan, or valsartan.

41. The use of claim 38, wherein the aldosterone antagonist is spironolactone.