VANRAFIA™ (atrasentan) tablets 0.75 mg

To reduce proteinuria in adults with primary IgAN at risk of rapid disease progression (generally a UPCR ≥1.5 g/g),[1]

Consider solidifying your foundation with a single addition to RASi ± SGLT2i for appropriate patients. **Add on VANRAFIA (atrasentan)**[1]

IgAN, immunoglobulin A nephropathy; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UPCR, urine protein-to-creatinine ratio.

INDICATION

VANRAFIA is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

This indication is approved under accelerated approval based on a reduction of proteinuria. It has not been established whether VANRAFIA slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

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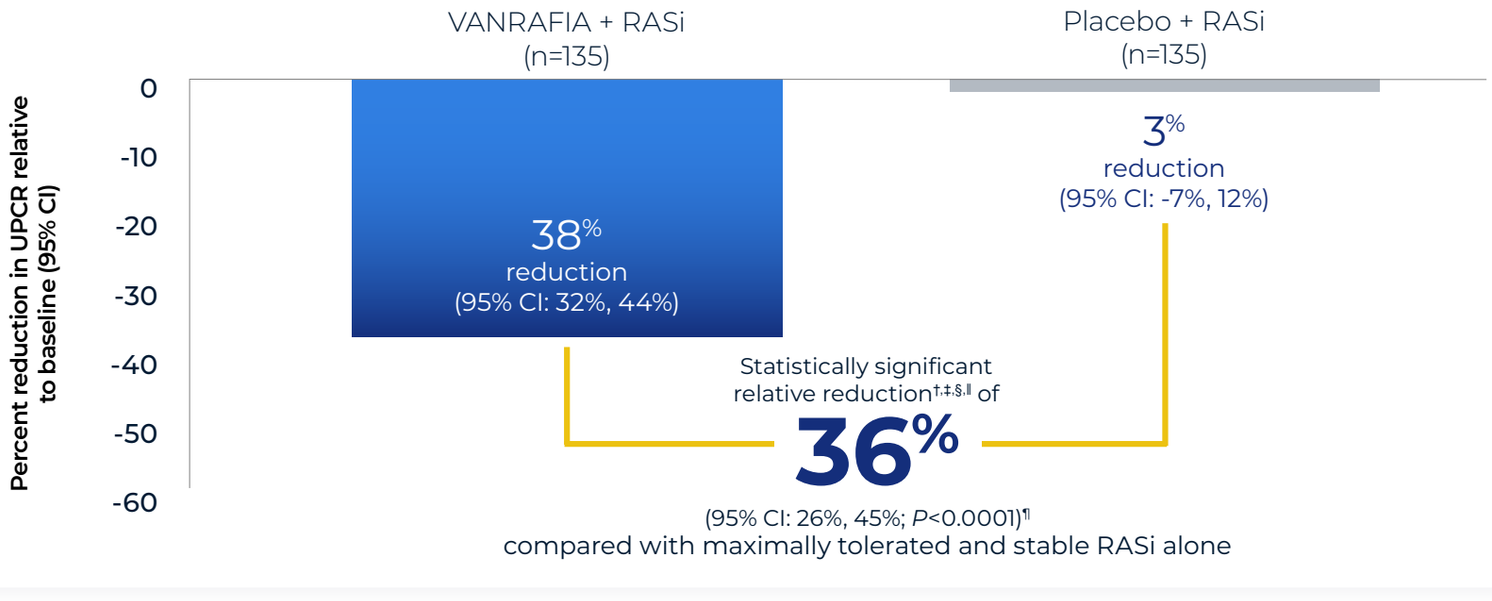
Please click here for full Important Safety Information. Please click here for full Prescribing Information, including Boxed WARNING and Medication Guide.

When added to a maximally tolerated and stable RASi regimen,

VANRAFIA delivered a significant reduction in UPCR at Week 36 for patients with IgAN in the main cohort (n=270)[1,2]

PERCENT REDUCTION IN UPCR FROM BASELINE AFTER 9 MONTHS OF TREATMENT*,†



*LS geometric mean ratio in UPCR (sampled from a 24-hour urine collection) to baseline was reported as a percent reduction along with the respective 95% CI.
†MMRM analysis included all observed UPCR data except for subjects with intercurrent events (eg, restricted medication use, chronic dialysis, kidney transplant). These subjects had UPCR data excluded beginning at the start date of the earliest event. The only intercurrent events observed were restricted medication use, which occurred in 3.0% and 5.2% of VANRAFIA- and placebo-treated subjects, respectively.
‡Statistically significant results coming from an interim analysis for accelerated approval through 36 weeks of treatment. The study for full approval is ongoing and will be based on data from 132 weeks of treatment.
§The estimate of the ratio of LS geometric mean ratio in UPCR (sampled from a 24-hour urine collection) to baseline comparing VANRAFIA with placebo was reported as a relative percent reduction along with the respective 95% CI and 2-sided *P* value.
‖The relative percent difference between VANRAFIA and placebo is equal to the ratio of the geometric mean minus 1 multiplied by 100: 100*[(0.62/0.97)-1]=-36%.
¶Two-sided *P* value statistically significant at the 0.01 level.
eGFR, estimated glomerular filtration rate; LS, least squares; MMRM, mixed model of repeated measures; RASi, renin-angiotensin system inhibitor; UPCR, urine protein-to-creatinine ratio.

- VANRAFIA was assessed in the ALIGN trial, which enrolled 340 adult patients with biopsy-proven primary IgAN, urine protein ≥1 g/day, and an eGFR of ≥30 mL/min/1.73 m^2 on a maximally tolerated and stable dose of RASi, which was continued throughout the study. Patients were randomized 1:1 to either RASi + VANRAFIA 0.75 mg daily (n=135) or RASi + placebo (n=135). The interim efficacy analysis included the first 270 in the main cohort who reached the Week 36 visit
- Patients in both the VANRAFIA and placebo groups were on a **maximally tolerated and stable dose of RASi** at baseline that was continued throughout the duration of the study
- The treatment effect on UPCR at Week 36 was consistent across subgroups, including age, sex, race, and baseline disease characteristics (such as eGFR and proteinuria levels), within the main cohort

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

Pregnancy

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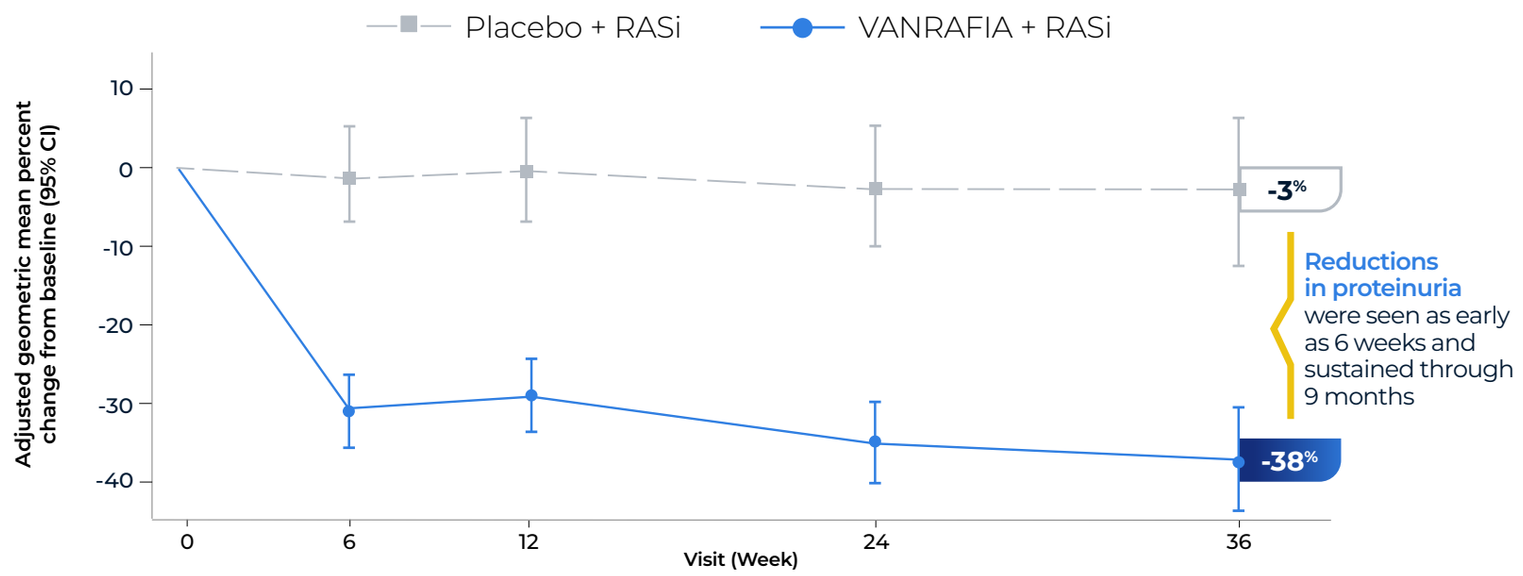
VANRAFIA™ (atrasentan) tablets 0.75 mg

When added to a maximally tolerated and stable RASi regimen,

VANRAFIA delivered RAPID AND SUSTAINED proteinuria reduction through 9 months of treatment[1,2]

GEOMETRIC MEAN PERCENT CHANGE FROM BASELINE IN UPCR BY VISIT*,†



Placebo N=	132‡	129	130	126	114
VANRAFIA N=	132‡	129	125	125	124

- Patients in both the VANRAFIA and placebo groups were on a **maximally tolerated and stable dose of RASi** at baseline that was continued throughout the duration of the study
- The treatment effect on UPCR at Week 36 was consistent across subgroups, including age, sex, race, and baseline disease characteristics (such as eGFR and proteinuria levels), within the main cohort
- In an exploratory analysis, a similar treatment effect on 24-hour UPCR was observed in an exploratory cohort of patients on an existing RASi + SGLT2i regimen

*Adjusted percent change relative to baseline in UPCR (sampled from a 24-hour urine collection) was estimated based on the MMRM analysis in Table 2 of the VANRAFIA Prescribing Information. N represents the number of evaluable subjects included in the analysis (ie, with nonmissing UPCR values and baseline covariates and did not have restricted medication use, chronic dialysis, or kidney transplant) for each visit and treatment group.

†Values reported in the figure were expressed as percent change from baseline and 95% CI, estimated from the regression model in Table 2 of the VANRAFIA Prescribing Information.

‡A total of 3 patients in each group had no postbaseline data for the urinary protein-to-creatinine ratio; these patients were excluded from the number of patients at baseline.

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS (continued)

Hypersensitivity

VANRAFIA is contraindicated in patients with a history of a hypersensitivity reaction to atrasentan or any component of the product.

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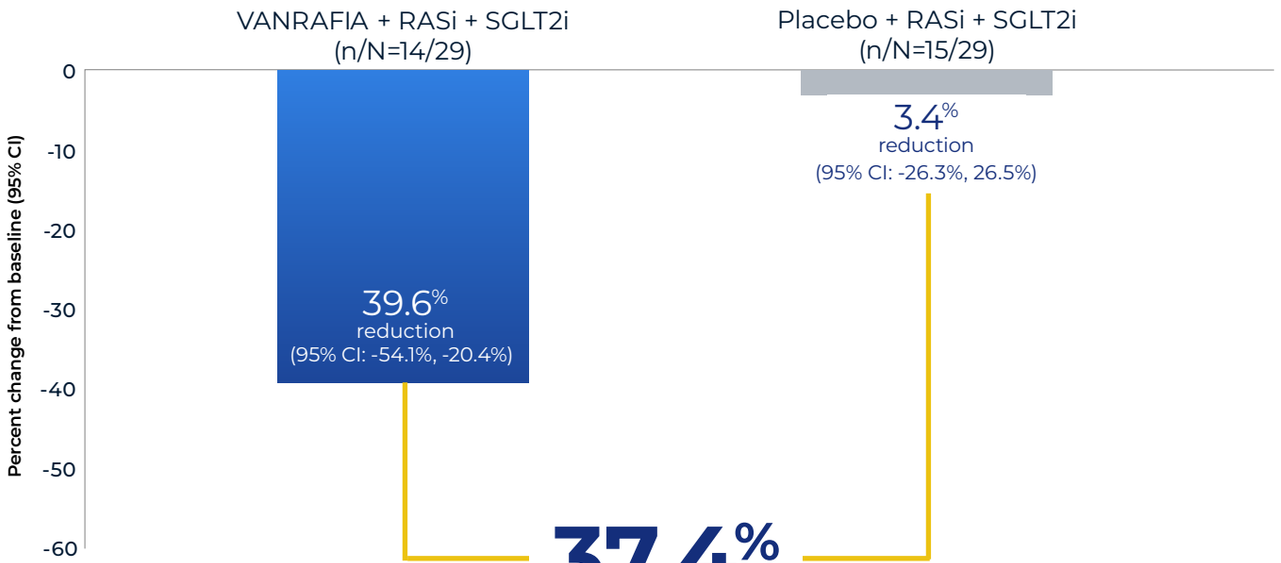
In an exploratory analysis of the ALIGN study,

A similar treatment effect on UPCR was seen in patients (N=29) treated with an optimized dose of RASi + SGLT2i prior to randomization[1,2]

GEOMETRIC MEAN PERCENT CHANGE FROM BASELINE IN UPCR AFTER 9 MONTHS OF TREATMENT*



37.4%
(95% CI: -57.2%, -8.5%)

relative reduction in mean percentage change in UPCR between VANRAFIA and RASi + SGLT2i alone in the exploratory SGLT2i cohort

- Patients in both the VANRAFIA and placebo groups were on a **maximally tolerated and stable dose of RASi + SGLT2i** at baseline that was continued throughout the duration of the study
- Limitations: In ALIGN, UPCR was observed in an exploratory cohort of patients on RASi + SGLT2i treatment at study start. Graph shows UPCR in this cohort at Month 9. No clinical or statistical conclusions can be drawn. Results cannot be generalized to patients with total urine protein <1 g/day. Underrepresentation of Black patients limits generalizability to these patients

Explore the safety profile of VANRAFIA in ALIGN

*Based on a repeated measures analysis with the change from baseline of natural log UPCR at each post baseline timepoint as outcomes; UPCR values are censored (excluded) for subjects with intercurrent events (eg, restricted medication use, chronic dialysis, kidney transplant) beginning at the start date of the earliest event. Missing UPCR values implicitly imputed assuming missing at random.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity

Based on data from animal reproduction studies, VANRAFIA may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. The available human data for endothelin receptor antagonists (ERAs) do not establish the presence or absence of major birth defects related to the use of VANRAFIA. Counsel patients who can become pregnant of the potential risk to a fetus. Exclude pregnancy prior to initiation of treatment with VANRAFIA. Advise patients to use effective contraception prior to initiation of treatment, during treatment, and for 2 weeks after discontinuation of treatment with VANRAFIA. When pregnancy is detected, discontinue VANRAFIA as soon as possible.

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A similar treatment effect on UPCR was seen in patients (N=29) treated with

SAFETY PROFILE OF VANRAFIA IN ALIGN[1]

Adverse reactions reported in ≥2% of adult patients with IgAN treated with VANRAFIA and higher than placebo in ALIGN*,†

Adverse reaction	VANRAFIA + RASi ± SGLT2i (N=201), n (%)	Placebo + RASi ± SGLT2i (N=202), n (%)
Peripheral edema[a]	21 (10)	14 (7)
Anemia[a]	12 (6)	2 (1)
Liver transaminase elevation[b]	4 (2)	2 (1)

[a]Includes related terms.
[b]Elevations in ALT or AST >3-fold ULN.

- Fluid retention may occur with VANRAFIA. If clinically significant fluid retention develops, consider initiating or increasing diuretic treatment and interrupting treatment with VANRAFIA

Advise patients about contraception

- Do not initiate VANRAFIA if a patient is pregnant. Advise patients to use effective contraception prior to and during treatment, and for 2 weeks following discontinuation of VANRAFIA
- Stop VANRAFIA as soon as possible if your patient becomes pregnant

Counsel patients about fertility

- Similar to other endothelin receptor antagonists, VANRAFIA may have a reversible adverse effect on sperm count. Counsel patients about potential effects on fertility
  - —A decrease in sperm count in some patients with diabetic kidney disease has been observed with VANRAFIA
  - —Patient sperm counts returned to normal levels within ~3 months after drug discontinuation
  - —This effect has not yet been studied in patients with IgAN

First and only ET_A receptor antagonist in IgAN without a REMS program

Use of VANRAFIA is contraindicated in patients who are pregnant and patients with hypersensitivity. Serious warnings associated with VANRAFIA include embryo-fetal toxicity, hepatotoxicity, fluid retention, and decreased sperm counts. Most common adverse reactions (incidence ≥5%) were peripheral edema and anemia. Please see additional Important Safety Information throughout.

*The safety analysis was based on patients from both cohorts (n=403) for the duration that they received VANRAFIA.
†The median duration of treatment was 47 weeks (range: 0 to 128 weeks).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ET_A, endothelin A; REMS, Risk Evaluation and Mitigation Strategy; ULN, upper limit of normal.

Indication and Important Safety Information

INDICATION

VANRAFIA is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

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IMPORTANT SAFETY INFORMATION

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CONTRAINDICATIONS

Pregnancy

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Additional Important Safety Information

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VANRAFIA™ (atrasentan) tablets 0.75 mg

Important Safety Information (continued)

WARNINGS AND PRECAUTIONS (continued)

Hepatotoxicity

Some ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. Asymptomatic and transient transaminase elevations have been observed with VANRAFIA. Obtain liver enzyme testing before initiating VANRAFIA, and repeat during treatment as clinically indicated. In patients with elevated aminotransferases at baseline (>3 × upper limit of normal [ULN]), consider periodic liver test monitoring. Do not initiate VANRAFIA in patients with severe hepatic impairment.

Advise patients to report symptoms suggesting hepatic injury (eg, nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue VANRAFIA. Consider reinitiation of VANRAFIA when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity or jaundice.

Fluid Retention

Fluid retention may occur with ERAs and has been observed in clinical studies with VANRAFIA. VANRAFIA has not been evaluated in IgAN patients with heart failure. If clinically significant fluid retention develops, consider initiating or increasing diuretic treatment and interrupting VANRAFIA treatment.

Decreased Sperm Counts

VANRAFIA, similar to other ERAs, may have an adverse effect on spermatogenesis. Counsel men about the potential effects on fertility.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5%) with VANRAFIA were peripheral edema and anemia.

EFFECT OF OTHER DRUGS ON VANRAFIA

Strong or Moderate CYP3A Inducers: Avoid concomitant use with a strong or moderate CYP3A inducer. Atrasentan is a CYP3A substrate. Concomitant use with a strong and moderate CYP3A inducer is expected to decrease atrasentan exposure, which may reduce VANRAFIA efficacy.

OATP1B1/1B3 Inhibitors: Avoid concomitant use with organic anion transporting polypeptides (OATP) 1B1/1B3 (OATP1B1/1B3) inhibitors. Atrasentan is an OATP1B1/1B3 substrate. Concomitant use with an OATP1B1/1B3 inhibitor increases atrasentan exposure, which may increase the risk of VANRAFIA adverse reactions.

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To reduce proteinuria in adults with primary IgAN at risk of rapid disease progression (generally a UPCR ≥1.5 g/g),[1]

IT'S TIME TO *MOVE A LITTLE FASTER*

Consider if it's time for an add-on treatment.

VANRAFIA + maximally tolerated and stable RASi provided greater total reduction in 24-hour UPCR compared with maximally tolerated and stable RASi alone, with a 38% (95% CI: 32%, 44%) reduction from baseline in the treatment arm vs only 3% (95% CI: -7%, 12%) in the placebo arm.[1,*,†]

RAPID AND SUSTAINED PROTEINURIA REDUCTION[1]

Improvements were seen as early as Week 6 and sustained through Month 9. At Month 9, VANRAFIA achieved a statistically significant relative reduction[†,‡,§,‖] of 24-hour UPCR compared with a maximally tolerated and stable RASi alone of 36% (95% CI: 26%, 45%; *P*<0.0001)[¶] relative to baseline.

FIRST AND ONLY ET_A RECEPTOR ANTAGONIST IN IgAN WITHOUT A REMS PROGRAM[1]

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TARGETS THE ET_A RECEPTOR. NOT A STEROID[1]

VANRAFIA is an ET_A receptor antagonist that can be added to your patient's maximally tolerated and stable RASi ± SGLT2i.

Solidify your foundation with a single addition to RASi ± SGLT2i for appropriate patients. ***ADD ON VANRAFIA***[1]

Download the start form at www.VANRAFIA-startform.com

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NOVARTIS

VANRAFIA™ (atrasentan) tablets 0.75 mg

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

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TARGETS THE ET$_A$ RECEPTOR, NOT A STEROID[1]

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References: 1. Vanrafia. Prescribing information. Novartis Pharmaceuticals Corp. **2.** Heerspink HJL, Jardine M, Kohan DE, et al. Atrasentan in patients with IgA nephropathy. *N Engl J Med*. 2024;1-11. doi:10.1056/NEJMoa2409415

References

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