1. NAME OF THE MEDICINAL PRODUCT

FABHALTA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Size 0 pale yellow, opaque hard capsule with “LNP200” on the body and “NVR” on the cap, containing white or almost white to pale purplish-pink powder.

Patient safety information card and Patient and caregiver guide

The marketing of Fabhalta is subject to a risk management plan (RMP) including "Patient safety information Card" and "Patient and caregiver guide". These materials emphasize important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review these materials before starting treatment.

Healthcare Professional Guide
This product is marketed with Healthcare Professional Guides providing important safety information.
Please ensure you are familiar with this material as it contains important safety information.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paroxysmal nocturnal haemoglobinuria:

FABHALTA is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

Complement 3 glomerulopathy

FABHALTA is indicated for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated (see section 5.1).

4.2 Posology and method of administration

Posology

The recommended dose is 200 mg taken orally twice daily.

Healthcare professionals should advise patients about the importance of adherence to the dosing schedule. In patients with PNH, adherence is important to minimise the risk of haemolysis (see section 4.4).

If a dose or doses are missed, the patient should be advised to take one dose as soon as possible (even if it is shortly before the next scheduled dose) and then to resume the regular dosing schedule. Patients with PNH who have missed several consecutive doses should be monitored for potential signs and symptoms of haemolysis.

PNH is a disease that requires chronic treatment. Discontinuation of this medicinal product is not recommended unless clinically indicated (see section 4.4).

Patients with PNH switching from anti-C5 (eculizumab, ravulizumab) or other PNH therapies to iptacopan

To reduce the potential risk of haemolysis with abrupt treatment discontinuation:

- For patients switching from eculizumab, iptacopan should be initiated no later than 1 week after the last dose of eculizumab.
- For patients switching from ravulizumab, iptacopan should be initiated no later than 6 weeks after the last dose of ravulizumab.

Switches from complement inhibitors other than eculizumab and ravulizumab have not been studied.

Patients with C3G after kidney transplantation (recurrent C3G)

Diagnosis of recurrent C3G should be made based on histological C3 deposition in the glomeruli of the transplanted kidney. C3 deposition may be detected in a routine post-transplantation biopsy; otherwise, a biopsy should be performed when clinical signs indicate recurrent C3G. As done in study X2202 (see section 5.1), treatment with iptacopan can be started before the onset of clinical signs such as estimated glomerular filtration rate (eGFR) decrease or urine protein-to-creatinine ratio (UPCR) increase. There is limited experience with the use of iptacopan in patients with recurrent C3G after transplantation in clinical studies (see section 5.1).

Special populations

Elderly

No dose adjustment is required for patients 65 years of age and older (see section 5.2).

Renal impairment

No dose adjustment is required in patients with mild (eGFR between 60 and <90 ml/min) or moderate (eGFR between 30 and <60 ml/min) renal impairment. No data are currently available in patients with severe renal impairment or on dialysis and no dose recommendations can be given(see section 5.2).

Hepatic impairment

The use of iptacopan is not recommended in patients with severe hepatic impairment (Child-Pugh class C). No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of iptacopan in children aged below 18 years have not been established. No data are available.

Method of administration

For oral use.

This medicinal product may be taken with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who are not currently vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae*, unless the risk of delaying treatment outweighs the risk of developing an infection from these encapsulated bacteria (see section 4.4).
- Patients with unresolved infection caused by encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae* or *Haemophilus influenzae* type B, at treatment initiation.

4.4 Special warnings and precautions for use

Serious infections caused by encapsulated bacteria

The use of complement inhibitors, such as iptacopan, may predispose individuals to serious, life-threatening or fatal infections caused by encapsulated bacteria. To reduce the risk of infection, all patients must be vaccinated against encapsulated bacteria, including *Neisseria meningitidis* and *Streptococcus pneumoniae*. It is recommended to vaccinate patients against *Haemophilus influenzae* type B if vaccine is available. Healthcare professionals should refer to local vaccination guideline recommendations.
Vaccines should be administered at least 2 weeks prior to administration of the first dose of iptacopan. If treatment must be initiated prior to vaccination, patients should be vaccinated as soon as possible and provided with antibacterial prophylaxis until 2 weeks after vaccine administration.

If necessary, patients may be revaccinated in accordance with local vaccination guideline recommendations.

Vaccination reduces, but does not eliminate, the risk of serious infection. Serious infection may rapidly become life-threatening or fatal if not recognised and treated early. Patients should be informed of and monitored for early signs and symptoms of serious infection. Patients should be immediately evaluated and treated if infection is suspected. The use of iptacopan during treatment of serious infection may be considered following an assessment of the risks and benefits (see section 4.8).

PNH laboratory monitoring

Patients with PNH receiving iptacopan should be monitored regularly for signs and symptoms of haemolysis, including measuring lactate dehydrogenase (LDH) levels.

Monitoring of PNH manifestations after treatment discontinuation

If treatment must be discontinued, patients with PNH should be closely monitored for signs and symptoms of haemolysis for at least 2 weeks after the last dose. These signs and symptoms include, but are not limited to, elevated LDH levels along with sudden decrease in haemoglobin or PNH clone size, fatigue, haemoglobinuria, abdominal pain, dyspnoea, dysphagia, erectile dysfunction, or major adverse vascular events (MAVEs), including venous or arterial thrombosis. If treatment discontinuation is necessary, alternative therapy should be considered.

If haemolysis occurs after discontinuation of iptacopan, restarting treatment should be considered.

Co-administration with other medicinal products

Concomitant use of iptacopan with strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3 has not been studied clinically; therefore, concomitant use is not recommended due to the potential for reduced efficacy of iptacopan (see section 4.5). If an alternative concomitant medicinal product cannot be identified, patients with PNH should be monitored for potential signs and symptoms of haemolysis.

Treatment of patients with C3G

Patients with C3G treated with immunosuppressant medicinal products may show modest proteinuria reduction with iptacopan, which is likely linked to a more treatment-resistant nature of C3G in these patients.

There is no experience with the use of iptacopan in patients with C3G in native kidney who have proteinuria below 1 g/g at treatment initiation.

Educational materials

All physicians who intend to prescribe FABHALTA must ensure they have received and are familiar with the physician educational materials. Physicians must explain and discuss the benefits and risks of FABHALTA therapy with the patient and provide them with the patient information pack. The patient should be instructed to seek prompt medical care if they experience any sign or symptom of serious infection or serious haemolysis (patients with PNH) following treatment discontinuation.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on iptacopan

Strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3
Although concomitant administration of iptacopan with strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3, such as rifampicin, has not been studied clinically, concomitant use with iptacopan is not recommended due to the potential for reduced efficacy of iptacopan (see section 4.4).

Effects of iptacopan on other medicinal products

CYP3A4 substrates
In vitro data showed iptacopan has potential for induction of CYP3A4 and may decrease the exposure of sensitive CYP3A4 substrates. The concomitant use of iptacopan and sensitive CYP3A4 substrates has not been studied clinically. Caution should be exercised if co-administration of iptacopan with sensitive CYP3A4 substrates is required, especially for those with a narrow therapeutic index (e.g. carbamazepine, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

CYP2C8 substrates
In vitro data showed iptacopan has potential for time-dependent inhibition of CYP2C8 and may increase the exposure of sensitive CYP2C8 substrates, such as repaglinide, dasabuvir or paclitaxel. The concomitant use of iptacopan and sensitive CYP2C8 substrates has not been studied clinically. Caution should be exercised if co-administration of iptacopan with sensitive CYP2C8 substrates is required.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of iptacopan in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures between 2- and 8-fold the human exposure at the maximum recommended human dose (MRHD) (see section 5.3).

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, as well as adverse foetal outcomes, including foetal death and premature delivery.

C3G in pregnancy may be associated with adverse maternal outcomes, in particular pre-eclampsia and miscarriage, as well as adverse foetal outcomes including prematurity and low birth weight.

The use of iptacopan in pregnant women or women planning to become pregnant may only be considered following a careful assessment of the risk and benefits, if necessary.

Breast-feeding

It is unknown whether iptacopan is excreted in human milk. There are no data on the effects of iptacopan on the breast-fed newborn/infant or on milk production.

A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from FABHALTA therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of iptacopan on human fertility. Available non-clinical data do not suggest an effect of iptacopan treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

FABHALTA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in adult patients with PNH were upper respiratory tract infection (18.9%), headache (18.3%) and diarrhoea (11.0%). The most commonly reported serious adverse reaction was urinary tract infection (1.2%).

The most commonly reported adverse reaction in adult patients with C3G was upper respiratory tract infection (12.9%). The most commonly reported serious adverse reaction was pneumococcal infection (1%).

Tabulated list of adverse reactions

Table 1 shows the adverse reactions observed in the clinical studies with iptacopan in patients with PNH and C3G. Adverse reactions are listed by MedDRA system organ class (SOC) and frequency, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000) or very rare (<1/10 000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

System Organ Class Adverse reaction	Frequency category	
	PNH	**C3G**
Infections and infestations		
Upper respiratory tract infection[1]	Very common	Very common
Urinary tract infection[2]	Common	
Bronchitis[3]	Common	
Pneumococcal infection[4]		Common
Pneumonia bacterial	Uncommon	
Blood and lymphatic system disorders		
Platelet count decreased	Common	
Nervous system disorders		
Headache[5]	Very common	
Dizziness	Common	
Gastrointestinal disorders		
Diarrhoea	Very common	
Abdominal pain[6]	Common	
Nausea	Common	
Skin and subcutaneous tissue disorders		
Urticaria	Uncommon	
Musculoskeletal and connective tissue disorders		
Arthralgia	Common	

[1] Upper respiratory tract infection includes preferred terms influenza, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
[2] Urinary tract infection includes preferred terms urinary tract infection and cystitis escherichia.
[3] Bronchitis includes preferred terms bronchitis, bronchitis haemophilus and bronchitis bacterial.
[4] Pneumococcal infection includes preferred terms pneumonia pneumococcal and pneumococcal sepsis
[5] Headache includes preferred terms headache and head discomfort.
[6] Abdominal pain includes preferred terms abdominal pain, abdominal pain upper, abdominal tenderness and abdominal discomfort.

Description of selected adverse reactions

Infections
In PNH clinical studies 1/164 (0.6%) patients with PNH reported serious bacterial pneumonia while receiving treatment with iptacopan; the patient had been vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B and recovered following treatment with antibiotics while continuing treatment with iptacopan.

In C3G completed clinical studies, 1 patient with C3G reported serious pneumococcal infection with pneumonia and sepsis while receiving treatment with iptacopan; the patient had been vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B and recovered following treatment with antibiotics. Iptacopan treatment was interrupted and restarted after recovery.

Platelet count decreased in patients with PNH
Decrease in platelet count events was reported in 12/164 (7%) patients with PNH. Of these, 5 patients had events of mild severity, 5 had moderate events and 2 had severe events. Patients with severe events had concurrent anti-platelet antibodies or idiopathic bone marrow aplasia with pre-existing thrombocytopenia. The events started within the first 2 months of iptacopan treatment in 7/12 patients, and after a longer exposure (111 to 951 days) in 5/12 patients. At the cut-off date, 7 (58%) patients had recovered or events were resolving and iptacopan treatment was continued throughout in all patients.

Blood cholesterol and blood pressure increases in patients with PNH
In patients treated with iptacopan 200 mg twice a day in PNH clinical studies, mean increases from baseline of approximately 0.7 mmol/l were seen at month 6 for total cholesterol and LDL-cholesterol. The mean values remained within the normal ranges. Increases in blood pressure, particularly diastolic blood pressure (DBP), were observed (mean increase 4.7 mmHg at month 6). The mean DBP did not exceed 80 mmHg. Total cholesterol, LDL-C and DBP increases correlated with increases in haemoglobin (improvement in anaemia) in patients with PNH (see section 5.1).

In patients treated with iptacopan 200 mg twice a day in the C3G clinical study, no clinically relevant differences were observed in total cholesterol, LDL-cholesterol or blood pressure compared to placebo.

Heart rate decrease in patients with PNH
In patients treated with iptacopan 200 mg twice a day in PNH clinical studies, a mean decrease in heart rate of approximately 5 bpm was seen at month 6 (mean of 68 bpm).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
And to Novartis using the following email address: Safetydesk.israel@novaris.com.

4.9 Overdose

During clinical studies, a few patients took up to 800 mg iptacopan daily and this was well tolerated. In healthy volunteers, the highest dose was 1 200 mg administered as a single dose and this was well tolerated.

General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, complement inhibitors, ATC code: L04AJ08

Mechanism of action

Iptacopan is a proximal complement inhibitor that targets Factor B (FB) to selectively inhibit the alternative pathway. In PNH inhibition of FB in the alternative pathway of the complement cascade prevents the activation of C3 convertase and the subsequent formation of C5 convertase to control both C3-mediated extravascular haemolysis (EVH) and terminal complement-mediated intravascular haemolysis (IVH).
In C3G, overactivation of the complement alternative pathway leads to deposition of C3 within the glomeruli, triggering inflammation, glomerular injury, and kidney fibrosis. Iptacopan selectively blocks the alternative pathway overactivation by inhibiting the alternative pathway related C3 convertase activity, leading to decreased cleavage of C3 and reduced C3 deposition in the kidney.

Pharmacodynamic effects

The onset of inhibition of the alternative complement pathway, measured using an *ex vivo* alternative pathway assay, Bb levels (fragment b of Factor B) and plasma levels of C5b-9, was ≤2 hours after a single iptacopan dose in healthy volunteers.

A comparable effect of iptacopan was observed in patients with PNH previously exposed to anti-C5 agents and treatment-naïve patients.

In treatment-naïve PNH patients, iptacopan 200 mg twice daily reduced LDH by >60% compared to baseline after 12 weeks and maintained the effect through to the end of the study.

In patients with C3G, the mean serum C3 level increased by 249% compared to baseline at day 14 of iptacopan treatment, reflecting inhibition of pathological C3 cleavage. The plasma soluble C5b-9 and urine soluble C5b-9 decreased from baseline by 71.8% and 92.1%, respectively, on the first observation at day 30 of treatment with iptacopan 200 mg twice daily. The effect was sustained over the observation period of 12 months. A reduction of glomerular C3 deposition at 6 months was also observed based on C3 deposit score change.

Cardiac electrophysiology

In a QTc clinical study in healthy volunteers, single supra-therapeutic iptacopan doses up to 1 200 mg (which provided greater than 4-fold exposure of the 200 mg twice daily dose), showed no effect on cardiac repolarisation or QT interval.

Clinical efficacy and safety

Paroxysmal nocturnal haemoglobinuria

The efficacy and safety of iptacopan in adult patients with PNH were evaluated in two multicentre, open-label, 24-week phase III studies: an active comparator-controlled study (APPLY-PNH) and a single-arm study (APPOINT-PNH).

APPLY-PNH: anti-C5 treatment experienced patients with PNH
APPLY-PNH enrolled adult PNH patients (RBC clone size ≥10%) with residual anaemia (haemoglobin <10 g/dl) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomisation.

Patients (N=97) were randomised in 8:5 ratio either to receive iptacopan 200 mg orally twice daily (N=62) or to continue anti-C5 treatment (eculizumab N=23; or ravulizumab N=12) throughout the duration of the 24-week randomised controlled period (RCP). Randomisation was stratified based on prior anti-C5 treatment and transfusion history within the last 6 months.

Demographics and baseline disease characteristics were generally well balanced between treatment groups. At baseline, patients had a mean (standard deviation [SD]) age of 51.7 (16.9) years (range 22-84) and 49.8 (16.7) years (range 20-82) in the iptacopan and anti-C5 groups, respectively and 69% of patients were female in both groups. The mean (SD) haemoglobin was 8.9 (0.7) g/dl and 8.9 (0.9) g/dl, in the iptacopan and anti-C5 group, respectively. Fifty-seven percent (iptacopan group) and 60% (anti-C5 group) of patients received at least one transfusion in the 6 months prior to randomisation. Amongst those, the mean (SD) number of transfusions was 3.1 (2.6) and 4.0 (4.3) in the iptacopan and anti-C5 group, respectively. The mean (SD) LDH level was 269.1 (70.1) U/l in the iptacopan group and 272.7 (84.8) U/l in the anti-C5 group. The mean (SD) absolute reticulocyte count was 193.2 (83.6) 10^9/l in the iptacopan group and 190.6 (80.9) 10^9/l in the anti-C5 group. The mean (SD) total PNH RBC clone size (Type II + III) was 64.6% (27.5%) in the iptacopan group and 57.4% (29.7%) in the anti-C5 group.

During the RCP, 1 patient in the iptacopan group discontinued treatment due to pregnancy; no patients in the anti-C5 group discontinued.

Efficacy was based on two primary endpoints to demonstrate superiority of iptacopan to anti-C5 in achieving haematological response after 24 weeks of treatment, without a need for transfusion, by assessing the proportion of patients demonstrating: 1) sustained increase of ≥2 g/dl in haemoglobin levels from baseline (haemoglobin improvement) and/or 2) sustained haemoglobin levels ≥12 g/dl.

Iptacopan demonstrated superiority to anti-C5 therapy for the two primary endpoints, as well as for several secondary endpoints including transfusion avoidance, changes from baseline in haemoglobin levels, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores, absolute reticulocyte counts (ARCs) and annualised rate of clinical breakthrough haemolysis (see Table 2).

The treatment effect of iptacopan on haemoglobin was seen as early as day 7 and sustained during the study (see Figure 1).

Table 2 Efficacy results for the 24-week randomised treatment period in APPLY-PNH

Endpoints	**Iptacopan (N=62)**	**Anti-C5 (N=35)**	**Difference (95% CI) p-value**
Primary endpoints			
Number of patients achieving haemoglobin improvement (sustained increase of haemoglobin levels ≥2 g/dl from baseline[a] in the absence of transfusions) Response rate[c] (%)	51/60[b] 82.3	0/35[b] 2.0	 80.2 (71.2, 87.6) <0.0001
Number of patients achieving sustained haemoglobin level ≥12 g/dl[a] in the absence of transfusions Response rate[c] (%)	42/60[b] 68.8	0/35[b] 1.8	 67.0 (56.4, 76.9) <0.0001
Secondary endpoints			
Number of patients avoiding transfusion[d,e] Transfusion avoidance rate[c] (%)	59/62[b] 94.8	14/35[b] 25.9	 68.9 (51.4, 83.9) <0.0001
Haemoglobin level change from baseline (g/dl) (adjusted mean[f])	3.60	-0.06	3.66 (3.20, 4.12) <0.0001
FACIT-Fatigue score change from baseline (adjusted mean[g])	8.59	0.31	8.29 (5.28, 11.29) <0.0001
Clinical breakthrough haemolysis[h,i], % (n/N) Annualised rate of clinical breakthrough haemolysis	3.2 (2/62) 0.07	17.1 (6/35) 0.67	 RR=0.10 (0.02, 0.61) 0.01
Absolute reticulocyte count change from baseline (10^9/l) (adjusted mean[g])	-115.8	0.3	-116.2 (-132.0, -100.3) <0.0001

LDH ratio to baseline (adjusted geometric mean[g])	0.96	0.98	Ratio = 0.99 (0.89, 1.10) 0.84
MAVEs[h] % (n/N) Annualised rate of MAVEs[h]	1.6 (1/62) 0.03	0 0	 0.03 (-0.03, 0.10) 0.32

RR: rate ratio; LDH: lactate dehydrogenase; MAVEs: major adverse vascular events

[a,d,h] Assessed between days 126 and 168[(a)], 14 and 168[(d)], 1 and 168[(h)].

[b] Based on observed data among evaluable patients. (In 2 patients with partially missing central haemoglobin data between days 126 and 168, the haematological response could not be established unequivocally. The haematological response was derived using multiple imputation. These patients did not discontinue.)

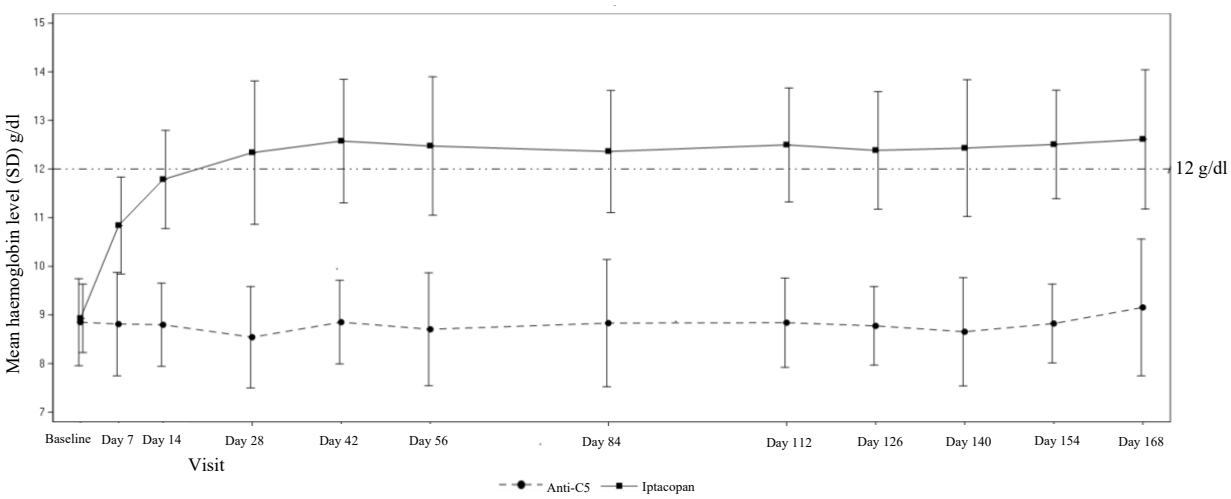
[c] Response rate reflects the model estimated proportion.

[e] Transfusion avoidance is defined as absence of administration of packed red blood cell transfusions between days 14 and 168 or meeting the criteria for transfusion between days 14 and 168.

[f,g] Adjusted mean assessed between days 126 and 168, values within 30 days after transfusion were excluded[(f)]/included[(g)] in the analysis.

[i] Clinical breakthrough haemolysis is defined as meeting clinical criteria (either decrease of haemoglobin level ≥2 g/dl compared to the last assessment or within 15 days, or signs or symptoms of gross haemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs and symptoms) and laboratory criteria (LDH >1.5 x ULN and increased as compared to the last 2 assessments).

Figure 1 Mean haemoglobin level* (g/dl) during 24-week randomised treatment period in APPLY-PNH



*Note: The figure includes all haemoglobin data collected in the study, including those values within 30 days after RBC transfusion.

APPOINT-PNH: Complement inhibitor-naïve study

APPOINT-PNH was a single-arm study in 40 adult PNH patients (RBC clone size ≥10%) with haemoglobin <10 g/dl and LDH >1.5 x ULN who were not previously treated with a complement inhibitor. All 40 patients received iptacopan 200 mg orally twice daily during the 24-week open-label core treatment period.

At baseline, patients had a mean (SD) age of 42.1 (15.9) years (range 18-81) and 43% were female. The mean (SD) haemoglobin was 8.2 (1.1) g/dl. Seventy percent of patients received at least one transfusion in the 6 months prior to treatment. Amongst those the mean (SD) number of transfusions was 3.1 (2.1). The mean (SD) LDH level was 1 698.8 (683.3) U/l, and the mean (SD) absolute

reticulocyte count was 154.3 (63.7) 10^9/l. The mean (SD) total PNH RBC clone size (Type II + III) was 42.7% (21.2%). No patients discontinued from the core treatment period of the study.

Efficacy was based on the primary endpoint assessing the effect of iptacopan treatment on the proportion of patients achieving haemoglobin improvement (sustained increase of ≥2 g/dl in haemoglobin levels from baseline, without a need for RBC transfusion, after 24 weeks).

See Table 3 for detailed efficacy results and see Figure 2 for the mean LDH level change during the 24-week core treatment period.

Table 3 Efficacy results for the 24-week core treatment period in APPOINT-PNH

Endpoints	**Iptacopan (N=40) 95% CI**
Primary endpoint	
Number of patients achieving haemoglobin improvement (sustained increase of haemoglobin levels ≥2 g/dl from baseline[a] in the absence of transfusions) Response rate[c] (%)	31/33[b] 92.2 (82.5, 100.0)[d]
Secondary endpoints	
Number of patients achieving sustained haemoglobin level ≥12 g/dl[a] in the absence of transfusions Response rate[c] (%)	19/33[b] 62.8 (47.5, 77.5)
Number of patients avoiding transfusion[e,f] Transfusion avoidance rate[c] (%)	40/40[b] 97.6 (92.5, 100.0)
Haemoglobin level change from baseline (g/dl) (adjusted mean[g])	+4.3 (3.9, 4.7)
Clinical breakthrough haemolysis[i,j], % (n/N) Annualised rate of clinical breakthrough haemolysis	0/40 0.0 (0.0, 0.2)
Absolute reticulocyte count change from baseline (10^9/l) (adjusted mean[h])	-82.5 (-89.3, -75.6)
LDH percent change from baseline (adjusted mean[h])	-83.6 (-84.9, -82.1)
Percentage of patients with MAVEs[j]	0.0

[a,e,j] Assessed between days 126 and 168[(a)], 14 and 168[(e)], 1 and 168[(j)].

[b] Based on observed data among evaluable patients. (In 7 patients with partially missing central haemoglobin data between days 126 and 168, the haematological response could not be established unequivocally. The haematological response was derived using multiple imputation. These patients did not discontinue.)

[c] Response rate reflects the model estimated proportion.

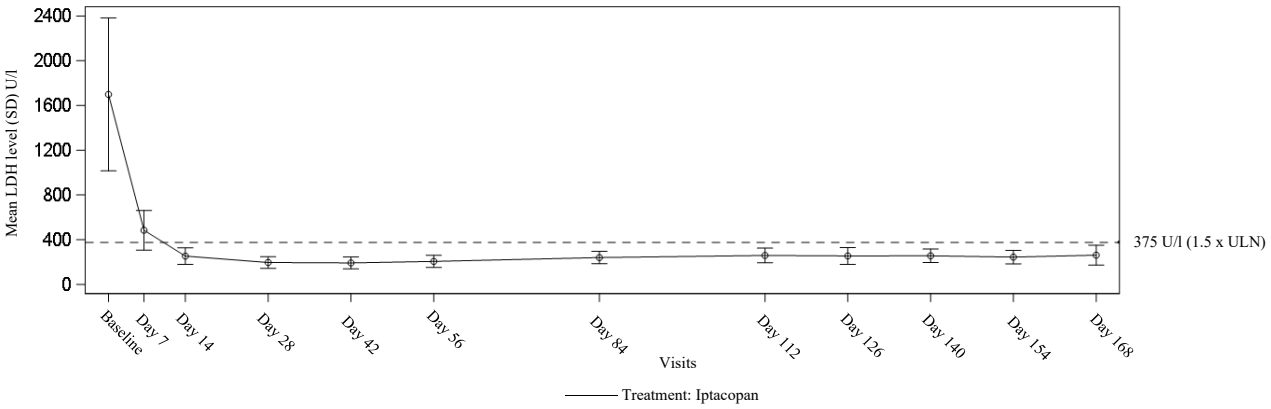
[d] The threshold for demonstration of benefit was 15%, representing the rate that would have been expected on anti-C5 treatment.

[f] Transfusion avoidance is defined as absence of administration of packed red blood cell transfusions between days 14 and 168 or meeting the criteria for transfusion between days 14 and 168.

[g,h] Adjusted mean assessed between days 126 and 168, values within 30 days after transfusion were excluded[(g)]/included[(h)] in the analysis.

[i] Clinical breakthrough haemolysis defined as meeting clinical criteria (either decrease of haemoglobin level ≥2 g/dl compared to the latest assessment or within 15 days; or signs or symptoms of gross haemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs and symptoms) and laboratory criteria (LDH >1.5 x ULN and increased as compared to the last 2 assessments).

Figure 2 Mean LDH level (U/l) during 24-week core treatment period in APPOINT-PNH



Complement 3 glomerulopathy

The efficacy and safety of iptacopan for the treatment of C3G were evaluated in a total of 101 patients with C3G in one pivotal phase III study (APPEAR-C3G, in patients with native kidney, N=74) and two supportive open-label studies (study X2202 in patients with native kidney (N=16) and patients with recurrent C3G (N=11), and a roll-over extension study).

APPEAR-C3G

APPEAR-C3G, a multicentre, randomised, double-blind, placebo-controlled study, enrolled 74 adult patients with biopsy-confirmed C3G, UPCR ≥1 g/g, and eGFR ≥30 ml/min/1.73 m^2.

Patients were randomised (1:1) to receive either iptacopan 200 mg orally twice daily (N=38) or placebo (N=36) for 6 months, followed by a 6-month open-label treatment period in which patients received iptacopan 200 mg orally twice daily. All 74 patients completed the double-blind period and 73 patients completed the open-label treatment period with iptacopan.

Patients were on a stable maximally tolerated dose of a renin-angiotensin system (RAS) inhibitor. Randomisation was stratified according to whether or not patients were receiving concomitant immunosuppressive therapy (i.e. corticosteroid and/or mycophenolate mofetil/sodium [MMF/MPS]). All of these therapies (i.e. RAS inhibitors, corticosteroids and MMF/MPS) were required to be at stable doses 90 days prior to randomisation and throughout the study.

At baseline, patients had a mean (standard deviation [SD]) age of 26.1 (10.4) years (range 18-52) and 29.8 (10.8) years (range 18-60) in the iptacopan and placebo groups, respectively. At the time of C3G diagnosis, 40% (iptacopan) and 17% (placebo) of patients were <18 years old. Females were 29% (iptacopan) and 44% (placebo). The geometric mean UPCR was 3.33 g/g and 2.58 g/g in the iptacopan and placebo groups, respectively. The mean modelled historical eGFR slope prior to randomisation was -10.75 vs. -7.64 ml/min/1.73m^2 per year in iptacopan and placebo arms, respectively. The mean (SD) eGFR was 89.3 (35.2) ml/min/1.73 m^2 and 99.2 (26.9) ml/min/1.73 m^2 in the iptacopan and placebo groups, respectively. Subtypes were C3 glomerulonephritis (C3GN) in 68% (iptacopan) and 89% (placebo) of patients, and dense deposit disease (DDD) in 23.7% (iptacopan) and 2.8% (placebo). A stable dose of immunosuppressive therapy with corticosteroid and/or MMF/MPS was used by 42% (iptacopan) and 47% (placebo) of patients.

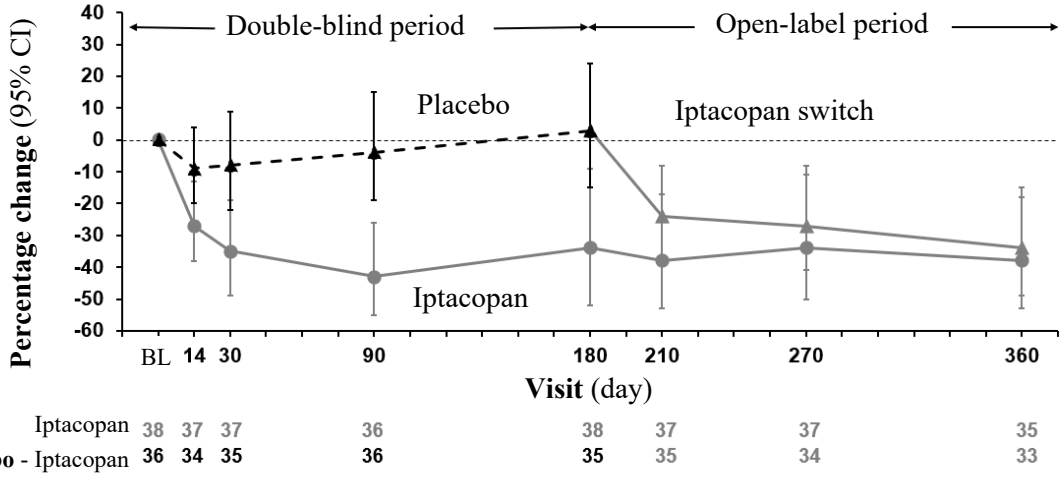
The primary efficacy endpoint was percent reduction in 24-hour UPCR compared to baseline after 6 months of treatment.

Iptacopan was superior to placebo, with a statistically significant 35.1% reduction (95% CI: 13.8%, 51.1%, 1-sided p=0.0014) in 24-hour UPCR from baseline compared to placebo after 6 months of treatment (-30.2% and +7.6% for iptacopan and placebo, respectively). The effect of iptacopan on 24-hour UPCR was sustained up to 12 months (-40.0% from baseline). Patients who switched from placebo to iptacopan in the 6-month open-label treatment period experienced a 31.0% reduction in 24-

hour UPCR from month 6 to month 12. First morning void (FMV) UPCR trajectory is described in Figure 3.

In a post-hoc analysis, iptacopan reduced the percentage of patients with nephrotic range proteinuria (defined as UPCR ≥3 g/g) from 55.3% at baseline to 31.6% and 36.8% at months 6 and 12, respectively. The percentage of patients with nephrotic range proteinuria randomised to placebo increased from 30.6% at baseline to 41.7% at month 6. After switching to iptacopan treatment, it decreased to 27.8% at month 12.

Figure 3 Geometric mean percent change from baseline in FMV UPCR up to 12 months (APPEAR-C3G)



Iptacopan treatment for 6 months resulted in a numerical improvement of 2.2 ml/min/1.73 m^2 (95% CI: -2.7, 7.1, 1-sided p=0.3241) in eGFR from baseline compared to placebo (1.3 and -0.9 ml/min/1.73 m^2 for iptacopan and placebo, respectively). The eGFR remained stable during the 12 months duration of the study in the iptacopan treatment arm (+0.4 ml/min/1.73 m^2 from baseline).

Iptacopan treatment for 6 months resulted in a mean difference in glomerular C3 deposition of -1.9 (95% CI: -3.3, -0.5; nominal 1-sided p=0.0053) from baseline compared to placebo. Change from baseline on iptacopan was -0.78 (95% CI: -1.81, 0.25) compared to an increase of 1.09 (95% CI: 0.11, 2.08) with placebo.

X2202 and roll-over extension study
The efficacy of iptacopan in adults with C3G was supported by an open-label phase II study X2202 in patients with C3G in native kidney (N=16) and patients with recurrent C3G post-kidney transplantation (N=11) for 3 months.

Diagnosis of recurrent C3G required histological assessment of glomerular C3 staining intensity on a recent biopsy of the transplanted kidney. The baseline mean age was 35 years (range 18-70), the geometric mean UPCR was 0.32 g/g, the mean (SD) eGFR was 52.2 (17.29) ml/min/1.73m^2, and the median C3 deposit score was 3 on a scale of 0-12 at baseline. All patients were on MMF/MPS and/or corticosteroids in addition to calcineurin inhibitors.

In patients with native kidney, iptacopan resulted in a statistically significant 45% (-162.6 g/mol) reduction in 24-hour UPCR (p=0.0003) at 3 months. In patients with recurrent C3G, iptacopan significantly reduced the histological C3 deposit score by 2.50 (p=0.0313) at 3 months.

Most (n=26) patients from the study transitioned to a roll-over extension study to receive iptacopan 200 mg twice daily for up to 39 months. Mean UPCR and eGFR remained stable throughout the study in the 16 patients with C3G in native kidney. Among the 10 subjects with recurrent C3G after transplantation, 2 patients dropped out due to deterioration of renal function. In the other

8 participants, eGFR and UPCR remained essentially constant until the end of the observation period (up to 48 months).

Paediatric population

FABHALTA is not indicated for PNH or C3G in children and adolescents under 18 years old.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, iptacopan reached peak plasma concentrations approximately 2 hours post dose. At the recommended dosing regimen of 200 mg twice daily, steady state is achieved in approximately 5 days with minor accumulation (1.4-fold). In healthy volunteers, steady-state $C_{max,ss}$ (geo-mean (%CV)) was 4 020 ng/ml (23.8%) and $AUC_{tau,ss}$ was 25 400 ng*hr/ml (15.2%). Inter- and intra-subject variability in iptacopan pharmacokinetics is low to moderate.

Results from a food-effect study with a high-fat high-calorie meal in healthy volunteers indicated that C_{max} and area under the curve (AUC) of iptacopan were not affected by food. Therefore, iptacopan may be taken with or without food.

Distribution

Iptacopan showed concentration-dependent plasma protein binding due to binding to the target FB in the systemic circulation. Iptacopan was 75 to 93% protein bound *in vitro* at the relevant clinical plasma concentrations. After administration of iptacopan 200 mg twice daily, the geo-mean apparent volume of distribution at steady state was approximately 265 litres.

Biotransformation

Metabolism is a predominant elimination pathway for iptacopan, with approximately 50% of the dose attributed to oxidative pathways. Metabolism of iptacopan includes N-dealkylation, O-deethylation, oxidation and dehydrogenation, mostly driven by CYP2C8 with a small contribution from CYP2D6. Direct glucuronidation (by UGT1A1, UGT1A3 and UGT1A8) is a minor pathway. In plasma, iptacopan was the major component, accounting for 83% of the $AUC_{0\text{-}48\ h}$. Two acyl glucuronides were the only metabolites detected in plasma and were minor, accounting for 8% and 5% of the $AUC_{0\text{-}48\ h}$. Iptacopan metabolites are not considered pharmacologically active.

Elimination

In a study in healthy volunteers, following a single 100 mg oral dose of [^{14}C]-iptacopan, mean total excretion of radioactivity (iptacopan and metabolites) was 71.5% in the faeces and 24.8% in the urine. Specifically, 17.9% of the dose was excreted as parent iptacopan in the urine and 16.8% in faeces. The apparent clearance (CL/F) after administration of iptacopan 200 mg twice daily at steady state is 7 960 ml/h. The half-life ($t_{½}$) of iptacopan at steady state is approximately 25 hours after administration of iptacopan 200 mg twice daily.

Linearity/non-linearity

At doses between 25 and 100 mg twice daily, the pharmacokinetics of iptacopan were overall less than dose proportional. However, oral doses of 100 mg and 200 mg were approximately dose proportional. Non-linearity was primarily attributed to the saturable binding of iptacopan to its target FB in plasma.

Drug interactions

A dedicated interaction study in which iptacopan was co-administered with other medicinal products was conducted in healthy volunteers and did not demonstrate any clinically relevant interactions.

Iptacopan as a substrate
CYP2C8 inhibitors
When iptacopan is co-administered with clopidogrel (a moderate CYP2C8 inhibitor), the iptacopan C_{max} and the AUC increased by 5% and 36%, respectively.

OATP1B1/OATP1B3 inhibitors
When iptacopan is co-administered with ciclosporin (a strong OATP 1B1/1B3 inhibitor, and a PgP and BCRP inhibitor), the iptacopan C_{max} and AUC increased by 41% and 50%, respectively.

Iptacopan as an inhibitor
PgP substrates
In the presence of iptacopan, the C_{max} of digoxin (a PgP substrate) increased by 8% while its AUC was unchanged.

OATP substrates
In the presence of iptacopan, the C_{max} and AUC of rosuvastatin (an OATP substrate) remained unchanged.

Special populations

A population pharmacokinetic (PK) analysis was conducted on data from 234 patients. Age (18 to 84 years), body weight, eGFR, race and gender did not significantly influence iptacopan PK. Studies that included Asian subjects showed that the PK of iptacopan were similar to Caucasian (white) subjects.

Renal impairment
The effect of renal impairment on the clearance of iptacopan was assessed using a population PK analysis. There were no clinically relevant differences in the clearance of iptacopan between patients with normal renal function and patients with mild (eGFR between 60 and 90 ml/min) or moderate (eGFR between 30 and 60 ml/min) renal impairment and no dose adjustment is required (see section 4.2). Patients with severe renal impairment or on dialysis have not been studied.

Hepatic impairment
Based on a study in subjects with mild (Child-Pugh A, n=8), moderate (Child-Pugh B, n=8) or severe (Child-Pugh C, n=6) hepatic impairment, a negligible effect on the total systemic exposure of iptacopan was observed compared to subjects with normal hepatic function. Unbound iptacopan C_{max} increased 1.4-, 1.7- and 2.1-fold, and unbound iptacopan AUC_{inf} increased by 1.5-, 1.6- and 3.7-fold in subjects with mild, moderate and severe hepatic impairment, respectively (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Reproductive toxicity

In oral dose animal fertility studies, iptacopan did not impact fertility in male rats up to the highest dose tested (750 mg/kg/day), which corresponds to 6-fold the MRHD based on AUC. Reversible effects on the male reproductive system (testicular tubular degeneration and hypospermatogenesis) were observed in repeated dose toxicity studies after oral administration in rats and dogs at doses >3-fold the MRHD based on AUC, with no apparent effects on sperm numbers, morphology or motility, or fertility.

In the female fertility and early embryonic developmental study in rats, iptacopan-related findings were limited to increased pre-and post-implantation losses and, consequently, decreased numbers of

live embryos only at the highest dose of 1 000 mg/kg/day orally, which corresponds to ~5-fold the MRHD based on total AUC. The dose of 300 mg/kg/day is the no-observed-adverse-effect level (NOAEL) which corresponds to ~2-fold the MRHD based on AUC.

Animal reproduction studies in rats and rabbits demonstrated that oral administration of iptacopan during organogenesis did not induce adverse embryo or foetal toxicity up to the highest doses, which correspond to 5-fold (for rats) and 8-fold (for rabbits) the MRHD of 200 mg twice daily based on AUC.

In the pre- and postnatal development study in rats, with iptacopan administered orally to females during gestation, parturition and lactation (from gestational day 6 to lactation day 21), there were no adverse effects on pregnant dams or offspring up to the highest dose tested of 1 000 mg/kg/day (estimated 5-fold the MRHD based on AUC).

Repeated dose toxicity

In the chronic toxicity study, one male dog at the highest dose level (margin to clinical exposure near 20-fold), was sacrificed 103 days after completed iptacopan administration due to irreversible non-regenerative severe anaemia associated with bone marrow fibrosis. During the treatment phase, haematology findings indicating inflammation and dyserythropoiesis were observed. No mechanism for the observed findings has been identified and a relation to treatment cannot be excluded.

Mutagenicity and carcinogenicity

Iptacopan was not genotoxic or mutagenic in a battery of *in vitro* and *in vivo* assays.

Carcinogenicity studies conducted with iptacopan in mice and rats via oral administration did not identify any carcinogenic potential. The highest doses of iptacopan studied in mice (1 000 mg/kg/day) and rats (750 mg/kg/day) were approximately 4- and 12-fold the MRHD based on AUC, respectively.

Phototoxicity

In vitro and *in vivo* phototoxicity tests were equivocal. In the *in vivo* phototoxicity study, with iptacopan at doses between 100 and 1 000 mg/kg (equivalent to 38-fold the human total C_{max} at the MRHD), some mice showed a non-dose-response pattern of transient minimal erythema, scabs and dryness and slight increase in average ear weight subsequent to irradiation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell

Gelatin
Titanium dioxide (E171)
Iron oxide ,yellow (E172)
Iron oxide ,red (E172)

Imrpinting:
Shellac
Iron oxide ,black (E172)
Propylene glycol
Ammonia solution, concentrated
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

FABHALTA is supplied in PVC/PE/PVDC blisters with aluminium foil backing.

Packs containing 56 hard capsules.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 REGISTRATION HOLDER AND IMPORTER AND ITS ADDRESS

Novartis Israel Ltd., P.O.B. 9240, Tel Aviv-Yafo , 6109102, Israel.

8 REGISTRATION NUMBER:

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