Vabysmo and Arterial Thromboembolic Events and CNS Haemorrhagic Events

This article responds to your request for information on Vabysmo® (faricimab) and the risk of ATE and CNS haemorrhagic events. This response was developed according to the principles of evidence-based medicine and contains data from Phase 3 clinical trials.

In brief

- Concerns have arisen that ATEs are a potential risk associated with IVT anti-VEGF agents.
- Following IVT administration of Vabysmo 6 mg, systemic exposure is low; therefore, systemic PD effects are unlikely, supported by the absence of significant changes in free VEGF and Ang-2 concentration in plasma upon faricimab treatment in clinical studies. The risk of the development of ATEs and non-ocular haemorrhagic events are unlikely, and the risk remains potential.
- The incidence of ATEs in the Vabysmo arms of all four Phase 3 studies was 3.7% (n=71) at week 48.
    - In the faricimab-treated safety population with nAMD, 1.1% of patients (n=7) experienced at least one adjudicated APTC-defined event.
    - In the faricimab-treated safety population with DME, 5.1% of patients (n=64) experienced at least one adjudicated APTC-defined event.
- History of ATEs, including stroke and myocardial infarction, or CNS haemorrhagic events is not a contraindication to Vabysmo treatment. In the Phase 3 pivotal studies, patients with a history of stroke, or cerebral vascular accident, or myocardial infarction were eligible for the study, provided it had been more than six months between the event and Day 1 of the study.

Abbreviations

AE = adverse event

APTC = Antiplatelet Trialists' Collaboration

ATE = arterial thromboembolic event

CNS = central nervous system

IVT = intravitreal

SAE = serious adverse event

VEGF = vascular endothelial growth factor

Background

Concerns have arisen that IVT anti-VEGF agents may be associated with a potential risk of ATEs.[1] It is well known that there is an increased risk of thromboembolic events and non-ocular haemorrhage associated with IV administration of high doses of VEGF-inhibitors used in the treatment of cancer.[2] Yet, there is currently no clear evidence of this same effect when IVT doses of VEGF-inhibitors are administered in patients with nAMD and DME.[3-5]

ATEs have been reported following IVT injection of anti-VEGF therapies.[4-9] A warning regarding the theoretical risk of ATE and CNS haemorrhagic events related to VEGF inhibition is included in certain local Vabysmo product labelling and risk management plans.[10]

Theoretical effect of VEGF inhibition on endothelial lining

VEGF plays an important role in endothelial cell health and homeostasis of the endothelial cell lining. Systemic inhibition of the VEGF pathway may disrupt vascular integrity, and promote platelet aggregation, thereby increasing the risk of ATEs.[11]

ATEs

ATEs are defined as

- non-fatal stroke
- non-fatal myocardial infarction, and
- vascular or cardiac death or death of unknown cause.[12]

Because of challenges with how ATEs may be defined and assessed, and in order to be as conservative as possible, Roche/Genentech uses the APTC definition of an ATE, which includes both thrombotic and haemorrhagic events.[12]

CNS haemorrhagic events

CNS haemorrhagic events are defined as haemorrhagic CNS vascular conditions and cerebrovascular accidents. These events are included with ATEs as a Vabysmo safety concern to account for variations in how thrombotic and haemorrhagic events may be reported.[13]

Systemic exposure of Vabysmo

As the route of administration of Vabysmo is IVT, systemic exposure to Vabysmo is extremely low compared to systemically administered VEGF inhibitors.[14] Based on population PK models, the maximum free faricimab concentrations in plasma are predicted to be approximately 600 and 6000-fold lower than in aqueous and vitreous humor, respectively.[14]

Following IVT administration of Vabysmo 6 mg, systemic exposure is low; therefore, systemic PD effects are unlikely, supported by the absence of significant changes in free VEGF and Ang-2 concentration in plasma upon faricimab treatment in clinical studies. The risk of the development of ATEs and non-ocular haemorrhagic events are unlikely, and the risk remains potential.[10]

Incidence of ATEs in Vabysmo Phase 3 studies

The incidence of ATEs in the Vabysmo arm of all four Phase 3 studies was 3.7% (n=71) at week 48. There were no notable differences between the Vabysmo-treated group and comparator groups. This incidence is consistent with incidence observed with approved IVT anti-VEGF monotherapies.[13]

TENAYA/LUCERNE - Phase 3 nAMD studies

Of the 664 faricimab-treated with patients from the Phase 3 safety population with nAMD, 1.1% of patients (n=7) experienced at least one adjudicated APTC-defined event. All seven patients had severe events, and all were considered serious.[13]

YOSEMITE/RHINE - Phase 3 DME studies

Of the 1262 faricimab-treated patients from the Phase 3 safety population with DME, 5.1% of patients (n=64) experienced at least one adjudicated APTC-defined event. Of these, 4.0% of patients (n=51) had

severe events and 1.0% of patients (n=12) had moderate events. Most of these events were considered serious.[13]

Use of Vabysmo in patients with previous ATEs or in the event of an ATE

History of ATEs, including stroke and myocardial infarction, or CNS haemorrhagic events is not a contraindication to Vabysmo treatment.[10]

Timing of Vabysmo

Roche/Genentech has no recommendations around starting Vabysmo in patients with history of previous ATEs, or continuing Vabysmo in the event of an ATE.[10] However, the timing of Vabysmo administration was accounted for during enrolment of the Phase 3 clinical studies.

Eligibility criteria in the Phase 3 pivotal studies

Patients with stroke, or cerebral vascular accident, or myocardial infarction within 6 months prior to Day 1 of Vabysmo were excluded from the Phase 3 studies. Therefore, patients who had these events >6 months prior to Day 1 were eligible to participate in the studies.[15,16]

Patients with a previous medical history of stroke have a higher risk of recurrence.[17] Therefore, this exclusion criteria was included to reduce the possibility of serious complications or death caused by stroke, thus impacting patients' ability to continue in the study.

Safety in cardiac or vascular disease subgroup of Phase 3 studies

Subgroup analyses were performed to study the effect of medical history, including risk factors for cardiac or vascular disease, on pooled safety data from the Phase 3 clinical studies.[18,19] The following safety events were evaluated

- ocular AEs
- non-ocular AEs
- SAEs, and
- ocular AEs of special interest.[18,19]

Through Year 2 of the Phase 3 DME studies (YOSEMITE/RHINE) and through Week 48 of the Phase 3 nAMD studies (TENAYA/LUCERNE), differences in the incidence of safety events, between the Vabysmo treatment arms and aflibercept Q8W arm, were consistent across cardiac and vascular diseases subgroups.[18,19] The specific risk factors evaluated for cardiac and vascular disease are listed below.

No subgroup analysis was performed in patients treated with or without anticoagulants.

Cardiac or vascular disease risk factors

Cardiac disease risk factors were defined as

- atrial fibrillation
- coronary artery disease
- systemic hypertension
- angina

- myocardial infarction
- congestive heart failure, and
- ocular history of glaucoma or neovascular glaucoma.[18,19]

Vascular disease risk factors were defined as

- transient ischemic attack
- cerebrovascular disease
- peripheral vascular disease
- cerebrovascular accidents (stroke)
- deep venous thrombosis, and
- ocular history of retinal vein occlusion.[18,19]

Recommendations from EURETINA clinical guidelines on IVT injections

According to the 2018 EURETINA clinical guidelines, no medical or ocular condition is an absolute contraindication for IVT injections, but they may affect the choice of drug or the timing of the procedure in some patients.[20] Although no guidelines on the safety of anti-VEGF agents have been established, the organisation issued several recommendations for treating ophthalmologists:

- Be aware of the potential cardiovascular and cerebrovascular risks associated with anti-VEGF agents.
- Exercise caution when anti-VEGF IVT injections is considered in patients with preexisting cardiovascular or cerebrovascular conditions, especially if recent or unstable at the time of the planned IVT injection.
- Consult with additional relevant physicians prior to the administration.
- Consider that anti-VEGF IVT injection is not a medical emergency and can be deferred for a few days to allow for multidisciplinary consultation to reduce the risk of any systemic complications.

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