# *Safety of Silicone Oil in the Preparation and Intravitreal Administration of Vabysmo*

This letter responds to your request for information on the presence and impact of silicone oil in the preparation, administration and use of Vabysmo® (faricimab-svoa) intravitreal injection. This response was developed according to the principles of evidence-based medicine and contains data from Phase 3 clinical trials.

## In brief

- Roche/Genentech recommends the use of the co-packaged transfer filter needle when preparing Vabysmo IVT injection.
- The potential risk of injected silicone oil following the preparation and administration of Vabysmo is most likely from two sources:
    - Syringe — Vabysmo drug product can come in direct contact with the silicone oil on the internal surface of the syringe barrel, and plunger movement disrupts the silicone layer.
    - Injection needle — Silicone oil on the external surface of the cannula gets in direct contact with the eye upon injection.
- Roche/Genentech do not have a recommendation related to the silicone oil content of the syringe or the injection needle used for intravitreal injections of Vabysmo. Please contact the respective manufacturers if you have questions related to their product.
- There have been no changes in the specifications of syringes and needles used for the preparation and intravitreal administration of Vabysmo from the beginning of clinical development through the duration of the clinical trials, to the current commercial configuration.
- Roche/Genentech established a cross-functional task force to assess the potential impact of BD syringes and needles on Vabysmo intravitreal injections in the clinical studies.
    - A preliminary assessment of data from the four, ongoing Vabysmo Phase 3 clinical studies (TENAYA/LUCERNE and YOSEMITE/RHINE) found slightly higher rates of vitreous floaters and endophthalmitis with Vabysmo compared with aflibercept (the active comparator arm in these studies); however, overall rates in both arms were low and the difference was not statistically significant.
- Review of data through Year 2 shows that the risk of vitreous floaters and endophthalmitis associated with Vabysmo remained comparable with aflibercept.

## Abbreviations

BD=Becton Dickinson
DME=diabetic macular edema
IVT=intravitreal
nAMD=neovascular age-related macular degeneration

## Recommendation for preparation of Vabysmo administration

Roche/Genentech recommends the use of the co-packaged transfer filter needle when preparing Vabysmo IVT injection.

Syringes and injection needles are not included in the Vabysmo kit. Please refer to your local Vabysmo instructions for use for more details on the specifications of syringes and needles used for the preparation and intravitreal administration of Vabysmo.

Roche/Genentech do not have a recommendation related to the silicone oil content of the syringe or the injection needle used for intravitreal injections of Vabysmo.[1] Please contact the respective manufacturers if you have questions related to their product.

## Background

The presence of silicone oil droplets has been observed in the vitreous of patients who have received IVT injections.[2] Currently, the majority of commercially available syringes and injection needles are not developed or approved specifically for ophthalmic use.[3] While not validated for intravitreal injections, siliconized syringes and needles have been used for this purpose for more than 20 years.[3]

### Purpose of silicone oil in syringe systems

Silicone oil is commonly applied as a lubricant in plastic and glass syringe and stainless steel needle manufacturing.[4,5] The inner surface of the syringe barrel is coated with silicone oil to ensure easy movement of plunger rods through the barrel.[4] Silicone oil is applied to the outer surface of needle cannula to reduce frictional drag when puncturing the vial stopper and minimize patient discomfort when injecting into the tissue.[5,6]

## Potential sources of silicone oil in Vabysmo IVT injection

The potential risk of injected silicone oil following the preparation and administration of Vabysmo is most likely from two sources:

**Syringe** — Vabysmo drug product can come in direct contact with the silicone oil on the internal surface of the syringe barrel, and plunger movement disrupts the silicone layer.[7]

**Injection needle** — Silicone oil on the external surface of the cannula gets in direct contact with the eye upon injection.[7]

## Limited or negligible sources of silicone oil in Vabysmo injection

### Vabysmo vial

The Vabysmo vial may contain trace amounts of silicone oil, as it is used in the manufacturing of the vial septum, excluding surfaces in contact with drug. The amount of silicone oil in the vial is considered negligible compared with amounts found in the injection syringe.[7]

### Co-packaged transfer filter needle

The co-packaged transfer filter needle has silicone oil on the outer surface of the cannula. However, the transfer filter needle is considered to be less impactful as a potential source of silicone oil because when the needle is inserted into the vial septum, silicone oil is partially wiped from the cannula. However, some silicone oil can remain and be in contact with the drug product for a short time.[7]

## Syringe and needle specifications

There have been no changes in the specifications of syringes and needles used for the preparation and intravitreal administration of Vabysmo. These have remained unchanged from the beginning of clinical development through the duration of the clinical trials, to the current commercial configuration.

## Clinical safety assessment

### Background

On January 8, 2021, in the course of the TENAYA/LUCERNE and YOSEMITE/RHINE Phase 3 clinical studies, a field safety notice sent by Becton Dickinson (BD) advised of an added caution associated with several BD syringes and needles when used for intraocular injections.[8] It advised of the potential risk for 'floaters' in patients' eyes, which is believed to be due to silicone. Separately, it also advised on the risk of endophthalmitis, which may be associated with previously unidentified failure modes.[8]

This led to Roche/Genentech's immediate engagement with BD and the establishment of a Roche/Genentech cross-functional task force to assess the impact on affected products in the ongoing Vabysmo clinical studies and the planned commercial setting. The affected products are listed in the Appendix. [7]

### Preliminary assessment of Phase 3 clinical study safety data

Roche conducted a preliminary assessment of data on vitreous floaters and endophthalmitis from the four, ongoing Vabysmo Phase 3 clinical studies (TENAYA/LUCERNE and YOSEMITE/RHINE).[7]

#### *Safety results*

The preliminary assessment found slightly higher rates of vitreous floaters and endophthalmitis with Vabysmo compared with aflibercept (the active comparator arm in these studies), however overall rates in both arms were low and the difference was not statistically significant (Table 1). The vast majority of vitreous floater events were mild and no patients required vitrectomy.[7]

### Table 1. Preliminary review of incidence of vitreous floaters and endophthalmitis in TENAYA/LUCERNE and YOSEMITE/RHINE

| | nAMD (N=1326) | | DME (N=1887) | |
|---|---|---|---|---|
| % | Faricimab (n=664) | Aflibercept (n=662) | Faricimab (n=1,264) | Aflibercept (n=623) |
| Vitreous floaters | 3.0 | 1.7 | 3.4 | 1.6 |
| Endophthalmitis | 0.0 | 0.2 | 0.3 | 0.2 |

#### *Vabysmo benefit-risk profile assessment based on safety results*

The benefit-risk assessment took into consideration all risks associated with the medicinal product, including the excipients and medical devices used for their preparation and administration. Based on the preliminary assessment of safety data, the benefit-risk profile of Vabysmo remained unchanged.[7]

### Incidence of safety events through Year 2

At Year 2, of the 3,213 patients in the safety population of the four Phase 3 clinical studies, 1,926 patients were treated with Vabysmo (n=664 in nAMD; n=1,262 in DME), and 1,287 were treated with aflibercept (n=662 in nAMD; n=625 in DME). Review of data through Year 2 shows that the risk of vitreous floaters and endophthalmitis associated with Vabysmo remained comparable with aflibercept.

### Table 2. Incidence of vitreous floaters and endophthalmitis in TENAYA/LUCERNE and YOSEMITE/RHINE through Year 2

| | nAMD (N=1326) | | DME (N=1887) | |
|---|---|---|---|---|
| % | Faricimab (n=664) | Aflibercept (n=662) | Faricimab (n=1,262) | Aflibercept (n=625) |
| Vitreous floaters | 4.5 | 2.6 | 3.9 | 2.9 |
| Endophthalmitis | 0.5 | 0.3 | 0.5 | 0.2 |

## Technical assessment

Roche conducted technical assessments of BD syringes, transfer filter needles and injection needles as part of several in-use compatibility studies.

### *Technical results*

No trend of increased subvisible or visible particle levels (e.g. by silicone oil droplets) were observed after simulated administration, including contact and hold time in BD syringes, as well as contact with the co-packaged transfer filter needle and injection needle.[7]

## References


1. Roche Internal Technical Report (Accessed July 10, 2023).

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3. Melo G, Cruz N, Emerson G, et al. Critical analysis of techniques and materials used in devices, syringes, and needles used for intravitreal injections. Prog Retin Eye Res 2021;80:100862. https://www.ncbi.nlm.nih.gov/pubmed/32311476

4. Sacha G, Saffell-Clemmer W, Abram K, et al. Practical fundamentals of glass, rubber, and plastic sterile packaging systems. Pharm Dev Technol 1970;15:6-34. https://www.ncbi.nlm.nih.gov/pubmed/20088708

5. Smith E, Henley M, Adams E, et al. Siliconization of Parenteral Drug Packaging Components (Technical Report No. 12). Journal of Parenteral Science and Technology 1988;42:S1-S13. https://s3-us-west-1.amazonaws.com/ptab-filings/IPR2016-00254/1004

6. Melo G, Emerson G, Lima FA, et al. Needles as a source of silicone oil during intravitreal injection. Eye (Lond) 2019;33:1025-1027. https://www.ncbi.nlm.nih.gov/pubmed/30760899

7. Roche Internal Communication (Accessed July 10, 2023).

8. Field safety notice - MPS-18-1209: BD Syringes and Needles. January 8, 2021. Available at https://ufs.admin.cam.ac.uk/files/mps-18-1209_-_intraocular_fsn_fisher.pdf. Accessed on February 16, 2023.

## Appendix

### Appendix 1. Affected products in the Vabysmo clinical trials and commercial setting[7,8]

| Setting | BD affected products (part #) |
|---|---|
| Phase 3 clinical studies | BD 1ml Syringe Luer-LokTM Tip (309628)<br><br>BD Blunt Fill Needle with Filter 18G x 1 1/2 (5µm) (305211) |
| Commercial: co-packaged kit containing vial with transfer filter needle | BD Blunt Fill Needle with Filter 18G x 1 1/2 (5µm) (305211) |