sysmex | Lighting the way with diagnostics

SYSMEX EDUCATIONAL ENHANCEMENT AND DEVELOPMENT | June 2021

SEED Haemostasis

Emicizumab

Introducing haemophilia

Haemophilia is a bleeding disorder that results in people bleeding for a longer time after an injury, easy bruising, and an increased risk of bleeding inside joints or the brain. In severe cases, bleeding can occur spontaneously. The most common types of haemophilia are

- Haemophilia A (HA) – a deficiency in coagulation factor VIII (FVIII)
- Haemophilia B (HB) – a deficiency in coagulation factor IX (FIX)
- Haemophilia C (HC) – a deficiency in coagulation factor XI (FXI)

As haemophilia A and B are both X-linked recessive disorders, females are rarely severely affected. However, females can show increased bleeding tendency under certain conditions. For haemophilia C are both; male and females are affected equally. [1–4] Haemophilia is classified based on the frequency and severity of bleeding events as well as the factor activity into three classes: severe, moderate and mild haemophilia. [5] Unfortunately, in most cases, the condition is severe.

Prevention and management of bleeding episodes as well as preventing joint bleeds is of utmost importance to maintain joint health in haemophilia patients. The Joint Outcome Study, a randomised clinical trial, showed that prophylactic administration of factor concentrates prevented joint damage and reduced bleeding episodes in adolescent males with severe haemophilia A. [6] In recent decades, treatment of haemophilia has significantly improved. Transitioning from plasma-derived treatment and therapy, recombinant factor concentrates free of infection risk were introduced, enabling much more efficient production and improved product half-life. Recently introduced extended half-life factor concentrates provide 1.5 times the half-life in FVIII or 4–5 times in FIX compared to conventional products. This results in far fewer intravenous injections required for patients contributing to reduced visits for the patient to the treatment centre. The treatment of haemophilia patients is based on number and recurrence of bleeding events in moderate and mild cases. On-demand treatment might be appropriate in such cases, because their bleeding tendency is not significantly elevated. However, constant prophylactic therapy might become necessary if significant bleeding episodes return. Even if improved factor concentrates widely became available, challenges for the treatment of haemophilia remain, such as frequent intravenous injections, although at less frequency than before. Additionally, widely available factor concentrates contributes to the decrease in efficacy of treatment due to inhibitor development. The development of high-titre inhibitory antibodies (inhibitors) against FVIII remains a challenge in the management of patients with haemophilia A (HA). Patients with high-titre inhibitors are more likely to experience uncontrolled bleeding, physical disability from chronic arthropathy and premature death compared with those without this complication. Immune tolerance induction (ITI), utilizing repeated infusions of FVIII, is an effective therapeutic approach to eliminating inhibitory antibodies.

Table 1 *Haemophilia classification [5]*

Classification	Factor activity	Bleeding tendency
Severe	< 1% of norm (< 0.01 IU/mL)	Spontaneous bleeding in joints, muscles or gastrointestinal tract
Moderate	≥ 1 to 5% of norm (≥ 0.01 to 0.05 IU/mL)	Rare spontaneous bleeding in joints, mostly bleedings after trauma
Mild	≥ 5 to 40% of norm (≥ 0.05 to 0.40 IU/mL)	Bleedings after injury or surgery, rare bleeding tendency in daily routine

Introducing Emicizumab

Emicizumab (Hemlibra®, Roche Pharma AG) is a humanised, modified, monoclonal immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure. Emicizumab substitutes part of the cofactor function of activated factor VIII (FVIIIa) by bridging activated factor IX (FIXa) and factor X (FX) to restore effective haemostasis in HA individuals. It is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children of all ages (neonates and older), with and without FVIII inhibitors. The drug has no structural relationship or sequence homology to FVIII, so functions even when inhibitors are present in blood and does not trigger or enhance the development of direct FVIII inhibitors. [7, 8]

Emicizumab prophylaxis improves haemostasis but does not completely correct it. The treatment regimen ensures that a steady state is achieved, eliminating the need for drug monitoring for dose adjustment in general. The drug half-life is of approximately 30 days and stable mean plasma concentrations of 40 µg/mL is archived after four weeks treatment. [7, 9, 10]

These pharmacological properties therefore allow sufficient long-term protection against spontaneous and traumatic bleeding events even with administration of 6 mg / kg Emicizumab once a month. [10] In contrast, FVIII has a half-life of only about 12 hours depending on individual patient factors thus require injections several times a week. [12]

A long half-life allows Emicizumab to remain in the patient's blood circulation for many months after discontinuation of therapy. This can affect the results of relevant haemostasis assays for up to six months. [7, 13]

Influence of Emicizumab on haemostasis assays

Emicizumab does not need to be activated by thrombin to be effective in clot formation whereas FVIII does. This lead to a significant reduction in the coagulation time in activated partial thromboplastin time (APTT)-based assays even at subtherapeutic Emicizumab levels, regardless of which APTT reagent is used. [7, 14, 15]

Clotting times of APTT assay are reduced to the normal range or below and may erroneously lead to the assumption that normal thrombin generation occurs during therapy. However, this is incorrect, since the thrombin generation potential at stable mean plasma concentrations corresponds more closely to that of a patient with a mild HA. [12, 16]

Because of the interference of Emicizumab with APTT-based assays, one-stage APTT-based FVIII assays (FVIII OSA) are also interfered with and have shown to produce results of > 150% of norm (> 1.5 IU/mL) in samples from patients on Emicizumab therapy. [7, 17] Therefore, FVIII OSA assay should not be carried out in patients on Emicizumab therapy as there is no correlation between this Emicizumab induced coagulation activity and the patients' haemostatic status. [16] Furthermore, there is evidence suggesting that the degree of FVIII overestimation in patients receiving Emicizumab varies with different APTT reagents. [18]

Additionally, because of the sensitivity of APTT to Emicizumab, there is a risk that the factor IX (FIX), factor XI (FXI), and factor XII (FXII) results measured by one-stage APTT-based assays may also overestimated. [12] Consequently, when treating patients with Emicizumab, APTT-based factor assays and Bethesda tests, inhibitor titre testing which is also based on OSA, should be avoided. APTT-based activated protein C resistance (APC-R) and APTT-based protein S assays should also not be used for determination in patients on Emicizumab therapy. [19]

Emicizumab is unaffected by the presence of FVIII inhibitors and maintains its full activity even during pre-analytical heat treatment. Therefore, the FVIII OSA-based Nijmegen-Bethesda Assay (NBA) may also give false negative results when Emicizumab is present. [20]

Non-APTT-based assays such as thrombin time, fibrinogen assays and tests of the extrinsic coagulation factors are not influenced by Emicizumab. [19] Prothrombin time (PT) and associated extrinsic pathway factor assays are generally unaffected by the presence of Emicizumab. However, this may vary depending on the reagent and a reliable validation of the reagent used in patients under Emicizumab therapy should be performed. [19]

Chromogenic assays, including antithrombin activity, anti-Xa assays and protein C activity, are unaffected by the presence of Emicizumab and should be used to in Emicizumab-treated HA patients e.g. requiring heparin therapy. [19, 21] Merely FVIII-chromogenic assays with human factor IXa (hFIXa) and human factor X (hFX) are sensitive to and detects Emicizumab in the patient's plasma parallel to the FVIII activity.

Global coagulation assays like rotational thromboelastometry (ROTEM) and thrombin generation assays (TGA) are considered to accurately measure coagulation in the presence of Emicizumab. [22]

Measuring Emicizumab

Emicizumab does not require routine monitoring unless unexpected bleeding occurs and subsequent treatment with coagulation factors is needed or prior surgery or for monitoring of inhibitors. [11, 23, 24]

There are currently two different approaches to determining the amount of Emicizumab present. The first approach is to determine the factor VIII equivalent activity (FVIII:C-like), the second to determine the concentration of Emicizumab in the plasma.

Chromogenic FVIII assays consisting hFIXa and hFX (FVIII CSAh) are sensitive to Emicizumab and might be used to detect the presence accordingly as the results increasing in a dose dependent manner. However, these assays not only measure Emicizumab but also any FVIII may be present in the sample (remaining or infused). Therefore and because of the biological differences between Emicizumab and human or recombinant FVIII, the measured results are neither Emicizumab concentrations nor FVIII activity. They are so-called FVIII equivalent (FVIII-like). The FVIII-like activity and the Emicizumab concentration in the patient sample show a linear correlation to one another. However, the FVIII-like activity is not directly equivalent to the Emicizumab concentration and a direct comparison of the two values in the clinical setting is therefore difficult. Reasons for that are the sensitivity to residual or infused FVIII as well as differences in the hFIXa concentration of the reagent between different lot numbers. All this is leading to current recommendation to use FVIII CSAh to indicate the presence of Emicizumab. Local validation should be performed before the use of this assay in patients receiving Emicizumab. [16, 21, 25, 26]

Another approach to determine the Emicizumab in patient plasma is to use a FVIII OSA with a higher sample dilution of 1:80. This so-call modified one-stage APTT-based FVIIII assay (FVIII mOSA) is calibrated against a Emicizumab specific calibrator and can reveal the Emicizumab concentration in patient sample. This method is considered as most robust and accurate method and recommended by certain expert groups. [16, 25, 27–29] However, like FVIII CSAh, also FVIII mOSA recognises residual or infused FVIII in the sample and the concentration of Emicizumab might be overestimated in its presence. Therefore, this assay should not be used in patients receiving concurrent treatment with infused FVIII and Emicizumab. [16] In addition, an increased dilution of the patient sample poses a certain risk of a matrix effect and the responsiveness of the FVIII mOSA is also dependent on the reagent used. Accordingly, verification of the assay method with reagents in local use must be performed by the testing laboratory.

TGA and ROTEM appear to be sensitive to Emicizumab and may be used to assess the global haemostatic status as well as for TGA to monitor the effects of bypassing agents in haemophilia patients receiving Emicizumab. [28, 30, 31]

Measurement of FVIII activity in the presence of Emicizumab

Chromogenic FVIII assays based on bovine factors (FVIII CSAb) are not affected by the presence of Emicizumab, as Emicizumab binds to hFIXa and hFX only. Therefore, this test measures only the residual or infused FVIII and can be used in patients receiving clinically necessary parallel treatment with Emicizumab and infused FVIII. [16, 21, 25, 28]

FVIII chromogenic assays incorporating hFIXa and bovine FX (bFX) have been described as able to accurately measure infused FVIII in the presence of Emicizumab. [32, 33] But there might be a potential risk that the FVIII level obtained may be artificially raised using this reagent due to interaction of Emicizumab with the human FIXa of the kit and patient FX. Consequently, verification of this assays as suitable for measuring FVIII in the presence of Emicizumab is recommended. [21]

An alternative to FVIII CSAb is to use FVIII OSA after spiking the patient sample with monoclonal anti-idiotype Emicizumab antibodies (mAbs; rcAQ8, a mAb that binds to the anti-FIXa arm of Emicizumab, and rcAJ540, an anti-FX arm mAb). These antibodies almost completely neutralize the binding potential of Emicizumab for human FIXa and FX, so that only the residual or infused FVIII remains present in the plasma. [35, 36]

Measurement of FVIII Inhibitors in the presence of Emicizumab

Under certain clinical conditions, an evidence-based decision is necessary as to whether therapy with Emicizumab must continue in patients with FVIII inhibitor or whether therapy with infused FVIII can be initiated. For example, patients undergoing surgery may have to administrate factor VIII concentrate in addition to Emicizumab since haemostasis potential of Emicizumab is not enough to achieve haemostasis during operation. The FVIII inhibitor is potentially neutralised by infused FVIII and treatment with FVIII may be considered in patients with low inhibitor titre (≤ 5 BU/mL). Conventional Nijmegen-Bethesda methods based on an FVIII OSA in the various dilutions with pooled normal plasma may provide incorrect results. Accordingly, the use of FVIII OSA is not recommended and should be replaced by FVIII CSAb to determine the inhibitor titre by the Nijmegen-Bethesda method. [16] In theory, an FVIII CSA with hFIXa and bFX can also be used. However, it is recommended to validate such reagent as suitable for the measurement of FVIII inhibitors in the presence of Emicizumab. [21]

Measurement of Anti-Emicizumab antibodies

Anti-drug antibodies (ADA) are not uncommon in clinical practise. ADAs can be either neutralizing or non-neutralizing and affect the effectiveness, safety and pharmacokinetics of the drug admin-

istered. Neutralising ADAs have been reported for Emicizumab, but the immunogenicity is expected to be lower than that of FVIII products. [13]

Unless the laboratory has a commercial assay to directly identify ADA against Emicizumab, functional tests can provide an indication of its presence. Neutralising ADAs have been shown to negate the shortening effect of Emicizumab on APTT and thus imply the presence of inhibitory ADAs in the patient's sample. However, low titre neutralizing ADA may not be detected by APTT. [37] In addition, the APTT normalises even with sub-therapeutic Emicizumab concentrations and should therefore be used to rule out ADA only. Due to the very high dilution of the patient's plasma, FVIII mOSA calibrated with Emicizumab are better suited for the detection of ADA-related Emicizumab reductions in the patient sample and should therefore be preferred to the usual APTT. [16, 21, 22]

Overview of haemostasis assays in context with Emicizumab

The table below provides an overview about the impact of Emicizumab to basic haemostasis assays. Following points should be considered prior reading:

- The sensitivities of the assay to Emicizumab might be reagent dependent (e.g. source of activator used in APTT reagents etc.). Verification of the assay method with reagents in local use is advised to be performed by the testing laboratory.
- The table below summarizes the current methods, it's uses and proposed alternatives to the best of our knowledge and belief. However, the reader is requested to confirm this information is up-to-date and in accordance with local guidelines.

Table 2 *Overview of haemostasis assays in context with Emicizumab [7, 19]*

Assay	Effect on results	Use in Emicizumab patients	Alternatives in Emicizumab patients
APTT	↓↓	Rule out ADA	–
One-stage APTT-based FVIII assay (FVIII OSA)	↑↑	Measure Emicizumab concentration[1,2] Measure Emicizumab concentration in patients with suspected ADA[1,2]	FVIII chromogenic assay, bovine origin to measure FVIII
One-stage APTT-based FIX assay (FIX OSA)	↑↑	Determine FIX activity after adding mAbs	Factor IX chromogenic assay
One-stage APTT-based FXI assay (FXI OSA)	↑↑	Determine FXI activity after adding mAbs	–
One-stage APTT-based FXII assay (FXII OSA)	↑↑	Determine FXII activity after adding mAbs	–
APTT-based Nijmegen Bethesda assays	↓↓	Not usable	FVIII chromogenic assay, bovine origin with Nijmegen Bethesda modification
Activated clotting time (ACT)	↓↓	Rule out ADA	–
FVIII chromogenic assay, bovine origin	–	Measure residual or infused FVIII Measure FVIII inhibitor titres	FVIII chromogenic assay, with hFIXa and bFX origin[3]
FVIII chromogenic assay, human origin	↑	Measure of FVIII-like activity Measure Emicizumab concentration[2]	FVIII OSA to measure Emicizumab concentration[1,2]
Immuno-based FVIII assays	–	Measure FVIII levels	FVIII chromogenic assay, bovine origin
Fibrinogen (Clauss)	–	No restrictions	–
Thrombin Time	–	No restrictions	–
Factor IX chromogenic assay	–	Measure FIX activity	FIX OSA after adding mAbs
Protein C (clotting) assay	↓↓	Measure protein C activity after adding mAbs	Protein C chromogenic assay
Protein C chromogenic assay	–	Measure protein C activity	–
Protein S (clotting) assay	↓	Measure protein S activity after adding mAbs	Free Protein S assay
Free-Protein S antigen assay	–	Measure free protein S	–
DVRRT assays	–	No restrictions	–
Prothrombin Time	–	No restrictions[3]	–
One-stage PT-based factor assays (FII, FV, FVII, FX)	–	No restrictions[3]	–
FXIII chromogenic assays	–	No restrictions	–
Anti-Xa activity assays	–	Measure heparin levels	–
Antithrombin assays	–	No restrictions	–
Plasminogen activity and antigen assays	–	No restrictions	–
D-Dimer assay	–	No restrictions	–
vWF activity and antigen assays	–	No restrictions	–

↑↑ Severe overestimation
↑ Overestimation
– Not influenced
↓ Underestimation
↓↓ Severe underestimation

[1] Using a modified version of the assay
[2] Using a dedicated Emicizumab calibrator
[3] Validation of the assay/reagent is recommended

References

[1] **CDC – Centers for Disease Control and Prevention.** *What is Hemophilia? Issued on 27. August 2016, last reviewed 6. September 2018.*

[2] **U.S. National Library of Medicine.** *Hemophilia. Issued 4. October 2016.*

[3] **Bolton-Maggs PH, Pasi KJ.** *Haemophilias A and B. Lancet. 2003 May 24;361(9371): 1801–9. Review.*

[4] **Bolton-Maggs PH et al.:** *Hemophilia C. Medscape. 1. March 2019.*

[5] **White GC, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J.:** *Definitions in Hemophilia. Recommendations of the Scientific Subcommittee on FVIII and Factor IX of the SSC of ISTH. Thromb Haemost 2001 Mar; 85(3): 560.*

[6] **Manco-Johnson MJ et al.:** *Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia. N Engl J Med 2007; 357: 535–44.*

[7] **Hemlibra®** *– Product Information. Annex 1 – SUMMARY OF PRODUCT CHARACTERISTICS. European Medicines Agency. EMA/162298/2019. First published: 01.03.2018. Last updated: 05.06.2019.*

[8] **Hemophilia.org,** *MASAC Recommendation on the Use and Management of Emicizumab-kxwh (Hemlibra®) for Hemophilia A with and without Inhibitors. December 7, 2018.*

[9] **Kitazawa T, Esaki K, Tachibana T et al.:** *Factor VIIIa-mimetic cofactor activity of a bispecific antibody to factors IX/IXa and X/Xa, Emicizumab, depends on its ability to bridge the antigens. Thromb Haemost 2017; 117(07): 1348–1357.*

[10] **Uchida N, Sambe T, Yoneyama K et al.:** *A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects. Blood 2016; 127(13): 1633–1641.*

[11] **Pipe S, Shima M, Lehle M et al.:** *A multicentre, open-label, phase 3 study to evaluate the efficacy, safety, and pharmacokinetics of Emicizumab prophylaxis administered every 4 weeks in persons with haemophilia A. Lancet Haematol 2019 Jun; 6(6):e295–e305.*

[12] **van Dijk K, van der Bom JG, Lenting PJ et al.:** *Factor VIII half-life and clinical phenotype of severe hemophilia A. Haematologica 2005; 90(04):494–498.*

[13] **Paz-Priel I, Chang T, Asikanius E et al.:** *Immunogenicity of Emicizumab in people with hemophilia A (PwHA): results from the HAVEN 1–4 studies. Blood. 2018; 132:633.*

[14] **Shima M, Hanabusa H, Taki M et al.:** *Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. N Engl J Med 2016; 374(21): 2044–2053.*

[15] **Bowyer A, Kitchen S, Maclean R.:** *Effects of Emicizumab on APTT, one-stage and chromogenic assays of factor VIII in artificially spiked plasma and in samples from haemophilia A patients with inhibitors. Haemophilia. 2020; 26(3): 536–542.*

[16] **Nougier C, Jeanpierre E, Ternisien C et al.:** *Emicizumab treatment: Impact on coagulation tests and biological monitoring of haemostasis according to clinical situations (BIMHO group proposals). Eur J Haematol. 2020; 105:675–681.*

[17] **Al-Samkari H, Croteau SE.** *Shifting landscape of hemophilia therapy: implications for current clinical laboratory coagulation assays. Am J Hematol 2018; 93: 1082–1090.*

[18] **Bowyer AE, Kitchen S, Maclean RM.** *Effects of Emicizumab on APTT, one-stage and chromogenic assays of factor VIII in artificially spiked plasma and in samples from haemophilia A patients with inhibitors. Haemophilia 2020 May; 26(3): 536–542.*

[19] **Adamkewicz JI, Chen DC, Paz-Priel I.** *Effects and interferences of Emicizumab, a humanised bispecific antibody mimicking activated factor VIII cofactor function, on coagulation assays. Thromb Haemost. 2019; 119(7): 1084–1093.*

[20] **Miller CH.** *Laboratory testing for factor VIII and IX inhibitors in haemophilia: a review. Haemophilia 2018; 24(02): 186–197.*

[21] **Jenkins PV, Bowyer AE, Burgess C et al.:** *Laboratory coagulation tests and Emicizumab treatment A United Kingdom Haemophilia Centre Doctors' Organisation guideline. Haemophilia. 2019; 26(1): 151-155.*

[22] **Mueller J et al.:** *Laboratory Monitoring in Emicizumab-Treated Persons with Hemophilia A. Thromb Haemost. 2019; 119: 1384–1393.*

[23] **Mahlangu J, Oldenburg J, Paz-Priel I et al.:** *Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med 2018; 379(09): 811–822.*

[24] **Oldenburg J, Mahlangu JN, Kim B et al.:** *Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med 2017; 377 (09): 809–818.*

[25] **Calatzis A, Chen DC, Paz-Priel I et al.:** *Effects and interferences of Emicizumab – a humanised bispecific antibody mimicking activated factor VIII cofactor function – on coagulation assays. 62nd Annual Meeting of the Gesellschaft für Thrombose- und Hämostaseforschung (GTH) February 20–23, 2018; Vienna, Austria.*

[26] **Ferrière S, Lenting PJ.** *Antibodies in the treatment of haemophilia A-a biochemical perspective. Hamostaseologie 2019; 39(01): 36–41.*

[27] **Calhoon W, McInerney M, Calatzis A et al.:** *Evaluation of a dedicated calibrator and controls for Emicizumab quantification. 4th Scientific Meeting of the Thrombosis and Hemostasis Societies of North America (THSNA) April 22–25, 2018; Chicago, IL.*

[28] **Escuriola-Ettingshausen C, Auerswald G, Königs C et al.:** *Optimizing the management of patients with haemophilia A and inhibitors in the era of Emicizumab: Recommendations from a German expert panel. Haemophilia. 2020; 00: 1–9.*

[29] **Shinohara S, Saito T, Noguchi-Sasaki M, Ishiwata T, Morris M.** *Evaluation of Emicizumab calibrator and controls with a modified one-stage FVIII assay on an automated coagulation analyzer. Res Pract Thromb Haemost. 2019, 3:203 (abstract).*

[30] **Ogiwara K et al.:** *A modified thrombin generation analysis to measure the plasma coagulation potency in the presence of anti-FIXa/FX bispecific antibody, Emicizumab. Blood. 2018; 132: 1200.*

[31] **Yada K, Nogami K, Ogiwara K et al.:** *Global coagulation function assessed by rotational thromboelastometry predicts coagulation-steady state in individual hemophilia A patients receiving Emicizumab prophylaxis. Int J Hematol. 2019; 110 (4): 419–430.*

[32] **Haran C, Byrne M, Doyle M et al.:** *Measurement of factor VIII replacement therapy for patients with haemophilia A on Emicizumab. Prophylaxis (PB1490). Res Pract Thromb Haemost. 2019; 3(S1): 467–468.*

[33] **Unterberger M, Wagner L, Binder NB.** *PB1299 – Use of Chromogenic Factor VIII Activity Determination in Haemophilia A Plasma of Patients under Emicizumab Treatment. Res Pract Thromb Haemost. 2019; 3: 1–891.*

[34] ***Nogami K, Soeda T, Matsumoto T, Kawabe Y, Kitazawa T, Shima M.*** *Routine measurements of factor VIII activity and inhibitor titer in the presence of Emicizumab utilizing anti-idiotype monoclonal antibodies. J Thromb Haemost 2018; 16(07): 1383–1390.*

[35] ***Ogiwara K et al.:*** *PB 0729 – Anti-Idiotype Monoclonal Antibodies to Emicizumab Enable Measurements of aPTT-Based Coagulation/ Anticoagulation Assays in the Presence of Emicizumab. Res Pract Thromb Haemost. 2019; 3(Suppl. 1): 1–891.*

[36] ***Novembrino C, Boscolo-Anzoletti M, Rossi F, Mancuso E, Shinohara S, Peyvandi F.*** *Evaluation of the Effect Emicizumab Neutralizing Antibodies on aPTT Clotting-based Tests Results in Patients Treated with Emicizumab. Res Pract Thromb Haemost. 2020; 4(Suppl 1).*

[37] ***Valsecchi C, Gobbi M, Beeg M et al.:*** *Characterization of the neutralizing anti-Emicizumab antibody in a patient with hemophilia A and inhibitor. J Thromb Haemost. 2021; 00: 1-8. Online Version of Record before inclusion in an issue.*