

## Factor VIII replacement is still the standard of care in haemophilia A

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### Abstract

Prophylactic factor VIII (FVIII) has dramatically improved haemophilia A treatment, preventing joint bleeding and halting the deterioration of joint status. FVIII products with an extended plasma half-life further improve patients' quality of life and increase therapeutic adherence. New licensed classes of non-replacement products include prophylactic emicizumab, which is administered subcutaneously up to every 4 weeks. However, this drug is not suitable for acute bleeding episodes or management of major surgery, and long-term data on the impact of emicizumab on joint health, FVIII inhibitor development and thrombotic risk are awaited. Prophylaxis with FVIII replacement remains the standard of care in haemophilia A, with the aim of achieving a level of haemostasis control that allows patients to meet their lifestyle goals.

**Keywords:** factor VIII, haemophilia A, prophylaxis, standard of care, half-life.

### Introduction

The availability of factor replacement products has dramatically improved care for people with haemophilia. Where these treatments are accessible and affordable, individuals have a life expectancy similar to that of males in the general population<sup>1</sup>. Replacement of factor VIII (FVIII) in haemophilia A has been used for decades to control bleeding, including during and after surgery, and for immune tolerance induction (ITI) in patients who develop alloantibodies that neutralise FVIII coagulant activity (inhibitors). The development of inhibitors is the most serious and expensive treatment-related complication<sup>2</sup>, affecting at least one-third of individuals with severe haemophilia A<sup>3</sup>. Bypassing agents, such as activated prothrombin complex concentrates (aPCCs) and recombinant activated factor VII (rFVIIa), are generally used to treat acute bleeding in individuals with inhibitors<sup>4</sup>; however, some evidence supports the use of prophylaxis with bypassing agents in these patients<sup>4</sup>. ITI with FVIII is currently the only proven method to eradicate FVIII inhibitors, and is successful in approximately 70% of individuals with haemophilia A<sup>5-8</sup>.

Randomised clinical trials and real-world evidence have demonstrated that prophylaxis prevents joint bleeding and deterioration of joint status<sup>9,10</sup>, and primary prophylaxis with FVIII has, therefore, been recognised as the standard of care for individuals with severe haemophilia A in countries with adequate resources<sup>11</sup>. The landmark Joint Outcomes Study by Manco-Johnson *et al.* provided evidence of an approximately 6-fold reduction in the risk of joint damage in children with severe haemophilia A assigned to prophylaxis compared with those randomly assigned to on-demand treatment<sup>10</sup>. Prophylactic therapy also reduces the incidence of central nervous system bleeds (intracranial and spinal haematoma), which are less common than joint bleeding but much more life-threatening<sup>12,13</sup>. Additional advantages of prophylaxis vs on-demand treatment include reduced hospitalisations and absenteeism from school or work, greater participation in social activities and, on the whole, an improved health-related quality of life<sup>14-16</sup>.

Currently, targeted trough plasma levels of approximately 1-2% FVIII activity are advisable and achievable in the context of prophylaxis programmes in order to prevent breakthrough bleeding, including joint bleeding. However, prophylaxis with higher troughs of approximately 12% may provide better outcomes and avoid disabilities<sup>17</sup>. The ability to measure FVIII levels in plasma facilitates tailoring of prophylaxis according to patient-agreed lifestyle priorities. Indeed, application of pharmacokinetic measures plays a key role in tailoring management to individual patients<sup>18</sup>.

With its increasing availability, prophylaxis has evolved, and now focusses on improving a person's quality of life by reducing the burden of infusions and increasing treatment adherence<sup>19</sup>. Intravenous administration has been cited as a key barrier to prophylaxis. Drawbacks include the frequent need for a central venous access device and related complications, plus the fear of needles and the related pain<sup>9,20,21</sup>. Regimens requiring frequent intravenous injections may be a reason for poor adherence to prophylaxis<sup>21,22</sup>, because standard half-life (SHL) coagulation FVIII products typically involve the burden of 2-4 injections *per week*.

With these limitations in mind, new treatments with extended plasma half-lives (EHLs) of the infused FVIII were developed to promote more convenient and individualised dosing schedules, with longer intervals between doses or higher threshold levels with the same dosing interval<sup>22-26</sup>. Several techniques have been used to extend the plasma half-life of currently licensed products. The two main approaches are Fc-fusion technology and PEGylation, which is the conjugation of the FVIII protein with polyethylene glycol (PEG). Here we critically review the advantages of EHL FVIII products and outline their limitations, and discuss the development and licensing of new non-replacement treatment products, such as emicizumab.

### Fc-fusion extended plasma half-life product

The recombinant FVIII Fc-fusion protein (rFVIII-Fc; Eloctate<sup>®</sup>, Sanofi Genzyme, Cambridge, MA, USA), composed of human FVIII fused with a monomeric human immunoglobulin (IgG1) Fc domain<sup>24</sup>, was the first EHL product to be licensed (2014), with indications for the treatment and prevention of bleeding and for perioperative management of individuals with haemophilia A<sup>27,28</sup>. In a phase I/IIa safety and pharmacokinetic study in previously treated patients with severe haemophilia A, rFVIII-Fc demonstrated a 1.5-1.7-fold longer plasma half-life compared with a SHL rFVIII<sup>24</sup>. Results from the phase III studies A-LONG and Kids A-LONG, and *interim* results from the ongoing extension study ASPIRE, established the long-term efficacy and safety of rFVIII-Fc for the treatment and prevention of bleeding in previously treated patients with severe haemophilia A<sup>29-31</sup>. The median annualised bleeding rates (ABR) observed for individualised prophylaxis, weekly prophylaxis and episodic treatment arms were 1.6, 3.6 and 33.6, with no bleeding episodes occurring in 45.3% and 17.4% of patients on prophylaxis in arms 1 and 2 (Table I). In Kids A-LONG, participants received twice-weekly rFVIII-Fc (25 IU/kg and 50 IU/kg on days 1 and 4). Median ABR was 1.96 overall<sup>30</sup>. This low ABR was maintained in ASPIRE, which enrolled participants from the A-LONG and Kids A-LONG, with no bleeding events occurring in 22.2-59.3% of patients across the different regimens (Table I)<sup>31</sup>. rFVIII-Fc was well tolerated and efficacious for the management of perioperative haemostasis across a wide spectrum of major and minor surgery in patients with severe haemophilia enrolled on the primary and ASPIRE studies<sup>32</sup>. During most major surgeries (95.7%), haemostasis was maintained with one rFVIII-Fc infusion. No FVIII inhibitors were observed<sup>29-32</sup>, although at-risk patients with a history or evidence of FVIII inhibitors, as well as previously untreated patients, were excluded from the pivotal clinical trials.

rFVIII-Fc has also been used for ITI in patients with severe haemophilia A and high-titre inhibitors, with varying levels of success<sup>33</sup>.

### PEGylated extended plasma half-life products

BAX 855 (rurioctocog alpha pegol, Adynovate<sup>®</sup>, Takeda Pharmaceutical Company Ltd., Lexington, MA, USA), a PEGylated, full-length, recombinant FVIII produced in Chinese hamster ovary (CHO) cells and manufactured by attaching a branched 20 kDa PEG molecule to a SHL rFVIII (Advate<sup>®</sup>, Takeda US Inc., Lexington, MA, USA)<sup>34</sup>, was licensed in 2017, with indications for the treatment and prevention of bleeding and perioperative management of haemophilia A<sup>35,36</sup>. The efficacy, pharmacokinetics and safety of BAX 855 for prophylaxis and on-demand therapy were assessed in previously treated patients with severe haemophilia A in the PROLONG-ATE trial<sup>23</sup>. The mean half-life of BAX 855 was 1.4-fold longer than that of Advate<sup>®</sup>. Median ABR in the group assigned to twice-weekly prophylaxis was 1.9 vs 41.5 in the group assigned to on-demand treatment, with no bleeds reported in 39.6% of patients receiving prophylaxis (Table I). No FVIII inhibitors were detected. Furthermore, the efficacy, pharmacokinetics and safety of prophylaxis with BAX 855 were also assessed in previously treated paediatric patients with severe haemophilia A<sup>37</sup>. The mean half-life of BAX 855 was 1.3-1.5-fold longer than that of Advate<sup>®</sup>, depending on the FVIII assay method used; the median ABR was 2.0 and no inhibitor was detected. BAX 855 was well tolerated and effective for perioperative use in patients with haemophilia A<sup>38</sup>.

BAY 94-9027 (Jivi<sup>®</sup>, Bayer HealthCare Pharmaceuticals, Berlin, Germany), a recombinant EHL FVIII product conjugated with a 60-kDa branched PEG molecule, was licensed in 2018 for previously treated adults and adolescents (aged  $\geq 12$  years) for routine prophylaxis, on-demand treatment, and perioperative management of bleeding<sup>22,39-42</sup>. In a phase I study carried out in patients with severe haemophilia A, this product demonstrated a longer FVIII half-life and higher area under the curve (AUC) than a SHL rFVIII (rFVIII-FS [Kogenate<sup>®</sup> FS, Bayer, Berkeley, CA, USA])<sup>22,43</sup>. Furthermore, in a head-to-head pharmacokinetic study in patients with severe haemophilia A, BAY 94-9027 demonstrated improvements in AUC, clearance and half-life compared with the rFVIII-Fc Eloctate<sup>®</sup> (Swedish Orphan Biovitrum Ltd., Great Abington, UK)<sup>25</sup>. In the phase II/III PROTECT VIII trial, patients received the product for 36 weeks on demand or prophylactically at individually determined intervals<sup>44</sup>. Low ABRs were reported in participants across three regimens (median ABRs were 4.1, 1.9 and 3.9 in the twice-weekly, every 5 days and every 7 days interval groups, respectively;

**Table I** - Bleeding rates observed with licensed extended plasma half-life (EHLs) factor VIII (FVIII) products and non-replacement factor therapy.

Product and clinical trial	Regimen	Overall ABR (median)	Zero bleeding rates <sup>a</sup>
<b>rFVIII-Fc (Eloctate<sup>®</sup>)</b>			
A-LONG <sup>29</sup>	Individualised prophylaxis (25-65 IU/kg every 3-5 days) (n=117)	1.6	45.3%
	QW prophylaxis (65 IU/kg) (n=23)	3.6	17.4%
	Episodic treatment (10-50 IU/kg) (n=23)	33.6	0
Kids A-LONG <sup>30</sup>	Twice-weekly prophylaxis (25 IU/kg and 50 IU/kg on days 1 and 4) (n=69)	1.96	NR
ASPIRE (extension study) <sup>b,31</sup>	<i>A-LONG patients:</i>		
	Individualised prophylaxis (n=108)	0.66	38.9%
	QW prophylaxis (n=27)	2.03	22.2%
	Modified prophylaxis (n=17)	1.97	23.5%
	Episodic treatment (n=14)	18.36	-
	<i>Kids A-LONG patients:</i>		
	Individualised prophylaxis <6 years (n=29)	0	NR
	Individualised prophylaxis 6-12 years (n=30)	1.54	NR
	Individualised prophylaxis <6-12 years (n=59)	NR	59.3%
	Modified prophylaxis <6 years (n=1)	6.55	NR
	Modified prophylaxis 6-12 years (n=1)	0	NR
Modified prophylaxis <6-12 years (n=2)	NR	50%	
<b>BAX 855 (Adynovate<sup>®</sup>)</b>			
PROLONG-ATE <sup>23</sup>	Twice-weekly prophylaxis (45±5 IU/kg for 6 months [≥50 EDs]) (n=120)	1.9	39.6%
	On-demand treatment (10-60±5 IU/kg) (n=17)	41.5	-
Pediatric trial (NCT02210091) <sup>37</sup>	Twice-weekly prophylaxis (50±10 IU/kg for 6 months [≥50 EDs])	2.0	38%
<b>BAY 94-9027 (Jivi<sup>®</sup>)</b>			
PROTECT VIII <sup>44</sup>	Twice-weekly prophylaxis (30-40 IU/kg), not eligible for randomisation (n=13)	4.1	15.4%
	Twice-weekly prophylaxis (30-40 IU/kg), eligible for randomisation (n=11)	1.9	45.5%
	Every 5 days prophylaxis (45-60 IU/kg) (n=43)	1.9	44.2%
	QW prophylaxis enrolled (60 IU/kg) (n=43)	3.9	37.2%
	QW prophylaxis completed (60 IU/kg) (n=32)	1.0	50%
	On-demand treatment (n=20)	23.4	-
PROTECT VIII extension <sup>46</sup>	Any PROTECT VIII regimen (n=36)	1.2 <sup>c</sup>	
	Twice-weekly prophylaxis (n=4)	1.5	
	Every 5 days prophylaxis (n=10)	1.1	NR
	QW prophylaxis (n=8)	0.4	
Variable frequency (n=14)	2.0		
<b>N8-GP (Esperoct<sup>®</sup>)</b>			
Pathfinder 2 <sup>49</sup>	Every 4 days prophylaxis (50 IU/kg) (n=175)	1.33	40%
	On-demand treatment (n=12)	30.87	0
Pathfinder 2 extension <sup>50</sup>	Every 4 days prophylaxis (50 IU/kg) (n=17)	0.0	52.9%
	QW prophylaxis (75 IU/kg) (n=38)	0.0	57.9%
Pathfinder 5 <sup>52</sup>	Twice-weekly prophylaxis (50-75 IU/kg) (n=68)	1.95	42.6%
<b>Emicizumab (Hemlibra<sup>®</sup>)</b>			
HAVEN 3 <sup>57</sup>	QW prophylaxis (1.5 mg/kg) (n=36)	2.5 <sup>d</sup>	50%
	Q2W prophylaxis (3.0 mg/kg) (n=35)	2.6 <sup>d</sup>	40%
	No prophylaxis (n=18)	47.6 <sup>d</sup>	0
HAVEN 4 <sup>58,59</sup>	Q4W prophylaxis (6 mg/kg) (n=41; 5 with inhibitors)	4.5 <sup>d,e</sup>	29%

Data cannot be directly compared between studies due to differences in trial design and patient populations. <sup>a</sup>Patients with no bleeding episodes during the trial. <sup>b</sup>Interim data. <sup>c</sup>Median annualised bleeding rate (ABR) during the full 5-year period. <sup>d</sup>All bleeding events, regardless of treatment with FVIII. <sup>e</sup>Median ABR during the expansion phase. NR: not reported; QW: once weekly; Q2W: every 2 weeks; Q4W: every 4 weeks.

zero bleeds occurred in 15.4%, 44.2% and 37.2% of patients, respectively), while median ABR in the on-demand treatment group was 23.4. No participant developed FVIII inhibitors. BAY 94-9027 was also efficacious and well tolerated in the treatment of patients undergoing major surgeries in the PROTECT VIII trial<sup>45</sup>. The previously demonstrated efficacy and safety of this EHL rFVIII was maintained across the PROTECT VIII extension period: the median ABR was 1.2 and no participant developed FVIII inhibitors<sup>46</sup>. It must be noted, however, that during the PROTECT VIII Kids trial, a phase III study carried out in 61 previously-treated children aged <12 years with an ongoing extension, 8 children aged 2-6 years left the study because of suspected immunological responses against PEG. No major safety concerns, including FVIII inhibitor development, were observed in these patients<sup>47</sup>.

N8-GP (turoctocog alfa pegol; Esperoct<sup>®</sup>, Novo Nordisk, Bagsvaerd, Denmark) is another EHL FVIII product featuring a 40 kDa PEG conjugated to a B-domain truncated FVIII *via* site-directed glycoPEGylation. It received US Food and Drug Administration (FDA) approval in 2019 and is indicated for use in previously treated adults and children with haemophilia A for prophylaxis, on-demand treatment and the perioperative management of bleeding<sup>48</sup>. In a phase I pharmacokinetic study (pathfinder 1) in previously treated patients with severe haemophilia A, the product demonstrated a 1.6-fold longer half-life than patients' previous FVIII products<sup>26</sup>. The efficacy and safety of N8-GP prophylaxis and on-demand therapy were then assessed in previously treated patients with severe haemophilia A in the pathfinder 2 study<sup>49</sup>. Patients in the prophylaxis arm had a median ABR of 1.33, 40% of them reporting zero bleeds (Table I). One patient, who developed inhibitory antibodies against FVIII ( $\geq 0.6$  Bethesda units [BU]) after 93 exposure days with this product, continued into the extension phase of the trial, but was then withdrawn when the FVIII inhibitor titre increased to 13.5 BU. During the pathfinder 2 extension trial, once weekly N8-GP was efficacious in patients with a low bleeding phenotype ( $\leq 2$  bleeds during the preceding 6 months of the trial's main phase), with 58% experiencing zero bleeds during the 24-week treatment period (Table I)<sup>50</sup>. N8-GP was effective and well tolerated for the prevention and treatment of bleeds during major surgery<sup>51</sup>. Finally, the efficacy, safety and pharmacokinetics of N8-GP prophylaxis and on-demand therapy were assessed in previously treated paediatric patients with severe haemophilia A in the pathfinder 5 trial<sup>52</sup>. Patients in the prophylaxis arm had a median ABR of 1.95 and 42.6% of them experienced zero bleeds during the study (Table I). No inhibitors were detected.

### General comments on extended plasma half-life factor VIII products

These licensed EHL FVIII products were efficacious in previously treated patients with severe haemophilia A, with a median ABR that ranged from 0 to 6.6 in the context of prophylactic regimens (Table I) and compared favourably with values ranging from 18.4 to 41.5 for on-demand regimens. Use of EHL FVIII was accompanied by a lower number and frequency of intravenous infusions than SHL products. However, not all patients were fully protected from bleeding on the dosing regimens tested (twice weekly, every 4 or 5 days or once weekly), which were less frequent than those generally used for prophylaxis with SHL products (thrice weekly or every other day). The ideal target of zero bleeding during the pivotal trials was achieved by approximately half of the patients (Table I), but improvements in ABR during the extension phases suggest that zero bleeds may be achieved for more patients when dosing regimens are individually tailored. There was no increased risk of FVIII inhibitor development in previously treated patients who switched from SHL to EHL FVIII products, but it remains to be seen whether or not this low immunogenicity is replicated in previously untreated patients and in those with a positive family history, i.e. those at higher risk of inhibitor development. Finally, limitations common to all EHL recombinant products are that treatment monitoring through the measurement of plasma FVIII levels may give unreliable results with the widely available one-stage coagulation assays. However, this can be circumvented by employing 2-stage chromogenic assays, although these are more costly and less widely available.

### Non-replacement factor therapy: emicizumab

Currently, emicizumab (Hemlibra<sup>®</sup>, Chugai Pharmaceutical Co., Tokyo, Japan) is the only non-replacement factor therapy licensed for individuals with haemophilia A with or without inhibitors by the FDA and the European Medicines Agency (EMA)<sup>53-55</sup>. Emicizumab is a bispecific monoclonal antibody that bridges activated factor IX and factor X to mimic the function of missing activated factor VIII, thereby increasing thrombin formation<sup>56</sup>. The unequivocal advantage of emicizumab for patients without inhibitors is its subcutaneous administration once-weekly (1×W), every 2 weeks (E2W), or every 4 weeks (E4W). However, emicizumab is not suitable for the management of major surgery, nor for treating acute bleeding episodes, because multiple doses are needed in order to achieve a steady state of haemostasis.

The efficacy and safety of emicizumab prophylaxis

in patients with severe haemophilia A without inhibitors were assessed in the HAVEN 3 trial<sup>57</sup>. Patients previously receiving on-demand therapy with FVIII were randomly assigned to prophylaxis with subcutaneous emicizumab at one of two dosing regimens or to no prophylaxis. Participants on 1×W or E2W prophylaxis had lower ABRs for all bleeding events than those with no prophylaxis (2.5, 2.6 vs 47.6, respectively) and a greater percentage had zero bleeding events during the study (50% and 40%, vs 0% with no prophylaxis). In addition, the HAVEN 4 study assessed emicizumab administered E4W in participants with haemophilia A with and without inhibitors<sup>58,59</sup>. Median ABR for the 41 participants (5 with inhibitors) included in the expansion phase was 4.5<sup>59</sup>.

On the whole, the efficacy results obtained in the multiple HAVEN trials are impressive and there are clear advantages in using the subcutaneous route of administration vs the traditional intravenous route. In spite of a high rate of zero bleeding in the frame of the HAVEN prophylaxis studies, some breakthrough bleeds did require additional haemostatic treatments. Data on the long-term preservation of joint health are currently not available beyond 2 years, and there are some concerns regarding safety. Although thrombotic microangiopathy and thrombosis risk are safety concerns that may be limited to patients with inhibitors treated with high or frequent doses of aPCC<sup>60,61</sup>, pharmacovigilance is needed to assess the impact on broader populations and over time. In addition, the current difficulty in assaying the haemostatic activity of emicizumab relative to the activity that would be expected from a given level of FVIII is a drawback, both for guiding treatment and recognising inhibitor activity. Indeed, the concomitant use of non-replacement factor therapy with add-on FVIII, e.g. to resolve breakthrough bleeds or manage surgery, requires further investigation to determine whether or not these patients are more likely to develop inhibitors to exogenous FVIII due to limited prior exposure. Finally, whether emicizumab can be used in previously untreated children to delay the use of FVIII replacement and/or to prevent intercurrent bleeding during ITI still needs to be explored. Furthermore, the data from HAVEN do not indicate the level of protection provided by emicizumab prophylaxis in real-world situations, such as in highly active patients and in those who take part in high-impact activities/organised sports<sup>62</sup>. In addition, continued surveillance is required to establish whether or not the occurrence of anti-drug antibodies, which, in rare cases, neutralise the FVIII-mimicking action of this drug, will be clinically significant.

## Discussion and conclusions

Factor VIII replacement remains the standard of care to treat and prevent bleeds in people with haemophilia A, with the unequivocal evidence supported by decades of clinical and real-world data that FVIII prophylaxis is highly effective in reducing bleeding and long-term complications such as arthropathy. It is also evident that FVIII prophylaxis regimens should be tailored to meet the individual needs and expectations of the patients<sup>63</sup>. The following factors should be considered when individualising a prophylactic regimen: bleeding pattern, joint health, individual pharmacokinetic profile, physical activity, and likelihood of adherence. Recent developments, such as EHL FVIII products and pharmacokinetic-guided dosing, provide new opportunities to optimise regimes for each individual patient<sup>64</sup>.

So far, in adolescents or adults, no major safety issues have been identified with any of the technologies used to extend the plasma half-life of FVIII<sup>65</sup>. However, the available data were obtained in the frame of clinical trials enrolling highly selected patients, chosen with the goal of demonstrating safety and efficacy, i.e. the end points required for product licensing. Thus, long-term post-marketing surveillance will be extremely important in order to confirm the safety of EHL products when used more extensively and for longer periods of time in real-world situations. For instance, PEGylation is being safely and widely used to prolong the plasma half-life of various therapeutic agents, including epoetin beta, growth hormone, interferon  $\alpha$ -2a and anti-tumour necrosis factor monoclonal antibodies<sup>66</sup>. However, none of these products are being administered lifelong from birth, even though the concentrations of PEG employed to prolong the plasma half-life of FVIII products are very low and, indeed, among the lowest used in currently available pegylated medications<sup>67</sup>.

Extended half-life products have not raised any concerns about the possibility of an increased risk of FVIII inhibitor formation, at least in previously treated patients who are tolerant to FVIII and thus at low risk of developing this complication. However, the immunogenicity of EHL products compared with SHL products in patients at high risk for inhibitor development, e.g. previously untreated or minimally treated children, and those with a family history of inhibitor, remains to be established.

Taken together, strict and long-term post-marketing surveillance should be put in place and should be supervised independently. This is essential in order to monitor the long-term safety of EHL FVIII products and of non-replacement products such as emicizumab, given that its FVIII-mimicking activity differs from that of FVIII, a protein that plays important physiological roles beyond haemostasis, including in cardiovascular and skeletal health<sup>11,56,68</sup>. For example, FVIII deficiency

is associated with altered bone metabolism, as indicated by reduced formation and increased reabsorption of bone observed in FVIII-deficient mice, and osteoporosis is a common comorbidity in patients with FVIII deficiency<sup>69,70</sup>. Data are needed to provide information as to whether or not the FVIII-mimicking activity of emicizumab can fulfil the roles of FVIII beyond haemostasis in patients with haemophilia.

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### Disclosures of conflicts of interest

*LA has participated in a Data Safety Monitoring Board for Octapharma and Takeda. He has also received honoraria from Bayer, Kedrion, and Takeda, and has acted as Chair for a scientific advisory committee for Kedrion. PMM sits on the scientific board for the Bayer Awards. He has also received honoraria for lectures at educational symposia from Bayer, Kedrion and Novo Nordisk. WS has participated in a Data Safety Monitoring Board for Biotest and received honoraria for lectures from Biotest, Novo Nordisk, Roche, Takeda and Bio&Bio. MT has been an advisor for Amgen, Genentech, Kedrion, Novo Nordisk, Octapharma and Takeda. He has received fees for lectures at symposia for Takeda. Research with Novo Nordisk and Takeda.*

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