

# Plerixafor prescription modalities in autologous haematopoietic stem cell mobilization in Belgium

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**Objectives:** The efficacy and safety of plerixafor, an antagonist of the CXCR4 receptor, in combination with G-CSF has been demonstrated in patients suffering from lymphoma and multiple myeloma (MM) eligible for autologous haematopoietic stem cell collection. However, different reimbursement criteria have been applied in different countries to select patients eligible for treatment with plerixafor. The objective of this observational study was to describe the plerixafor prescription modalities in daily practice in Belgium.

**Methods:** This open-label, prospective, observational study was conducted in 11 Belgian centres in 114 patients with lymphoma (Hodgkin's and non-Hodgkin's lymphoma) or MM who were treated with plerixafor according to the SmPC between April 2011 and October 2012. Patients included in another clinical trial with plerixafor were excluded from the study.

**Results:** The use of plerixafor in patients with MM or lymphoma was effective, with a success rate (defined as a total yield  $>2 \times 10^6$  CD34+ cells/kg) of 77%, and well tolerated (one SAE reported). Optimal collection (defined as a total yield  $>4 \times 10^6$  CD34+ cells/kg) was obtained for 43% of the study population (31% in lymphoma patients, compared to 61% in patients with MM). The use of plerixafor was in line with the SmPC and the Belgian reimbursement criteria for all patients.

**Conclusion:** This study is showing that the use of plerixafor according to Belgian reimbursement criteria results in similar efficacy and safety as in other centres and countries worldwide.

**Keywords:** Poor mobilizers, Plerixafor, Non-Hodgkin's lymphoma, Multiple myeloma, Hodgkin's lymphoma

## Introduction

Intensive chemotherapy followed by autologous stem cell transplantation is an important treatment modality for patients suffering from lymphoma or multiple myeloma (MM).<sup>1-3</sup> This strategy is associated with improved overall survival, event-free and progression-free survival.<sup>4,5</sup> Transplantation of autologous haematopoietic stem cells (HSC) is required for the recovery from bone marrow aplasia caused by high dose chemotherapy.<sup>6-8</sup> However, autologous transplantation can only be performed if an adequate

autologous graft is available. Transplantation with stem cells from peripheral blood has largely replaced transplantation with bone marrow stem cells.

Stem cells can be mobilized to the peripheral blood by the use of a haematopoietic growth factor such as Granulocyte Colony Stimulating Factor (G-CSF). G-CSF can be used with or without mobilizing chemotherapy. However, these mobilization strategies are not always satisfactory. According to recent literature data, the proportion of patients for whom the collection of an adequate graft fails varies from 4 to 48%.<sup>1-11</sup> In these papers, an adequate graft was defined as a graft containing more than  $2 \times 10^6$  CD34 cells per kg body weight collected in a maximum of 4 to 5 leucapheresis procedures. The failure rate is

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higher in elderly patients, in patients previously treated with myelosuppressive chemotherapy,<sup>10,12</sup> in case of marrow involvement at diagnosis<sup>4</sup> and especially after failure of a previous mobilization attempt. With the current strategies of mobilization and remobilization, the risk of remobilization failure is much higher than for the first attempt: only 30% of remobilized patients can undergo autologous stem cell transplantation (HSCT) with the total number of cells obtained during the first and second attempt.<sup>8</sup>

Plerixafor, the active substance of Mozobil<sup>®</sup>, is a bicyclam derivative and is a selective, competitive and reversible antagonist of the CXCR4 receptor expressed on HSC. Plerixafor inhibits the binding of the CXCR4 receptor to its SDF1alpha ligand, produced by stromal cells. By disrupting the CXCR4/SDF1alpha axis plerixafor mobilizes HSC to the peripheral blood, where they can be collected by apheresis.<sup>13</sup> Plerixafor in combination with G-CSF is approved to improve mobilization of HSC to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and MM whose cells mobilize poorly.

The efficacy and safety of plerixafor in combination with G-CSF has been demonstrated in patients suffering from Non-Hodgkin's Lymphoma (NHL) and MM eligible for autologous HSCT. Plerixafor significantly increases the number of CD34+ cells collected, reduces the number of apheresis procedures required to collect an adequate number of stem cells, increases the chance to collect an optimal graft and reduces the collection failure rate. A significantly higher number of patients are able to proceed to autologous HSCT with plerixafor compared with standard mobilization with G-CSF.<sup>13,14</sup> In addition, plerixafor overcomes mobilization failures in about 70% of patients who had already failed a previous collection or mobilization attempt.<sup>15–18</sup>

Worldwide, different criteria are applied to select patients for treatment with plerixafor. In some countries, the use of plerixafor is restricted to patients who need remobilization, while in other countries the use is less restricted. In Europe, the use of plerixafor is mainly restricted to known poor mobilizers. In Belgium, the current reimbursement criteria are as

follows: patients with lymphoma or MM who are candidates for an autologous HSCT and who are failing mobilization (less than 10–15 cells CD34+ cells/ $\mu$ l blood mobilized) or who are failing collection (less than  $2 \times 10^6$  CD34+ cells/kg collected) after G-CSF administration (10  $\mu$ g/kg) during at least 4 days or after chemomobilization with G-CSF. The objective of this observational study was to describe the plerixafor prescription modalities in daily practice in Belgium.

## Materials and Methods

This open-label, prospective, multi-centre, observational study was conducted in Belgium in patients treated with plerixafor between April 2011 and October 2012. The study was approved by the Ethics Committee of the University Hospital of Leuven (no. B322201110611) and was performed in compliance with GCP and all local applicable rules and regulations. The study was conducted in 11 Belgian centres. All patients treated with plerixafor who gave their written informed consent and for whom data were available were included in the study. Patients who were already included in another clinical trial with plerixafor were excluded from the study. The following information was recorded: demographics, current and past treatment, previous stem cell mobilization attempts, current mobilization treatment, results of mobilization, and safety. Data were statistically analyzed in a descriptive manner (mean, standard deviation and range).

## Results

### Demographics

In total, 114 patients who were treated with plerixafor according to the SmPC between April 2011 and October 2012 were included in the study (Table 1). This corresponded to 77% of the total number of Belgian patients treated with plerixafor in the time frame of the study. Of the 114 patients, 46 (40.4%) were treated for MM, while 68 (59.6%) patients were treated for lymphoma [59 (51.8%) patients with NHL and 9 (7.9%) with HL].

All patients with lymphoma (HL+NHL) were previously treated with chemotherapy, compared with 42 MM-patients (91%). Only 13% of the total

**Table 1** Demographic information for patients with myeloma, lymphoma and the entire study population

|   | MM (n=46)                     | NHL+HL (n=68)                  | Total (n=114)                  |
|---|-------------------------------|--------------------------------|--------------------------------|
| Gender (M/F) Number (%)                 | 21/25 (46%/54%)               | 36/32 (53%/47%)                | 57/57 (50%/50%)                |
| Mean age $\pm$ SD (range)<br>(in years) | 62.5 $\pm$ 7.7<br>(42.9–74.7) | 56.1 $\pm$ 15.0<br>(17.6–77.0) | 58.7 $\pm$ 12.9<br>(17.6–77.0) |
| Mean height $\pm$ SD (range)<br>(in cm) | 165.6 $\pm$ 27.7<br>(157–193) | 166.6 $\pm$ 32.4<br>(152–196)  | 166.2 $\pm$ 30.6<br>(152–196)  |
| Mean weight $\pm$ SD (range)<br>(in kg) | 72.5 $\pm$ 16.3<br>(45–119)   | 76.9 $\pm$ 16.7<br>(47–127.7)  | 75.1 $\pm$ 16.6<br>(45–127.7)  |

Note: MM, multiple myeloma; NHL, Non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

**Table 2 Mobilization history for patients with myeloma, lymphoma and the entire study population**

|                                   | MM (n=46)  | NHL+HL (n=68) | Total (n=114) |
|-----------------------------------|------------|---------------|---------------|
| No previous mobilization          | 36 (78.3%) | 47 (69.1%)    | 83 (72.8%)    |
| Previous mobilization with        | 10 (21.7%) | 21 (30.8%)    | 31 (27.2%)    |
| G-CSF                             | 4 (8.7%)   | 3 (4.4%)      | 7 (6.1%)      |
| G-CSF + mobilization chemotherapy | 1 (2.2%)   | 3 (4.4%)      | 4 (3.5%)      |
| G-CSF + therapeutic chemotherapy  | 3 (6.5%)   | 7 (10.3%)     | 10 (8.8%)     |
| Other*                            | 2 (2.9%)   | 8 (11.8%)     | 10 (8.8%)     |

Note: MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

\*These 10 patients underwent a previous mobilization session with plerixafor and have been included in this study.

population previously received radiotherapy. More patients with MM ( $n=4$ ; 9%) had received a prior stem cell transplant than patients with lymphoma ( $n=1$ ; 4.4%).

#### Mobilization history in remobilization patients

In the total population, only 27% of the patients ( $n=31$ ) were remobilized patients (Table 2). Previous mobilization was mainly done in steady state using G-CSF alone ( $n=7$ ; 6.1%) or on the backbone of therapeutic chemotherapy ( $n=10$ ; 8.8%). Specific chemotherapy for mobilization purposes was the least frequently used mobilization regimen ( $n=4$ ; 3.5%). Ten patients (8.8%) had been mobilized with plerixafor in first line and had failed. They were included in this registry as remobilization patients. Of the 31 remobilized patients, 24 (77.5%) underwent one previous mobilization attempt, while five (16%) had two attempts and two (6.4%) had more than two previous mobilization attempts.

In nine of 31 patients, no apheresis had been performed due to low peripheral blood CD34 counts. In 21 of 31 patients, apheresis was performed with an average yield of CD34+ cells of  $3.22 \times 10^6$  cells/kg; seven of these 21 patients had an apheresis yield higher than  $2 \times 10^6$  cells/kg. However, these seven patients were considered as poor mobilizers and mobilized with plerixafor in the second round of apheresis due to low pre-apheresis CD34 counts ( $<15$  cells/ $\mu$ l) after at least 4 days of G-CSF or due to insufficient yield for double transplant in the first apheresis.

#### Current mobilization procedure for all patients

Specific chemotherapy for mobilization purposes only was administered in 13.2% of all patients ( $n=15$ ), with the most frequent use in patients with MM (Table 3). Overall, 47.8% of the MM patients ( $n=22$ ) were mobilized with G-CSF and plerixafor

alone, potentially avoiding the side effects of chemomobilization. In lymphoma patients, mobilization with G-CSF and plerixafor was more frequent ( $n=37$ ; 54.4%) than mobilization with G-CSF/plerixafor and chemotherapy. Most cases of chemomobilization in lymphoma were performed in the frame of the chemotherapeutic treatment of the disease. For the 31 patients who already underwent a previous mobilization attempt, the most frequently used mobilization regimen applied the second time was G-CSF in combination with plerixafor ( $n=18$ ; 58.1%) (Table 4).

Ninety-six patients (84.2%) received one or two administrations of plerixafor in the mobilization regimen (Table 5). Only one patient was treated up to 4 days with plerixafor. For most patients ( $n=101$ ; 88.6%), plerixafor was administered in a hospital setting (hospitalization or day care unit).

#### Mobilization efficacy

Before mobilization with plerixafor, the mean CD34+ cell count was  $10.1 \pm 16.4$  cells/ $\mu$ l. The CD34+ cell count increased 2.78-fold after a first administration of plerixafor ( $28.2 \pm 25.1$  cells/ $\mu$ l). For 92 patients (80.7%), the pre-apheresis CD34+ cell count before plerixafor was lower than 15 cells/ $\mu$ l. Another seven patients (6.1%) were known as poor mobilizers with a collection yield in previous mobilization ( $<2 \times 10^6$  cells/kg) or did not undergo apheresis. For 15 patients (13%; 10 patients in the MM-group and 5 patients in the lymphoma-group), the pre-apheresis CD34+ cell count before plerixafor was higher than 15 cells/ $\mu$ l. However, in 11 of them, one or two apheresis sessions with a collection yield below  $2 \times 10^6$  cells/kg were performed after which the mobilization session was rescued by administration of plerixafor. Two patients with a high pre-apheresis CD34+ cell count were

**Table 3 Mobilization regimen used in combination with plerixafor for the total population, divided per myeloma and lymphoma group**

|                                   | MM (n=46)  | NHL+HL (n=68) | Total (n=114) |
|-----------------------------------|------------|---------------|---------------|
| G-CSF                             | 22 (47.8%) | 37 (54.4%)    | 59 (51.7%)    |
| G-CSF + mobilization chemotherapy | 9 (19.6%)  | 6 (8.8%)      | 15 (13.2%)    |
| G-CSF + therapeutic chemotherapy  | 15 (32.6%) | 25 (36.7%)    | 40 (35.1%)    |

Note: MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

**Table 4 Mobilization regimen used in combination with plerixafor for the remobilization patients, divided per myeloma and lymphoma group**

|                                   | MM (n=21)  | NHL+HL (n=10) | Total (n=31) |
|-----------------------------------|------------|---------------|--------------|
| G-CSF                             | 13 (62.0%) | 5 (50.0%)     | 18 (58.1%)   |
| G-CSF + mobilization chemotherapy | 0 (0.0%)   | 1 (10.0%)     | 1 (3.2%)     |
| G-CSF + therapeutic chemotherapy  | 8 (38.0%)  | 4 (40.0%)     | 12 (38.7%)   |

Note: MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

already mobilized with plerixafor a few weeks earlier and were considered as known poor mobilizers. Therefore, the use of plerixafor in these patients with CD34+ cell count exceeding 15 cells/ $\mu$ l was also in line with the reimbursement criteria.

On average,  $1.79 \pm 0.88$  apheresis days were performed in the total study population. This was slightly lower in the lymphoma-group ( $1.73 \pm 0.90$ ; range: 0–4 days) compared with the MM-group ( $1.87 \pm 0.85$ ; range: 0–3 days).

On day 1 of plerixafor administration, 95 patients (83.3%) went to apheresis and more than or equal to  $2 \times 10^6$  cells/kg (mean apheresis yield  $3.25 \times 10^6$  cells/kg) could be collected in 60% of them. In the total population, the mean total CD34+ cells collected was  $4.28 \pm 3.32 \times 10^6$  cells/kg. Collection yields were higher in the MM-group ( $5.58 \pm 3.64 \times 10^6$  cells/kg) in comparison with the lymphoma-group ( $3.39 \pm 2.76 \times 10^6$  cells/kg). In the total study population, success rate (defined as total yield  $\geq 2 \times 10^6$  CD34+ cells/kg) was 77%. In first attempt mobilization, this success rate was 82%, while it was 63% in the group of patients who have been mobilized at least once. Overall success rate and first mobilization success rate was higher in patients with MM than in patients with lymphoma (84 vs 72%, and 88 vs 76%, respectively).

The 10 patients who were mobilized with plerixafor in the first and second mobilization attempt were separately analyzed. In all but one of these 10 patients, the apheresis yield of the first mobilization with plerixafor was  $< 2 \times 10^6$  CD34 cells/kg.

However, in all but one of the 10 patients a collection of  $\geq 2 \times 10^6$  CD34/kg was possible in the second mobilization round with plerixafor, demonstrating that plerixafor can be used successfully in patients that failed a first mobilization round with plerixafor.

The relationship between total yield collection and the pre-plerixafor CD34+ cell count is shown in Table 6. In

the group with a pre-plerixafor pre-apheresis CD34+ cell count less than 5 and more than 2 cells/ $\mu$ l, the success rate, defined as collection yield above  $2 \times 10^6$  CD34+ cells/kg, was 75.8%. For patients with a pre-plerixafor pre-apheresis CD34+ cell count higher than 10 cells/ $\mu$ l, success rate with plerixafor was 100%. Analysis of the relationship between pre-plerixafor CD34+ cell counts and the total yield collected per patient shows a relatively high success rate (40%) in those patients with very low pre-plerixafor CD34+ cell counts (below 2 cells/ $\mu$ l). Optimal collection, defined as a total collection yield of  $4 \times 10^6$  cells/kg, was obtained for 43% of the total study population ( $n=49$ ) (31% in patients with lymphoma, compared with 61% in patients with MM).

### Safety

A total of 14 adverse events (AEs) were reported by seven patients (6.1%). One patient showed an allergic reaction (including rash, facial oedema and hypotension), which was classified as a serious adverse event (moderate grade). Most frequent adverse events were gastro-intestinal (diarrhoea, nausea and abdominal pain). Hypotension was reported in two additional patients (1.7%). Plerixafor was discontinued in three patients and medication was needed in three patients to treat the adverse event (allergic reaction and low blood pressure). All reported events resolved within 24 hours.

### Discussion

The population in this observational study is representative of all patients treated with plerixafor in Belgium as the participating centres covered 77% of total sales in Belgium over the study period. A total of 114 patients with lymphoma or MM undergoing stem cell mobilization were included in the registry.

Success was defined as a total yield collected over the complete mobilization session of  $2 \times 10^6$  CD34+

**Table 5 Number of administration days of plerixafor for patients with myeloma, lymphoma and the entire study population**

| Number of administration days of plerixafor | MM (n=46)  | NHL+HL (n=68) | Total (n=114) |
|---|------------|---------------|---------------|
| 1   | 23 (50.0%) | 29 (42.6%)    | 52 (45.6%)    |
| 2   | 17 (37.0%) | 27 (39.7%)    | 44 (38.6%)    |
| 3   | 6 (13.0%)  | 11 (16.2%)    | 17 (14.9%)    |
| >3  | 0 (0.0%)   | 1 (1.5%)      | 1 (0.9%)      |

Note: MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

cells/kg or more. Overall success rate of mobilization with plerixafor in the difficult to mobilize population included in this registry was 77%. The success rate was higher in patients in a first mobilization attempt (82%) as compared to patients having already undergone a previous mobilization attempt (63%).

When looking at the information by disease type, success rate was higher in patients with MM than in lymphoma patients (84 vs 72%), which corresponds to earlier observations in the registration phase III trials for plerixafor.<sup>13,14</sup>

Analysis of the relationship between pre-plerixafor CD34+ cell counts and the total yield collected per patient shows a relatively high success rate (40%) in those patients with very low pre-plerixafor CD34+ cell counts (below 2 cells/ $\mu$ l). Interestingly, the cut-off value of 10 cells/ $\mu$ l blood correlates with a 100% success rate with plerixafor.

In general, results observed in a real world context are often less positive than those observed in a well-controlled clinical trial context. Efficacy results reported for plerixafor in clinical trials are indeed somewhat better than those observed in our registry. This is not surprising as the population in our registry was a selected group meeting the reimbursement criteria for plerixafor in Belgium. These patients by definition can be classified as patients with mobilization difficulties.

In patients with known collection failure in a previous attempt, Hubel *et al.*<sup>19</sup> reported a success rate of 73.8% in a median of two apheresis days based on data from the European Compassionate Use Program for plerixafor with better results in patients with MM (success rate 81.6%) than in patients with NHL (success rate 64.8%). For the Belgian patients included in this European Compassionate Use Program, a success rate of 64% in a mean of two apheresis sessions has been reported,<sup>20</sup> which is in line with the observation in this registry in the group of patients with known mobilization failure (63%).

Plerixafor use in a first mobilization attempt has been described by Russell *et al.*<sup>21</sup> who has reported results of the European multicentre PREDICT trial

in which plerixafor was used in first line in all mobilization attempts. Success rate was 96% in a median of 1 day of apheresis (range 1–3). By disease type, a 98% success rate was observed in patients with MM and 80% in patients with NHL. The mean fold increase of CD34+ cell counts after one dose of plerixafor was 2.6. Despite the fact that the population enrolled in the Belgian registry was restricted to difficult to mobilize patients (as defined by the reimbursement criteria in Belgium), the data observed in this registry are in line with the PREDICT trial. In the Belgian registry, the observed success rate of the first mobilization attempt was 88 and 76.5% in patients with MM or lymphoma, respectively. Mean fold increase of CD34+ cell count after one dose of plerixafor in the registry was 2.78, which is very close to that observed in the PREDICT trial.

Data in patients with low pre-plerixafor CD34+ cell counts after 4 days of G-CSF have been published recently, based on a post hoc analysis of the double blind controlled phase III trials for plerixafor in MM and NHL.<sup>22,23</sup> In these publications, failure rate in the placebo groups (patients mobilized with G-CSF alone) for patients with low CD34+ cell counts at Day 4 are high. In patients with MM with less than 15 CD34+ cells/ $\mu$ l after 4 days of G-CSF administration, total collection yield obtained in the G-CSF alone group was below the minimum target in 22% of the patients.<sup>23</sup> It was below the minimum target in 5% of the patients mobilized with plerixafor and G-CSF.<sup>23</sup> In this Belgian registry, for 12% of the MM patients a total yield below target was obtained after first line mobilization with plerixafor. Per inclusion criteria, these patients presented with less than 15 CD34+ cells before plerixafor administration. In the *post hoc* analysis of the phase III trial in NHL,<sup>22</sup> failure rate in the placebo group of patients with a CD34+ cell count below 15 CD34+ cells/ $\mu$ l after 4 days of G-CSF administration was 59%. The failure rate was 19% in the comparative group with low pre-apheresis CD34+ count mobilized with plerixafor and G-CSF.<sup>22</sup> In the Belgian registry, 23.5% of the patients

**Table 6 Total yield CD34+ cells collected in relation to pre-plerixafor CD34+ cell counts. Collection failure was defined as a collection yield below  $2 \times 10^6$  CD34+ cells/kg. Collection success was defined as a collection yield above  $2 \times 10^6$  CD34+ cells/kg**

| Pre-plerixafor CD34+ cell counts (cells/ $\mu$ l) | Patients with collection failure, n (%) | Patients with collection success, n (%) | Total number of patients, n (%) |
|---|---|---|---------------------------------|
| <2  | 15 (60.0%)                              | 10 (40.0%)                              | 25 (100%)                       |
| 2–5   | 7 (24.1%)                               | 22 (75.8%)                              | 29 (100%)                       |
| 5–10  | 4 (15.3%)                               | 22 (84.6%)                              | 26 (100%)                       |
| 10–15   | 0 (0%)                                  | 19 (100%)                               | 19 (100%)                       |
| >15   | 0 (0%)                                  | 14 (100%)                               | 14 (100%)                       |
| Total population*                                 | 26 (23.0%)                              | 87 (76.9%)                              | 113 (100%)                      |

Note:

\*Information is missing for one patient.

with lymphoma who received plerixafor with a baseline CD34+ count less than 15 cells/ $\mu$ l did not collect the minimum of  $2 \times 10^6$  cells/kg. In summary, failure rates with plerixafor mobilization in poor mobilizers in the Belgian registry compared to those observed in the *post hoc* analysis of the phase III trials are higher (12 vs 5% in MM, 23.5 vs 19% in lymphoma). This can partially be attributed to the fact that in the phase III trial no remobilization patients were included, while 27.2% of the patients in the registry had already experienced a previous mobilization attempt.

Analysis of the literature regarding cut-off values for CD34+ cell counts after at least 4 days of treatment with G-CSF indicates that cut-off values for pre-plerixafor CD34+ cell counts implemented in some centres in US and EU and defining a group of 'proven poor mobilizers' are close to those used in the Belgian reimbursement criteria.<sup>8,24-29</sup> In addition to decision making based on pre-apheresis CD34+ cell counts, in many centres 'known poor mobilizers' (patients with previous mobilization failure, i.e. a collection yield of less than  $2 \times 10^6$  cells/kg) are treated with plerixafor. Belgian reimbursement criteria also include these 'known poor mobilizers'.

One Serious Adverse Event (allergic reaction to plerixafor) was reported. Overall, plerixafor was well tolerated with adverse events (of mild or moderate intensity) reported in 6% of the patients. AEs were mainly gastrointestinal. Hypotension as adverse event was reported in two patients and in the patient who presented with allergic reaction. These data are in line with literature data.

## Conclusion

The criteria for reimbursed use of plerixafor in Belgium are comparable with the strategies of use implemented in different countries and centres worldwide. Reported efficacy and safety information from the Belgian registry is in line with the published results of clinical studies in comparable patient populations.

## Acknowledgements

The authors wish to thank S. Deforme, PhD (PharmaXL, Belgium) for his assistance in writing and publishing this manuscript. The authors acknowledge Sanofi for the financial support of the study.

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