**Overview of participants, experiences and adverse drug reaction reports in the pilot Dutch Biologic Monitor**

## 1. Background of the pilot Dutch Biologic Monitor

The pilot Dutch Biologic Monitor is a prospective cohort event monitoring study for patient-reported ADRs attributed to biologics that was established by the Netherlands Pharmacovigilance Centre Lareb in 2017. Nine Dutch hospitals participated in the monitor between 1 January 2017 and 31 October 2019. Patients were selected and invited to participate by health care professionals (HCPs) of the respective hospitals using consecutive sampling. Patients were eligible in case they were proficient in Dutch, eighteen years or older and used a biologic indicated for an immune-mediated inflammatory disease (IMID). Recruitment strategies varied per hospital. Patients were either recruited via letters, during appointments with nurses and specialists, at the outpatient pharmacy or during infusion therapy at the ambulatory care unit. Biologics that became available for IMID treatment after 1 January 2017 were incorporated in the study starting the release date.

The aim of the pilot was to develop a patient-reported outcome measure-based drug safety monitoring system using Lareb Intensive Monitoring (LIM) for biologicals used for immune-mediated inflammatory diseases (IMIDs).

Participating patients were asked to complete a comprehensive web-based baseline questionnaire covering demographic information (gender, birthdate, weight, height, smoking habits), drug use (biologic and combination therapy), indication for biologic therapy and comorbidities (Table 1). Information about ADRs attributed to biologics was collected, including the type of ADR, start and stop date, course, burden (using a five-point Likert type scale, ranging from 1 (no burden) to 5 (very high burden)), and treatment steps. Every reported unique ADR, including a recurrent ADR, was considered as one ADR per patient. Subsequent questionnaires focused exclusively on biologic use and ADRs, and were sent out bimonthly. No more questionnaires were sent in case the previous questionnaire had expired (after 21 days) or if the patient withdrew from the study.

Additional to analysing the completed questionnaires, we conducted a stakeholders analysis, we inventoried patient preferences in ADR information regarding biologics and inventoried participants' experiences with the pilot Dutch Biologic Monitor.

Table 1. Overview of biologicals with anatomical therapeutic chemical classification (ATC), indications (immune-mediated inflammatory disease, IMIDs) and combination therapy in the web-based questionnaire of the pilot Dutch Monitor Biologics.

| Drug | ATC | Indications | Combination therapy |
|---|---|---|---|
| Abatacept | L04AA24 | Ankylosing spondylitis/axSpA | Azathioprine |
| Adalimumab | L04AB04 | Crohn's disease | Chloroquine |
| Anakinra | L04AC03 | Psoriasis | Hydroxychloroquine |
| Brodalumab | L04AC12 | Psoriatic arthritis | Hydrocortison |
| Canakinumab | L04AC08 | Rheumatoid arthritis | Leflunomide |
| Certolizumab pegol | L04AB05 | Ulcerative colitis | Mercaptopurine |
| Dupilumab | D11AH05 | Other reported indications e.g: | Mesalazine |
| Etanercept | L04AB01 | Uveitis | Methotrexate |
| Golimumab | L04AB06 | Hidradenitis | Methylprednisolone |
| Guselkumab | L04AC16 | Atopic eczema | Olsalazine |
| Infliximab | L04AB02 | | Prednisone/Prednisolone |
| Ixekizumab | L04AC13 | | Sulfasalazine |
| Natalizumab | L04AA23 | | |
| Rituximab | L01XC02 | | |
| Sarilumab | L04AC14 | | |
| Secukinumab | L04AC10 | | |
| Tocilizumab | L04AC07 | | |
| Ustekinumab | L04AC05 | | |
| Vedolizumab | L04AA33 | | |

Table 2. Number of users in the Netherlands of biologicals followed in the pilot Dutch Biologic Monitor[1]

| ATC | Drug | Number of users |
|---|---|---|
| D11AH05 | Dupilumab | 638 |
| L04AA23 | Natalizumab | 1,034 |
| L04AA24 | Abatacept | 2,119 |
| L04AA33 | Vedolizumab | 2,301 |
| L04AB01 | Etanercept | 16,456 |
| L04AB02 | Infliximab | 12,908 |
| L04AB04 | Adalimumab | 21,445 |
| L04AB05 | Certolizumab pegol | 1,560 |
| L04AB06 | Golimumab | 1,976 |
| L04AC03 | Anakinra | 434 |
| L04AC05 | Ustekinumab | 4,412 |
| L04AC07 | Tocilizumab | 2,822 |
| L04AC08 | Canakinumab | 126 |
| L04AC10 | Secukinumab | 2,232 |
| L04AC12 | Brodalumab | 51 |
| L04AC13 | Ixekizumab | 407 |
| L04AC14 | Sarilumab | 55 |
| L04AC16 | Guselkumab | 175 |
| L01XC02 | Rituximab | 8,743 |
| | Total | 79,894 |

[1] Source: Zorginstituut Nederland. Intramurale dure en weesgeneesmiddelen, 2014-2018. Available from: https://www.gipdatabank.nl/databank#/g/00-totaal/R_04_addon/gebr/https://www.horizonscangeneesmiddelen.nl/

## 2. Results of the pilot Dutch Biologic Monitor

### a. Characteristics of patients participating in the pilot Dutch Biologic Monitor

Until 31 October 2019 1,369 patients participated in the pilot Dutch Biologic Monitor. A total of 7,437 questionnaires were completed and 1,844 unique ADRs were reported of which 67 ADRs resulted in hospitalisation, concerning 55 patients. Characteristics of participants are summarized in Table 3, the reported ADRs are summarized in Table 4.

Table 3. Characteristics of participants in the pilot Dutch Biologic Monitor

| **Characteristics (N= 1,369)** | **N (%)** |
|---|---|
| Female gender, *n* (%) | 799 (58.4) |
| Age, median (± S.D.) (years) | 57 ± 19 |
| Smoking (yes) | 222 (16.2) |
| BMI (± S.D.) (kg/l$^{-2}$) | 26.2 ± 5.1 |
| *TNF α-inhibitors* | |
| Adalimumab | 498 (36.4) |
| Certolizumab pegol | 37 (2.7) |
| Etanercept | 426 (31.1) |
| Golimumab | 40 (2.9) |
| Infliximab | 161 (11.8) |
| *Interleukin inhibitors* | |
| Anakinra | 17 (1.2) |
| Canakinumab | 8 (0.6) |
| Dupilumab | 10 (0.7) |
| Guselkumab | 3 (0.2) |
| Ixekizumab | 2 (0.1) |
| Sarilumab | 2 (0.1) |
| Secukinumab | 38 (2.8) |
| Tocilizumab | 52 (3.8) |
| Ustekinumab | 62 (4.5) |
| *Antilymophycyte agents* | |
| Abatacept | 38 (2.8) |
| Rituximab | 33 (2.4) |
| *Integrin antagonist* | |
| Natalizumab | 26 (1.9) |
| Vedolizumab | 3 (0.2) |
| Combination therapy[a] | |
| Methotrexate | 431 (31.5) |
| Corticosteroids[b] | 268 (19.6) |
| Thiopurines[c] | 124 (9.1) |
| Aminosalicylates[d] | 105 (7.7) |
| Hydroxychloroquine | 76 (5.6) |
| Leflunomide | 69 (5.0) |
| No combination therapy | 636 (46.5) |
| Unknown | 128 (9.3) |
| Indications for biologic therapy | |
| Rheumatoid arthritis | 586 (42.8) |
| Psoriatic arthritis | 242 (17.7) |
| Ankylosing spondylitis/axSpA | 172 (12.6) |
| Crohn's disease | 194 (14.2) |
| Psoriasis | 82 (6.0) |
| Ulcerative colitis | 60 (4.4) |
| Other | 108 (7.9) |

[a] The percent of total adds up to more than 100% since patients can have either a combination therapy consisting of more than one drug or more than one indication for biologic therapy.

[b] Corticosteroids include predniso(lo)ne (n=247), hydrocortisone (n=35), and methylprednisolone (n=11)

[c] Thiopurines include azathioprine (n=73), mercaptopurine (n=32) and thioguanine (n=18).

[d] Aminosalicyclates include sulfasalazine (n=63) and mesalamine (n=41).

Table 4. Adverse drug reactions attributed to biologics reported in the pilot Dutch Biologic Monitor

| Biologicals | Injection site reactions (HLGT administration site reactions) | Infections and infestations (SOC) | Skin and subcutaneous tissue disorders (SOC) | Musculoskeletal and connective tissue disorders (SOC) | Gastrointestinal disorders (SOC) | Nervous system disorders (SOC) | Respiratory, thoracic and mediastinal disorders (SOC) | Eye disorders (SOC) | Psychiatric disorders (SOC) | All others | Totals |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Adalimumab | 90 | 94 | 72 | 62 | 34 | 28 | 45 | 23 | 10 | 128 | 586 |
| Etanercept | 119 | 77 | 49 | 26 | 38 | 19 | 16 | 13 | 2 | 82 | 441 |
| Infliximab | 4 | 13 | 31 | 21 | 21 | 28 | 9 | 14 | 6 | 57 | 204 |
| Tocilizumab | 12 | 20 | 9 | 5 | 10 | 12 | 13 | 1 | 2 | 35 | 119 |
| Rituximab | 2 | 10 | 12 | 5 | 9 | 9 | 4 | 3 | 5 | 28 | 87 |
| Ustekinumab | 4 | 11 | 16 | 14 | 5 | 7 | 5 | 5 | 1 | 18 | 86 |
| Secukinumab | 3 | 16 | 9 | 2 | 10 | 3 | 8 | 3 | 2 | 15 | 71 |
| Certolizumab pegol | 5 | 11 | 14 | 4 | 4 | 1 | 3 | 1 |  | 12 | 55 |
| Golimumab | 8 | 4 | 5 | 5 | 6 | 3 | 2 | 3 | 1 | 14 | 51 |
| Vedolizumab | 1 | 8 | 4 | 4 | 2 | 9 | 3 |  | 1 | 11 | 43 |
| Abatacept | 5 |  | 12 | 5 | 2 |  | 4 |  | 1 | 6 | 35 |
| Anakinra | 11 | 1 |  | 1 | 1 | 3 |  |  |  | 6 | 23 |
| Dupilumab | 1 | 1 | 1 | 2 | 1 | 2 |  | 3 | 1 | 6 | 18 |
| Canakinumab | 2 | 1 | 4 | 3 | 1 | 3 | 1 |  | 1 |  | 16 |
| Guselkumab |  | 1 | 1 | 1 |  |  |  |  |  | 1 | 4 |
| Natalizumab |  |  |  | 1 |  | 1 |  |  | 1 |  | 3 |
| Sarilumab |  | 1 |  |  |  |  | 1 |  |  |  | 2 |
| **Totals** | **267** | **269** | **239** | **161** | **144** | **128** | **114** | **69** | **34** | **419** | **1,844** |

**b. Quality of self-reported medical information in the pilot Dutch Biologic Monitor**

The quality of the reported biologic therapy and combination therapy by immune-mediated inflammatory disease (IMID) patients has to our knowledge not yet been assessed in literature. Therefore, a substudy of the pilot Dutch Biologic Monitor was performed (as a proxy) to estimate the quality of the patient-reported medical information and to evaluate the representativeness of participating inflammatory rheumatic diseases patients in relation to their reference populations.

Consecutive adult patients using a bDMARD for an IMID were included in eight Dutch centres. Data of 550 patients with inflammatory rheumatic diseases (IRD) were used. Patient-reported bDMARD prescription, indication and combination therapy were verified for patients that permitted access to their electronic health record (EHR) using percentage agreement and/or Cohen's kappa (*n*=483). Conservative post-hoc sensitivity analysis was performed to account for missing data. Population representativeness was tested for the entire substudy population by comparing age, gender and prescribed bDMARD to the centres' reference populations using Mann-Whitney U test, Chi-Square Goodness-of-Fit or Fisher's exact test with Monte Carlo simulation (*n*=550).

The correct bDMARD was reported by 95.8% of the participants. Agreement between patients and EHR was almost perfect for indications (κ=0.832) and substantial for combination therapies (κ=0.725). Agreement on combination therapies remained substantial after post-hoc sensitivity analysis (κ=0.640). Gender distribution ($p>0.05$) and bDMARD use ($p>0.05$) were similar to the reference populations. Median age was different (58.0 vs. 56.0 years, $p=0.04$), but considered clinically irrelevant.

The *Dutch Biologic Monitor* seems to be a valid tool to obtain patient-reported medical information. Reported medical information generally corresponded to the electronic health records and the participants represented their reference populations regarding age, gender and prescribed bDMARD.[1]

[1]Kosse LJ, Jessurun NT, Hebing RCF, Huiskes VJB, Spijkers KM, van den Bemt BJF, et al. Patients with inflammatory rheumatic diseases: quality of self-reported medical information in a prospective cohort event monitoring system. *Rheumatology (Oxford)* 2019 Published on 30 September 2019. doi: 10.1093/rheumatology/kez412

### c. Analysis of unlabelled biologic-induced adverse drug reaction

Six associations of biologic–induced adverse drug reactions reported in the pilot Dutch Biologic Monitor were further analysed together with the received cases of these associations in the spontaneous reporting system. The associations and conclusions are summarized in table 5. The association between etanercept and headache led to a signal disseminated to the Dutch Medicines Evaluation Board.

Table 5. Reports of unlabelled associations of adverse rug reaction and biologics reported in the pilot Dutch Biologic Monitor

| Biological | Adverse drug reaction (ADR) | Conclusion and Lareb and Medicine Evaluation Board |
|---|---|---|
| Adalimumab | Fatigue (MedDRA PT) | Lareb received 143 adalimumab cases of fatigue of which 11 in the pilot Dutch Biologic Monitor. Fatigue is not included in the Summary of product characteristics (SmPC) insomnia is included in the SmPC. In the patient information leaflet (PIL) the following ADRs are mentioned: feeling sick, weakened or tired, having trouble sleeping. |
| Etanercept | Fatigue (MedDRA PT) | Lareb received a total of 62 reports of etanercept and fatigue of which 9 patients describe a specific course of the fatigue (5 spontaneous reports, 4 reports in the Biologic Monitor). The fatigue occurs shortly after administration. The PIL mentions fatigue as part of a lupuslike syndrome. |
| Tocilizumab | Fatigue (MedDRA PT) | Lareb received a total of fourteen reports of tocilizumab and fatgue. Six Lareb cases of tocilizumab and fatigue are not confounded and they describe a plausible time to onset. Fatigue occurs after every administration. Five Lareb cases are confounded with MTX. Fatigue is not mentioned in the SmPC of tocilizumab. |
| Etanercept | Eye inflammation (MedDRA PT) | Lareb received 19 cases of etanercept and eye inflammation. Various kinds of eye inflammation are currently included in the SmPC (in 4.8) e.g. uveitis, scleritis, optic neuritis. Eye inflammation is mentioned in the PIL with a prevalence of more than 1%. |
| Etanercept | Gastro-intestinal disorders (MedDRA SOC) | Lareb received 107 reports of gastro-intestinal ADRs. In 88 reports it was reported for etanercept. Nausea/vomiting were 38 times reported, 26 reports concerned diarrhoea, and 43 reports described abdominal complaints. No gastro-intestinal ADRs are included in the SmPC of etanercept. |
| Etanercept | Visual impairment (MedDRA PTs: visual impairment; vision blurred; diplopia; visual field defect; accommodation disorder; visual acuity reduced; blindness unilateral; blindness; photopsia) | Lareb received 21 cases of visual impairment. There was no specific course of time to onset and pharmacological mechanism in the cases. Both positive and negative dechallenge are described. The association is described in the SmPC. |
| Etanercept | Headache (MedDRA HLT) | Lareb received 35 reports of headache with etanercept. In twelve reports the headache seems to be related with the administration, 8 of them had a positive rechallenge. There is a plausible temporal relation with the administration. Headache is mentioned in the SmPC of etanercept in paediatric patients with juvenile idiopathic arthritis. However, the reports received by Lareb did not include paediatric patients and only one patient used etanercept for juvenile idiopathic arthritis. |

#### *Biologic-induced fatigue*

Fatigue is reported in the pilot Dutch Biologic Monitor as an ADR. At the same it is well-known symptom of the underlying disease of patients with IMIDs. Evidence suggests that bDMARDs have a positive effect on fatigue in rheumatoid arthritis (RA). However, patients that report biologic induced fatigue describe a specific course of the fatigue in relation with the administration. Biologic-related fatigue might not be discovered using most fatigue measurement scales. Therefore, fatigue as an adverse drug reaction (ADR) of biologics might be easily overlooked or may be attributed to the underlying disease rather than the drug.
To gain insight in biologic-induced fatigue in patients with IMIDs, we assessed all reported ADRs concerning fatigue in the pilot Dutch Biologic Monitor. Furthermore we compared the patient characteristics between patients with fatigue, with other ADRs and without ADRs using Fisher's exact test, Mann-Whitney U or independent t-test where appropriate. A p value below 0.05 was considered statistically significant.
In total 696 patients reported 1,844 unique ADRs in the pilot Dutch Biologic Monitor between 1 January 2017 and 1 November 2019. Biologic-induced fatigue was reported by 100 patients and 48% described a pattern of recurring fatigue after every administration with recovery in several days. Patients recovered from fatigue up to one week after biologic administration, with a maximum of 10 days. More than half of these patients (26 patients) recovered up to 2 days after biologic administration. Basic demographics and patient characteristics that differ significantly between patients with fatigue, patients with other ADRs and patients with no ADRs are summarized in Table 6. Patients with fatigue had a lower mean age and smoked more than patients without fatigue. Patients with fatigue used infliximab, rituximab or vedolizumab more often than patients with other or without ADRs. Patients with fatigue used less etanercept than patients without fatigue and used more tocilizumab than patients without ADRs. RA was less prevalent and Crohn's disease was more prevalent in

patients with fatigue. Patients with fatigue used methotrexate as combination therapy less often and had a psychiatric disorder more often than patients without ADRs. The mean burden of fatigue was higher than burden of other ADRs. No significant difference was seen for gender, BMI, adalimumab, tocilizumab, ustekinumab or other biologic use; an indication of psoriatic arthritis, axial spondyloarthritis, ulcerative colitis or psoriasis; combination therapy with corticosteroids, thiopurines, hydroxychloroquine, leflunomide, sulfasalazine, mesalazine or no combination therapy or cardiovascular, respiratory, nervous system or malignant comorbidity or no comorbidities.
Although fatigue can be related to the underlying IMID, descriptions of the course of fatigue in patients receiving biologic therapy, point to a possible relationship between the administration of the biologic and the occurrence of the fatigue.

Table 6. Characteristics of patients that reported biologic-induced fatigue compared to patients with other adverse drug reactions.

| | **Patients with fatigue N(%)** | **Patients with other ADRs N(%)** | **p-value** | **Patients without ADRs** | **p-value** |
|---|---|---|---|---|---|
| Number of patients | 100 (100%) | 596 (100%) | | 673 (100%) | |
| Age (years) (mean ± SD) | 50.0 ± 14.6 | 53.4 ± 13.6 | 0.023 | 55.7 ± 14.2 | <0.001 |
| Gender (Female) | 59 (59%) | 398 (67%) | 0.14 | 342 (51%) | 0.134 |
| Smoking | 25 (25%) | 97 (16%) | 0.046 | 100 (15%) | 0.013 |
| BMI (kg/m$^2$) (mean ± SD) | 25.7 ± 4.4 | 25.9 ± 4.7 | 0.657 | 26.6 ± 5.5 | 0.131 |
| Biologic | | | | | |
| Infliximab | 22 (22%) | 53 (9%) | <0.001 | 84 (12%) | 0.018 |
| Etanercept | 13 (13%) | 177 (30%) | <0.001 | 228 (34%) | <0.001 |
| Rituximab | 9 (9%) | 18 (3%) | 0.009 | 6 (1%) | <0.001 |
| Tocilizumab | 8 (8%) | 29 (5%) | 0.224 | 13 (2%) | 0.003 |
| Vedolizumab | 7 (7%) | 12 (2%) | 0.012 | 7 (1%) | 0.001 |
| Indication | | | | | |
| Rheumatoid arthritis | 29 (29%) | 270 (45%) | 0.002 | 272 (40%) | 0.036 |
| Crohn's disease | 29 (29%) | 77 (13%) | <0.001 | 88 (13%) | <0.001 |
| Other indication | 16 (16%) | 53 (9%) | 0.044 | 39 (6%) | 0.001 |
| Combination therapy | | | | | |
| Methotrexate | 23 (23%) | 167 (28%) | 0.333 | 227 (34%) | 0.039 |
| Comorbidity | | | | | |
| Psychiatric disorder | 11 (11%) | 49 (8%) | 0.340 | 31 (5%) | 0.016 |
| Other comorbidity | 30 (30%) | 124 (21%) | 0.050 | 102 (15%) | 0.001 |
| Mean burden ± SD | 2.9 ± 0.9 | 2.4 ± 1.1 | <0.001 | | |

***Etanercept-induced headache***

Headache is mentioned in the Dutch SmPCs of etanercept as a possible adverse drug reaction that occurred in clinical trials in pediatric patients with juvenile idiopathic arthritis but not with other indications.
From 15 August 2000 to 1 November 2019 the Netherlands Pharmacovigilance Centre Lareb received 39 reports of headache (MedDRA HLT Headaches NEC) in association with the use of etanercept. Nine reports were received via the pilot Dutch Biologic Monitor and thirty reports were spontaneous reports. A possible association with the moment of administration of etanercept was explicitly mentioned in 16 reports, including 7 reports in the pilot Dutch Monitor Biologics and 9 spontaneous reports. Headache was recurrent in 3 cases and occurred after one or more administrations of etanercept in 13 cases. In 15 cases the patient recovered from headache within several days and in 1 case headache persisted and aggravated after every administration of etanercept. The association between headache and etanercept is disproportionately present in the Eudravigilance database, but not in the WHO and Lareb database.
Literature supporting headache related to etanercept is sparse. Headache is mentioned in the SmPC of etanercept in paediatric patients with juvenile idiopathic arthritis. Headache is labelled in the SmPCs of all other TNF-α inhibitors and could be part of an immediate reaction due to massive cytokine release.
In conclusion; headache can have many causes and therefore, a relationship with etanercept can be easily overlooked. Despite a long latency after start in several cases, many reports received by Lareb indicate a correlation between headache and the moment of administration of etanercept, the association of headache and etanercept should be further investigated.

**d. Patient-reported burden of adverse drug reactions attributed to biologics used for IMIDs**

Although the burden of adverse drug reactions (ADRs) has significant impact on patient's quality of life, thorough knowledge about patients' perspectives on the burden of biologic-induced ADRs is lacking. A study was conducted to gain insight in patient experienced burden of biologic-induced ADRs. The patient perspective gives important insights in the burden of biologic-induced ADRs. This information could be used by HCPs to optimise treatment with biologics.

Participants of the monitor were asked to complete the bimonthly questionnaires and to score the burden of ADRs on a five-point Likert type scale, ranging from 1 (no burden) to 5 (very high burden). We assessed potential factors associated with patient-reported burden of ADRs.

A total of 1,355 patients completed 6,293 questionnaires in 798 patient years (mean 7.1 months). Almost half of the patients (665 patients, 49%), of which 69% with rheumatic diseases and 31% with other diseases, collectively reported 1,720 unique ADRs. Infections and musculoskeletal complaints were the most burdensome ADRs and injection site reactions were the least burdensome. ADRs leading to health care professional (HCP) contact were more burdensome than ADRs without HCP contact. Smoking, respiratory and psychiatric comorbidities were associated with higher burden of ADRs. Crohn's disease, use of adalimumab and use of sulfasalazine as combination therapy were associated with lower burden of ADRs.

### e. A drug safety monitoring system for IMIDs: a stakeholder analysis

To investigate the multi-stakeholder perspective on the preferred setup, potential and added value of a PROM-based national drug safety monitoring system for ADRs based on the Dutch Biologic Monitor a stakeholder analysis was conducted.

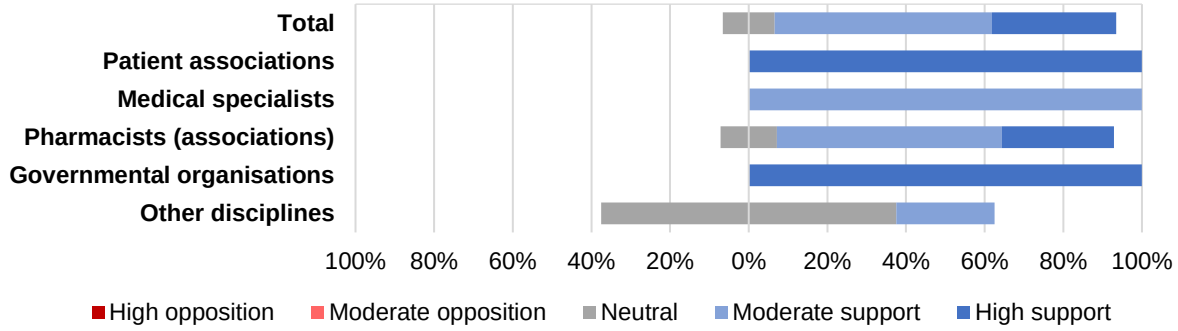
Nineteen stakeholders (representatives of patient organisations, medical specialists, pharmacists, governmental organisations and PROM-using research institutes) were interviewed using a structured interview guide. Transcribed data were coded and analysed to count frequencies and to generate recurring themes relating to the study aims.

The majority of stakeholders (84.2%) support the establishment of a national drug safety monitoring system based on PROMs. Feasibility of the system depends on the process of implementation. Furthermore, the need for integration of PROMs on ADRs in clinical practice and the preference to also monitor small molecules and new drugs was emphasized. Preferably, all pharmacological options for an indication should be monitored.

Our study shows that the majority of stakeholders recommend to establish a PROM-based national drug safety monitoring system focused on ADRs attributed to biologics, small molecules and new drugs. To enhance the added value, PROMs on ADRs ideally need to become integrated in clinical practice.

The stakeholders were asked to express their position towards the establishment of a PROM-based drug safety monitoring system focused on ADRs that is based on the Dutch Biologic Monitor using a five-point scale (ranging from high support to high opposition; Figure 1). All stakeholders had a neutral or supporting stand towards a PROM-based national drug safety monitoring system, as they agreed on the necessity to monitor the safety of drugs and to obtain more insight in the patient perspective on ADRs (84.2%). Three stakeholders had a neutral position due to the proposed methodology. Among these stakeholders were two representatives of the national oncology association, who discouraged the incorporation of oncology drugs due to the presence of various (Dutch) initiatives and registries to monitor ADRs attributed to oncolytics. However, they did support a monitoring system for non-oncolytic indications.

Figure 1. Position map of the interviewed stakeholders towards the establishment of a PROM-based national drug safety monitoring system focused on ADRs that is based on the pilot Dutch Biologic Monitor. ADR: adverse drug reaction; PROM: patient-reported outcome measure




## 3. Discussion and conclusion

The aim of this report was to provide an update of the ADR-reports received in the pilot Dutch Monitor biologics. Patient reported previously not labelled ADRs in the pilot Dutch Monitor Biologics which are together with reports received with the spontaneous reporting system were further analysed. These analyses led to at least one Signal disseminated to the Dutch Medicines Evaluation Board (etanercept and headache). Furthermore, additional studies show that reported medical information generally corresponded to the electronic health records, the participants represented their reference populations regarding age, gender and prescribed bDMARD, that infections and musculoskeletal ADRs are the most burdensome ADRs and that injection site reactions are the least burdensome ADRs. Interviewed stakeholders recommend to establish a national drug safety monitoring system focused on patient-reported ADRs. To enhance the added value, these ADRs ideally need to become integrated in clinical practice.

*This signal has been raised on February 6, 2020. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB [www.cbg-meb.nl](http://www.cbg-meb.nl)*