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**TITLE:**
**BEPACT Lung: Impact of Patient Characteristics on pneumo-oncologists NSCLC systemic treatment decision in Belgium: A cross-sectional study.**

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# PROTOCOL SUMMARY

| | |
|---|---|
| Title | BEPACT Lung: Impact of Patient Characteristics on pneumo-oncologists NSCLC systemic treatment decision in Belgium: A cross-sectional study. |
| Vendor/Collaborator | |
| Rationale | The treatment landscape of metastatic NSCLC is rapidly evolving. There are new diagnostic and treatment options available in the coming months and years.<br><br>New combination treatments will give different solutions to pneumo-oncologists who might be guided by certain patient and tumor characteristics.<br><br>The link between patient and tumor characteristics in untreated stage IV NSCLC patients and systemic treatment needs further investigation, allowing the identification of possible treatment issues, data gaps and/or areas of improvement. |
| Primary Objective(s) | Investigate the relation between patient, tumor and site characteristics and systemic treatment choices of stage IV untreated NSCLC. |
| Study Design | This is a multicenter, non-interventional, cross-sectional study.<br><br>Consecutive patients with metastatic stage IV NSCLC selected for systemic treatment or best supportive care will be included in the trial at the time the patient signed the informed consent form (ICF). Patients that were selected for systemic treatment, should have received at least their first dose and a maximum of one cycle of the same treatment.<br><br>The pneumo-oncologist that treats the patient will fill in the CRF, indicating the systemic treatment option and the link with the variable categories that impacted the choice for a systemic treatment option. |
| Study Population | 210 patients with stage IV NSCLC starting first-line systemic treatment or best supportive care will be enrolled in line with inclusion and exclusion criteria. |
| Study Duration | Target estimated at 5 months, 210 eligible patients to be included. |
| Exposure and Outcome | The study outcome is defined as the systemic treatment choice. Systemic treatment choices are defined as :<br>1) Chemotherapy (chemo)<br>2) Immunotherapy (IO)<br>3) immuno combined therapies (IO+IO)<br>4) IO+chemo<br>5) IO+bevacizumab+chemo (IO+bev+chemo)<br>6) best supportive care (BSC).<br><br>There is no exposure in this study. |
| Statistical Methods | - Descriptive statistics.<br>- Hierarchical logistic regression for discrete choices |
| Sample Size and Power Calculations | The study is descriptive and no sample size calculations will be performed. |

| | |
|---|---|
| | In order to have a representative picture of the pneumo-oncologists' NSCLC systemic treatment decision in Belgium, a minimum of 200 patients need to be enrolled in the study.<br><br>A maximum of 10% of the total study population can be enrolled in a site to avoid bias.<br><br>A minimum of 30 patients need to be included in a subgroup for any given analysis. |
| Limitations | The experiment is not interventional and cross sectional. |

# 1 Background and Rationale

## 1.1 Background

Lung cancer remains one of the most frequent and most deadly tumor entities, with 1.6 million tumor-related deaths annually worldwide. The World Health Organization (WHO) estimates that lung cancer is the cause of 1.37 million deaths globally per year. An estimated 71% of these deaths are caused by smoking, indicating that ~400 000 deaths annually are attributed to lung cancer in lifetime never smokers. New epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic tumour characteristics have been identified **(Novello S. Ann Oncol. 2016)**.

In Belgium we had 8,196 new diagnoses of lung cancer in 2013, 70% males and 30% females. The 5-year relative survival proportion for the Belgian 2009-2013 cohort is about 16% in males and 23% in females. Most patients with NSCLC are diagnosed in a very advanced stage; stage III or stage IV. The incidence rate in Belgium for stage IV non-small cell lung cancer (NSCLC) is ± 4000 per year **(Belgian Cancer Register)**.

Lung cancer comprises small-cell lung cancer (SCLC; approximately 15% of all lung cancers) and non–small-cell lung cancer (NSCLC; approximately 85%). The latter can be further subdivided into two major histological subtypes being adenocarcinoma and squamous cell carcinoma. When tissue samples or cytologic samples of lung cancer show clear morphologic features of adenocarcinoma or squamous-cell carcinoma, the diagnosis can be firmly established. If morphologic evaluation reveals neuroendocrine features, the tumor may be classified as SCLC or NSCLC (probably large-cell neuroendocrine carcinoma). If there is no clear morphologic evidence of adenocarcinoma or squamous-cell carcinoma, the tumor is classified as NSCLC not otherwise specified (NOS). The category of tumors classified as NSCLC NOS can be further subdivided according to immunocytochemical or immunohistochemical analysis, mucin staining, or molecular data. NSCLC that is positive for cytokeratin 7 and thyroid transcription factor 1, with negative markers for squamous-cell cancer, is classified as NSCLC favoring adenocarcinoma. A tumor that is positive for one or more markers of squamous-cell cancer, such as p63, cytokeratin 5, or cytokeratin 6, with negative adenocarcinoma markers, is classified as NSCLC favoring squamous-cell carcinoma. If all markers are negative, the tumor is classified as NSCLC NOS **(Novello S. Ann Oncol. 2016)**.

The discovery of treatable oncogenic alterations led to the recommendation to include molecular testing in the standard approach allowing further classification of nonsquamous NSCLC. This includes testing for mutations in the gene encoding for epidermal growth factor receptor (EGFR), for the BRAF V600E mutation, and for translocations in the genes encoding anaplastic lymphoma kinase (ALK) and rat osteosarcoma 1 (ROS1). Furthermore, EGFR and ALK molecular testing should be used to select patients for targeted tyrosin kinase inhibitor (TKI) therapy. However, the proportion of patients harboring these mutations in their tumor cells is low, and most tumours become resistant to targeted treatment **(Pauwels P. Belg J Med Oncol. 2016)**.

Immunotherapy is a new paradigm for the treatment of NSCLC, and targeting the PD-1 pathway is a promising therapeutic option. The PD-1 receptor is an immune checkpoint inhibitor expressed on activated B and T cells that normally downmodulates excessive immune responses. Binding of PD-1 to its ligands on tumour cells suppresses T cells through a negative feedback loop, leading to evasion of the immune response. Pembrolizumab (MK-3475) is a highly selective, humanised, IgG4 monoclonal antibody against PD-1. Nivolumab, atezolizumab and durvalumab block either PD1 or its ligand. Moreover, the proportion of tumor cells expressing PD-L1 has been shown to correlate with better responses and survival for anti-PD-(L)1 treated NSCLC patients. As a consequence, testing for PD-L1 expression has been added to standard diagnostic practice (**Reck M. Immunotherapy. 2018**).

Current first-line treatment decisions for metastatic NSCLC patients are based on tumor histology, presence of genetic abberations and PD-L1 expression status. In patients with metastatic NSCLC who do not harbor genetic abberations, standard first-line treatment is platinum-doublet chemotherapy. Patients with high PD-L1 expression [PD-L1 Tumour Proportion Score (TPS) ≥ 50%] and no EGFR or ALK genomic tumor aberrations, Pembrolizumab monotherapy has become a standard of care. Pemetrexed maintenance therapy often follows first-line treatment with platinum-based chemotherapy in patients with non–squamous-cell NSCLC. With the introduction of novel therapies, however, accepted practices with respect to second and subsequent lines of therapy have changed substantially already during the last two years. Figure 1 gives an overview of the current treatment algorithm in metastatic NSCLC (**Reck M. and Rabe K. F. N Engl J Med. 2017**). Note that Bevacizumab is not reimbursed in Belgium for the treatment of NSCLC due to a suboptimal safety profile.

**Figure 1. Individualized Treatment Algorithm for NSCLC**

| Histology | Molecular Pathology | PD-L1 Status (TPS) | First-Line Therapy | Maintenance Therapy | Second-Line Therapy |
|---|---|---|---|---|---|
| Squamous-cell NSCLC | NA | <50% | Platinum-based chemotherapy<br>Gemcitabine and cisplatin+ necitumumab (EMA) | Necitumumab | Immunotherapy<br>Chemotherapy<br>Docetaxel+ramucirumab<br>Afatinib |
| | NA | ≥50% | Pembrolizumab | Pembrolizumab | Platinum-based chemotherapy |
| Non–squamous-cell NSCLC | Positive for EGFR mutation | NA | Erlotinib+bevacizumab<br>Erlotinib<br>Afatinib<br>Gefitinib | Erlotinib+bevacizumab<br>Erlotinib<br>Afatinib<br>Gefitinib | Osimertinib<br>Platinum-based chemotherapy |
| | ALK | NA | Crizotinib (also for ROS1-positive patients)<br>Ceritinib (FDA and EMA) | Crizotinib (also for ROS1-positive patients)<br>Ceritinib (FDA and EMA) | Ceritinib<br>Alectinib (after failure of crizotinib)<br>Platinum-based chemotherapy |
| | Wild type | <50% | Platinum-based chemotherapy (bevacizumab optional in eligible patients) | Pemetrexed (continuation or switch maintenance)<br>Bevacizumab (continuation maintenance) | Immunotherapy<br>Chemotherapy<br>Docetaxel+ramucirumab<br>Docetaxel+nintedanib (adenocarcinoma, EMA)<br>Erlotinib (EMA) |
| | Wild type | ≥50% | Pembrolizumab | Pembrolizumab | Platinum-based chemotherapy |

**Reference: (Reck M. and Rabe K. F. N Engl J Med. 2017)**

In October 2016, the FDA approved Pembrolizumab for the treatment of patients with previously untreated metastatic NSCLC that expresses PD-L1 with a TPS greater than or equal to 50% (TPS ≥ 50%). The results from the KEYNOTE-024 study demonstrated a significant improvement of both progression-free survival (PFS) and overall survival (OS) in favor of Pembrolizumab compared to platinum-based doublet chemotherapy. In December 2016, the Committee for Medicinal Products for Human Use (CHMP) also adopted a positive opinion for this new indication based on the KEYNOTE-024 study results and recommended a change to the terms of the marketing authorisation to be granted by the European Commission on January 31st 2017. Before that, the European Commission has adopted their Decision on 29 July 2016, approving KEYTRUDA monotherapy for the second-line treatment of NSCLC patients in the 28 EU member states, available in Belgium since May 2017. The treatment is available for patients in Belgium for first and second line since May 2017. Preliminary results of the KEYNOTE- 042, which is a randomized, open-label, phase 3 study evaluating the efficacy and safety of Pembrolizumab monotherapy versus platinum-based chemotherapy in 1274 untreated, advanced and metastatic NSCLC patients with a PD-L1 TPS ≥ 1% in the first-line treatment setting, were presented at ASCO 2018. The study met its primary endpoints of OS, demonstrating an improved survival benefit for patients with a PD-L1 TPS ≥ 1% treated with Pembrolizumab compared to platinum-based chemotherapy.

In the nearby future, combination therapies of immunotherapy with chemotherapy or other molecules may become usual practice in first-line treatment. KEYNOTE-021, Cohort G, a rigorously conducted trial, which demonstrated both a clinical benefit as well as a manageable safety profile in favor of the combination regimen with pemetrexed and carboplatin. Specifically, significant improvements in overall response rate (ORR) and PFS were observed for the KEYTRUDA combination regimen compared to pemetrexed and carboplatin alone, and no new safety signals were observed for the combination regimen. In addition, based on data presented at ESMO 2017, a trend in improvement in the secondary endpoint of OS, continued to be seen for the KEYTRUDA combination regimen compared to pemetrexed and carboplatin alone despite its cross-over design. KEYNOTE-189, which is a randomized, double-blind, phase 3 study evaluating the efficacy and safety of KEYTRUDA in combination with pemetrexed and either cisplatin or carboplatin versus pemetrexed and either cisplatin or carboplatin alone in 616 untreated, metastatic, nonsquamous, EGFR- and ALK-negative NSCLC patients in the first-line treatment setting, has demonstrated an impressive improvement of both OS and PFS regardless of PD-L1 expression **(Gandhi L. N Engl J Med. 2018)**. According to the results, the estimated rate of survival at 12 months was 69.2% in the patients who received Pembrolizumab plus chemotherapy versus 49.4% in the chemotherapy only group. The improvement in OS for Pembrolizumab combination therapy was observed across the three PD-L1 TPS categories: 61.7% vs 52.2% TPS<1%, 71.5% vs 50.9% TPS 1-49%, and 73.0% vs 48.1% TPS≥50%, respectively. Furthermore, the median PFS was 8.8 months and 4.9 months, respectively. Addition of Pembrolizumab did not appear to increase the frequency of adverse events of grade 3 or higher. Access for patients in Belgium might be possible by the end of 2018. Preliminary results of the KEYNOTE- 407, which is a randomized, double-blind, phase 3 study evaluating the efficacy and safety of Pembrolizumab in combination with carboplatin and either paclitaxel or nab- paclitaxel versus carboplatin

and either paclitaxel or nab- paclitaxel in 560 untreated, metastatic, squamous NSCLC patients in the first-line treatment setting, were presented at ASCO 2018. The study met its dual primary endpoints of OS and PFS, demonstrating an improved survival benefit for patients treated with Pembrolizumab in combination with chemotherapy compared to chemotherapy alone.

Nivolumab (Opdivo) was registered for squamous NSCLC by the end of May 2015, the registration for nonsquamous NSCLC followed one year later and acces was obtained for patients in Belgium since January 2017. The CHECKMATE-026 study, which is an international, randomized, open-label, phase 3 study evaluating the safety and efficacy of nivolumab versus platinum-based chemotherapy as first-line therapy in patients with (non)squamous stage IV or recurrent NSCLC with a PD-L1 expression level of 1% or more, did not meet its primary endpoint of PFS among patients with a PD-L1 expression level of ≥5%. Similar results regarding PFS were obtained for patients with a PD-L1 expression level of ≥1% **(Carbone D. P. N Engl J Med. 2017)**. On the other hand, the CHECKMATE-227 study met his co-primary endpoint, showing a significantly longer PFS with nivolumab plus ipilimumab compared with chemotherapy among patiens with advanced NSCLC and a tumor mutational burden of at least 10 mutations per megabase, irrespective of tumor PD-L1 expression level **(Hellmann M.D., N Engl J Med.2018)**.

Atezolizumab (Tecentriq) is registered for second line NSCLC since September 22nd 2017 based on the OAK-trial and is on the market in Belgium since March 1st 2018. By the end of July 2017, AstraZeneca reported the initial results from the ongoing MYSTIC trial in Stage IV lung cancer. Imfinzi (durvalumab) plus tremelimumab combination did not meet its primary endpoint of PFS compared to chemotherapy, but the trial continued as planned to assess the additional primary endpoints of OS for both Imfinzi monotherapy and Imfinzi plus tremelimumab combination.

December 2017, Roche announced detailed results from the Phase III IMpower150 study, which met its co-primary endpoint, showing that the combination of Tecentriq (atezolizumab) and Avastin (bevacizumab) plus chemotherapy provided a significant and clinically meaningful reduction in the risk of disease progression or death compared to Avastin plus chemotherapy in the first-line treatment of patients with stage IV or recurrent metastatic nonsquamous NSCLC. According to the results, patients who received Tecentriq and Avastin plus chemotherapy had a 38 percent risk reduction of their disease progression or death compared to those who received Avastin plus chemotherapy, with a respective median PFS of 8.3 months and 6.8 months. Furthermore, a doubling of the 1-year PFS rate was observed in favor of the combination of Tecentriq and Avastin plus chemotherapy, compared to Avastin plus chemotherapy (37% versus 18%) **(Reck M. ESMO IO Conference. 2017).** Registration and reimbursement in Belgium can be expected during 2018. As mentioned before, Avastin is not reimbursed in Belgium for the treatment of NSCLC as the combination of bevacizumab, paclitaxel and carboplatin was observed to be more toxic compared to the combination of carboplatin and pemetrexed for an equal efficacy **(Zinner R. G. J Thorac Oncol. 2015).** Recently presented at ASCO 2018, the IMpower-131 study, which is a randomized, double-blind, phase 3 study evaluating the efficacy and safety of Atezolizumab in combination with carboplatin and either paclitaxel (Arm 1) or nab- paclitaxel (Arm 2) versus carboplatin and nab- paclitaxel

(Arm 3) in 196 untreated, metastatic, squamous NSCLC patients in the first-line treatment setting, met its co-primary endpoint PFS, showing a significant improved progression-free survival benefit for patients treated with atezolizumab in combination with carboplatin and nab-paclitaxel compared to patients treated with carboplatin and nab-paclitaxel alone.

An overview of the current ongoing trials is shown in Figure 2. It includes an estimate of the new treatment modalities during 2018 and 2019.

**Figure 2: Ongoing trials - New treatment modalities during 2018-2019**

| Trial | Type | Phase | Line | Study arms | | | | | | SQ | NSQ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| KEYNOTE-189 | IO-chemo | 3 | 1 | Pembro + platinum doublet chemo + pemetrexed | | | | Platinum doublet chemo + pemetrexed then pembro (PD) | | | ✓ |
| KEYNOTE-407 | IO-chemo | 3 | 1 | Pembro + platinum doublet chemo then pembro mono (PD) | | | | Platinum doublet chemo then saline then pembro (PD) | | ✓ | |
| KEYNOTE-042 | IO-chemo | 3 | 1 | Pembro | | Platinum-based Chemotherapy | | | | ✓ | ✓ |
| CHECKMATE-227 | IO-chemo IO-IO | 3 | 1 | Nivo[b] | Nivo + ipi[b] | Chemo[b] | Nivo + ipi[a] | Nivo + chemo[a] | Chemo[a] | ✓ | ✓ |
| CHECKMATE-722 | IO-chemo IO-IO | 3 | 2 | Nivo + ipi + platinum doublet chemo | | Nivo + ipi | | Platinum doublet chemo | | ✓ | ✓ |
| IMpower110 | IO-chemo | 3 | 1 | Atezo | | | | Gemcitabine + cis/carb (PD) | | ✓ | ✓ |
| IMpower130 | IO-chemo | 3 | 1 | Atezo + nab-P + carboplatin | | | | nab-P + carboplatin | | | ✓ |
| IMpower131 | IO-chemo | 3 | 1 | Atezo + nab-P + carboplatin | | Atezo + paclitaxel + carboplatin | | nab-P + carboplatin | | ✓ | |
| IMpower132 | IO-chemo | 3 | 1 | Atezo + carboplatin/cisplatin + pemetrexed | | | | Carboplatin/cisplatin + pemetrexed | | | ✓ |
| NEPTUNE | IO-IO | 3 | 1 | Durva + tremelimumab | | | | Platinum doublet chemo | | ✓ | ✓ |
| MYSTIC | IO-IO | 3 | 1 | Durva | | Durva + treme | | Platinum doublet chemo | | ✓ | ✓ |
| ARCTIC | IO-IO | 3 | 3 | SOC[a] | Durva[a] | SOC[a] | Durva[b] | Durva + treme[b] | Treme[b] | ✓ | ✓ |
| POSEIDON | IO-chemo | 3 | 1 | Durva + treme + SOC | | Durva + SOC | | SOC | | ✓ | ✓ |

## 1.2 Rationale

The treatment landscape of metastatic NSCLC is rapidly evolving. There are new diagnostic and treatment options available in the coming months and years. New combination treatments will give different solutions to pneumo-oncologists who might be guided by certain patient and tumor characteristics. The link between patient and tumor characteristics in untreated stage IV NSCLC patients and systemic treatment choices need to be investigated, allowing the identification of possible treatment issues, data gaps and/or areas of improvement.

This cross-sectional study will document systemic treatment choice linked to patient, tumor and site characteristics. A better understanding of the current clinical practice in the Belgian sites should allow the medical community to have a better insight on which characteristics impact treatment choice in real life, helping to determine certain health care and scientific educational needs.

# 2 Objectives and Hypotheses

## 2.1 Primary Objective(s) & Hypothesis(es)

The objective of this study is to investigate the relation between patient, tumor and site characterstics and systemic treatment choices of stage IV untreated NSCLC.

Systemic treatment choices and best supportive care are defined as :

1) Chemotherapy (chemo)
2) Immunotherapy (IO)
3) Immuno combined therapies (IO+IO)
4) IO+chemo
5) IO+bevacizumab+chemo (IO+bev+chemo)
6) Best supportive care (BSC).

It is hypothesized that there is a relation between the systemic treatment choice and the explanatory variable categories listed below. It is assumed that the variable categories have a different weight for the different systemic treatment options:

- Patient demography characteristics
- Medical history
- Co-morbidities
- Autoimmune disease
- Current/recent medication
- Prior cancer treatment in earlier stage
- Site characteristics

The details of the variables can be found in the section 4.2.

For each of the variable categories, it will be queried whether the variable category had an impact on the systemic treatment choice.

# 3 METHODOLOGY

## 3.1 Summary of Study Design

This is a multicenter non-interventional cross-sectional study in stage IV NSCLC patients on first-line systemic treatment coming to the consultation.

Consecutive patients with metastatic stage IV NSCLC selected for systemic treatment or best supportive care will be included in the trial at the time the patient signed the informed consent form (ICF). Patients that were selected for systemic treatment, should have received at least their first dose and a maximum of one cycle of the same treatment.

The pneumo-oncologist that treats the patient will fill in the CRF, indicating the systemic treatment option and the link with the variable categories that impacted positively or negatively the systemic treatment option. The actual value of variables linked to a variable category will also be recorded in the CRF.

A questionnaire has to be filled in characterizing the site and allowing the site to be assigned to a group based on the number of newly diagnosed patients per year with lung cancer and whether the site participates in interventional clinical trials. All sites will be retrospectively divided in four groups; high number of patients per year (more than median NSCLC patients per year) and participating in interventional clinical trials, high number of patients but not participating in interventional clinical trials, low number of patients (less than median NSCLC patients per year) and participating in interventional clinical trials or low number of patients and not participating in interventional clinical trials.

## 3.2 Study Population

210 eligible stage IV NSCLC subjects treated in approximately 21 Belgian hospitals starting first-line treatment or best supportive care will be enrolled in line with inclusion and exclusion criteria. The estimated recruitment period to reach the target of 210 eligible patients is 5 months. Upon inclusion of 210 eligible patients the recruitment will be closed. Only a maximum of 10% of subjects can be enrolled by one site.

## 3.3 Inclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

In order to be eligible for participation in this trial, the subject must:

- Have voluntarily agreed to participate by giving written informed consent/assent for the trial.

- Have a histologically or cytologically confirmed diagnosis of stage IV NSCLC on first-line (1L) systemic treatment.
- Have received at least their first dose of the selected systemic treatment and a maximum of 1 cycle of the same treatment. Patients that were selected to receive best supportive care will not have to comply to this inclusion criterion.
- Be ≥ 18 years of age on day of signing informed consent.

### 3.4 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

- Has received prior systemic treatment for their metastatic NSCLC before the first dose of trial treatment. However, subjects who received adjuvant or neoadjuvant therapy during an earlier stage of their disease, but evolved to stage IV, are eligible.
- TKI selected as first-line systemic treatment.
- Is participating in an interventional trial or medical need program.

# 4 Variables and Epidemiological Measurements

## 4.1 Outcomes

Systemic treatment choices and best supportive care are defined as :

1) Chemotherapy (chemo)
2) Immunotherapy (IO)
3) immuno combined therapies (IO+IO)
4) IO+chemo
5) IO+bevacizumab+chemo (IO+bev+chemo)
6) best supportive care (BSC).

## 4.2 Covariates

The actual values of the following covariates will be recorded within the eCRF, which can be discrete or continuous in nature. In addition to the actual values, the investigator will also have to indicate whether the covariates had an impact on the treatment choice in a binary fashion.

✓ Patient demography characteristics at study entry:
- Age
- Gender:
  - F
  - M
- Weight loss
  - (%)
- Smoking status:
  - Current
  - Former (≥ 1 year)
  - Never
  - Not known

- ECOG status:
  - 0
  - 1
  - 2
  - 3-4
- Patient's preference
  - Yes
  - No

✓ Medical history:
- Metastatic disease stage:
  - M1a
  - M1b

  - M1c
- Tumor Burden:
  - Tumor size
  - Number of metastatic sites
- Brainmets:
  - No
  - Symptomatic
  - Asympotomatic
  - Treated with SRT
  - Treated with WBRT
- Livermets
  - Present
  - Not present
- Concomitant malignancies
  - Present
- Histology:
  - Squamous
  - Nonsquamous
  - NOS
- IHC PD-L1:
  - PD-L1 TPS <1%,
  - PD-L1 TPS 1 - 49%
  - PD-L1 TPS ≥50%
- High TMB (≥ 10 mutations/Mb (Cfr. CHECKMATE-227)
  - Present
  - Not present
- Testing
  - Turn-around-time
  - Not tested
  - Biopsy availability
  - Type of NGS testing (e.g. whole exome, gene panel, platform, …)

✓ Comorbidities
- Myocardial infarction in the last year
- Congestive heart failure
- Peripheral vascular disease
- Hypertension
- Cerebrovascular event in the last year
- Transient ischemic attack in the last year
- Diabetes without complications
- Renal disease
- Liver disease
- Hematological disease
- Chronic obstructive pulmonary disease
- Chronic infections
- Mental disorders

✓ Autoimmune disease
- Active inflammatory interstitial lung disease
- Non-active inflammatory interstitial lung disease
- Active inflammatory bowel disease (IBD)
- Non-active IBD
- Active inflammatory joint disease
- Non-active inflammatory joint disease
- Active psoriasis
- Non-active psoriasis
- Active connective tissue disease
- Non-active connective tissue disease

✓ Current/recent medication
- Low dose corticosteroids
- High dose (≥10 mg/day Prednisolone or eq) corticosteroids
- Other immunosuppressants (i.e. Anti-TNF-α, MMF, …)
- Antibiotics

✓ Prior cancer treatment in earlier stage NSCLC
- Single Modality treatment
- Multi-Modality treatment
- Surgery / radiotherapy
- Previous IO treatment
- Year of treatment

For each variable category, the physician has to determine whether it had an impact on his/her treatment decision, yes or no. For all variable categories, for whom the answer was yes, the physician has to select the three most important variable categories that impacted his treatment decision.

# 5 Study Flow Chart

| | V1 | V2* |
|---|---|---|
| **Informed consent** | X | |
| **Inclusion** | X | |
| **Exclusion** | X | |
| **Systemic treatment option** | | X |
| **Variable categories impacting treatment choice** | | X |
| **Patient demography characteristics** | | X |
| **Medical history** | | X |
| **Co-morbidities** | | X |
| **Autoimmune disease** | | X |
| **Baseline medications** | | X |
| **Prior cancer treatment in earlier stage** | | X |
| **Site characteristics** | | X |

*time of V2 and V1 can coincide. V2 will only be created if V1 is successfully passed.

It is allowed that information is collected retrospectively.

# 6 STUDY PROCEDURES

## 6.1 Study Procedures

The Study Diagram in Section 5 summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety.

### 6.1.1 Administrative Procedures

#### 6.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

#### 6.1.1.2 Consent and Collection of Specimens for Future Biomedical Research (Required for Studies Collecting DNA)

Not applicable.

#### 6.1.1.3 Medical History

Only relevant information based on the CRF will be collected.

#### 6.1.1.4 Prior and Concomitant Medications Review

Only relevant information based on the CRF will be collected.

##### 6.1.1.4.1 Prior Medications

Only relevant information based on the CRF will be collected.

##### 6.1.1.4.2 Concomitant Medications

Only relevant information based on the CRF will be collected.

#### 6.1.1.5 Assignment of Screening Number

All consented patients will be given a unique depersonalized identification number. The patient number identifies the patient for all procedures occurring during observation. Data protection and other applicable regulatory requirements will be fulfilled.

#### 6.1.1.6 Assignment of Randomization Number

Not applicable.

# 7 Safety Reporting and Related Procedures

**Introduction**

This is a primary data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

## 7.1 Adverse Event Reporting

### 7.1.1 INVESTIGATOR RESPONSIBILITY:

If the investigator becomes aware of any serious adverse event (SAE), including death due to any cause, or non-serious adverse reaction (NSAR) following the use of any Merck product, the event must be reported according to Table 1. The investigator must evaluate each SAE for causality and record causality on the AE form for each event reported.

Similarly, pre-specified Health Outcomes of Interest (HOIs) that meet criteria for SAE/NSAR, special situations, and any spontaneously reported AEs must be reported according to Table 1.

**Table 1: AE Reporting Timeframes and Process for Investigators and Vendors**

| EVENT TYPE | INVESTIGATOR TIMEFRAME | VENDOR TIMEFRAME |
|---|---|---|
| | **Investigator to Vendor [1], [2] OR Investigator to Merck [3]** | **Vendor to Merck [4]** |
| SAE, regardless of causality (primary data collection)<br>Serious pre-specified HOI<br>Serious Special Situation, regardless of causality | 24 hours from receipt | 2 BD/3 CD from time of receipt from investigator |
| NSAR<br>Non-Serious pre-specified HOI if NSAR<br>Non-serious Special Situation, regardless of causality | 10 CD from receipt | 10 CD from time of receipt from investigator |
| Spontaneously reported adverse events for Merck products-submit using above timeframes | | |
| If the investigator elects to submit AEs for **non-Merck products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations. Note: Per **[2],** below, AEs for comparators must be entered in study database. | | |
| Follow-up to any event-submit using above timeframes | | |
| BD-Business Day; CD-Calendar Day | | |
| **[1]** AE reports from investigators must be transmitted via fax, secure email (if available), or entered directly into vendor's electronic data collection (EDC) platform, if utilized.<br>**[2] Investigator to Vendor**: Applies to events for **Merck study product**, **non-Merck comparators**, and ***other*** **Merck products** when a VENDOR is managing AE reporting from investigator to Merck. Events for **Merck study product** and **non-Merck comparators** are entered in study database for tabulation in study report. Events for ***other*** **Merck products** are *not entered in study database* but must be forwarded to Merck for regulatory reporting.<br>**[3] Investigator to Merck:** Applies to studies that do not have a vendor managing AEs.<br>**[4] Vendor to Merck:** Applies to events for **Merck study product** and ***other*** **Merck products** if the vendor is managing AE reporting between investigator and Merck. Not applicable for studies not using a vendor for AE reporting. | | |

**Submitting AE reports to Merck Global Safety: All AEs must be submitted to AER Mailbox FAX** #215-661-6229 **(US), or toll-free fax 1-800-547-5552 (ex-US and US availability), in English using an AE form (attached) for reporting to worldwide regulatory agencies as appropriate.**

## 7.2 DEFINITIONS

### 7.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

### 7.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

### 7.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

### 7.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 7.2.3.

### 7.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent
- Unexpected Therapeutic Benefit/Effect

### 7.2.6 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are pre-specified clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnosis, treatment or procedures. Examples of HOIs include syncope or hypoglycaemia collected as study endpoints. HOIs must be assessed as part of AE collection and may meet criteria for AE reporting. Specifically, the investigator must assess each HOI for serious criteria and causality. If the HOI meets criteria specified in the protocol for AE reporting, then it must be reported as such.

### 7.2.7 Sponsor's product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

### 7.2.8 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

**Primary Data Collection**

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

# 8 Product Quality Complaint Reporting

## 8.1 INVESTIGATOR RESPONSIBILITY:

Any occurrence of a product quality complaint for a Merck product identified during the conduct of the study, must be reported by the study investigator or qualified designee using the Product Quality Complaint (PQC) Reporting Form following the directions in Table 2. The PQC Reporting Form must be fully completed in English. Once the PQC Reporting Form is submitted, the investigator or designee may be contacted for further information.

If both an AE and a PQC occur, the AE should be reported according to the AE reporting requirements in the protocol and the PQC should be reported per Table 2.

**Table 2: PQC Reporting Timeframes and Process for Investigators**

| **EVENT TYPE** | **INVESTIGATOR TIMEFRAME** |
|---|---|
| | **Investigator to Merck** |
| **PQC** | 24 hours from receipt |
| PQC reports must be submitted via e-mail by the investigator to the local designated point of contact (DPOC) using a PQC form. | |
| **Submitting PQC reports to Merck: All PQCs must be submitted to the local DPOC in English using a PQC form. The following e-mail addresses should be used by country:** **dpoc_belux@merck.com** | |

## 8.2 DEFINITIONS

### 8.2.1 Product Quality Complaint (PQC).

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

### 8.2.2 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

# 9 Statistical Analysis Plan

## 9.1 Statistical Methods

The statistical analysis will be performed using SAS software 9.2.

### 9.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, hazard ratios, incidence rates, test/retest reliability)

Systemic treatment choices and best supportive care are defined as :

1) Chemotherapy (chemo)
2) Immunotherapy (IO)
3) immuno combined therapies (IO+IO)
4) IO+chemo
5) IO+bevacizumab+chemo (IO+bev+chemo)
6) best supportive care (BSC).

Descriptive statistics of the relation between variable category and systemic treatment choice will be provided. The descriptive statistics will involve the number of times (frequency) a variable category is indicated as being linked to a systemic treatment option.

For each of the variable categories that are linked to a systemic treatment choice, descriptive statistics of the underlying variables will be provided. These descriptive statistics will consist of:

- For the quantitative variables, summary statistics including mean, standard deviation, 95% confidence interval on the mean, minimum, first quartile, median, third quartile, maximum, and number of available and number of missing observations.
- For the categorical variables, frequencies and percentages.

In an exploratory analysis, a penalized hierarchical logistic regression model for discrete choices will be used to evaluate the effect of the potential explanatory variables on the 1$^{st}$ line systemic treatment.

### 9.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

No secondary objectives.

#### 9.1.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

Investigate if there are differences in the link between variable categories and systemic treatment choices for the 4 types of sites that are defined.

### 9.2 Bias

#### 9.2.1 Methods to Minimize Bias

It will be emphasized to the participating centres that consecutive patients need to be included in the study.

210 eligible subjects will be included in approximately 21 participating sites with a maximum of 10% inclusion by each site. The risk of statistical bias is minimized by the fact that all sites start the inclusion period at the same time. However, toward the end of the inclusion period, the imposed maximum inclusion site limit may potentially lead to statistical bias, which will be described in detail in the study manuscript

#### 9.2.2 Adjustment for Multiple Comparisons

Not applicable.

#### 9.2.3 Limitations

The study is cross-sectional.

### 9.3 Sample Size and Power Calculations

The study is descriptive and no sample size calculations will be performed. In order to have a representative picture of the pneumo-oncologists' NSCLC systemic treatment decision in Belgium, a minimum of 200 patients need to be enrolled in the study.

A maximum of 10% of the total study population can be enrolled in a site to avoid bias. A minimum of 30 patients need to be included in a subgroup for any given analysis.

# 10 ADMINISTRATIVE AND REGULATORY DETAILS

## 10.1 Confidentiality

### 10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol. The study and its results will be registered on a publicly accessible database.

### 10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative) or Institutional Review Board/Independent Ethics Committee (IRB/IEC), may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

### 10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

## 10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

## 10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice; and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

## 10.4 Compliance with Study Registration and Results Posting Requirements

Not applicable.

## 10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted and data are generated,

documented, and reported in compliance with the protocol, accepted standards of Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

## 10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

For an outsourced study the institutional policies of the vendor should be followed for development of data management plans. However, the vendor should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

# 11 References

1. Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 3), EMA/876333/2011 Rev 3

2. EU Directive 2001/20/EC on Clinical trials and detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal product for human use, ENTR/CT 3 Revision 2 dated April 2006.

3. The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. Geneva, WHO, 2002.

4. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiology Assessment. Rockville, MD, Food and Drug Administration (FDA), March 2005.

5. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

6. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf.

# 12 Appendices

Not applicable

# 13 Attachments

MSD **GLOBAL PHARMACOVIGILANCE INTAKE FORM**

| | | | | | | |
|---|---|---|---|---|---|---|
| Initial ☐ F/U ☐ | Local Ref Number: | MARRS ID: | HA/BP Ref. #: | DPOC/PQC Ref. #: | Receipt Date: (dd-MM-yyyy) | Central Receipt Date: (dd-MM-yyyy) |
| | | | | | | |

**Case Details**

| Country of... | Source Type: | | | | Case Classification: | | | |
|---|---|---|---|---|---|---|---|---|
| Incidence | Spontaneous ☐ | Solicited ☐ | | | PSP ☐ | Market Research ☐ | | |
| Patient " | Literature Study ☐ | Literature Marketed ☐ | | | PSMP ☐ | LCE ☐ | | |
| Reporter " | | | | | Social Media ☐ | Non-valid ☐ | | |
| Program/ Study ID | Program/Study Name or Description<br>This is a non-interventional study/program with no HCP assessment of seriousness or causality ☐ | | | | | | | |

**PATIENT** *(Complete in accordance with local privacy law(s))*

**Patient**

| | | | | |
|---|---|---|---|---|
| Patient Name or Initials | Anonymized: ☐ | | Unknown: ☐ | |
| | First/Last Name: | | Initials: | |
| Patient Demographics | Gender: | Male ☐ | Female ☐ | Unknown ☐ |
| | Date of Birth: / / | | Age: - | Age Group: - |
| | Weight: - | | Height: - | |

**REPORTER** *(Complete in accordance with local privacy law(s))*

**Reporter**

| | | | | |
|---|---|---|---|---|
| Reporter Contact Details | Anonymized: ☐ | Unknown: ☐ | Telephone: | |
| | Name: | | Fax: | |
| | Address: | | E-mail address: | |
| Reporter Type | Company Rep ☐ | Consumer ☐ | Lawyer ☐ | Other ☐ |
| | Other Health Prof ☐ | Pharmacist ☐ | Physician ☐ | Authority ☐ |

**EVENT(S)**

**Event(s)**

| Reported term | Onset date | Stop date | Outcome | Seriousness | Reported Causality |
|---|---|---|---|---|---|
| | / / | / / | - | - | - |
| | / / | / / | - | - | - |
| | / / | / / | - | - | - |
| | / / | / / | - | - | - |
| | / / | / / | - | - | - |
| | / / | / / | - | - | - |
| | / / | / / | - | - | - |

**PRODUCT(S)**

**Product(s)**

| Trade/generic name | S/C* | Formulation** | Indication | Start Date | Stop Date | Action Taken | Batch/Lot# |
|---|---|---|---|---|---|---|---|
| | - | | | / / | / / | - | |
| | - | | | / / | / / | - | |
| | - | | | / / | / / | - | |
| | - | | | / / | / / | - | |
| | - | | | / / | / / | - | |
| | - | | | / / | / / | - | |
| | - | | | / / | / / | - | |

* S = Suspect Product, C = Concomitant Product ** Include Dose + Frequency when available or specify in Description of Event(s) Section

**DESCRIPTION OF EVENT(S) (incl relevant tests, history and observations)**

| | | | |
|---|---|---|---|
| Follow-up comment: | | | |
| Form Entered By: | Date (dd-MM-yyyy): | QC check by: | Date: (dd-MM-yyyy): |

Confidential Page 1 of 1 PV-GLB-01-ER04, v2.0

# 14 SIGNATURES

### Sponsor's Representative

| TYPED NAME | SIGNATURE | DATE |
|---|---|---|
| _____ | _____ | _____ |

### Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 7 – Safety Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

| TYPED NAME | SIGNATURE | DATE |
|---|---|---|
| _____ | _____ | _____ |