OBSERVATIONAL PLAN

TGCT Observational Platform Project

A Disease Registry for patients with tenosynovial giant cell tumors (TGCT), also known as pigmented villonodular synovitis (PVNS) and giant cell tumor of the tendon sheath (GCT-TS)

DS-ONC-01-15-EU

Sponsor:

Daiichi Sankyo Europe GmbH

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Germany

PPD

Version Number: 4.0 VALID ONLY FOR US

Date of Version: 15 OCT 2020

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1. SIGNATURES

1.1. Daiichi Sankyo

PPD
Daiichi Sankyo Europe GmbH

Date

PPD
Daiichi Sankyo Europe GmbH

Date

PPD
Daiichi Sankyo Europe GmbH

Date

PPD
Daiichi Sankyo Europe GmbH

Date

1.2. Steering Committee

PPD Date
Leiden University Medical Center

PPD Date
Leiden University Medical Center

PPD Date
Istituto Ortopedico Rizzoli

PPD Date
Istituto Ortopedico Rizzoli

PPD Date
Istituto Nazionale Tumori-Fondazione IRCCS

PPD Date
West German Cancer Center

PPD Date
Memorial Sloan Kettering Cancer Center

PPD Date
University Castilla-La Mancha

2. SUMMARY OF CHANGES

New Version	Previous version	Change
4.0 dated 15 Oct 2020	3.0 dated 18 Jul 2017	Documentation of Adverse Drug Reactions updated following approval of pexidartinib in the US on 02Aug2019; Administrative changes: change in study statistician, data manager to sign protocol; glossary updated; dates for milestones and final report updated
3.0 dated 18 Jul 2017	2.0 dated 14 Oct 2016	Country list updated to add the US
3.0 dated 18 Jul 2017	3.0 dated 18 Jul 2017	Total Patient Number required for the study changed from 100 to 200
3.0 dated 18 Jul 2017	2.0 dated 14 Oct 2016	Overall site number increased from “approximately 15” to “up to 20”
3.0 dated 18 Jul 2017	2.0 dated 14 Oct 2016	PPD added to the lists of the steering committee members and national coordinators
3.0 dated 18 Jul 2017	2.0 dated 14 Oct 2016	PPD excluded from Steering Committee members list
3.0 dated 18 Jul 2017	2.0 dated 14 Oct 2016	PPD and PPD added to the list of the national coordinators for Spain and Austria respectively
2.0 dated 14 Oct 2016	1.0 dated 23 May 2016	Inclusion criteria updated to confirm patients must be diagnosed histologically
2.0 dated 14 Oct 2016	1.0 dated 23 May 2016	Inclusion criteria updated to remove the restriction on patients in an interventional study

2.0 dated 14 Oct 2016	1.0 dated 23 May 2016	Section 10.4 updated to reflect that co-morbidities, employment status and MRI results will be collected throughout the observational period not just at baseline
2.0 dated 14 Oct 2016	1.0 dated 23 May 2016	Addition that the site needs to confirm the patient is not participating in the registry at another site
2.0 dated 14 Oct 2016	1.0 dated 23 May 2016	Removal of question regarding the patients race
2.0 dated 14 Oct 2016	1.0 dated 23 May 2016	The entire Brief Pain Inventory Questionnaire shall be completed not just the worst pain scale item.

3. GLOSSARY

AE	Adverse Event
ADR	Adverse Drug Reaction
CA	Competent Authority
CRO	Contract Research Organisation
DB	Database
DM	Data Management
DS	Daiichi Sankyo
DSE	Daiichi Sankyo Europe GmbH
eCRF	Electronic Case Report Form
FPI	First Patient In
GCT-TS	Giant cell tumor of the tendon sheath
GEP	Good Epidemiological Practice
HEOR	Health Economic Outcome Research
ICF	Informed Consent Form
IEC	Independent Ethics Committee
LPO	Last Patient Out
NIS	Non-interventional Study
PRO	Patient Report Outcome
PVNS	Pigmented villonodular synovitis
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SC	Steering Committee
SAS®	Statistical Analysis Software
SDTM	Study Data Tabulation Model (CDISC)
TGCT	Tenosynovial Giant Cell Tumor

4. RESPONSIBLE PARTIES

Project Leader Daiichi Sankyo Europe GmbH	PPD
Coordinating Investigator/Chair of Steering Committee Leiden University Medical Center	PPD
Study Statistician	PPD
Contract Research Organisation Project Leader SSS International Clinical Research	PPD

4.1. Steering Committee (if applicable)

The Steering Committee is the primary group with supervisory responsibility for all aspects of the conduct of the T.O.P Project (DS-ONC-01-15-EU). It has contributed to the design of the registry, is ensuring the maintenance of the scientific quality and integrity of conduct and will support the Daiichi Sankyo project team during the course of the study. The Steering Committee will evaluate the results together with the Daiichi Sankyo project team and will review the study report as well as publications based on the results of the registry.

The Steering Committee (SC) consists of external renowned members of the scientific community with a strong medical background in the treatment of TGCT. The responsibilities of the SC are:

- Participation in Steering Committee meetings
- Scientific and medical advice prior, during and after the Registry, including evaluation and interpretation of the results of the Registry
- Advice in observational plan & eCRF development
- Support the performance of the Registry as a contact person for sites and other personnel involved in the Registry
- Scientific and medical advice regarding the Registry results
- Support and advice on publication, abstracts, posters, journals and congresses in connection with the Registry.

In addition, selected persons of the Daiichi Sankyo Project Team were specially assigned as Steering Committee members from the following functions: Clinical Operations, Health Economics and Outcome Research (HEOR), Biostatistics. These members will participate in the meetings as non-voting members.

4.2. List of participating centres

A list of the principal investigators and all collaborating institutions and investigators is kept in a stand-alone document and can be made available upon request. Listed below are the details of the coordinating investigators for each country.

Chair of Steering Committee and National Coordinator for Netherlands	PPD	PPD
National Coordinator for France	PPD	PPD
National Coordinator for Germany	PPD	PPD
National Coordinator for Italy	PPD	PPD
National Coordinator for Spain	PPD	PPD
National Coordinator for the United Kingdom	PPD	PPD
National Coordinator for Austria	PPD	PPD
National Coordinator for the United States of America	PPD	PPD

5. SUMMARY

Study/Registry Title	TGCT Observational Platform Project: A Disease Registry for patients with tenosynovial giant cell tumors (TGCT), also known as pigmented villonodular synovitis (PVNS) and giant cell tumor of the tendon sheath (GCT-TS)
Protocol version identifier	DS-ONC-01-15-EU
Date of last protocol version	18-Jul-2017
Centres/Study Sites/Countries	Up to 20 sites located in the Netherlands, Germany, Italy, France, Austria, Spain, the UK and US.
Milestones	First Patient In (FPI) / Start of Data Collection: Nov 2016 Last Patient Out (LPO) / End of data Collection: Apr 2021 Snapshot Report: Dec 2017
Final Report	Q3 2021
Rationale and Background	The purpose of the TGCT Disease Registry is to explore the real world management of patients diagnosed with diffuse TGCT, to understand the management of TGCT patients, the patient flow and to understand the relapse rates of the surgical series. Scientific Background: Tenosynovial giant cell tumor (TGCT) is a rare, benign, but potentially locally aggressive and recurrent disease. It is characterized by synovial hyperplasia and pigment deposition inside the joints, tendon sheaths and bursae. Evidence shows that it mainly affects large joints such as the knee and the hip and is extremely rare in the temporomandibular joint and spine. There are two forms of TGCT, localized and diffuse. When the tumor involves the tendons that support the joint, or occurs in just one area of the joint, it is called localized TGCT. This type usually responds well to surgical treatment. The diffuse type is more widespread and involves an entire joint. It tends to be more destructive and is more difficult to treat. TGCT is rare, with an estimated annual incidence of 1.8 cases per million for PVNS and 9.2 cases per million for GCT-TS, in the United States (Myers 1980). TGCT is a challenging disease to manage and the aggressiveness of the tumour is often underestimated. The current standard of care is surgical resection of the tumor as completely as possible in order to: (1) reduce pain, stiffness, and joint destruction caused by the disease process; (2) improve function; and (3) minimize the risk of recurrence. Patient outcome following surgery depends on multiple factors including the location and extent of disease as well as on a thorough diagnostic evaluation and quality of surgery. Currently, there are no systemic

	agents approved for the treatment of TGCT. Currently studies in TGCT mainly focus on its radiological and pathological characteristics and surgical outcomes. Little effort has been made to address its clinical characteristics and natural history. Therefore, this prospective registry will be conducted to evaluate the clinical profile and management of the disease in Europe.
Research Question and Objectives	To gain detailed insight on the characteristics and management patterns of patients with diffuse TGCT (including functional details measured pre and post treatment), to explore the patient pathway in a real world setting and collect data on patients' quality of life.
Study Design	Multinational, multicentre, prospective, non-interventional observational disease registry.
Setting	• 2 year recruitment period • 2 year follow up per patient • Electronic data capture • Number of recommended data collection points: 1 baseline and 2 follow up data collections at 12 and 24 months
Population/Patients	It is the aim to document 200 patients with TGCT. However, the enrolment of patients will be stopped at the latest 24 months after enrolment of the first patient regardless of the total number of patients enrolled.
Inclusion/exclusion criteria	As this is a non-interventional study, there are no explicit selection criteria besides: - Written informed consent for participation in the study (ICF) - Age ≥ 18 years - Patients with diffuse TGCT (diagnosed histologically) confirmed naïve or recurrent case
Variables (Observation Criteria)	Data on the patients' TGCT (both current status and history) will be collected at an initial baseline data collection point. Patient reported outcomes on TGCT symptoms and quality of life will also be assessed at this time as well as health resources used in the past 24 months. The patient will also attend two further data collections at 12 months and 24 months (as this is routine clinical practice). Details of the patients' TGCT will be recorded and associated patient reported outcomes and health resource utilization will be assessed again. This will also be done at any time the patient attends the site. Optionally, the patients may also complete the PRO questionnaires on pain, stiffness, physical function, quality of life and health resource utilization between the data collection points at 6 and 18 months.
Data Sources	As this is a non-interventional observational study, only data from routine clinical practice will be documented. To facilitate accurate recording of data, patients can fill in a memory aid to note important details. This can then serve also as a memory aid during the visits. Patients can also optionally complete patient reported outcome

	questionnaires to report on the details of their TGCT and Quality of Life.
Planned Sample Size, Data analysis	As this is a rare disease the recruitment of patients within the scheduled 2-years treatment period will be difficult. Therefore, no formal sample size consideration has been performed. All collected variables will be used in the statistical analysis. Binary, categorical, and ordinal parameters will be summarised by means of absolute and percentage numbers within the various categories. Numerical data will be summarised by means of standard statistics. In addition, adequate graphs (e.g. bar charts, box-whisker plots) may be presented. The purpose of all analyses will be purely descriptive/exploratory.
Quality Control	This study will be conducted according to the rules Good Epidemiological Practice (GEP) and STROBE guidelines. Related quality control mechanisms (e.g. data plausibility checks, monitoring of data) will be performed accordingly

6. AMENDMENTS TO THE OBSERVATIONAL PLAN

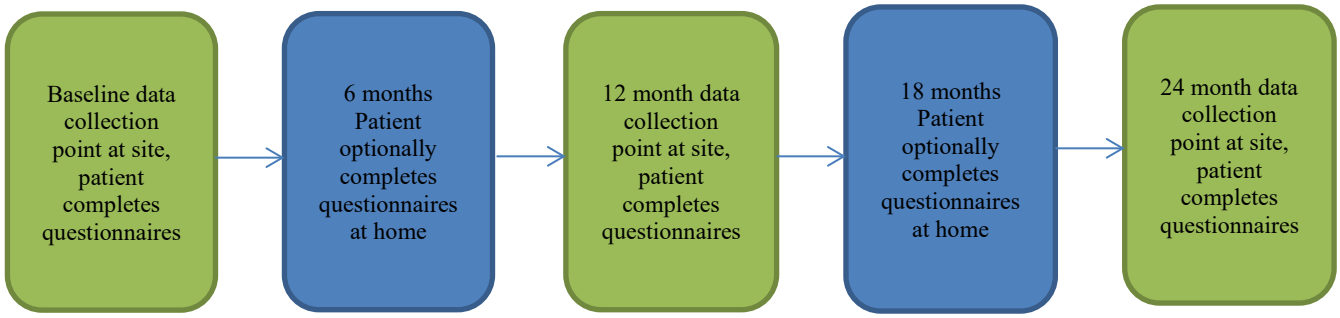
In case of essential changes to the existing Observational Plan the investigators have to be informed as well as the respective local and/or competent authorities and Independent Ethics Committees (IEC) if required by local laws or regulations.

7. MILESTONES

Table 1: Study milestones

FPI / Start of data collection	Q4 2016
LPI	Q1 2019
LPO/ Planned end of data collection	Q2 2021
Data Snapshot	Q4 2017
Final Study Report	Q3 2021

7.1. Study Flow Chart



* Additional Data Collection points may occur at any time the patient visits the site, even if it is outside this schedule

8. RATIONALE AND BACKGROUND

8.1. Background

Pigmented villonodular synovitis (PVNS) and giant cell tumors of the tendon sheath (GCT-TS) are members of a single condition referred to as tenosynovial giant cell tumor (TGCT), localized and diffuse type, and have a common pathogenesis.[1] They are proliferative neoplasms involving the synovium and tendon sheaths that typically present in young and middle-aged adults of both sexes. Diffuse-type TGCT tends to be more aggressive, often recurring locally (8%–56%) after surgery, and is capable of malignant transformation.[2] In a retrospective analysis of 49 previously untreated patients with PVNS of the knee (12 localized, 37 diffuse), the overall relapse rate after surgery was 43%, with 52% of diffuse-type relapsing within 5 years.[3]

Although rare, TGCTs are likely underreported and underdiagnosed, with an estimated overall annual incidence in the United States of 11 cases per million, including 1.8 cases per million for PVNS, and 9.2 cases per million for GCT-TS.[4] More recent nationwide pathology data from the Netherlands estimate the annual incidence of TGCTs to be 49.7 cases per million.[5]

The current standard of care for TGCT is surgical resection of the tumor as completely as possible to reduce symptoms and joint destruction, improve function, and minimize the risk of recurrence.[6] Although surgery is the standard of care, it has been observed that expression of the colony-stimulating factor 1 gene is elevated in most TGCT tumors[7] and may, in many cases, be driven by a gene translocation.[8,9] This possibility has led to the development of therapies targeting the colony-stimulating factor 1 receptor for which regression in tumor volume is the primary indicator of response.[10]

Treatments for rare diseases, especially innovative treatments must now also compete with technologies for other indications, in terms of their benefits and risks for the patients and resources needed. A range of access hurdles are already in use by payers/budget holders to curb physicians' prescriptions. At their heart is the goal of improving effectiveness and value in healthcare as a way of balancing growing costs and increasingly limited resources. Constantly higher levels of performance are demanded in terms of improved patient-relevant outcomes without additional risks. The need for proven evidence of effectiveness and cost-effectiveness has become imperative.

Current studies in TGCT focus on its radiological and pathological characteristics and surgical outcomes. Little effort has been made to address its clinical characteristics and natural history.

Therefore, this prospective registry will be conducted to evaluate the routine clinical care the clinical profile, management of the disease, clinical and patient-reported outcomes and resource usage in Europe. This registry will be the first comprehensive European disease registry to increase transparency on TGCT patients' pathways, treatment patterns, health outcomes and health economics. Data collected through this registry could also be used to assess the unmet medical need.

8.2. Study Rationale

As previously noted TGCT is a rare disease that is difficult to manage, surgical resection is the primary treatment currently available. To date no disease registry exists and there is little data available detailing the management of patients with TGCT, the burden of TGCT for patients (including pain, joint stiffness, swelling, reduced mobility and quality of life) or the economic impact of TGCT. This study aims to collect data by an observational disease registry involving no intervention to the patient or changes to investigators treatment decisions.

9. RESEARCH QUESTION AND OBJECTIVES OF THE OBSERVATION

9.1. Primary Objective

The primary objective of this disease registry is to gain detailed insight on the characteristics and management patterns of patients with diffuse TGCT. Specifically this registry will explore the following:

- Patient pathway to diagnosis
- To provide insight into the routine clinical care for patients with TGCT
- Requirement for surgery
- Severity of disease on MRI
- Rate of complications due to surgery
- Rate of recurrence
- Patient reported outcomes on pain, stiffness and physical function

9.2. Secondary Objectives

The secondary objective is to assess the economic health and quality of life burden for patients with diffuse TGCT. Specifically this registry will collect information on the following:

- Patient Reported Outcomes on Quality of Life
- Health Resource Utilization
- Patient daily life activity
- Collection of ADR for those patients treated with Pexidartinib after 02 Aug 2019

10. RESEARCH METHODS

10.1. Study Design

Multinational, multicentre, prospective, observational disease registry.

10.2. Settings

TGCT is a rare, benign, but potentially locally aggressive and recurrent disease. Treatment pattern and treatment initiation, continuation or changes are solely at the discretion of the physician and the patient. There will be no attempt to influence the prescribing patterns of any individual treating physician. All medication will be prescribed in the usual standard of care and will not be provided by the study sponsor. Participation in the study will in no way influence payment or reimbursement for any treatment received by patients during the study.

It is the responsibility of the investigator and his study staff to enter all relevant patient data required for this registry in the eCRF and in the patients' medical records.

Patients from several European countries and care settings will be enrolled and followed up for 2 years. A 2-year patient recruitment period is planned.

10.2.1. Participating Centres

Up to 20 sites located in France, Germany, Austria, Italy, the Netherlands, Spain, the United Kingdom and US) are planned to participate in the study. The sites will be specialized sites that treat TGCT regularly; no referral sites will be used.

10.2.2. Eligibility Criteria

As this is a non-interventional study, there are no explicit selection criteria besides:

- Written informed consent for participation in the study (ICF)
- Age ≥ 18 years
- Patients with diffuse TGCT (diagnosed histologically) confirmed naïve or recurrent case

10.2.3. Schedule

The total study period from FPI to LPO is 48 months. The patient recruitment period is 24 months. The follow up period for each patient is 24 months.

The patients will have a baseline data collection point and follow up data collection points performed at 12 and 24 months as this is routine clinical practice. Patients will be followed up according to normal clinical practice; therefore if they attend the site more frequently then this data will also be documented in the clinical notes and entered in the eCRF. Patients will be given questionnaires to optionally complete at the 6 month and 18 month point allowing them to report on their TGCT symptoms and quality of life regularly without the need to visit the site.

Patients eligible for the study at the site will be documented in a screening log to allow for judgement on representativeness of patient inclusion.

10.3. Variables

Data on the patients TGCT (both current status and history) will be collected at an initial baseline data collection point; this will take place when the patient first attends the site and agrees to participate by signing the informed consent form, it does not need to be a visit scheduled specifically for the study. Patient reported outcomes on TGCT symptoms and quality of life will also be assessed at this time as well as health resources used in the past 24 months. When the patient attends the site at the 12 month and 24 month follow up data collection changes in the patients TGCT will be recorded and patient reported outcomes and health resource utilization will be assessed again. The patient will also complete the PRO questionnaires on pain, stiffness, physical function and quality of life at 6 months and 18 months.

10.4. Data Sources

Scheduled assessments for the study are presented in the Data Collection Flow Chart provided. All data elements will be collected from information routinely recorded in the patient files / medical records. No visits or examinations, laboratory tests or procedures are mandated as part of this study. To facilitate accurate recording of data, patients use a memory aid to note important details that can be used during the visits.

Table 2: Data Collection Flow Chart

Visit/CRF Forms	Baseline data	6 Month PROs	12 Month data	18 Month PROs	24 Month data	Any further data
Date	x		x		x	x
Eligibility	x					
Informed Consent	x					
Confirmation patient is not participating at another site	x					
Demographics	x					
Employment status	x		x		x	x
Physical Exam						
Vital Signs	x		x		x	x
Medical History and comorbidities	x		x		x	x
TGCT Disease						
Date of first symptoms	x					
Date of first diagnosis	x					
Tumor details	x					
MRI details	x		x		x	x
Diagnosis Confirmation	x					

Visit/CRF Forms	Baseline data	6 Month PROs	12 Month data	18 Month PROs	24 Month data	Any further data
Histology	x					
Primary diagnosis or Recurrence	x					
Number of recurrences	x					
Current Status	x		x		x	x
Current Symptoms	x		x		x	x
Most disturbing symptom	x		x		x	x
TGCT Treatment						
Surgery	x		x		x	x
Current Treatment	x		x		x	x
Concomitant medications (symptom management)	x		x		x	x
Health Resource Utilization						
Number of referrals / specialist visits prior to diagnosis	x					
Details of health resource utilised (since diagnosis or last visit)	x		x		x	x
Patient Reported Outcomes						
Brief Pain Inventory	x	x	x	x	x	x
Worst Stiffness Scale	x	x	x	x	x	x
PROMIS Physical Function Scale	x	x	x	x	x	x
EQ-5D-5L	x	x	x	x	x	x
ADR reporting for pexidartinib			x		x	x
* ADRs will only be collected from 02 August 2019 on						

10.4.1. Baseline/Enrolment

The following data will be collected for at baseline for all enrolled patients

- Date of visit
- Date of Informed Consent
- Confirm patient is not participating in the study at another site
- Demographics:
  - Age
  - Gender
  - Highest Graduation/Education
  - Employment Status

- Insurance status
- Vital Signs:
  - Blood Pressure
  - Heart rate
  - Height
  - Weight
- Medical History
  - General clinical history
  - Trauma
  - Auto-immune disease
  - Auto-immune disease in family members
- TGCT History, diagnosis:
  - Date of first symptoms
  - Date of first diagnosis
  - Tumor details (side, joint affected)
  - MRI
  - Diagnosis confirmation
  - Histology
  - Primary diagnosis or Recurrence
- Current status of TGCT:
  - Current status
  - Current symptoms
  - Most disturbing symptom
- TGCT past treatment
  - Surgery required
    - Date
    - Type of resection performed
    - Adjuvant therapy received
    - Outcome of the surgery
    - Complications experienced
- TGCT current treatment

- Current treatment plan
- Concomitant therapies for managing TGCT related symptoms

- Health Resource utilization
  - Number of referrals/specialist visits prior to diagnosis (to identify the pathway to diagnosis)
  - Number of health appoints due to TGCT in the previous 12 and 24 months including:
    - Number of office visits due to TGCT
    - Number of emergency room visits due to TGCT
    - Number of hospitalizations due to TGCT
    - Number of days in hospital due to TGCT
    - Number of days in rehabilitation / physical therapy due to TGCT
  - Number of days of work missed due to TGCT symptoms or treatment in the last 12 and 24 months
  - Domestic help required
- Patient Reported Outcomes
  - Brief Pain Inventory
  - Worst Stiffness Scale
  - PROMIS Physical Function Scale
  - EQ-5D-5L

10.4.2. 12 month, 24 month and any further data collection points

As part of standard of care patients will attend a 12 month and 24 month data collection point. Patients may also attend further data collection points at any time as part of their usual care. At these follow up points the following data will be collected:

- Date of visit
- Vital signs:
  - Blood pressure
  - Heart rate
  - Weight
- Any changes in employment status
- Any new comorbidities diagnosed
- Any change in the current status of TGCT including:

- Current status (for example: stable, resolved, any recurrence)
- If recurrence, date of recurrence
- Current symptoms
- Most disturbing symptom

- Any changes in TGCT treatment including
  - Hospitalization since last visit? (including number of days)
  - Surgery occurred since last visit?
    - Date
    - Type of resection performed
    - Adjuvant therapy received
    - Outcome of the surgery
    - Complications experienced
  - Changes to current treatment plan
  - Changes to Concomitant therapies for managing TGCT related symptoms
  - Changes in MRI
  - ADR for patients on pexidartinib after 02 Aug 2019
- Health Resource utilization
  - Number of health appointments due to TGCT since the previous visit including:
    - Number of office visits due to TGCT
    - Number of emergency room visits due to TGCT
    - Number of hospitalizations due to TGCT
    - Number of days in hospital due to TGCT
    - Number of days in rehabilitation/physical therapy due to TGCT
  - Number of days of work missed due to TGCT symptoms or treatment since last visit
  - Changes in amount of domestic help required
- Patient Reported Outcomes
  - Brief Pain Inventory
  - Worst Stiffness Scale
  - PROMIS Physical Function Scale

- EQ-5D-5L

The patient may be provided with a memory aid to facilitate them recording and recalling data between data collection points.

10.4.3. Patient Reported Outcomes (optional)

Questionnaires may be completed by the patient at 6 months and 18months to give the patient the opportunity to report on their TGCT symptoms and Quality of Life

- Brief Pain Inventory
- Worst Stiffness Scale
- PROMIS Physical Function Scale
- EQ-5D-5L

10.4.4. Adverse Drug Reaction Reporting

In case a patient experiences an adverse drug reaction that the investigator judges to be related to pexidartinib, this needs to be documented independent from the data collection point, in the respective eCRF section. ADRs will be collected starting from August 02, 2019, which is the date pexidartinib became available on the US market. ADRs occurred prior this date, were collected within the follow-up phase of the ENLIVEN study in which all study patients who were treated with pexidartinib, were participating.

The ADR documentation and processing follows the Guideline on Good Pharmacovigilance Practices (GVP) Module VI (Collection, management and submission of reports of suspected adverse reactions to medicinal products)

10.5. Sample Size Calculation

As this is a rare disease the recruitment of patients within the scheduled 2-years treatment period will be difficult. Therefore, no formal sample size consideration has been performed. All collected variables will be used in the statistical analysis.

10.6. Data Management

Data will be collected on standardised electronic CRFs (eCRF, Clincase) in English. During data entry performed at the investigational sites automated plausibility checks (e.g., range checks, conditional checks, etc.) will be performed. Additional manual queries resulting from medical/manual data review may be raised by Data Management.

All patient reported outcome questionnaires will be completed on paper forms in local language and will be entered in the clinical database directly by Data Management.

Data from the project specific database will be exported into SAS data sets for further validation and analysis. Data Management details will be described in a separate Data Management Plan.

For (S)ADRs a reconciliation between the data available in the Daiichi Sankyo safety database and the data in the eCRF will be performed as described in the separate (S)ADR Reconciliation Plan.

10.7. Data Analysis

All statistical methodology will be described in detail in the Statistical Analysis Plan (SAP) which will be finalised at the latest prior to data snapshot. All variables collected in the eCRF as well as the data obtained from the patient reported outcomes assessments and all derived parameters will be used in the statistical analysis.

Binary, categorical, and ordinal parameters will be summarised by means of absolute and percentage numbers within the various categories (including 'missing data' as valid category at baseline). Numerical data will be summarised by means of standard statistics. In addition, adequate graphs (e.g. bar charts, box-whisker plots) may be presented. The purpose of all analyses will be purely descriptive/exploratory. Adverse drug reactions will be analysed overall and by type of ADR, based on MedDRA preferred terms and primary system organ class.

10.8. Quality Control/Monitoring

This study will be performed according to Good Epidemiological Practice and the STROBE guidelines, specifically following the RECORD statement (http://www.record-statement.org).

Remote monitoring will be performed on regular basis. The purpose is to ensure that the rights of the patients are protected, that the reported data is complete and that the conduct of the study is in compliance with the Observational Plan and applicable regulatory requirements.

Onsite monitoring may be performed at the sponsor's discretion (e.g. at sites that have enrolled a pre-specified number of patients or depending on findings during remote monitoring).

10.9. Limitations of the Research Methods

As this study aims at collecting and evaluating real world evidence, some limitations common to non-interventional studies apply. In addition to this, the following aspects need to be considered:

- Only specialized centres will be used for the study which limits the number of sites per country. This may influence the sites' representativeness for this specific patient population.
- Eligible patients may choose not to participate in the Registry. Therefore, this may impact the consecutive enrolment at a site. To be able to assess the consecutiveness of enrolment, eligible patients will be listed in the patient screening log.
- At the follow up documentation time point all relevant changes/events since the last documentation time point need to be entered. Due to the long time between data collection an underreporting of data might occur that are not considered essential or that are difficult to remember. The patient memory aid and the patients' medical records at the site shall support the precise documentation of the time between two data documentation time points. The utility of both records is however influenced by the precision and accuracy with which the memory aid and the medical records have been completed in the meantime. It is expected that possible underreporting will not appear in case of severe events and hospitalizations and that this data is considered to be representative for the whole study population.
- Due to the nature of the disease the number of patients enrolled in this study is limited.
- As the study is non-interventional, only data from the clinical routine treatment can be obtained. Therefore, some information may be missing or unavailable. This needs to be taken into account when data is analysed and reported.
- No explicit non-eligibility criteria are defined to avoid selection of patients and thus violation of the 'real-life' principle.

11. MANAGEMENT AND REPORTING OF ADVERSE DRUG REACTIONS

In case a patient experiences an adverse drug reaction that the investigator judges to be related to pexidartinib, this needs to be documented independent from the data collection point, in the respective eCRF section. ADRs will be collected starting on August 02, 2019, which is the date pexidartinib became available on the US market (please refer to section 10.4.4)

In the US, Turalio (pexidartinib) was approved by the FDA with a boxed warning for hepatotoxicity and is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) program Safety reporting of initial hepatotoxicity event(s) will occur through the REMS program (i.e., REMS Liver Adverse Event form) and/or through routine pharmacovigilance. Reporting of non-hepatic, TURALIO-related safety events will occur only through routine pharmacovigilance, regardless of seriousness. Safety reporting of initial hepatotoxicity event(s) will occur through the REMS program (i.e., REMS Liver Adverse Event form) and/or through routine pharmacovigilance. Reporting of non-hepatic, TURALIO-related safety events will occur only through routine pharmacovigilance, regardless of seriousness.

All Adverse Drug Reactions will need to be documented in the eCRF, independently whether they have already been reported through the REMS program or not.

Adverse drug reactions that occurred from August 022019 onwards are to be collected as pexidartinib has become commercially available in the US on that date. The documentation and reporting follows the Guideline on Good Pharmacovigilance Practices (GVP Module VI).

The ADR documentation and processing follows the Guideline on Good Pharmacovigilance Practices (GVP) Module VI (Collection, management and submission of reports of suspected adverse reactions to medicinal products).

11.1 Definitions

Adverse Drug Reaction (ADR)

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for

the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

Serious Adverse Drug Reaction (SADR)

Serious adverse reaction means an adverse reaction which

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly/birth defect.

Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation or development of dependency or abuse.

11.2 Reporting of Suspected ADRs by the Investigator

- For Routine Pharmacovigilance: To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc, at PPD .
- As part of the REMS commitment, the US prescribers are required to report hepatoxicity to the Turalio REMS program at PPD or fax it to the TURALIO REMS Call Center at PPD or call the TURALIO REMS Call Center at PPD to provide the information.

All Suspected Adverse Drug Reactions will need to be documented in the eCRF, independently whether they have already been reported through the REMS program or not.

As soon as a (suspected) Adverse Drug Reaction has been entered into the eCRF, an automatic notification will be sent to DSE-CSPV , e-mail DLEU-CSPV@daiichi-sankyo.eu.

11.3. Pregnancy

Daiichi Sankyo must be notified of those patients only who become pregnant while receiving or within 30 days of discontinuing pexidartinib. The patient should discontinue pexidartinib upon confirmation of pregnancy.

Although pregnancy is technically not an adverse reaction, pregnancies for patients treated with pexidartinib must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female patient using the Exposure In Utero (EIU) Reporting form.

Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the patient until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion.

The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets any criteria for immediate classification as a SADR (e.g., post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting ADRs outlined in Section 11.2.

12. PROTECTION OF HUMAN SUBJECTS

12.1. Review by Independent Ethics Committees/Competent Authorities

Notification to or approval by IECs and CAs or other organizations will be performed as required by national regulations in the participating countries before commencement of enrolment at a study centre.

12.2. Insurance and Liability

All treatments of patients included in this disease registry are local standard of care and occur as part of the daily routine practice. Claims of the patient upon his physician will not be covered by Daiichi Sankyo. A specific patient's insurance for disease registry is not necessary.

12.3. Patient Information, Informed Consent

It is the responsibility of the investigator to inform the patient about his/her disease, possibilities for diagnostic and therapeutic measures, independent of a possible participation in any survey and therefore this information will not be part of the ICF.

The written ICF will be provided to the study centres in the local language(s). The ICF and any revision(s) should be approved by the Independent Ethics Committee (IEC) prior to being provided to potential patients.

The patient's written informed consent will be documented in the patient's medical records of the investigator. The ICF should be signed and personally dated both by the patient and by the investigator who conducted the informed consent discussion. The original signed ICF should be retained at the study site (preferably in the patient's medical records). A copy of the signed consent form should be provided to the patient. The date of informed consent will also be recorded in the electronic CRF (eCRF).

12.4. Data Protection

The patients' privacy will be kept according to the requirements of Directive 95/46 EC and national legislation for data protection. Data will be collected in a pseudonymous way. An identification number assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting study-related data.

Only authorised personnel such as hospital staff, representatives of the sponsor and contract research organisation (CRO), and Competent Authorities (CAs) should have access to personalised patient data e.g. in original source documents (medical records). The patient will agree to this by signing a respective statement on the ICF.

12.5. Numbering and Identification of Patients

A unique identification number will be assigned to each patient, for the eCRF.

At each study site a patient identification list ('Enrolment log') will be kept linking the identification number to the patient's identity.

12.6. Assessments (according to the study type)

The investigators will be instructed about the correct documentation of the required data for each patient in the CRF. These data are available as part of the routine treatment. No diagnostic or monitoring procedures are applied to the patients in the study other than those performed as standard of care.

12.6.1. Patient Reported Outcomes

While physicians in daily routine assess health-related quality of life (QoL) in a non-standardised manner (usually by questioning the patient), in the context of this registry they will be provided with validated questionnaires (EQ-5D-5L, Brief Pain Inventory (BPI), Worst Stiffness NRS item and PROMIS Physical Function Scale), these will be available in the local language.
Generally, questions in quality-of-life questionnaires are not more upsetting than those posed by a patient's physician or by friends and family members on a day-to-day basis. The use of the questionnaires is considered to be non-interventional, as the questions raised are similar to those asked in routine care. Patients are free to accept or refuse to fill in the proposed questionnaires in this registry.

12.6.1.1. EQ-5D-5L

The EQ-5D-5L is a preference-based general health status or health-related quality of life instrument consisting of two parts (Appendix 16.1). The first part comprises five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can have five levels ranging from no problems through profound difficulties. Accordingly, 3125 potential health profiles can be generated to which public preferences or utilities are applied. These data can subsequently be used in an economic evaluation or cost-utility analysis. The second part of the EQ-5D-5L is a Visual Analogue Scale on which the subject rates their current health, with 0 representing the "worst health you can imagine" and 100 representing the "best health you can imagine."

12.6.1.2. Brief Pain Inventory (BPI) short form

The BPI short form is a 5 minutes self-administered questionnaire that assesses severity of pain, impact of pain on daily function, location of pain, pain medications and amount of pain relief in the past 24 hours or the past week.

12.6.1.3. Worst Stiffness NRS item

The Worst Stiffness NRS item is a one-item self-administered questionnaire assessing the "worst" stiffness in the last 24 hours (Appendix 16.3). The NRS for this item ranges from 0 ("no stiffness") to 10 ("stiffness as bad as you can imagine").

12.6.1.4. PROMIS Physical Function Scale

Physical function items relevant to the assessment of lower and upper limb function are to be selected from the PROMIS physical function item bank (Appendix 16.4). Items assessing lower limb function will be administered to subjects with the lower extremity tumors, and items assessing upper limb function will be administered to subjects with upper extremity tumors. The results from both sets of items will be combined and analysed together.

13. DOCUMENTATION AND ARCHIVING

The sponsor is responsible for archiving study specific documentation (Observational Plan, potential amendments, Final Report and Database) for at least 10 years. Archived data may be held on electronic record, provided that a back-up exists and that hard copies can be obtained, if required.

The investigator is responsible for archiving the patient identification list, all signed ICFs and his contract for at least 10 years and in accordance with local legislation, if applicable.

Physicians are obliged to keep patient files according to national requirements.

14. LEGAL REQUIREMENTS

This NIS fulfils the requirements of the Directive 2001/83 EC, Module VIII of Guidelines on Good Pharmacovigilance Practices (GVP), Directive 95/46 EC, the Declaration of Helsinki and will be conducted in accordance with the respective SOPs of DSE.

14.1. Reimbursement

Compensation according to local regulations and to the time spent to inform patients and to document patient data will be paid. This compensation also includes the honorarium for responding to queries and for monitoring.

14.2. Registration

This NIS/registry will be listed in a public registry which meets International Committee of Medical Journal Editors (ICJME) requirements, before the onset of patient enrolment.

15. FINAL REPORT

A final NIS report will be presented latest one year after data base lock, if not required earlier by local legislation.

16. PUBLICATION

CCI

17. PREMATURE TERMINATION OF THE REGISTRY

The physician may withdraw his/her participation in this registry at any time. In the case of a premature termination of the entire NIS/registry by the sponsor, the project leader has to inform all participating sites, Ethics Committees, and authorities.

18. APPENDICES

18.1. EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

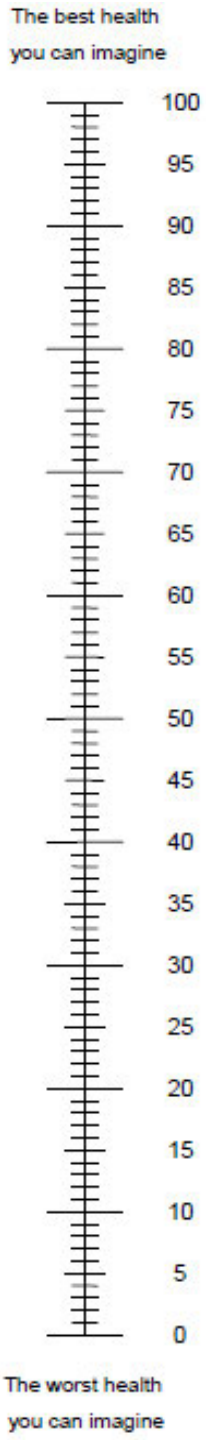
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



18.2. Brief Pain Inventory Short Form

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE Site #:_____

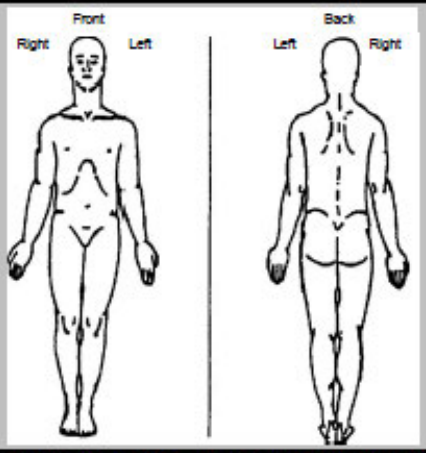
Brief Pain Inventory (Short Form)

Date:____/____/____ Time:_____
Patient ID:_____ _____ _____

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE Site #:_____

Date: ____/____/____ **Time:** _____
Patient ID: _____ _____ _____

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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18.3. Worst Stiffness NRS item

Worst Stiffness NRS item

The following question asks about stiffness at the site of your tumor.

Please rate your stiffness by circling the one number that best describes your stiffness at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No stiffness										Stiffness as bad as you can imagine

18.4. PROMIS Physical Function Scale

PROMIS Item Bank v. 1.2 – Physical Functioning (Lower Extremity)

Please respond to each item by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16rl	Are you able to dress yourself, including tying shoelaces and buttoning up your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFB54	Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA4	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA12	Are you able to push open a heavy door?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA14rl	Are you able to carry a heavy object (over 10 pounds/5 kg)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA42	Are you able to carry a laundry basket up a flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA10	Are you able to stand for one hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFA3	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA13	Are you able to exercise for an hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS Item Bank v. 1.2 – Physical Functioning (Upper Extremity)

Please respond to each item by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFB34	Are you able to change a light bulb overhead?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning up your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFB54	Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA4	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA12	Are you able to push open a heavy door?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB28r1	Are you able to lift 10 pounds (5 kg) above your shoulder?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA14r1	Are you able to carry a heavy object (over 10 pounds/5 kg)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA42	Are you able to carry a laundry basket up a flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA13	Are you able to exercise for an hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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