General Approval application example:

Clinical Trial

IMPORTANT NOTE

This is a fictitious example of a General Approval application. It is intended as a guide only to provide an indication of the level and type of detail required in the RDTI General Approval form.

1. PROJECT DESCRIPTION

1.1. Project Identifier

Project 5-21 – Study of a new treatment for Rheumatoid Arthritis.

1.2. Project Objective

The purpose of this project was to test a new active pharmaceutical ingredient (API) for treating Rheumatoid Arthritis (RA).

RA is an autoimmune disease that causes chronic inflammation. Over time, this can lead to joint damage and deformity – including bone erosion – that reduces joint mobility.

Patients with RA typically experience painful swelling and stiffness of the affected joints. Symptoms tend to be worse in the morning or after extended periods of rest.

RA can also cause fatigue, subcutaneous nodules, eye inflammation, reduced white blood count and lung disease. In severe cases, there may be significant loss of mobility.

A particular focus of our project was developing an effective treatment for adults with moderate to severe RA symptoms, who don't respond well to current treatments.

2. PROJECT CORE ACTIVITIES

2.1. Core activity

Phase 3 clinical trial

2.1.1. DESCRIBE YOUR CORE ACTIVITY

The core activity of the project involved a clinical trial to determine the efficacy, safety and tolerability of the new API in adults with moderate to severe RA.

Earlier laboratory investigations and clinical studies (Phases I and II) had indicated that the new API may provide improved benefits for patients suffering with RA.

However, a clinical trial (Phase III) was necessary to test the treatment among a larger patient population and over a longer period.

The trial ran from 1 April 2019 to 31 March 2021, and involved comparing the results of the new API with a placebo.

2.1.2. DESCRIBE THE SCIENTIFIC OR TECHNOLOGICAL UNCERTAINTY THAT YOUR CORE ACTIVITY HAD A MATERIAL PURPOSE OF RESOLVING

Despite the wide body of work undertaken prior to our core activity (Phase III clinical trial), there was insufficient evidence of the efficacy, safety, and tolerability of the new API in adult RA patients.

The earlier work had included pre-clinical studies to determine the non-human feasibility and safety of the new API. This involved extensive literature searches to gather existing knowledge of the drug as well as the disease target.

The drug had also been tested on a very small group of healthy volunteers (Phase I clinical trial) to determine its effects on humans. This included assessing the drug's safest dose, its mode of administration and pharmacokinetics.

Following the successful completion of the first clinical trial, a Phase II trial was conducted to test the drug on a reduced patient set, comprising those affected by RA. This trial investigated the drug's efficacy and safety over a relatively short time period, with the aim of determining the most effective dosage while limiting side effects.

Laboratory testing had indicated that the new API selectively inhibits dihydrofolate reductase (DHFR) – a key way of reducing arthritis-related inflammation. However, there was limited understanding of how differences across the patient population influence individual responses to the drug. As a result, uncertainty remained as to whether or not the new API would enable effective, safe and tolerable treatment of RA in patients with moderate to severe symptoms and where current treatments are either unsuitable or ineffective.

2.1.3. DESCRIBE THE SYSTEMATIC APPROACH YOU TOOK CONDUCTING THE CORE ACTIVITY

The phase III clinical trial involved a randomized, double-blind, placebo-controlled and multi-centre study.

Subjects who met the specified eligibility criteria were randomized and received weekly oral doses of the API at either 5 mg or 15 mg, or the matching placebo.

The study comprised an initial 40-day screening period, a 20-week DB period and a blinded extension period up to week 100. Following this, there was a 40-day follow-up visit period.

Throughout the study, a range of clinical data was collected and analysed:

Efficacy endpoints

Efficacy endpoints were any objective response to the study drug therapy.

This included, but was not limited to, the proportion of subjects who achieved:

- At least a 75% increase in joint function, compared to the baseline at week 24
- A validated Investigator Global Assessment for Rheumatoid Arthritis rating of 0 or 10, with at least a 2 point reduction from baseline at Week 24.

Evaluations

Evaluations included, but were not limited to: adverse

- event (AE) monitoring
- physical examinations
- vital sign measurements
- haematology and chemistry testing, as a measure of safety and tolerability for the entire duration of the study.

Pharmacokinetic samples

Pharmacokinetic samples were collected from subjects at key sites during visits.

Using the data obtained, a nonlinear mixed-effects modelling approach was then used to estimate: the

- population's central values
- the empirical Bayesian estimates of the individual values of the API's oral clearance and volume of distribution.

Additional parameters may be estimated if useful for interpretation of the data. Combined data from this and other studies may be used for the population PK analyses.

Assessment of key biomarker samples

These samples helped to clarify understanding of the subject's condition and their response to the new API.

Genes of interest may include:

- those associated with pharmacokinetics (e.g. drug metabolizing enzymes, drug transport proteins)
- genes within the target pathway

Research also included epigenetic DNA changes that may be associated with the subject's response to treatment or disease. Samples for RNA and proteomics were used to investigate if any genetic variants resulted in changes to gene expression or protein concentrations.

Given the nature and extent of the work as part of the clinical trial, data collection and experimental activities are expected to continue into the next financial year.

2.1.4. DESCRIBE HOW YOUR CORE ACTIVITY INTENDS TO CREATE EITHER NEW KNOWLEDGE OR NEW OR IMPROVED PROCESSES, SERVICES OR GOODS

Data obtained from the Phase III clinical trial is expected to yield new knowledge about the safety and efficacy of the API for treating RA.

Many treatments are currently available for RA, as the particular treatment given to adults is dependent on the extent and severity of their symptoms. However, there is an unmet number of patients who are non-responders or partial responders to current treatments.

The new API (XXX-1234) is a novel selective DHFR inhibitor and is being developed primarily for RA, where the enhanced selectivity of this drug against DHFR may offer an improved benefit-risk profile for patients.

Data from the Phase I and II clinical studies demonstrated superior efficacy of the API, while the Phase III trial aims to demonstrate an acceptable safety profile at the selected doses, compared to the placebo.

The efficacy and safety data gathered from the phase II RA study, along with cumulative safety data from ongoing Phase II and III programmes in other disease indications, supports further development of the API in subjects with moderate to severe RA.

When we commenced our core activity, New Drug Ltd had some knowledge of the new API's ability to selectively inhibit DHFR, with lesser inhibition of methionine synthase due to successful laboratory in vitro testing. We understand that less selective DHFR inhibitors can increase the risk of liver damage.

Our core activity aimed to increase understanding and generate data on the short and long-term efficacy, safety and tolerability of the API in patients with moderate to severe RA, and how this differs from the effects of a placebo. Previous research had suggested a high possibility of success, however, knowledge of long-term safety, tolerability and widespread efficacy could not be determined without undertaking the core activity.

New Drug Ltd seeks to develop safety knowledge including: treatment

- emergent adverse events (TEAEs)
- serious adverse events (SAEs)
- adverse events (AEs), adverse events of special interest
- (AESIs) AEs leading to discontinuation, vital signs and laboratory tests.

3. PROJECT SUPPORTING ACTIVITIES

3. Supporting activity (1)

Clinical trial facilitation and management

3.1. DESCRIBE YOUR SUPPORTING ACTIVITY

To support the core R&D activity, New Drug Ltd personnel undertook the following tasks to ensure the clinical trial could be performed efficiently and correctly:

- Local project management of clinical trials
- Auditing of data collected by New Drug Ltd staff and contractors Preparation
- of study protocols
- Shipment of supplies to and from clinical sites
- Literature searches
- Progress meetings with clinical teams
- Planning and monitoring of clinical trials and results Screening
- patients to set up trial population

3.2. DESCRIBE HOW THIS SATISFIES THE SUPPORTING ACTIVITY DEFINITION

Without performing the above tasks New Drug Ltd would not have been able to perform the clinical studies.

3.3. SELECTED ASSOCIATED CORE ACTIVITIES

Phase 3 clinical trial.