Cannabis clinical trial considerations

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To our Medical Cannabis Industry Partners,

As time passes, keeping track of all the changes in the Global Cannabis market is becoming more and more challenging. The current newsletter will provide clarity where possible, regarding the design and implementation of Clinical Trials. Valid Clinical Trials are necessary for the expansion of labelling in the US. In Europe in general, and in Germany in particular, labeling requirements are less precise and the authorities allow for physicians’ discretion in prescribing Cannabis to the patient.

Currently, Israel is known worldwide as a pioneer in Cannabis research and Clinical trials. More than 50 Israeli startups are developing medical Cannabis products. Most Israeli start-ups are gradually maturing and progressing to clinical trials, mainly for PK, Phase 1 and Phase 2. Since 2011, over 45 clinical trials have been conducted in the field of Cannabis worldwide, with most of these studies being preliminary studies, about 5 phase 3 studies (including GW Pharmaceuticals and Takeda studies) and about 10 phase 2 studies. The main research question investigated usually is the efficacy of the research product, but most studies also explore safety aspects where the most popular indications are central nervous system disease, Inflammation and cancer. The quality of the results and the scientific value of these studies are “varied”; therefore, practitioners should develop the ability to monitor the quality of execution and planning of clinical trials.

As a result of what we have learned and observed, we believe that a proper planning and execution of a Clinical Trial is critical to achieve regulatory approval in a timely manner.

We wish everyone a fruitful and prosperous year, and of course, may it be the year of Cannabis.

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Designing medical Cannabis clinical trials

Clinical studies are a significant and necessary portion of the process of developing and approving medical products. Cannabis-based medical products also require clinical trials and the submission of detailed clinical study reports of the clinical trials in order to be included in the Registration file that will be submitted to the authorities. This review will address two key aspects:

- Basic principles in clinical trials design
- Guiding considerations in the design of medical Cannabis clinical trials

Clinical trials should be designed and conducted according to three general principles:

1. Protection of Clinical Study Subject
   This principle provides guidance for planning and execution in a way that ensures the patient’s well-being and rights while emphasizing special populations in a way that requires compliance with the ICH E6 Good Clinical Practice requirements and ISO 14155 when the clinical investigation involves medical device.

2. Scientific Approach in Clinical Study Design Conduct and Analysis
   This principle requires a scientific approach in designing the research objectives, executing, collecting the results and analyzing them, to ensure obtaining reliable data and
3. Patient Input into Study Design

Aimed at integrating, receiving feedback and involvement of patients and patient organizations in the design and implementation of the study. This is done in order to plan and conduct a feasible study that addresses the real needs of patients.

The characteristics of clinical research in Cannabis as well as preclinical steps in product development are derived from the regulatory submission path and therefore great importance should be given to determining the correct regulatory strategy for each product and at the earliest stage. Although clinical trials are sometimes not mandatory, clinical trials are almost always performed. These clinical trials will be performed for the purpose of accumulating safety and efficacy information, for marketing needs, financial needs and or needs to confirm assumptions about the efficacy of the product under different indications, different administration routes, combination with other treatments, etc. This review focuses on the design and conduct of the clinical trials in accordance with the regulatory requirements of a non-herbal pharmaceutical product, these requirements are the most rigorous and demanding and ensures as much as possible the reliability of the scientific insights that can be derived from the research. Cannabis research requires special attention to these requirements because prior information on cannabinoids / Cannabis use in medical products is limited. This is due to, among other things, a lack of reliable scientific and clinical information in the field of Cannabis research and is the result of conducting studies that are lacking in their design and without the use of common methods to reduce BIAS.

Once the indication has been thoroughly studied and the relevant literature reviewed, the research rationale and assumptions sought by the research can be formulated. In each case, the research and its objectives will be planned with reference to, and in connection with, the broader clinical program and the stages of the project or product. The research design should focus on the guidelines outlined below at both the planning and execution levels:

1. Study Population

The characteristics of the study target population are derived first from the target product population, the study as a whole will characterize the effect of the investigated product on a particular population and the conclusions, in principle, will be relevant to that population. Later on, the criteria for inclusion and exclusion will also include considerations related to safety, ethics, DDI (Drug-Drug Interaction), background and medical history, etc. Cannabis studies should also take into account, the extent to which patients have been exposed to Cannabis use in the past, the psychoactive consequences of THC and the patients’ ability to consume the product as required. In general, the characteristic of the study population can be said to be a delicate balance between reducing the variability between patients in order to increase the chances of demonstrating the therapeutic effect on the one hand, and the implications of these decisions on the ability to recruit patients for research and approve treatment based on research in a population characterized by limited variability on the other hand.

2. Intervention

The dosage, treatment duration, route of administration, and number of treatments has a major impact on “Product Success / Research”. Dosage, treatment regimen and administration have a direct effect on product usability, the absorption of active ingredients, their effectiveness, as well on their safety, and economics. Cannabis studies show a wide variety of forms of administration, ranging from topical ointment form through to nasal and oral vaporizers, sub-lingual and even rectal administration. Each of the forms of administration has pros and cons. For example, using a vaporizer significantly reduces smoking damage and allows for an “Entourage Effect” and has a close proximity to the traditional Cannabis
consumption, but requires patients be supplied with a vaporizer which significantly increases the operative and regulatory requirements both during and after the study. Oral administration is relatively simple to use and operate but is characterized by a slower and less effective absorption of the active ingredients. Apart from these, the “intervention” consideration also corresponds to the indication itself and the target patient population, which dictates restrictions on how the patient consumes the product being tested.

3. Control Group
The requirement for controlled research is a “gold standard” in clinical studies design and usually research cannot be carried out with good reliability without a control arm. The need for a control arm / group results from a phenomenon that has been documented since the 1930s and is called the “Hawthorne effect.” In general, this effect shows that solely just the participation of the subject in the clinical trial results in a change not related to the medication. The purpose of the control group and its value derive from the fact that it allows us to analyze the effects of the treatment only regardless of the effect of other external factors not related to the medication/treatment. There are different types of controls, for example;

Comparison of the research drug or treatment with another drug or other conventional treatment as well as placebo. This aspect is particularly challenging in Cannabis trials as it is difficult to create a “placebo” in Cannabis products especially when the tested product is consumed via inhalation and / or contains a THC component that gives a unique feeling and allows for easy differentiation of treatment arms by the patient. Due to this reason cross over and double dummy studies for example are more relevant in the cannabis territory.

4. Response Variables
Endpoints are derived directly from the study objectives and are used to assess and characterize the treatment effects. The endpoints selection has a critical impact on the success of the study and is the result of a complex set of considerations. The endpoints are first and foremost intersected with the indication, regulatory requirements and statistical considerations, but also take into account broader elements of the clinical development program such as: follow-up and future planned studies, patient needs and limitations, competitors and competition, etc. Early studies will usually use measures related to safety and tolerability as a Primary endpoint, while efficacy questions can be also expressed in Secondary endpoints. In the more advanced stages of product development, the priority is changed and the main objective will focus on the question of effectiveness while safety information collection continues throughout the life cycle of the product in order to produce safety knowledge at different levels of product exposure.

5. Reduce or Assess Bias
Bias is an accumulation of factors that can compromise the reliability of clinical trial results. The bias is derived from the unique research structure and needs to be addressed to reduce it as much as possible. The two most powerful tools for reducing bias are “RANDOMIZATION” and “BLIND”. Randomization means randomly assigning patients to the treatment arms. This randomization is expressed as an equal probability for each patient to be included in each arm, thus avoiding conscious and unconscious bias of patient allocation and balancing the baseline characteristics of the treatment groups (The larger the group in the trial, the value of the randomness set increases). BLIND or MASKING, however, requires that the patient or the research team (SINGLE BLIND \ DOUBLE) do not know to which treatment arm the patient is assigned. Creating a proper blind study creates operative challenges that need to be addressed in order to avoid psychosomatic effects and biases.
Apart from this, every procedure in the study that can influence the results of the study should be considered to ensure that its application is not affected by bias.

6. Statistical Analysis
When the structure of the trial and the selected endpoints are determined, a suitable statistical model should be formulated to analyze the results of the study and a preliminary plan for the analysis of the results should be formulated. It is difficult to overstate the importance of bio-statistician involvement in model selection, sample size, decision making during the study, and of course in analyzing the results and presenting them. As mentioned before, these aspects have great importance in the planning phase and any changes may affect other aspects. Apart from this, during the Study Execution, the Sponsor is expected to ensure that the study conduct is done according to the approved plan and in compliance with the study protocol. In Cannabis trials this challenge is particularly tangible as these are studies with relatively high operative and regulatory complexity. In cases where the design and conduct are properly performed, authentic results are guaranteed which reflect product performance appropriately.

Examples of clinical trials performed in recent years and their characteristics:

<table>
<thead>
<tr>
<th>Title</th>
<th>Phase</th>
<th>#Participants</th>
<th>Allocation</th>
<th>Masking</th>
<th>Control</th>
<th>Arms</th>
<th>Subjects</th>
<th>Site/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Phase I, Double Blind, Randomized, Placebo Controlled, Maximal Dose Study to Determine the Safety, Tolerability of Topical Cream Containing MGC (Medical Grade Cannabis) in Healthy Volunteers</td>
<td>I</td>
<td>26</td>
<td>Randomized</td>
<td>Double Blind</td>
<td>Placebo</td>
<td>2</td>
<td>Healthy Volunteers</td>
<td>Single</td>
</tr>
<tr>
<td>Combined THC and CBD Drops for Treatment of Crohn's Disease, a Phase II Double Blind Placebo Controlled Trial</td>
<td>II</td>
<td>50</td>
<td>Randomized</td>
<td>Triple Blind (Participant, Care Provider, Investigator)</td>
<td>Placebo</td>
<td>2</td>
<td>Adults with Crohn's disease</td>
<td>Single</td>
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<tr>
<td>A Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P) in Children and Young Adults with Dravet Syndrome.</td>
<td>III</td>
<td>199</td>
<td>Randomized</td>
<td>Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)</td>
<td>Placebo</td>
<td>3</td>
<td>Children and Young Adults With Dravet Syndrome.</td>
<td>Multi/Global</td>
</tr>
<tr>
<td>A Multicenter, Non-comparative, Open-label Extension Study to Assess the Long Term Safety of Sativex® Oromucosal Spray (Sativex®, Nabiximols) as Adjunctive Therapy in Patients With Uncontrolled Persistent Chronic Cancer Related Pain</td>
<td>III</td>
<td>660</td>
<td>Single Group Assignment</td>
<td>Open-label</td>
<td>Single Group Assignment</td>
<td>1</td>
<td>Patients With uncontrolled persistent chronic cancer related pain</td>
<td>Multi/Global</td>
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