Application for the Marketing Approval of Vodaxa for the Treatment of Steroid Resistant Asthma

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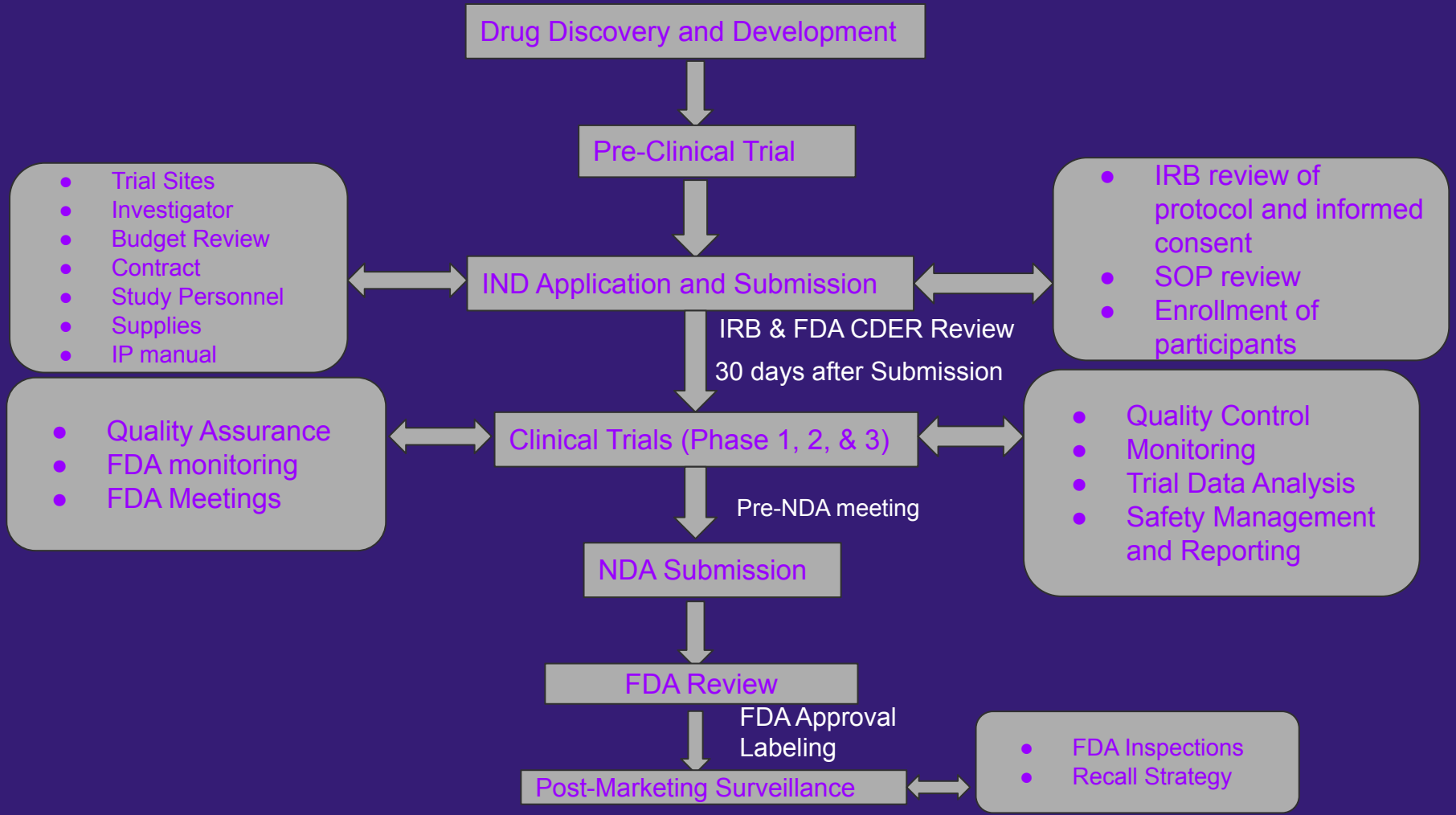
Content

1. **Timeline**
2. **Pharmaceutical Company**
3. **Drug Target**
4. **Standard of Care**
5. **Drug Discovery and Development (2 years)**
6. **Preclinical Studies** (3 years)
7. **IND Application**
   - -Pre Clinical Studies
   - -Chemical, Manufacturing and Controls Information Clinical Protocols
   - -Clinical Protocols and Investigator Information
   - -Informed Consent
8. **Development of SOPs**
9. **Selection of trial sites, qualified investigators and study personnel**
10. **Enrollment of Subjects**
11. **Clinical Trial**
12. **Quality Control**
13. **Quality Assurance**
14. **Safety Management and Reporting**
15. **NDA Submission**
16. **FDA Review**

Timeline of Study



Introduction (Pharmaceutical Company)

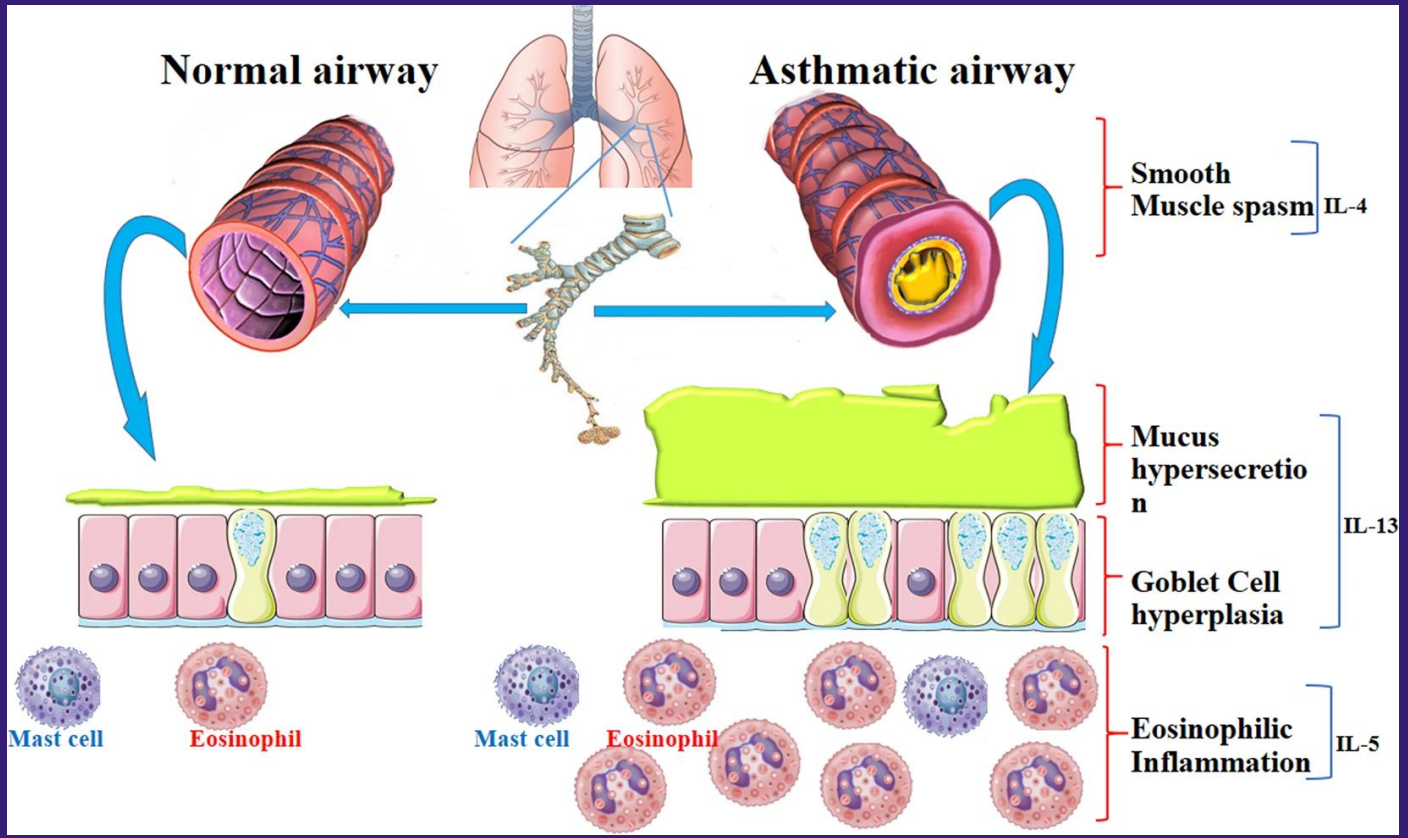
- PulsePharma is a small biopharmaceutical company founded in 2007.
- We are presenting our first drug “Vodaxa” which is designed to help people suffering from steroid resistant asthma.
- This process began over 15 years ago.
- Our research and development headquarters are located in Stony Brook, Long Island.

Drug Target - Asthma disease

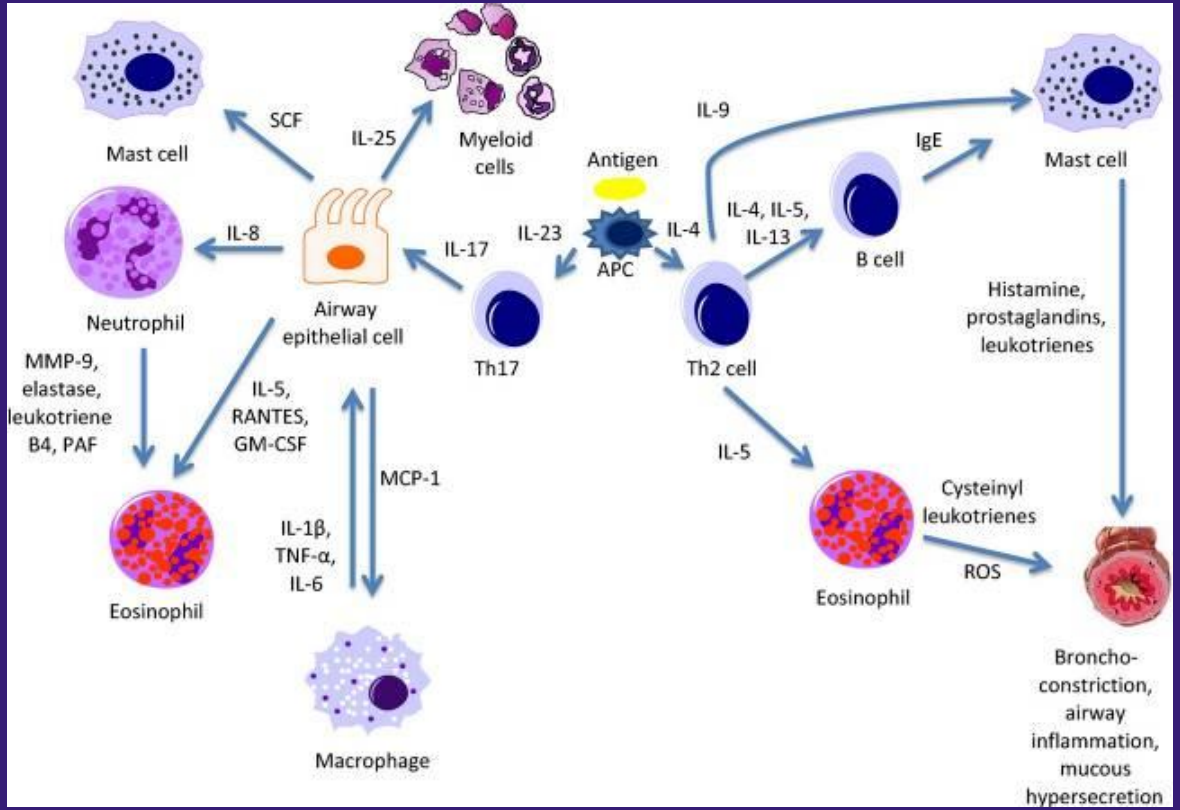
Symptoms for this disease include:

- Chronic inflammatory disease of the airways.
- Wheezing
- Breathlessness
- Chest tightness and/or coughing

Drug Target - Asthma disease



Drug Target (Asthma)

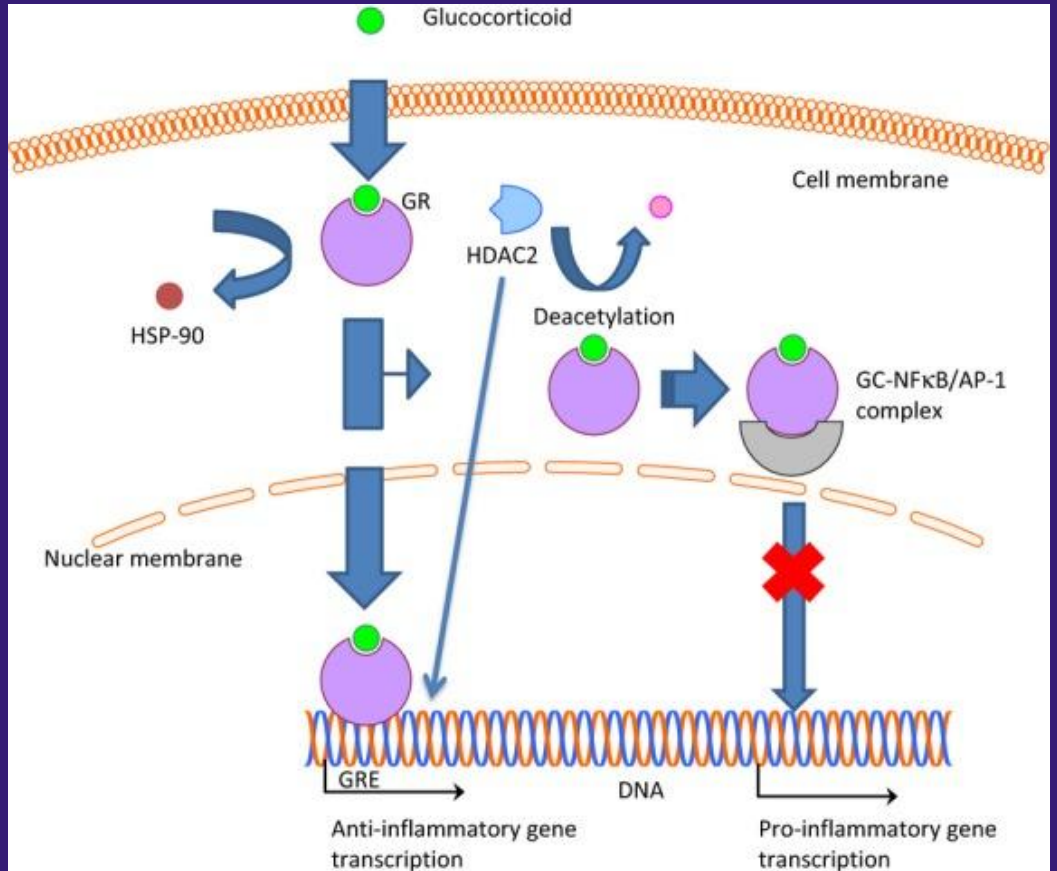


Standard of Care

Types of Asthma treatments include:

1. **Quick-relief medicines** (Albuterol (ProAir HFA, Proventil HFA, Ventolin HFA)
2. **Controller medicines** Beclomethasone (Becotide),Budesonide (Pulmicort), Fluticasone (Flixotide)
3. **Combination of quick-relief and controller medicines** Fluticasone & Salmeterol (Seretide) Budesonide & Formoterol (Symbicort: can be used)

Standard of Care



Drug Discovery

- IL-4 a very attractive target to inhibit type 2 inflammation because it drives the differentiation and clonal expansion of naïve CD4+ T cells into TH2 cells and further production of cytokines IL-4, IL-5 and IL-13 from TH2 cells in the upstream pathways.
- This subsequently leads to the downstream pathways of Immunoglobulin (Ig) E production, eosinophil activation, and mucus secretion.

IND Application & Submission

- Dr Matthew Goodman our regulatory affairs consultant submitted our Treatment Investigational New Drug (IND) Application in 2007.
- Our company met with new drug review divisions through the Pre-Investigational New Drug Application (IND) Consultation Program in order to gain a better perspective for the data necessary to submit our IND.
- There were also guidance documents that were looked at that helped us prepare our IND submission.
- The submitted IND application includes four main topics which are our preclinical data, Chemistry, Manufacturing and Controls Information (CMC), Clinical Protocols and Investigator Information, and Informed Consent.

IND Application & Submission

- Lastly these codes of federal regulations were followed under Federal Law in preparation for IND submission :

21CFR Part 201 (Drug Labeling)
21CFR Part 312 (Investigational New Drug Application)
21CFR Part 314 (INDA and NDA applications for FDA approval to Market a New Drug (New Drug Approval))
21CFR Part 316 (Orphan Drugs)
21CFR Part 50 (Protection of Human Subjects)
21CFR Part 54 (Financial Disclosure by Clinical Investigators)
21CFR Part 56 (Institutional Review Boards)
21CFR Part 58 (Good Lab Practice for Nonclinical Laboratory [Animal] Studies)

IND Application (Pre-Clinical Studies)

- Preclinical studies involves evaluating potential therapeutic interventions in cells and animals.
- Preclinical studies were carried out following good laboratory practices (GLP)
- Pre clinical trials began in 2007 and concluded in 2013
- Over one thousand biological agents were synthesized and purified for treatment of this disease
- The biological agents were then tested for their effectiveness to bind at their biological target site
- Experiments showed only 10 agents were effective at biological target

IND Application (Pre-Clinical Studies)

- In Vitro studies were carried out on the 10 biological agents
- The biological agent with the highest binding affinity to the target was chosen for clinical studies
- This process (pre-clinical studies) took about 5 years.

IND Application (Chemical, Manufacturing and Controls Information)

Regulatory Sponsor: PulsePharma
Funding Sponsor: Sanofi
Study Product: Dupilumab - Vodaxa

Investigational Agent

-Dupilumab - Vodaxa
-Clear liquid at room temperature, and IL-4, IL-5 and IL-13 cytokine antagonist
- Manufactured at 2500 Nesconset Hwy Ste 30-31, Stony Brook, NY 11790

IND Application (Chemical, Manufacturing and Controls Information)

General Method of Preparation and Packaging

-Drug is manufactured from cell line of rodents. There were strict measures taken into consideration for the preparation of this drug.

-Drug was tested at various points in order to ensure the highest quality and that it was in the appropriate metrics needed to support the purity and strength of the drug.

-The drug is stable at 10 - 20 degrees Celsius. At room temperature the drug starts to break down and must be injected before this occurs.

IND Application (Chemical, Manufacturing and Controls Information)

Drug Components and Drug Product

-Drug component- IL-4 IL-5 and IL-13 cytokine antagonist along with necessary carrier solution.

IND Application (Clinical Protocols & Investigators Information)

- The Clinical protocol is a document that describes how a clinical trial will be conducted (the objective(s), design, methodology, statistical considerations and organization of a clinical trial,) and ensures the safety of the trial subjects and integrity of the data collected.
- Primary Healthcare Physicians along with experts in the Asthma and Allergy fields contributed to the creation of our Clinical Protocol. They created a protocol on the basis of following our necessary primary objective and ensuring patient safety.
- Along with creating flow diagrams, Process diagrams, timeline diagrams and study arms and design.
- Detailed information on the qualifications of the principal investigator was also included in the application

IND Application (Informed Consent)

- Our informed consent documents did not contain unproven claims of effectiveness or certainty of benefit, either explicit or implicit, since that may unduly influence potential subjects.
- The informed consent was written by the clinical investigators.
- It was translated to 2 more languages including English - Spanish and Chinese in order to reach populations predisposed to asthma.
- The informed consent was prepared in an understandable language and given to the patient with sufficient time to digest the information and seek legal counsel or other opinion.
- All participants were informed that they are allowed to no longer participate whenever they so choose.

IND Submission & Ethics Review by IRB

- The IND application was submitted to the Office of New Drugs(OND) within the Center for Drug Evaluation and Research (CDER) in the FDA
- Our IND application was also reviewed by the Investigational Review Board (IRB)
- The IRB reviews the study protocols and informed consent in an IND application to ensure that the patients well being is put first.
- 30 days after our IND application was received by the FDA we began clinical trials

Development of Standard Operating Procedures (SOPs)

- Standard Operating Procedures (SOPs) are uniformly written procedures, with detailed instructions to record routine operations, processes and practices followed within a business organization.
- Our SOPs for each clinical trial contains adequate information to clearly guide our research staff (e.g nurses administering the drug, physician, monitors) through the procedures and thereby establish uniformity in the everyday functions of the trial

Development of Standard Operating Procedures (SOPs)

- The SOPs used in this clinical trial was written by an experienced study director and meets the requirement of the FDA
- The SOPs include all 25 SOPs provisions under section 211 required by the FDA.
- SOP’s have to be approved by IRB, If there is any change to any portion of the SOP’s the IRB must be notified and it must be approved before proceeding.

Selection of Trial Sites and Study Personnel

- Participants profile, staffing and facility requirements, enrollment target date and desired geography were first selected to identify appropriate sites.
- Past performance in clinical trials for both study personnels and investigational sites were also evaluated.

Selection of Trial Sites

- These sites were identified through various tools such as;
  - online and offline directories,
  - Clinicaltrials.gov postings,
  - Publication of related clinical trials,
  - Word-of-mouth,
  - External database through a Contract Research Organization (CRO) that has its on list of potential sites.
- After all the information was gathered, reviewed, and evaluated an objective selection of investigational sites was done

Selection and Enrollment of Participants

- Patients were given an Informed consent prior to being enrolled in study. As well as enough time to thoroughly read through the informed consent and get second opinions etc.
- Potential trial participants were found through information provided from patient organizations, patient registry, hospitals and pharmacy.
- Advertisements such as posters in doctor’s office and on social networks were also used to find participants.
- Prior to formal enrollment into our clinical trial, patients who were interested in participating went through a thorough screening process.
- The Inclusion and exclusion criteria for our study such as age, the type and stage of a disease, previous treatment history et.c determined if the participant was eligible for our trial

Quality Control (QC)

- Our QC team ensured that our research team is compliant with our SOPs, protocol,FDA requirement, have up to date training on the GCP required.
- They ensured that at each investigational site the requirements for quality trial activities were followed.
- They detected and measured the variability in the trials along with the characteristics and measurement of the trial generated.
- They ensured corrective response was taken to any discrepancy found during the clinical trials.

Phase 1 & 2 Trial (Summary)

Phase 1:

- The phase 1 trials took approximately 11 months to complete
- Here we primarily tested the safety of our drug on healthy volunteers
- The total number of participants in this study was 50

Phase 2:

- This trial took approximately 2 years to complete
- Here we studied the effectiveness of the drug and monitored for adverse events in the target population.
- The total number of participants in this study was 200
- Based on the efficacy and toxicology studies done a safe and effective dose was chosen for our phase 3 trials

Phase 3 Trial

- This trial was a randomized double blind parallel assignment.
- The drug was administered via injection
- The total number of participants in this study was 1903
- This trial was carried out in multiple investigational sites nationwide.
- The total study duration for the participants was 3 years and 9 months.

Phase 3 Trial (Monitoring)

At each investigational site there was at least one site monitor, that ensured that

- all data was collected and reported properly,
- the rights of the participants in the trial are protected,
- all procedures and protocols are followed
- any adverse event is completely reported.

Phase 3 Trial (Inclusion Criteria)

Inclusion Criteria:

- Adults 12 years or older as well as participants with a physician diagnosis of asthma for >=12 months
- Patients who have been diagnosed with severe asthma and a well-documented, regular prescribed treatment of maintenance corticosteroids in the 6 months prior to Visit 1
- Existing treatment with high-dose inhaled corticosteroid

Phase 3 Trial (Exclusion Criteria)

Exclusion Criteria:

- Any participant younger than 12 years old
- Pregnant or breastfeeding women
- Weighed less than 30 kg
- Any lung diseases that would impair lung function
- Previous smoker or current smoker (within 6 months prior to Visit 1).
- Clinical evidence or imaging within 12 months of Visit 1 with clinically significant findings of lung disease(s) other than asthma, as per local standard of care.
- A participant who experiences a deterioration of asthma that results in emergency treatment or hospitalization within 4 weeks of Screening Visit 1.

Phase 3 Trial (Exclusion Criteria)

Exclusion Criteria

- A participant who requires 12 puffs or more of rescue medication on any 1 day in the week prior to Visit 1.
- A participant who has experienced an upper or lower respiratory tract infection within the 4 weeks prior to screening.
- Any patient with history of hemophilia disorder

Phase 3 Trial (Arms of Study)

- In this trial the participants were divided into two treatment groups
- The first group was given the standard of care (Glucocorticoids)
- The second group was given a subcutaneous injection at the thigh containing a 150ml dose of the new drug
- This dose has been determined safe and effective from our previous trials.

Phase 3 Trial (Primary and Secondary Objectives)

Primary Objectives:

- To evaluate the efficacy of vodaxa, compared with the standard of care in order to reduce the use maintenance oral corticosteroids (OCS) in participants with severe steroid-dependent asthma
- To evaluate the safety and tolerability of Vodaxa
- A percentage reduction from baseline from the given dose at week 24 while maintaining asthma control

Phase 3 Trial (Primary and Secondary Objectives)

Secondary Objectives:

- Change in bronchial inflammation over time
- Change in Asthma quality of life
- Severity of treatment emergent adverse events
- Serum concentration of total IL-4 and IL-13 after single dose
- Immunogenicity of Vodaxa against standard of care

Phase 3 Results

- The results from this trial were observed.
- The change in baseline from corticosteroids versus Vodaxa.
- Overall there was a 70.1% change in eosinophilic basophilic and inflammation with vodaxa. As opposed to only a 23.1% change with corticosteroid.
- 69% of patients of vodaxa vs 33% on corticosteroids has a dose reduction to less than 50 ml per day.
- Injection site reactions were more common with vodaxa than with corticosteroid. (9% vs. 4%)

Quality Assurance (QA)

- Quality assurance carries out an independent examination of quality after and during a clinical trial.
- They ensure that all data in the trial is recorded and analyzed in accordance with the trial protocol and that the Good Clinical Practices (GCP) are followed
- The use of GCP guidelines in our clinical trial ensured that ethical and scientific quality standards for the design, conduct, recording, and reporting of the IRB and FDA approved clinical trials were upheld.

Safety management and Reporting

- We had no severe adverse events
- There were about 20 cases of mild adverse events that were reported and controlled.
- All adverse events were reported to our local health authority the FDA.
- Annual progress reports were submitted to the FDA within 60 days of the anniversary date our IND went into effect.
- At the end of our phase three trial, we submitted to the FDA the report summarizing the results of our trial.

Pre-NDA Submission meeting

- Prior to submitting our New Drug Application (NDA), we requested a meeting with the FDA
- This meeting helped to resolve any potential problem that could occur, and reduces the delays associated with the initial review of our application to the FDA.

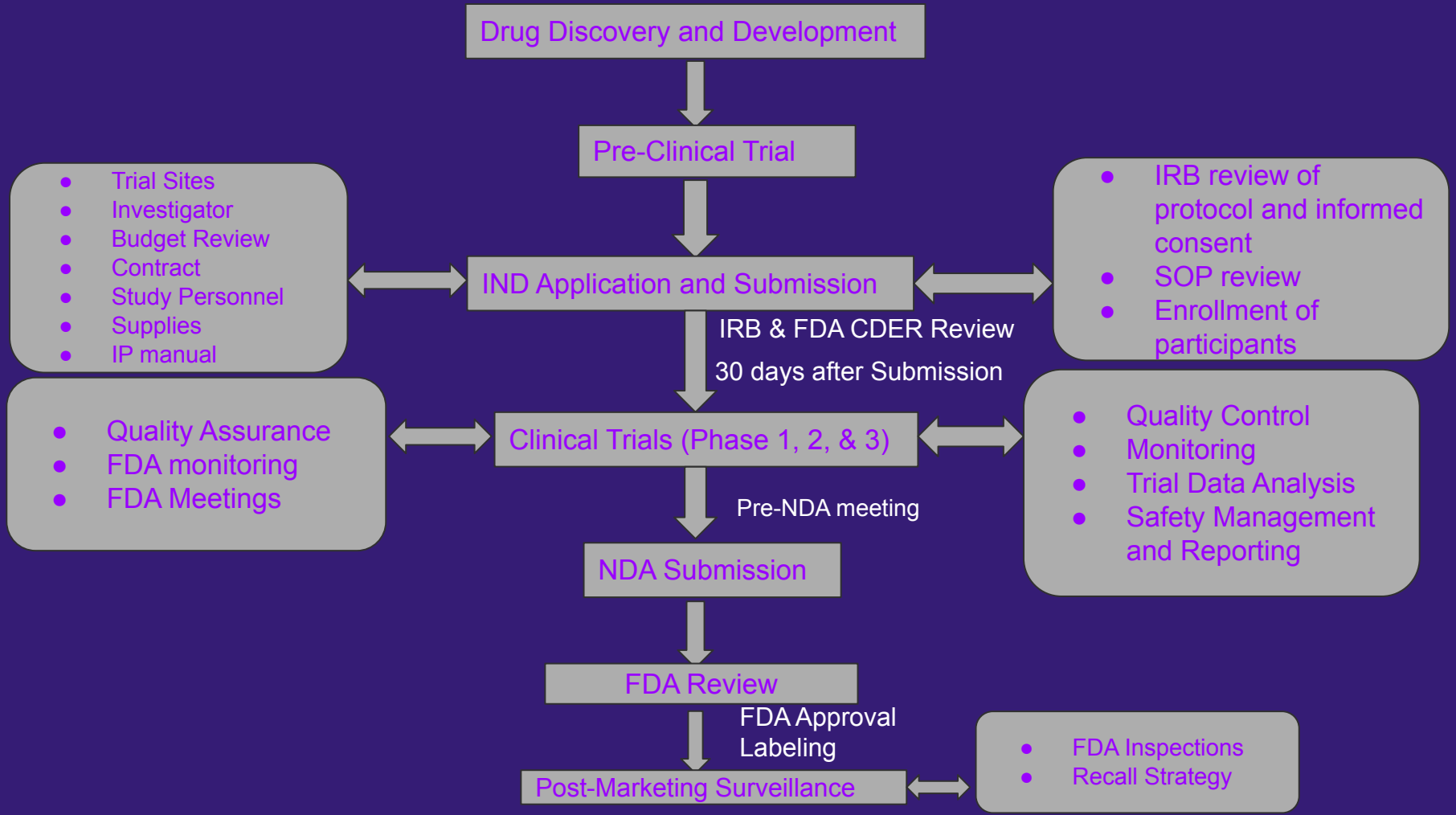
Objective of Pre-NDA Meeting

- To uncover any major unsolved problems
- To review the status of any ongoing studies
- To determine the adequacy of our dossier for the submission of our NDA
- To allow the FDA reviewers a chance to get acquainted with the information that will be submitted in the application
- To discuss the content, structure and format of our application
- To ensure that the amount of CMC information included in our NDA will be sufficient to demonstrate an understanding of the product and manufacturing process.

New Drug Application (NDA) Submission

- After the pre-NDA meeting, our NDA was submitted to the FDA.
- An NDA is submitted to the FDA to get approval to market a new drug in the United States
- Our company is a small growing company and was able to get a NDA fee waiver from the FDA because this is our first human drug application.
- Our NDA tells the FDA reviewers what occurred during our clinical trials, the ingredients inside the drug, how the drug behaves in the body, and how the drug is produced and packaged.

Timeline of Study



Thanks For Listening, Will you approve our drug “Vodaxa” for marketing in the United States?

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