NON INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	An Immuno-Dermatological disease registry to understand the burden of Atopic dermatitis (AD), Alopecia areata (AA), and Vitiligo in Indian Patients
Protocol Number	B7451103
Protocol Version Identifier	2.0
Date	19 April 2023
EU Post Authorization Study (PAS) Register Number	EUPAS48566
Research Question and Objectives	**Primary Objective:** • The objective of this registry is to evaluate the epidemiological burden of mild, moderate and severe AD, vitiligo, and AA across enrolled dermatology centers. **Secondary objectives:** • To elucidate the current diagnostic criteria and grading modalities for AD, vitiligo, and AA in India. • To define the burden of disease with a demographic overview of AD, vitiligo, and AA – with factors like Age (adult/adolescent/Pediatric), Gender (Male/female), Severity, region of body affected, Comorbidities, relevant personal history.

Redacted

	• To elucidate the treatment for AD, vitiligo, and AA – topical therapies, advanced therapies across the spectrum of the diseases, surgical interventions and laser or other cosmetic procedures across the disease severity spectrum. • To define the unmet needs in diagnosis (sequence of treatment and adverse events on therapy) and management of dermatological disorders Need for newer alternative therapies for patient's refractory to current therapeutic alternatives. • To identify and focus on patients' perspectives on benefits, quality of life and on the sequence of treatments.
Author	Redacted
Co-author	

Redacted

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Alopecia Areata
AAPPO	Alopecia Areata Patient Priority Outcomes
AASIS	Alopecia Areata Symptom Impact Scale
AD	Atopic Dermatitis
ADR	Adverse Drug Reaction
AE	Adverse Event
AEM	Adverse Event Monitoring
BSA	Body Surface Area
CDLQI	Children's Dermatology Life Quality Index
CRF	Case Report Form
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EDC	Electronic Data Capture
EDP	Exposure during pregnancy
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Definition
ICF	Informed Consent Form
ICH	International Council of Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICMR	Indian Council of Medical Research
IDQOL	Infants' Dermatitis Quality of Life Index
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NA	Not Applicable
NI	Non-Interventional
PGIS	Patient global impression of severity (PGIS) score
POEM	Patient-Oriented Eczema Measure
PV	Pharmacovigilance
QC	Quality Control
QoL	Quality of Life
SAE	Serious Adverse Event
SALT	Severity of Alopecia Tool
SAP	Statistical Analysis Plan
SCORAD	SCORing Atopic Dermatitis
SOP	Standard Operating Procedure
VIDA	Vitiligo Disease Activity Score
vIGA-AD	Validated Investigator Global Assessment Scale for Atopic Dermatitis

Redacted

Abbreviation	Definition
VIS-22	Vitiligo Impact Scale (VIS)-22
VITI QoL	Vitiligo Quality of Life

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
Redacted			

Redacted

4. ABSTRACT

Stand Alone document, see ANNEX 1.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1.0 Substantial	19 April 2023	Study Information and header	Version number and date have been updated	To reflect the actual amendment date and version number.
		2. LIST OF ABBREVIATIONS	Removed VSAS, VAS and VASI from the list and added AAPPO, PGIS and VIS 22.	Scales have been removed from protocol and replaced.
		3. RESPONSIBLE PARTIES	Added Dr. Gaur as responsible party. Changes in job titles.	Not listed previously. Only one team member can be listed as NI Study Lead.
		6. MILESTONES	Planned dates have been updated	Previous dates were in the past and not realistic anymore.
		7. RATIONALE AND BACKGROUND	Reference 1 *Dhar S, Parikh D, Rammoorthy R, Srinivas S, Sarkar R, Inamadar A, Shah M, Banerjee R, Kanwar AJ, Mendiratta V, George R, Gulati R. Treatment guidelines for atopic dermatitis by ISPD Task Force 2016. Indian J Paediatr Dermatol 2017;18:174-6* has been removed	Not applicable anymore
		9. RESEARCH METHODS	Corrected number of patients to be enrolled: 3000	Previous number of patients (2500) was incorrect.
		9.1 Study Design	Added number of planned centers (20).	For clarification.
		9.3 Variables	Removed CDLQI, DLQI, IDQOL, vIGA-AD, VIDA, VASI (acronym only) Dermatitis Family Impact Questionnaire and VITI QoL and added AAPPO, PGIS (disease-specific) and VIS 22.	Scales have been removed from protocol and replaced.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
			Nail Changes replaced with Itch Severity Removed "with or without consent" from photography listed as one of the clinician reported outcomes for Vitiligo.	By signing the ICF, patients will provide their consent for the physician to take photos, if required.
		9.5 Study Size	Minimum number of follow-up visits specified.	For clarification.
		9.6 Data Management and 9.8 Quality control	Details on data review and quality control process have been added.	For clarification.
		10.5 Ethical conduct of the study	Requirements were restricted to GCP, ICH and ICMR guidelines.	Not applicable requirements were deleted and only local and study specific requirements were kept.
		12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	ICMR was added mentioned amongst publications guidelines to follow.	To be consistent with the requirements mentioned in section 10.5.
		ANNEX 1 LIST OF STANDALONE DOCUMENTS	Removed the Informed Consent and Assent forms, SAP and CRFs.	Only the abstract is required to be listed as standalone document.
		Throughout the protocol	Minor changes added.	For clarification and/or corrections.

6. MILESTONES

Milestones	Planned Date
Completion of feasibility assessment	05 May 2023
Start of Data Collection	30 June 2023
End of Data Collection	31 August 2026
Registration in the EU PAS Register	30 April 2023
Final Study Report	28 February 2027

7. RATIONALE AND BACKGROUND

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that occurs most frequently in children but also affects many adults. It has a relapsing course and is often associated with elevated serum IgE levels and a personal or family history of allergic rhinitis and asthma. AD is one of the most common skin diseases which affects up to 20% of children and 1%–3% of adults in most countries of the world. The exact disease burden of AA, vitiligo and AD in India is not known.[1] Vitiligo is an acquired, idiopathic, and common depigmentation disorder. The values of various epidemiologic parameters of vitiligo are often doubtful due to the methodological weaknesses of the studies.[2] AA is a common form of non-scarring alopecia involving the scalp and/or body, characterized by hair loss without any clinical inflammatory signs. It is one of the most common forms of hair loss seen by dermatologists and accounts for 25% of all the alopecia cases.[3] The information on prevalence would be useful for planning strategies to manage these diseases.[2]

Nationwide systematic studies identifying the disease burden, epidemiology, and challenges and unmet needs in the diagnosis and management of AD, vitiligo, and AA in India are lacking.

This established the rationale to develop an Indian Immuno-Dermatological registry amongst Indian patients, suffering from AD, vitiligo, and AA to:

- Evaluate the epidemiological burden of AD, vitiligo, and AA;
- Current diagnostic modalities;
- Burden of diseases – pediatric population, adult patients, mild, moderate, or severe;
- Treatment – topical therapies, advanced therapies across the spectrum of the disease;
- Unmet needs in diagnosis and management of diseases – Need for newer alternative therapies for patient's refractory to current therapeutic alternatives.

This non-interventional study is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objective:

- The objective of this registry is to evaluate the epidemiological burden of mild, moderate and severe AD, vitiligo, and AA across enrolled dermatology centers.

Secondary objectives:

- To elucidate the current diagnostic criteria and grading modalities for AD, vitiligo, and AA in India.
- To define the burden of disease with a demographic overview of AD, vitiligo, and AA – with factors like Age (adult/adolescent/Pediatric), Gender (Male/female), Severity, region of body affected, Comorbidities, relevant personal history.
- To elucidate the treatment for AD, vitiligo, and AA – topical therapies, advanced therapies across the spectrum of the diseases, surgical interventions and laser or other cosmetic procedures across the disease severity spectrum.
- To define the unmet needs in diagnosis (sequence of treatment and adverse events on therapy) and management of dermatological disorders Need for newer alternative therapies for patient's refractory to current therapeutic alternatives.
- To identify and focus on patients' perspectives on benefits, quality of life and on the sequence of treatments.

9. RESEARCH METHODS

A prospective observational multi-centric study across 20 centers (including dermatologists and pediatric dermatologists) in India collecting data from 3000 patients diagnosed with AD/vitiligo/AA.

The data will be recorded for patients of AD, vitiligo, and AA which would include:

- The current diagnostic modalities and treatment modalities (topical therapies, medications, phototherapy) for these disorders.
- Variables regarding efficacy will be captured based on the physician's discretion. The same variables would be captured again at the follow up visit for a minimum of 3 follow up visits.

9.1. Study Design

A prospective, observational, longitudinal study (Immuno-Dermatological disease registry) conducted across 20 centers in India.

There is no study-related intervention. Enrolled patients are observed for the entire study period for a minimum of 3 follow-ups. Post baseline visit, follow-up visits take place at intervals as per the investigator's discretion.

At each follow-up visit, the investigator documents the clinical examination findings as per the Case Report Form (CRF), the prescribed therapy, as well as reasons for a change or continuation of therapy and possible adverse drug reactions (ADR) if any.

The patient questionnaire for follow-up visits is similar to the questionnaire for the baseline visit.

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the countries where this NI study is being conducted.

9.2. Setting

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Be aged between 2 and 64 years old.
2. Clinical diagnosis of Vitiligo, AA or AD.
3. Evidence of a personally signed and dated informed consent/assent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Not willing to provide written informed consent.
2. Not willing for follow up visit.

9.3. Variables

To note the age at diagnosis, the severity of disease, treatment initiation, treatment switch to advanced therapies, time to remission, time to relapse, patients with refractory disease, diagnosis at admission, patient demographics, underlying co-morbidities, treatment history, history of atopy, concomitant medications, clinical characteristics, clinical outcomes, use of topical therapy, the duration for moisturizers, quality of life parameters.

For Atopic Dermatitis[5]

Clinician Reported Outcomes

- Demographic criteria
- Clinical diagnosis
- Disease severity at baseline
    - QoL: loss of daily work/school days
    - Body Surface Area (BSA) Involvement
    - Eczema Area and Severity Index (EASI)
    - SCORing Atopic Dermatitis (SCORAD)
    - Itch Severity (Visual Analogue Scale)
- Associated comorbidities
- Past treatment history
- Current choice of therapy as I/II line agents
- Use of any other medications (phototherapy, antibiotics, antihistaminics)
- Treatment change if any
- Maintenance drugs (Topical/Systemic)
- Use of moisturizers
- Hospitalizations.

Patient Reported Outcomes

- Patient-Oriented Eczema Measure (POEM)
- Patient global impression of severity (PGIS) score for AD.

For Alopecia Areata[6]

Alopecia areata:

Clinician Reported Outcomes:

- Demographic details
- Clinical diagnosis
- Clinical history
- Associated Comorbidities
- Past Treatment
- Skin examination
- Skin biopsy (if done)
- Severity of Alopecia Tool (SALT)
- Current Treatment

Patient Reported Outcomes:

- Alopecia Areata symptom impact scale (AASIS)
- Patient global impression of severity (PGIS) score for AA
- Alopecia Areata Patient Priority Outcomes (AAPPO)

For Vitiligo[7]

Clinician Reported Outcomes:

- Demographic details
- Clinical diagnosis
- Clinical history at baseline

- Skin Examination
  - Body Surface Area
  - Vitiligo Area Scoring Index score
- Past vitiligo treatments (dose, duration, response, adverse effects)
- Current medications
- Koebner score
- Photography

Patient Reported Outcomes:

- Patient global impression of severity (PGIS) score for Vitiligo and Face
- VIS-22.

9.4. Data Sources

According to the inclusion and exclusion criteria specified in the protocol, investigators are to recruit patients for the specified conditions, AD, vitiligo and AA.

Primary data collected by the investigator through patient enrollment as per the protocol inclusion and exclusion criteria, observation and questionnaire during baseline and follow-up visit of the patient to the investigator as per the CRFs.

The data would be collected using either Electronic Data Capture (EDC) or in paper CRF's.

It is the investigator's responsibility to ensure that the study is conducted in compliance with all legal requirements and that the data are correctly recorded in the CRFs at the study site and the sponsor would be responsible for the compliance of the overall study conduct.

All data generated in the course of this study (including concomitant diseases, results of examinations and adverse events) must be recorded in the CRFs (paper or EDC) by appropriately authorized persons.

9.5. Study Size

The total study duration is estimated to be 3 years. The enrollment of all participants would be completed by 18 months with a minimum of 3 follow-up visits. A total of 3000 patients will be recruited and the sample distribution will be as follows:

- 1500 AD patients – The enrollment would proceed in a phased manner with evaluation on enrollment every 6 months.

- 750 vitiligo patients.
- 750 AA patients.

9.6. Data Management

Data pertaining to all fields required in order to fulfill the primary and secondary endpoints of the study will be captured in a paper CRF. Data from the paper CRF will then be transferred to an excel managed by Insignia. Data entry, data query generation and resolution, source document verification and database lock will be performed as per standard Good Clinical Practice (GCP) guidelines.

- Rules for completing CRFs:
  - Print legibly using preferably a black/blue ballpoint pen. Ensure that all questions are answered and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks.
  - If the question is irrelevant (eg is not applicable) indicate this by writing "NA" (not applicable) in the respective answer field.
  - The investigator staff must ensure that all information derived from source documentation is consistent with the source information. By signing the affirmation statement, the Investigator confirms that the information is complete and correct.
- Corrections to CRFs:
  - Corrections to the data on the CRFs must only be made by drawing a straight line through the incorrect data and by writing the correct value next to data that has been crossed out. Each correction must be initialed, dated and explained by the Investigator or the Investigator's authorised staff.
- Monitoring of CRFs:
  - Filled case record forms will be checked for accuracy by designated staff before sending them to Insignia for data entry, validation and analysis. The case record forms will be checked and collected at a mutually agreed frequency.
  - If a mistake is identified in already transcribed data, the data management team will follow CRO's internal SOP for correcting the mistake. This process includes:
    - Identifying the mistake and determining the correct information.
    - This includes source document verification on site

- Discrepancy management including query generation and resolution
- Sign off
- Making the correction on the paper CRF first with date and authorized signature
- Making the correction in the excel file with track changes thereby ensuring audit trail
- Independently reviewing the paper CRF and excel to ensure there are no discrepancies
- Updating any necessary documentation to reflect the correction

- We follow an intrinsic process to ensure that the paper CRF and excel file match to avoid discrepancies that could lead to errors or confusion. To document the correction process to ensure that it is clear and transparent.
- Investigator will be responsible for the retention of patient notes for a period of 5 years from study close out.

9.6.1. Case Report Forms (CRFs)

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in [encrypted electronic and/or paper] form and will be [password protected or secured in a locked room] to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, Informed Consent Form (ICF), CRFs and hospital records), copies of all ICFs, CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for as long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 5 years after completion or discontinuation of the study, unless Insignia Communications and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 5 years or as required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality Control

Before the first patient is recruited into the study, Insignia representative or delegate will:

- Establish the adequacy of the facilities and the investigator’s capability to appropriately select the sample.
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of Insignia or its representatives.

QC of the transcribed CRF to excel

- The data entry team and the data QC team would be independent of each other. They both will look at the same paper CRF but these would be independent and sequential activities.

- A set of validation rules will be set up in excel to identify potential data entry errors or inconsistencies. For example, these rules can include checking for missing data or data outside of the expected range of values.

- Manual spot checks will be performed periodically to ensure that data is being entered accurately and consistently.

- Regular data review and cleaning will be performed throughout the study to identify any errors or inconsistencies and take corrective actions as necessary.

During the study, Insignia representative or delegate can implement different activities to assure compliance with Insignia's standards of quality. These activities could include but are not limited to:

Contacts with the sites to:

- Provide information and support to the investigator(s).

- Confirm that the research team is complying with the protocol and that data are being accurately recorded in the CRFs.

- Ensure that the patient informed consent forms are signed and stored at the investigator's site.

- Ensure that the CRFs are completed properly and with adequate quality.

Monitoring activities for:

- Checking a sample of ICFs

- Checking that patients exist in medical records (a sample)

The extent and nature of monitoring will be mutually decided. If the study in charge is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

Should the sponsor decide to discontinue the study prior to what was established in this protocol, the investigator, and relevant authorities should receive written notice describing the reasons why the study was terminated at an earlier date. The investigator will immediately notify the patients taking part in the study; they will continue to receive their treatment according to usual clinical practice.

9.9. Limitations of the Research Methods

The potential limitation for this study would be patient's loss to follow up.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and *will be* password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of a disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

Patient personal data will be stored at Insignia Communications Pvt. Ltd. (CRO) in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. CRO will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, CRO shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. CRO will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the vendor contract, research agreement and applicable privacy laws.

10.2. Patient Consent

The informed consent/assent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

The investigator must ensure that each study patient or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient [or his or her legally acceptable representative, or parent(s) or legal guardian if a minor,] is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient or a legally acceptable representative/parent(s) or legal guardian, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

Investigators can follow their site's normal practice for documenting that the person signing the informed consent document is the patient's legally acceptable representative, but the source records should describe how it was determined.

If the study includes minor patients who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/IEC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative, parent(s), or legal guardian and the patient's assent, when applicable, before any study-specific activity is performed unless a waiver of informed consent has been granted by an IRB/IEC. The investigator will retain the original of each patient's signed consent/assent document.

10.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcomes, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.3.1. Criteria for Discontinuation:

Patients may be discontinued from the study at any time. Specific reasons for discontinuing a patient from this study could be, but are not limited to:

- Patients who discontinue treatment with the same investigator;
- Relocate to another city;
- Side effects, unexpected morbidity, etc.

Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.

10.4. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained by the investigator. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the Declaration of Helsinki, International Council of Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) and the Indian Council of Medical Research (ICMR).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

The table below summarizes the requirements for recording safety events on the data collection tool (eg, case report form) and for reporting safety events on the NI adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure to a Pfizer product, including exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	**Recorded on the *case report form***	**Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness**
SAE	All (regardless of whether the event is determined by the investigator to be related to any Pfizer product)	Only events determined by the investigator to be related to a Pfizer product
Non-serious AE	All (regardless of whether the event is determined by the investigator to be related to any Pfizer product)	Only events determined by the investigator to be related to a Pfizer product
Scenarios **involving exposure to a Pfizer product**, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) involving exposure to a Pfizer product Note: Any associated AE is reported together with the exposure scenario.

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below).

Safety events must be reported to Pfizer within 24 hours of awareness of the event by the investigator as described in the table above. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For those safety events that are considered serious or that are identified in the far-right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's informed consent, which is obtained prior to the patient's enrollment in the study, and lasts through the end of the observation period of the study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, the patient changes his/her mind about participation) the reporting period ends on the date of the decision to not enroll the patient. If the investigator becomes aware of an SAE occurring at any time after completion of the study and s/he considers the serious AE to be related to a Pfizer product, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to *a Pfizer product*, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that a Pfizer product caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether a Pfizer product caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that a Pfizer product did not cause the event, this should be clearly documented on the CRF and the NI study AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.
- Additionally, for medicinal products, they may include the signs or symptoms resulting from:
- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breastfeeding;
- Medication error;

- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly exam);
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) a Pfizer product, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to a Pfizer product (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to a Pfizer product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

For exposure during pregnancy in studies of pregnant women, data on the exposure to drug during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed, with the exception of those studies conducted in pregnant women (as described in above), for which data on the exposure are not reportable unless associated with serious or non-serious adverse events.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with a Pfizer product, this information must be submitted to Pfizer, irrespective of whether an AE has occurred, must be submitted using the NI study AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to a Pfizer product, in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NI study AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the

terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Insignia will prepare a Study Report within 2 months after the completion of the last patient. If a report of the study is published, the contribution of participating investigators will be duly acknowledged. Insignia is obliged to analyse and report all study data as described in the protocol. In a publication of the results of the study, the authors are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Insignia endeavors to publish the results of study and is committed to ensure that the data are reported in a responsible and coherent manner. Insignia seeks to ensure that publications in biomedical journals follow the guidelines established by ICMR and the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals.

Insignia is committed to ensuring that authorship for all publications should comply with the criteria defined by the ICMJE. These state that: "Each author should have participated sufficiently in the work to take public responsibility for the content."

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

13. REFERENCES

1. Dhar S, Parikh D, Rammoorthy R, Srinivas S, Sarkar R, Inamadar A, Shah M, Banerjee R, Kanwar AJ, Mendiratta V, George R, Gulati R. Treatment guidelines for atopic dermatitis by ISPD Task Force 2016. Indian J Paediatr Dermatol 2017;18:174-6.

2. Kumar S, Nayak CS, Padhi T, et al. Epidemiological pattern of psoriasis, vitiligo and atopic dermatitis in India: Hospital-based point prevalence. Indian Dermatol Online J. 2014;5(Suppl 1):S6-S8.

3. Sarma N et.al. A Nationwide, Multicentric Case-Control Study on Vitiligo (MEDEC-V) to Elicit the Magnitude and Correlates. Indian J Dermatol. 2020 Nov-Dec;65(6):473-482.

4. Seetharam KA. Alopecia areata: An update. Indian J Dermatol Venereol Leprol 2013;79:563-575.

5. Vermeulen FM, International TREAT Registry Taskforce. TREatment of ATopic eczema (TREAT) Registry Taskforce: consensus on how and when to measure the core dataset for atopic eczema treatment research registries. Br J Dermatol. 2019 Sep;181(3):492-504.

6. MA CDONALD HULL. Guidelines for the management of alopecia areata. British Journal of Dermatology,2003; 149, 692–699.

7. Kawakami T, Hashimoto T. Disease severity indexes and treatment evaluation criteria in vitiligo. Dermatol Res Pract. 2011;2011:750342.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	19 April 2023	Abstract: An Immuno-Dermatological disease registry to understand the burden of Atopic dermatitis (AD), Alopecia areata (AA), and Vitiligo in Indian Patients

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	B7451103 Non Interventional Study Amendment 1, Version 2.0 (clean) 19Apr23
Document Title:	B7451103 Non Interventional Study Amendment 1, Version 2.0 (clean) 19Apr23

Signed By:	Date(GMT)	Signing Capacity
Redacted	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]