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Application of Immunology and Inflammation Late Phase in Programming

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ABSTRACT

The scientists and physicians are committed to helping people who are suffering from immune-mediated diseases that have long eluded treatment. Immunology & Inflammation Therapeutic Area today is one of the most active areas. At present, Sanofi has three main routes in immunization: systemic diseases such as asthma and atopic dermatitis; peripheral inflammatory diseases such as rheumatoid arthritis, and autoimmune challenges in type 1 diabetes and cancer, especially in Sanofi with many products in development and our flagship medicine, continuing to grow rapidly in numbers of diseases and patients treated. As we continue to uncover more about inflammation and how it drives inflammatory diseases such as asthma and atopic dermatitis, we are investigating other indications in dermatology, respiratory and even gastroenterology where immune pathways play an important role in disease biology.

Further taking to heart the individuality of patients, Sanofi is developing precision medicine technology, generating molecular and cellular views of immune conditions which, when combined with real-world patient data, can reveal meaningful connections, and yield more precise therapeutics to fit individual patient biology and individual patient's needs.

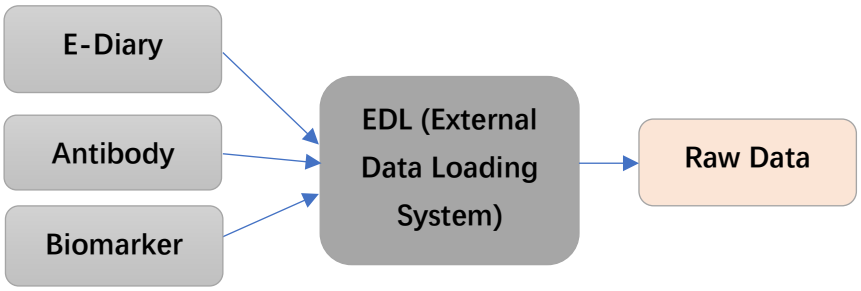
INTRODUCTION

As we know, Immunology and Inflammation (I&I) studies may have some very different scopes in programming based on the rules, and we are focusing on some standards which the other Therapeutic Area are not. In this paper, we will have some process and standards for I&I late phase studies' programming. Thus, you can much know about the I&I programming works.

There are four main parts in this paper, Database (the E-Diary, Antibody and Biomarker), Special AESI Flags for I&I, I&I Common Models and Hypersensitivity Listing. Hope this paper can make you more clearly about the I&I late phase study and know the corresponding programming knowledge.

1. PART ONE - DATABEASE

Talking about the data, the E-Diary, Antibody and Biomarker are I&I main special topics. Usually, the three parts of data are often collected by the vendors, and we can get the raw data by the External Data Loading system.



The E-Diary will be mapped in QS domain, E-Diary Findings domain or RE domain and categorized as “DAILY EDIARY” or others, and then we derive the SDTM into ADED for statistical analysis. Besides these three domains, we also map to more other domains if needed.

For Antibody, we often have two tests, one is Anti-drug Antibodies and the other one is Neutralizing Antibody. We collect and load the external data from vendor and derive as IS domain in SDTM level, then we will create ADIS for further statistical analysis.

For Biomarker, the tests are normally collected in Laboratory, and categorized as “Biomarker” in SDTM level, but we select the biomarker tests from SDTM to derive into a separate biomarker ADaM named as ADBM. In I&I studies, we normally take the tests like Protein, Allergen Total IgE, IGE (Immunoglobulin E), IGG4, TARC, Blood Eotaxin-3 as the important analysis ones.

1.1 E-DIARY

The list of data to be collected depends on the study protocol and the need for the statistical analysis. This must be discussed during the data collection strategy meeting at study team level. Here is a list of examples:

- IMP (Investigational Medicinal Product) or AxMP (Auxilary Medicinal Product) administration: Y/N question
- Administration date (often automatically populated by the E-Diary)
- Intake time if needed (e.g., for pharmacokinetics endpoints, monitoring of overdoses, etc)
- Number of tablets/syringes/injections/other
- Dose (in case of injection)
- IP identifier (kit number, treatment number, etc.) if needed (to identify dispensation mistakes for instance)
- Injection site

Study participant drug diary can also include other information necessary for the study such as:

- Adverse event collection / change in health condition?
- Concomitant medication use
- Other information justified by your protocol (questionnaires, personalized questions (pregnancy test), etc)

NB: always avoid free text in the diary. Consider Y/N question and multiple-choice answers.
Tips: add in E-Diary design unscheduled forms. This will allow data collection outside of visit window and score recalculation in case of mis-completion of the first assessment.

1.2 ANTIBODY

With the development of biotechnology, monoclonal antibodies (mAbs) have become one of the main therapeutic weapons in modern medicine. However, monoclonal antibody treatment often stimulates the formation of anti-drug antibodies (Anti-Drug Antibodies, ADAs), causing side effects and limiting efficacy. ADA can change the pharmacokinetics, pharmacodynamics, efficacy, and safety of monoclonal antibody drugs, and may cause additional side effects. To improve the efficacy and safety of monoclonal antibody drugs, the detection of ADA may be of great significance to treatment strategies and treatment adjustments.
A neutralizing antibody (NAb) is an antibody that is responsible for defending cells from pathogens and are produced naturally by the body as part of its immune response. Their

production is triggered by both infections and vaccinations against infections. In an immunogenetic context it will bind to a drug and neutralize its therapeutic effect.

Immunogenicity analyses

Anti-drug antibody (ADA) status (negative or titer value, if positive in the ADA assay) at Baseline, Week XX and EOS visit will be provided. The neutralizing antibody results for ADA positive samples will be provided.

Incidence will be provided for the following ADA response categories. Treatment-emergent and treatment-boosted response will be defined based on samples collected in the on-treatment period. Take an example for the defines.

- Pre-existing immunoreactivity is defined as:

An ADA positive response in the assay at baseline with all post first dose ADA results negative, OR an ADA positive response at baseline with all post first dose ADA responses less than 4-fold over baseline titer levels.

- Treatment-emergent ADA responses are defined as:

A positive response in the ADA assay post first dose, when baseline results are negative or missing.

- Treatment-emergent ADA responses are further classified as persistent, indeterminate, or transient.

a) Persistent response - defined as a treatment-emergent ADA response with two or more consecutive ADA positive sampling time points, separated by greater than (>) 12-week period (84 days), with no ADA negative samples in between.

b) Indeterminate response - defined as a treatment-emergent response with only the last collected sample positive in the ADA assay.

c) Transient response - defined as a treatment-emergent response that is not considered persistent OR indeterminate.

- Treatment-boosted response is defined as:

An ADA positive response in the assay post first dose that is greater-than or equal to 4-fold over baseline titer levels when baseline results are positive.

Titer values (Titer value category)

- Low (Titer <1000)
- Moderate (1,000 ≤ Titer ≤10,000)
- High (Titer >10,000)

1.3 BIOMARKER

Most important Biomarker in I&I studies are FENO, Eosinophil, Protein, Allergen Total IgE, IGE (Immunoglobulin E), IGG4, TARC, Periostin, Blood Eotaxin-3 etc. Biomarker analysis are often exploratory analysis not primary analysis. In future, Biomarker analysis may be extended to machine learning.

Blood, urine, nasal secretions, and nasal brushing biomarkers will be summarized on the safety population. Baseline values will be the last value collected prior to the first IMP. Descriptive statistics (including Number, Mean, SD, Median, Q1, Q3, Min, Max) of biomarkers at baseline and each post-baseline visit will be summarized. Summary plots at each visit (mean, mean change from baseline and median percent change from baseline) will be provided for each biomarker by intervention group.

1. Summary of Protein over time - Safety population

Protein	**Placebo (N=XX)**	**Treatment (N=XX)**
Baseline		
Value		
Number	XX	XX
Mean (SD)	XX.XX (XX.X)	XX.XX (XX.X)
Median	XX.XX	XX.XX
Q1: Q3	X.X: X.X	X.X: X.X
Min: Max	XX: XX	XX: XX
Week 12		
Value		
Number	XX	XX
Mean (SD)	XX.XX (XX.X)	XX.XX (XX.X)
Median	XX.XX	XX.XX
Q1: Q3	X.X: X.X	X.X: X.X
Min: Max	XX: XX	XX: XX
Change from baseline		
Number	XX	XX
Mean (SD)	XX.XX (XX.X)	XX.XX (XX.X)
Median	XX.XX	XX.XX
Q1: Q3	X.X: X.X	X.X: X.X
Min: Max	XX: XX	XX: XX
Percentage change from baseline		
Number	XX	XX

Mean (SD)	XX.XX (XX.X)	XX.XX (XX.X)
Median	XX.XX	XX.XX
Q1: Q3	X.X: X.X	X.X: X.X
Min: Max	XX: XX	XX: XX

Repeat for Other weeks.

Two figures:

2. Figure of mean (+/- SE) in Protein over time - Safety population
3. Figure of mean change (+/- SE) from baseline in Protein over time - Safety population

2. PART TWO - SPECIAL AESI FLAGS

The “AESI event" denotes if an event is considered an adverse event of special interest (AESI). The list of values includes "Blank", "Yes" or "No".
An AESI is defined as follows: AESI in solicited clinical trial cases: An adverse event (serious or non-serious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation to characterize and understand them.
The AESIs flags are very important in I&I studies, and we follow the company clinical and medical rule to derive them. Here I list some most common ones to make you clear about the rules.

- Anaphylactic reaction: Anaphylactic reaction algorithmic approach (Introductory Guide for Standardized MedDRA Queries (SMQs)): includes anaphylactic reaction narrow SMQ (20000021) terms; for selection based on occurrence of multiple symptoms, the symptoms must have occurred within 24 hours of each other, which are related to IMP and requires treatments.
- Systemic hypersensitivity reactions: SMQ [20000214] hypersensitivity narrow search and [AE corrective treatment/therapy = ’Y’ or Action taken with IMP = ’Drug withdrawn’ or Action taken with IMP = ’Drug interrupted’] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events.
- Serious injection site reactions or severe injection site reactions that last longer than 24 hours: HLT = ‘Injection site reaction’ and either with serious status, or with severe status and (AE end date/time - AE start date/time) ≥ 24 hours or ongoing.
- Severe or serious infection: Primary SOC = ‘Infections and infestations’ and (Intensity=’Severe’ or Serious=’Y’).
- Parasitic infection: Infection type "Parasitic" checked on eCRF.
- Opportunistic infection: The Infection Type ‘Opportunistic’ was checked on eCRF page.
- Drug-related hepatic disorder: Drug-related hepatic disorders-Comprehensive search narrow SMQ (20000006).
- Conjunctivitis (narrow): CMQ10644 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis].

- Conjunctivitis (broad): CMQ10645 based on the following PTs [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia.
- Keratitis: CMQ10642 based on the following PTs [keratitis, allergic keratitis, ulcerative keratitis, atopic keratoconjunctivitis, herpes ophthalmic, ophthalmic herpes simplex, corneal infection]
- Eosinophilia: HLT = 'Eosinophilic disorders' or PT = 'Eosinophil count increased'

3. PART THREE - I&I COMMON MODELS

In I&I studies, we are using a few models, but here I just list the most four common ones we used, such as Mixed-effect Models for Repeated Measures, Generalized Linear Mixed Model, Logistic regression Model and Cox model.

3.1 MMRM MODEL

The mixed model for repeated measures (MMRM) is a popular choice for individually randomized trials with longitudinal continuous outcomes. This model's appeal is due to avoidance of model misspecification and its unbiasedness for data missing completely at random or at random. It is a good analytic choice for cluster randomized trials with a continuous outcome measured longitudinally.

Mixed-effect models for repeated measures' function is,

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 (x_1 * x_2) + \cdots + \varepsilon$$

Here is an example which consider the following shell from a randomized study having two treatment groups – Treatment and Placebo. The assessment was repeated on Week 12 following the initial intake of the study drug.

Change from baseline in Pre-bronchodilator % predicted FEV1 over time (MMRM including measurements up to Week 12) - Type 2 inflammatory asthma phenotype population

Pre-bronchodilator % predicted FEV1	**Placebo**	**Treatment**
Baseline		
Value		
Number	XX	XX
Mean (SD)	XX.XX (XX.X)	XX.XX (XX.X)
Median	XX.XX	XX.XX
Q1: Q3	X.X: X.X	X.X: X.X
Min: Max	XX: XX	XX: XX
Week 2		
Change from baseline		
Number of patients in the model	XX	XX
LS Mean (SE) a	XX.XX (XX.X)	XX.XX (XX.X)
LS Mean Diff vs. placebo (95% CI) a		XX (XX, XX)
P-value vs. placebo a		XX
Repeat from Week 2 up to Week 12.		

a Derived from MMRM model with change from baseline in Pre-bronchodilator % predicted FEV1 values up to Week 12 as the response variable, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates.

Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils >= 0.15 Giga/L or baseline FeNO >= 20 ppb.

The Model program is like as below,

```
proc mixed data=effdata method=ML;
  where avisitn>0;
  class usubjid trt01pn WTBLGR1N REGION1N ETHNIC EOSBGR2N FENOBG2N ICSBLGR avisitn;
  model chg = trt01pn WTBLGR1N REGION1N ETHNIC EOSBGR2N FENOBG2N ICSBLGR avisitn
        trt01pn*avisitn base base*avisitn /ddfm=kr residual;
  repeated avisitn/ subject=usubjid type=UN;
  lsmeans trt01pn*avisitn / pdiff cl;
  ods output LSMeans=LSMeans_mmrm  Diffs=Diffs_mmrm;
run;
```

According to the footnote, we know the MMRM model is fitted using PROC MIXED which includes change from baseline in % predicted FEV1 values up to Week 12 as response

variables, and treatment, baseline weight group, region, ethnicity, baseline eosinophil level, baseline ICS dose level, visit, treatment by-visit interaction, baseline % predicted FEV1 value and baseline-by-visit interaction as covariates. Treatment group, region, baseline weight group, baseline eosinophil level, ethnicity, baseline ICS dose level, and visit will be treated as categorical variables. The repeated measures are the change from baseline in Pre-bronchodilator % predicted FEV1 obtained at the Week 2, Week 4, Week 6, Week 8, and Week 12 respectively.

The METHOD=ML specifies the estimation method for the covariance parameters.

DDFM=KR option performs the degrees of freedom calculations detailed by Kenward and Roger.

TYPE=UN specifies the covariance structure as Unstructured.

DIFF option requests differences of LS means.

We can conclude that reject the Hypothesis null and the treatment group is significant different with the Placebo group if the P-value is < 0.05. We accept the Hypothesis null no significant different between the two groups if the P-value is >= 0.05.

3.2 GENERALIZED LINEAR MIXED MODEL

A Generalized linear mixed model (GLMM) is an extension to the generalized linear model (GLM) in which the linear predictor contains random effects in addition to the fixed effects. Consider a generalized linear model with linear predictor and link function,

$$E[Y|\gamma] = g^{-1}(\eta) = g^{-1}(X\beta + Z\gamma)$$

The output shell is like as below,

Annualized rate of severe exacerbation events during the 52-week treatment period - Type 2 inflammatory asthma phenotype population and baseline blood eosinophils >=0.3 Giga/L population

	Type 2 inflammatory population		**Baseline blood eosinophils >=0.3 Giga/L population**	
	Placebo (N=XX)	**Treatment (N=XX)**	**Placebo (N=XX)**	**Treatment (N=XX)**
Adjusted annualized rate of severe exacerbation events				
Estimate a (95% CI) a	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)	XX (XX, XX)
Relative risk a vs. placebo (95% CI) a		XX (XX, XX)		XX (XX, XX)

P-value a vs. placebo a	XX	XX
Risk difference b vs. placebo (95% CI)	XX (XX, XX)	XX (XX, XX)

a Derived using negative binomial model with the total number of events onset from randomization up to Week 52 visit or last contact date (whichever comes earlier) as the response variable, with the treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.

b Derived using delta method.

The Model program is like as below,

```
proc glimmix data=effdata method=RSPL;
    class trt01pn eosbgr1n icsgrp region1n;
    model numevents= trt01pn age eosbgr1n icsgrp region1n asmanum /offset=logdur dist=negbin link=log solution;
          estimate 'Treatment vs Placebo rate ratio' trt01pn -1 1 /alpha=0.05 exp;
    lsmeans trt01pn/alpha=0.05 cl ilink diff=all cov;
run;
```

According to the footnote, we know the GLMM model is fitted using PROC GLIMMIX with age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study and treatment group as covariate.

The CLASS statement instructs the procedure to treat the variables center and group as classification variables.

The SOLUTION option in the MODEL statement requests a listing of the fixed-effects parameter estimates.

The GLIMMIX procedure defaults to the binomial distribution, with the default logit link. If these defaults are not appropriate, you can change the distribution with the DIST= option and the link function with the LINK= option of the MODEL statement.

Relative risk is a ratio of the probability of an event occurring in the exposed group versus the probability of the event occurring in the non-exposed group. Relative Risk = (Probability of event in exposed group) / (Probability of event in not exposed group)

Risk difference is defined as the difference in risk of a condition such as a disease between an exposed group and an unexposed group. Risk difference = risk of exposure group - risk of unexposed group.

3.3 LOGISTIC REGRESSION MODEL

Logistic regression is a process of modeling the probability of a discrete outcome given an input variable. The most common logistic regression models a binary outcome; something that can take two values such as true/false, yes/no, and so on.

For binary response models, the response, Y, of an individual or an experimental unit can take on one of two possible values, denoted for convenience by 1 and 2 (for example, $Y = 1$ if a disease is present, otherwise $Y = 2$). Suppose x is a vector of explanatory variables and $\pi = \Pr(Y|1 = x)$ is the response probability to be modeled. The linear logistic model has the form,

$$logit\left(\frac{\pi}{1-\pi}\right) = \alpha + \beta' x$$

where α is the intercept parameter and $\beta = (\beta_1, \ldots, \beta_s,)'$ is the vector of s slope parameters. Notice that the LOGISTIC procedure, by default, models the probability of the lower response levels.

One kind of output shell is like as below,

Responder analysis for change from baseline in ACQ-5-IA over time - Type 2 inflammatory asthma phenotype population and baseline blood eosinophils >=0.3 Giga/L population

	Type 2 inflammatory asthma phenotype population		**Baseline blood eosinophils >=0.3 Giga/L population**	
	Placebo (N=XX)	**Treatment (N=XX)**	**Placebo (N=XX)**	**Treatment (N=XX)**
Week 12				
Responder a	XX/XX (XX.X%)	XX/XX (XX.X%)	XX/XX (XX.X%)	XX/XX (XX.X%)
Non-responder a	XX/XX (XX.X %)	XX/XX (XX.X %)	XX/XX (XX.X %)	XX/XX (XX.X %)
OR vs. placebo (95% CI) b		XX (XX, XX)		XX (XX, XX)
P-value vs. placebo b		XX		XX
Repeated for Week 24, Week 36, and Week 52				

a A responder is defined as a patient with improvement from baseline in ACQ-5-IA >= 0.5. Patients with improvement < 0.5 or with missing value are considered as non-responder.
b Derived from a logistic regression model with treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and baseline ACQ-5-IA score as covariates.
Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils >= 0.15 Giga/L or baseline FeNO >= 20 ppb.

The Model program is like as below,

```
proc logistic data=effdata;
     class arm01pn WTBLGR1N REGION1N FENOBG2N ICSBLGR/param=glm;
     model CRIT1FLN(event='1')=arm01pn AGE WTBLGR1N REGION1N FENOBG2N ICSBLGR BASE2 /alpha=0.05 waldcl;
     estimate "Treatment vs. Placebo" arm01pn -1 1/cl chisq exp;
     by AVISITN;
     ods output Estimates=or;
run;
```

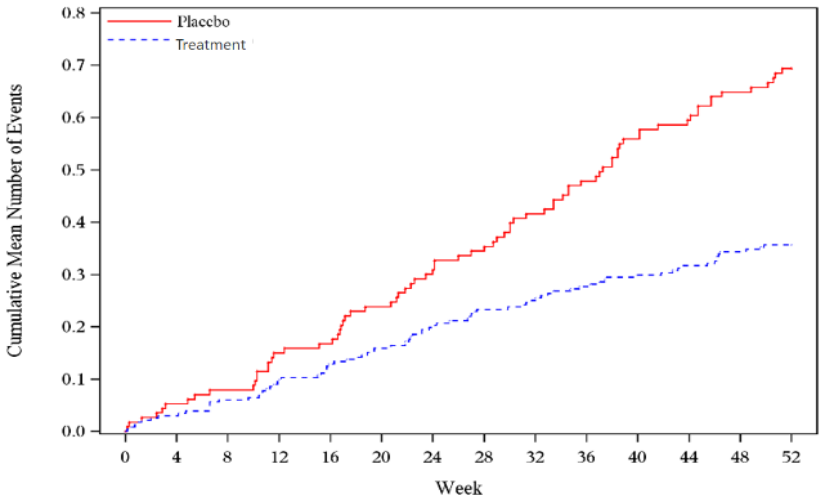
According to the footnote, we know the Logistic Regression Model is fitted using PROC LOGISTIC with treatment, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, and baseline ACQ-5-IA score as covariates. CLPARM=PL | WALD | BOTH requests confidence intervals for the parameters. Computation of these confidence intervals is based on the profile likelihood (CLPARM=PL) or individual Wald tests (CLPARM=WALD). If you specify CLPARM=BOTH, the procedure computes two sets of confidence intervals for the parameters, one based on the profile likelihood and the other based on individual Wald tests.
If you want to force SAS to predict an event that does not have the lowest numeric code, you can specify “EVENT='number'”, in this case, suppose we have coded outcome variable CRIT1FLN with 0 = not flag as Y, 1 = flag as Y. We want to predict the flag as Y.
Odds ratios provide a method of describing the strength of the partial relationship between an individual predictor and the predicted event. An odds ratio of 1 means that the proportion of this condition in the two groups is equal. If it is greater than 1, it means that the proportion of this condition in the Treatment group is higher than that in the placebo group. If it is less than 1, it means that the proportion of this condition in the Treatment group is lower than that in the placebo group.

3.4 COX REGRESSION MODEL

Cox Regression is a model is commonly used to evaluate the association between the survival time of patients and one or more predictor variables. Most survival analyses address a key analytical problem—censoring, which occurs when we do not know the exact time of exposure before an event.

The analysis of survival data requires special techniques because the data are almost always incomplete, and familiar parametric assumptions may be unjustifiable. Investigators follow subjects until they reach a prespecified endpoint (for example, death).
However, subjects sometimes withdraw from a study, or the study is completed before the endpoint is reached. In these cases, the survival times (also known as failure times) are censored; subjects survived to a certain time beyond which their status is unknown. The non-censored survival times are referred to as event times. Methods for survival analysis must account for both censored and non-censored data.

One figure is like as below,
Plot of cumulative mean number of severe exacerbation events during the 52-week treatment period - Type 2 inflammatory asthma phenotype population



Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils >= 0.15 Giga/L or baseline FeNO >= 20 ppb.

The Model program is like as below,

```
*-- Derive start and stop day for each event --*;
data formodel;
    set all;
    by subjid day;
    Tstart=lag(day/7);
    Tstop=day/7;
    if first.subjid then do;
    Tstart=0;
    end;
run;
*-- Model --*;
proc phreg data=formodel covs(aggregate) atrisk covm;
    by _trt01pn;
    model (Tstart,Tstop)*censor(1)=;
    baseline out=phout mcf=_all_ atrisk=atrisk / nomean;
    id subjid;
run;
```

In the model, Tstart and Tstop are survival time variables, censor is a censored variable, 1 is censored data, 0 is complete data, = followed by factor variables that affect survival time. In the PHREG process, the survival time variable, censored variable and the variable value corresponding to the censored data need to be defined before = in the model statement, and the influencing factor variables are after =.

4. PART FOUR: HYPERSENSITIVITY MEDICAL REVIEWED LISTING

The purpose of this document is to describe the process of blinded Clinical Case Review of hypersensitivity events that should identify relevant systemic hypersensitivity events that will be used for hypersensitivity analysis in the clinical study report as well as in submission documents. Narratives will be written for these events.

- The review of events will be performed by the SMM and GSO on the study as a separate step preceding the regular Clinical Case Review process.
- This review will be performed with the same frequency as Clinical Case Review - at approximately monthly frequency during the study. Approaching DBL the frequency of review may increase.
- If agreement is not reached between SMM and GSO the senior case review will be performed by senior physicians. The senior case review will be performed with frequency of every 2 months and may increase approaching database lock.
- Prior to the review performed by the SMM and GSO, the data management will have undergone data validation to ensure that reported information is accurate and all available information that can support Clinical Case Review has been obtained and will double check with file shared by the B&P.

Hypersensitivity (Medical reviewed)	SMQ [20000214] hypersensitivity narrow search and [AE corrective treatment/therapy = ’Y’ or Action taken with IMP = ’Drug withdrawn’ or Action taken with IMP = ’Drug interrupted’] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events

The listing will include the variables such as Study Identifier, Unique Subject Identifier, Dictionary-Derived Term, Reported Term for the Adverse Event, Preferred Term Code, Serious Event, Concomitant or Additional Treatment Given, Action Taken with Study Treatment, Treatment Emergent Flag, Outcome of Adverse Event, Causality,

Severity/Intensity, Start Date/Time of Adverse Event, End Date/Time of Adverse Event, AE Duration.

What's more, the document is reviewed by the medical team as below, they will give some comments and decision as below, then we programmer would get the Y decision to derive the flag for Hypersensitivity.

CSD decision (Y/N)	CSD comments	GSO decision (Y/N)	GSO comments	Conclusion (Agreement/For senior review)	Senior review comments/decision-senior physician (Leda)	Final conclusion (Yes/No)-If considered relevant systemic hypersensitivity event the answer should be YES	If No, provide reason/comment

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