ABIRISK Terms and Definitions for Reporting Immunogenicity Results	
Version Number: 2.0	**Date: June 2015**

ABIRISK: PROPOSED TERMS AND DEFINITIONS FOR REPORTING IMMUNOGENICITY RESULTS

TABLE OF CONTENTS

Introduction 3
General Terms 5
Terms for Subjects (Sample Donors) and Treatment History 6
Terms for ADA 7
Terms for ADA assays 8
Terms for ADA status of Samples 9
Terms for ADA status of Subjects 10
Terms for ADA status of Study Population 11
Terms for Pharmacokinetics 12
Terms for ADA-associated Clinical And pathophysiologicalEvents 13
Terms that are Cohort-specific 14
Terms from WP2 15
Terms from WP3 16
Definitions for General Terms 18
Definitions for terms for Subjects (Sample Donors) and Treatment History 19
Definitions for Terms for ADA 20
Definitions for ADA assays terms 22
Definitions for ADA Status of Samples terms 27
Definitions for ADA status of Subjects terms 29

Definitions for ADA status of Study Population terms 32
Definitions for Pharmacokinetics Terms 32
Definitions for ADA-associated Clinical and pathophysiological Events terms 35
Definitions for Terms that are Cohort-specific 36
Hemophilia – Specific Terms 36
IBD – Specific Terms 36
Multiple sclerosis (MS) – specific Terms 36
RA – Specific Terms 37
Definitions for terms from WP3 39
Appendix A – List of Hypersensitivity terms 42
References 44

ABIRISK Terms and Definitions for Reporting Immunogenicity Results	
Version Number: 2.0	**Date: June 2015**

INTRODUCTION

The ABIRISK consortium (Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Relevance to Minimize the Risk) was founded in 2012. One of the stated aims of the ABIRISK Consortium (Work Package 1, WP1) is:

To provide clear definitions around terms and concepts related to immunogenicity, its prediction and associated clinical events (e.g., transient ADA response, pre-existing ADA, assay sensitivity, loss of response, allergic reaction).

This document compiles the proposed terms and definitions that were generated by WP1 based on results ABIRISK intends to report and the definitions that ABIRISK needs for interpretation. Immunology literature, white papers (published and in preparation) and ABIRISK participants were consulted to develop the terms and definitions proposed here, which were originally focused on the Work Package 1 scope and have been reviewed by participants from WP1. The terms have been supplemented to include terms specific to WP2 and WP3. Under WP1 Scope, proposed terms are categorized according to:

- General Terms
- Terms for Donors/Subjects
- Treatment History Terms
- ADA and ADA Assays Terms
- Clinical Events Terms
- Cohort-Specific Terms

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Version Number: 2.0	**Date: June 2015**

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GENERAL TERMS

General
Adjuvanticity
Anti-Drug Immune Response (ADIR)
Immunogenicity potential
Intrinsic Immunogenicity

TERMS FOR SUBJECTS (SAMPLE DONORS) AND TREATMENT HISTORY

Based on Disease Status	Based on Treatment Status	Based on Treatment History
Healthy Subject	Naïve Patient Subject	Treatment Days (Cumulative Treatment Days)
Patient	Treated Patient Subject	Exposure Days (Cumulative Exposure Days)
		Total Doses
		Drug Holiday
		Time to Endpoint
		Immune Tolerized

TERMS FOR ADA

Based on ADA population	Based on impact	Based on ADA specificity	Based on Binding Strength
Anti-Drug Antibody (ADA)	Neutralizing ADA	HAHA	ADA Affinity
Binding ADA	Non-neutralizing ADA	HAMA	ADA Avidity
Total ADA	Sustaining ADA	HACA	
Isotype/Subclass-Specific ADA (e.g. IgG ADA)	Clearing ADA	Anti-component/-domain etc ADA	
	Clinically Relevant ADA	Anti-idiotypic ADA	
		Anti-allotypic ADA	

TERMS FOR ADA ASSAYS

Based on measured ADA	Based on tier position	Based on type of reported results	Analysis Terms	Assay validation Parameters	Analytical Issues
ADA	Screening	Qualitative (Positive/negative)	Cutpoint (screening, confirmatory, bioanalytical, clinical)	Cutpoint determination	Drug interference
Binding ADA	Confirmatory	Quasi-quantitative	Quality control; system suitability control	Sensitivity	Target interference
Total ADA	Characterization	Titer	Acceptance criteria for: Pre-study assay validation in-study assay validation	Precision	Pre-existing antibodies
Free ADA		Relative concentration		Selectivity/ interference	Rheumatoid factor interference
Isotype/Subclass-specific ADA (e.g. IgG ADA)		Signal		Stability	
Neutralizing antibody		TRU (ten-fold reduction unit(		Robustness	
Epitope/domain				Drug tolerance	

TERMS FOR ADA STATUS OF SAMPLES

Based on evaluability*	Based on result	Other
Evaluable	Positive	Time of collection
Non-evaluable	Negative	Time since last treatment
	Titer	Drug present
	(Inconclusive)**	Interference present
	Baseline positive	Immune Complexes
	Pre-existing positive	
	Post-treatment positive	
	Borderline positive	

TERMS FOR ADA STATUS OF SUBJECTS

Based on evaluability and status	Based on Positivity	Based on origin, kinetics/duration of immune response	
Evaluable	ADA Positive	Baseline (pre-existing) ADA	
Non-evaluable	ADA Negative	Treatment-induced ADA	
Treatment-naïve	ADA Inconclusive	Treatment-boosted ADA	
Treatment-experienced		Treatment-unaffected ADA	
		Time of onset	
		Persistent Positive	
		Transient Positive	
		Off-treatment Persistent Positive	

TERMS FOR ADA STATUS OF STUDY POPULATION

Based on Rate or Frequency	Based on Treatment
Incidence	Cumulative exposure days
Prevalence	Cumulative treatment days
Cumulative rate	

TERMS FOR PHARMACOKINETICS

Assay/type of measurement	PK parameters Individual subjects	ADA effect on PK	PK parameters population
Total Drug	Central volume of distribution	PK affected by ADA	Same parameters but analyzed for ADA pos vs neg populations
Free Drug	systemic clearance	No effect of ADA	Drug half-life
Bound Drug	peripheral volume	ADA cleared response	
Active Drug	Inter-compartmental clearance	ADA sustained response	
	elimination half-life		
	Non-linear clearance parameters		
	AUC and other assessments of exposure		
	R2/R1		

TERMS FOR ADA-ASSOCIATED CLINICAL AND PATHOPHYSIOLOGICALEVENTS

Efficacy/PD-related	Safety related	PK-related
Cohort-specific	Hypersensitivity	Sustained response
Loss of efficacy (LoE)	Neutralization of the endogenous counterpart	Clearing response
	Immune complex formation	Loss of response/efficacy
	Complement activation	

TERMS THAT ARE COHORT-SPECIFIC

Hemophilia	IBD	MS	RA
Inhibitors		Relapse	Anti-dsDNA antibodies
Bethesda unit		Remission	Lupus survival
		Relapsing-remitting MS (RRMS)	Lupus nephritis
		Primary progressive MS (PPMS)	Rheumatoid factor
		Secondary progressive MS (SPMS)	
		Expanded Disability Status Scale (EDSS)	
		Multiple Sclerosis Severity Score (MSSS)	
		Interferon beta treatment	
		Natalizumab treatment	
		Lesions or plaques	

TERMS FROM WP2

Samples	Assays	Epitopes/Cell Populations
ADA Positive	SOP: standard operating procedure	Agretopes
ADA Negative	CBA: cytometric bead array/Luminex	Regulatory B cells (B regs)
Disease Controls	FACS	Regulatory T cells (Tregs)
Healthy Controls	NGS	Memory B cells
	MAPPs	iNKT cells (invariant natural killer T cells)

TERMS FROM WP3

Terms for assays	Terms for Cells (Dentritic Cells)	Terms for Cells (T cells)	Terms for Epitopes
T cell assay	Dendritic cell	Naive T cell	Agretope
Predictive T cell assay	mDCs: myeloid dendritic cell	Memory T cell	T cell epitope
DC maturation assay	pDCs: plasmacytoid dendritic cells		Core region
MAPPS	HP-DCs: hematopoietic-derived dendritic cells		Flanking regions
Artificial lymph node assay	Immature dendritic cell:		Anchor residue
HLA affinity	Mature dendritic cell		Promiscuous peptide
T cell avidity	Monocyte-derived dendritic cell		Immunodominant epitope
			Immunoprevalence
			Subdominant epitope
			Cryptic epitope
			Major epitope
			Minor epitope

DEFINITIONS FOR GENERAL TERMS

Adjuvanticity: Capacity of compounds to increase the specific immune response

Anti-Drug Immune Response (ADIR): The host immune system response to an administered Biopharmaceutical, encompassing responses by multiple compartments including the innate and adaptive immune systems.

Immunogenicity Potential: Determines the maximal level of immunogenicity of a Biopharmaceutical.

Intrinsic Immunogenicity Potential: Immunogenicity due to factors related to the Biopharmaceutical product characteristics.

DEFINITIONS FOR TERMS FOR SUBJECTS (SAMPLE DONORS) AND TREATMENT HISTORY

Based on Disease Status

Healthy Subject : Subject who has not been diagnosed with disease.

Patient : Subject with confirmed diagnosis.

Based on Treatment Status

Naïve Patient or Subject: Patient or Subject who has not been previously exposed to the active substance in the Biotherapeutic.

Treated Patient or Subject: Patient or Subject who has been treated with the Biotherapeutic.

DEFINITIONS FOR TERMS FOR ADA

Based on ADA population

Anti-Drug Antibody (ADA): Host antibody specific for the Biopharmaceutical drug molecule. Includes all antibodies that bind the Biopharmaceutical regardless of their functional activity. May include pre-existing and natural host antibodies cross-reactive with the Biopharmaceutical (baseline ADA) as well as Biopharmaceutical-induced or boosted ADA. Preferred term to "Binding Antibody" [Bab] since all ADA bind the Biopharmaceutical.

Binding ADA (Bab): All ADA measured in screen ADA assay (and confirmed where confirmatory assay is available). All ADAs are inherently 'binding' antibodies because they bind the biologic drug molecule, as determined by an *in vitro* test method, regardless of their *in vivo* relevance (i.e., whether or not they result in clinical impact). A common misuse of this term is to apply it solely in reference to non-neutralizing antibodies; whereas, neutralizing antibodies are also binding antibodies.

Total ADA: Another term used to refer to all ADA measured in assay designed to detect all binding ADA (note – in practice binding or total ADA assays most likely will not detect IgE ADA due to low levels).

<Isotype/Subclass-Specific> ADA: ADA measured in assay designed to detect ADA of specific isotype(s); e.g. IgG ADA, IgG+M ADA, IgE ADA.

Based on ADA impact

Neutralizing ADA (Neutralizing Antibody, NAb): ADA that inhibits or reduces the functional activity of the Biopharmaceutical, as determined by an *in vitro* test method, regardless of its *in vivo* relevance (i.e., whether or not the NAb causes clinical impact).

Non-neutralizing ADA (Non-neutralizing Antibody, Non-NAb): ADA that binds to the Biopharmaceutical but does not inhibit its functional activity in an *in vitro* test method, regardless of its *in vivo* relevance (i.e. whether or not the non-NAb causes clinical impact).

Sustaining ADA: ADA associated with apparent decreased clearance of the Biopharmaceutical relative to its clearance rate in the absence of ADA; most frequently

sustaining ADA occurs when the Biopharmaceutical has a fast clearance rate relative to the rate of IgG clearance.

Clearing ADA: ADA (NAb or non-NAb) associated with increased clearance of the Biopharmaceutical.

Clinically Relevant ADA: Generally refers to ADA that has been associated with some alteration in clinical response to the Biopharmaceutical.

Based on ADA Specificity:

HAHA (Human Anti-Human Antibody): ADA specific for human epitopes present in a humanized or fully human mAb Biopharmaceutical. When cross-reactivity with other human sequence-containing antibodies is not confirmed, it is recommended to avoid the term HAHA for referring to ADAs against humanized or human mAb drugs.

HAMA (Human Anti-Murine Antibody): ADA specific for epitopes of murine origin present in a mAb Biopharmaceutical. When ADA cross-reactivity with other mouse antibodies is not confirmed, it is recommended to avoid the term HAMA for referring to ADAs against murine mAb Biopharmaceuticals.

HACA (**Human Anti-Chimeric Antibody**)**:** ADA specific for non-human epitopes present in a chimeric mAb Biopharmaceutical. Include xenotypic or junction neoepitope. When cross-reactivity with other chimeric antibodies is not confirmed, it is recommended to avoid the term HACA for referring to ADAs against chimeric mAb Biopharmaceuticals.

Anti-<Component/Domain etc> ADA: ADA against a particular component/domain of a Biopharmaceutical. E.g. anti-Fc, anti-Fab, anti-receptor, anti-PEG moiety.

Anti-Idiotypic ADA: ADA specific for epitope(s) unique to a specific monoclonal antibody therapeutic; usually ADA specific for the unique antigen-binding/complementarity determining region (CDR) of the mAb Biopharmaceutical.

Anti-Allotypic ADA: Generally refers to ADA specific for allotypic (defined as a genetically inheritable determinant common to some but not all human immunoglobulin molecules) epitopes of a mAb or mAb fragment Biopharmaceutical. Could also refer to ADA specific for allotypic determinants on non-immunoglobulin-based Biopharmaceuticals.

Based on Binding Strength

Affinity: Refers to strength of a specific intermolecular interaction. Often expressed as an equilibrium dissociation or association constant (Kd/Ka) or ratio of dissociation/association rate constants (kd/ka), however due to the multivalent binding and heterogeneity of affinities expected within a polyclonal ADA sample, other measurements may be appropriate for characterizing ADA-Biopharmaceutical interaction.

Avidity: Measured strength of intermolecular interaction, usually used for multivalent, complex interactions (e.g. between multi-valent antibody and antigen, ADA and Biopharmaceutical) and highly dependent on method used for the measurement.

DEFINITIONS FOR ADA ASSAYS TERMS

Based on measured ADA

Anti-Drug Antibody Assay (ADA assay): Bioanalytical method used to determine if a sample is qualitatively positive or negative for ADA and that can provide quasi-quantitative information about the amount of ADA (typically reported as an antibody titer). Often considered synonymous with **Binding ADA (Bab) Assay** or **Total ADA Assay** (see definitions below).

Binding ADA Assay: ADA assay designed to detect antibodies that bind the Biopharmaceutical, regardless of the functional activity of the ADA.

Total ADA Assay: ADA assay designed to detect antibodies of all classes and subclasses that bind to the Biopharmaceutical (usually not capable of binding IgE due to low levels). The ADA assay may consist of screening and confirmatory assays.

Free ADA Assay: ADA assay that measures ADA not bound to the Biopharmaceutical. Generally a binding ADA assay can be considered a free ADA assay unless specific ADA-Biopharmaceutical dissociating conditions are incorporated into the assay procedure.

<Isotype/Subclass x> ADA Assay: ADA assay designed to detect ADA of specific isotype(s) or group of isotypes; e.g.IgG ADA, IgG+M ADA, IgE ADA or subclass (e.g. IgG1, IgG2, IgG3, IgG4).

Neutralizing Antibody Assay: Assay used to determine whether ADA in a sample can neutralize some aspect of the Biopharmaceutical's activity. Encompasses bioassay (cell-based or enzymatic) or a competitive ligand-binding assay

<Epitope/Domain> ADA Assay: Assay designed to detect ADA specific for a particular epitope of domain of the Biopharmaceutical e.g. Fab assay

Based on position in tier

Screening Assay: In a tiered testing strategy, the assay used to distinguish potentially positive samples (based on screening cutpoint) vs negative samples.

Confirmatory Assay: An assay conducted on samples found to be potentially positive in the screening assay in a tiered testing strategy, to identify false and true positives (based on confirmatory cutpoint).

ADA Characterization Assay: Investigational assay that is designed to obtain additional information on the specificity or type of antibodies present in a sample. Information obtained from these assays may include, but is not limited to, the following:

- Titer assay (see definition below)
- Epitope/domain assay**:** (see definition above)
- Affinity determination assay: Assay that measures affinity of ADA

Based on type of reported results

Qualitative Assay: Assay that reports test results as positive/negative

Quasi-quantitative Assay: Assay that reports a relative magnitude of ADA present in a sample (e.g. titer)

Titer Assay: A quasi-quantitative assay providing titer as the unit of the amount of antibody in a sample. The titer is often defined as the reciprocal of the lowest dilution of a sample generating a signal that is above the assay cutpoint. Alternatively, the titer is defined as the reciprocal of the dilution of a sample generating a signal that is equivalent to the assay cutpoint, calculated by an interpolation formula provided in an assay-specific bioanalytical method.

Relative Concentration Assay: A quasi-quantitative assay providing sample results reported in relative mass units, determined by comparing the assay signal generated by the sample relative to a signal generated by a diluted positive control sample. Because the positive control generally contains a different mixture of antibodies than the sample, concentrations reported by this result are generally not accurate and should be reported as "relative concentrations" or defined units.

Signal or Signal:Noise Readout Assay: A quasi-quantitative assay providing sample results based on the signal generated by the sample or a ratio of the signal generated by the sample divided by the background signal. Value from background signal may be based on the negative control or blank.

Ten-fold Reduction Unit: Defined as the NAbs titre required to reduce the activity of, for example interferon beta, from 10 to 1 LU/mL (see Grossberg, Kawade et al. 2001; Grossberg, Kawade et al. 2001). 1 LU/mL is defined as the amount of interferon beta required to achieve 50 % maximum stimulation. The serum dilution required to reduce the activity from 10 to 1 LU/mL is corrected using the Kawade formula (see below) to give the final titre. The Kawade formula allows the results to be adjusted to compensate for small day to day changes in the activity IFN-β used, and ensures that NAbs titres are comparable.

Kawade and Grossberg equation: $t = f \times (n-1) / 9$ (expressed as TRU/mL)

Where: n = number of LU/mL (measured activity on the day of the assay) of IFN-β added to the cells, t = NAbs titre (corrected), f = serum dilution at 50% stimulation, TRU = Ten-fold Reduction Unit

Grossberg, S. E., Y. Kawade, et al. J. Interferon Cytokine Res. 2001;21(9): 729-742 and 743-755.

Other assay terms

Cutpoint: An assay signal threshold that distinguishes positive samples from negative samples, as defined in an assay-specific analytical procedure. The cutpoint is usually set based on statistical analysis with treatment naïve samples representative of the study popualtion (bioanalytical cutpoint) but could be based on a biological (e.g. change in pharmacodynamics marker; biological cutpoing) or clinical endpoint (e.g. loss of efficacy,

clinical cutpoint). Cutpoints are typically set for each assay in the tiered analysis strategy (screening assay, confirmatory assay, neutralizing assay cutpoints).

Quality Controls: Also called system suitability controls: Predetermined parameters used to determine acceptability of assay validation (validation acceptance criteria) or sample analysis run (referred to as run acceptance criteria or in-study validation acceptance criteria).

System Suitability Controls: Also known as Quality Control: Positive and negative assay control used for demonstrating the test equipment is functioning properly and monitoring performance of the assay, accepting or rejecting assay validation or sample analysis runs, based on pre-determined acceptance criteria.

Acceptance Criteria: Pre-established assay performance requirements used to demonstrate whether the assay is suitable for its intended use or not. Pre-study validation acceptance criteria must be met in order to accept the assay for use in sample analysis. In study validation acceptance criteria must be met in order to accept an assay run and report valid sample data.

Assay validation parameter terms

Cutpoint determination: Experimental evaluation performed to determine the cutpoints that will be used to distinguish ADA positive and negative samples.

Drug tolerance: Ability of assay to detect ADA in samples containing variable amounts of the Biotherapeutic; dependent on concentration and characteristics of ADA in the sample.

Precision : Measurement of random variability in the data from replicate determinations of the same sample under the established assay procedure. Usually determined for positive and negative controls, and cutpoint as interassay, intra-assay and intra-run evaluations.

Sensitivity: Estimation of the mass concentration of the ADA in a positive control that can be reliably detected in the assay**.**

Robustness: Performance of the assay when run under small but deliberate changes in normal conditions (e.g. upper and lower limits of incubation times, different machines, operators, and reagent lots).

Ruggedness: Reproducibility of the assay when performed by different laboratories.

Selectivity/interference: Ability of the assay to detect specific ADA in the presence of matrix or matrix components that might be present in a sample (e.g. nonspecific interference, Biotherapeutic target).

Stability: Measurement of stability of different assay components (e.g. controls, capture and detector reagents, coated plates) when stored or held for different times (e.g. 2 hrs to overnight) under different conditions (e.g. room temperature, 4°C, frozen).

Analytical issues terms

Drug Interference: Alteration in ADA detection (usually impaired detection) in an assay due to the presence of Biopharmaceutical complexed to ADA in the sample.

Target Interference: Alteration in ADA detection in an assay due to the presence of the Biopharmaceutical target in the sample. In bridge assay formats, multivalent target may cause false positive results.

DEFINITIONS FOR ADA STATUS OF SAMPLES TERMS

Based on evaluability:

Evaluable Sample: A sample that meets criteria for testing and results reporting based on established criteria for evaluability.

Unevaluable Sample: A sample that could not be tested or for which results cannot be reported due to sample loss, mishandling, quality issues, or errors in sample collection, processing, storage, etc.

Based on result

ADA Positive Sample: Sample in which ADA is detected i.e. sample generates assay signal equal to or greater than the cutpoint in the screening assay. Preferably, a second (confirmatory) should be used to confirm that sample also is positive. If both assays agree then the sample should be considered positive; when sample is positive in screening assay but not confirmed in a confirmatory assay, the sample should be considered negative.

ADA Negative Sample: A sample is considered negative when ADA is not detected (i.e. negative in screening assay or positive in screening but negative in confirmatory assay).

ADA Inconclusive Sample: A sample negative for ADA in the assay, but for which the assay result cannot be reported as incontrovertibly negative or positive for ADA i.e. Biopharmaceutical is present in the same sample at a concentration that can produce interference in the assay. *This term is provided for information but will not be used by ABIRISK; however presence of drug in sample should be noted in the database to aid in interpretation of results and correlation with other clinical or analytical outcomes.*

Baseline Positive: A sample positive at the beginning of the study (may be defined for naïve or treatment experienced patients).

Pre-existing Positive: Sample from drug-naïve patient that scores positively in an ADA assay.

Post-treatment Positive: ADA assay positive sample collected after at least 1 exposure to the drug.

Borderline Positive/Negative: Sample scoring between the cutpoint and a value just above the cutpoint (borderline positive); or between the cutpoint and a value just below the cutpoint (borderline negative). In the ABIRISK consortium, binary quantitative (positive vs negative) and quasi-quantitative (i.e. titer) are the preferred data formats.

Based on Other

Time of Collection: Timepoint for sample collection (reported based on study-specific reporting practices, e.g. days after first treatment)

Time since last treatment: Interval between last treatment and time of sample collection.

Drug/interference present: Flag for samples that are known or expected to have levels of Biopharmaceutical that may interfere with accurate ADA detection or characterization.

Immune Complexes: Sample contains ADA-target complexes. Refers to positive result for sample tested in an assay capable of detecting such immune complexes.

DEFINITIONS FOR ADA STATUS OF SUBJECTS TERMS

Based on Evaluability:

Evaluable Subject: - A study subject who meets the criteria for the particular evaluation being conducted. For example, to report incidence (for drug boosted response) defined as subject for whom a baseline sample and at least one sample collected after Biopharmaceutical administration during the treatment or follow-up observation period is available.

Non-evaluable Subject: A study subject who does not meet the criteria for the particular evaluation being conducted. For example, to report incidence, defined as: Subject without baseline and at least one sample taken after Biopharmaceutical administration during treatment or follow-up observation period, or those who had only unevaluable samples, and therefore cannot be evaluated for treatment induced response.

Treatment-naïve Subject: A study subject with no previous exposure to the Biopharmaceutical (or similar product) prior to study start

Treatment-experienced Subject: A study subject with some previous exposure to the Biopharmaceutical (or similar product) prior to study start

Based on Positivity:

ADA Positive Subject: Subject with at least 1 treatment-induced or treatment-boosted ADA positive sample at any time during the treatment or follow-up observation period.

ADA Negative Subject: Subject without a treatment- induced or treatment-boosted ADA positive sample during the treatment or follow-up observation period.

ADA Inconclusive Subject: An ADA non-positive subject who cannot irrefutably be classified as negative. Sound scientific rationale should be considered.

*Alternative: Utilize 2 categories 1) positive/negative for ADA (at any timept); 2) positive/negative for post-treatment increase (incorporating drug induced + drug boosted)

Based on ADA Origin or Kinetics/Duration of Immune Response:

Baseline ADA (pre-existing antibody) Positive Subject: Subject whose is positive for antibodies reactive with the Biopharmaceutical before initiation of treatment.

Treatment-Induced ADA Positive Subject: Subject with ADA developed *de novo* (seroconverted) following Biopharmaceutical administration (i.e., formation of ADA anytime after the initial drug administration in a subject without pre-existing antibodies).

Treatment-Boosted ADA Positive Subject: Subject with pre-existing antibodies that develops an increased level of ADA following Biopharmaceutical administration (i.e., anytime after the initial drug administration the ADA titer is disproportionately greater by a biologically relevant margin, such as a 2-fold or 3-fold relative to the baseline titer).

Treatment-Unaffected ADA Positive Subject: Subject with pre-existing antibody level that does not change following the BiopharmaceuticalP administration

Time of Onset of ADA: Refers to the time period between the initial administration of the Biopharmaceutical and the first instance of detected treatment-induced ADA.

Persistent Positive Subject: Subject with treatment-induced ADA detected at 2 or more sequential sampling time points during the treatment (including follow-up period, if any), where the first and last ADA positive samples are separated by an extended period (to be defined for each cohort) or (by conservative inference)with ADA present at the last sampling time point of the treatment study period.

Transient Positive Subject: Subject with detectable treatment-induced ADA detected only at one or more time points over a limited period (e.g. <16 weeks, or to be defined for each cohort) and then ADA negative. Subject's last time point should be ADA negative. This term may be defined for each cohort based on clinical relevance .

Off-Treatment Persistent Positive Subject: (Relevant for products with endogenous counterpart) Subject remaining positive after both Biopharmaceutical and any transient ADA would be expected to have cleared (for example a period of time equal to the sum of 5 half lives of the BIOPHARMACEUTICAL (which varies for each drug) *plus* 5 half lives of

human ADA (for human IgG1, IgG2, and IgG4 on average, 22 days x 5 = 16 weeks). ADA detected after the above defined period should be considered persistent off-treatment

Based on Treatment:

Treatment Days: Days on which the subject received treatment with the Biotherapeutic.

Exposure Days[1]: Days over which the subject was exposed to the Biotherapeutic.

Total Doses: Total number of doses of the Biotherapeutic received by the subject.

Drug Holiday: Interuption in regularly scheduled dose administrations of a Biopharmaceutical that is intended for chronic administration on a regular schedule (e.g. weekly or monthly).

Time to endpoint: The length of time from initial treatment to measured endpoint

Immune Tolerized Subject: Lack of ADA (or NAb) evidence after Biotherapeutic administration to a subject that was previously ADA positive, and has continued to receive the Biopharmaceutical. Ideally there is some evidence (biomarker, recall response) of immune tolerance or if not, no other likely cause (i.e. clearance of ADA, drug interference with detection) for observed lack of ADA.

[1] In the terminology used in clinical hemophilia literature and the relevant European guidelines for clinical evaluation of therapeutic products, the accepted definition of "exposure days" is equivalent to the definition of "treatment days".

DEFINITIONS FOR ADA STATUS OF STUDY POPULATION TERMS

Based on rate or frequency

Incidence of ADA (rate of ADA development): Measure of the rate of a Biopharmaceutical-specific ADA (or category of ADA) immune response during a defined observation period, usually equal to the sum total of treatment-induced and treatment-boosted ADA positive subjects (but not treatment unaffected) as a percentage of the evaluable subject population. Incidence is a cumulative measurement. Incidence rates for treatment-induced ADA, treatment-boosted ADA, or specific types of ADA (e.g. Nabs or IgE) may also be considered separately. Incidence includes transient and persistent positive patients and may also be referred to as cumulative incidence.

Prevalence of ADA (frequency of ADA positive subjects): The percentage of subjects positive for ADA at a particular timepoint or within a particular defined timeframe. For example, antibody prevalence at baseline (pre-treatment) is determined by dividing the number of evaluable subjects with antibody-positive pre-treatment samples by the number of subjects with a pre-treatment sample result, expressed as a percentage. May also be useful when subjects with diverse treatment histories are randomly sampled.

ADA Changes (frequency of subjects becoming ADA positive): The percentage of subjects becoming positive for ADA after dosing between a first ADA sampling after dosing (or at a particular timepoint) and the last ADA sampling available for each subject measurable. This should give information on "ADA progression" by subject and as a starting point of dynamic response.

Based on treatment

Cumulative Treatment Days: Total number of days on which the subject received treatment with the Biopharmaceutical.

Cumulative Exposure Days: Total number of days over which the subject was exposed to the Biopharmaceutical.

DEFINITIONS FOR PHARMACOKINETICS TERMS

Based on Assay/ type of Measurement

Total Drug: Pharmacokinetics of total drug (based on assay that measures free drug plus drug bound to target).

Free Drug: Pharmacokinetics of free drug (based on assay that measures only free drug).

Bound Drug: Pharmacokinetics of drug bound to target (based on assay that measures only the bound drug or based on calculation from total – free drug assay values).

Active Drug: Pharmacokinetics of active drug (based on assay that measures drug activity)

PK parameters

Central volume of distribution(Vc): Hypothetical volume into which a drug/Biopharmaceutical initially distributes upon administration. Generally composed of blood in vessels and highly perfused tissues.

Systemic clearance: The volume of plasma cleared of the Biopharmaceutical per unit time.

Peripheral volume: Hypothetical volume of tissues outside the central compartment.

Inter-compartmental clearance: The inter-compartmental clearance of the Biopharmaceutical per unit time.

Elimination half-life: The time required for the concentration of the Biopharmaceutical to reach half of its original value.

Non-linear clearance: Changes in Biopharmaceutical exposure/clearance not linearly proportionate with increases in drug dose.

AUC: Area under the time-concentration curve, an assessment of Biopharmaceutical exposure.

Based on ADA effect on PK

No effect of ADA: No changes observed in any PK parameters as a result of ADA presence.

ADA affected PK: A change in one or more pharmacokinetic parameter(s) suspected or determined to be caused by ADA.

ADA sustained response: A prolongation of drug half-life suspected or determined to be caused by ADA. This is more likely to occur with drugs that have a short intrinsic half-life.

ADA clearing response: A decrease in expected drug half-life suspected or determined to be caused by ADA. In some cases ADA interference in the PK assay with lower apparent concentration may be mistaken for an ADA clearing response.

DEFINITIONS FOR ADA-ASSOCIATED CLINICAL AND PATHOPHYSIOLOGICAL EVENTS TERMS

Note: Cohort-specific clinical event terms are listed in the respective cohort sections

Loss of efficacy (LoE): Observed change in efficacious response in patient previously exhibiting efficacious response to the treatment. May be defined for each cohort. To establish relatedness to ADA, change in efficacious response observation should be coupled with objective evidence that change is due to re-activation of disease for which the drug was given and not due to other causes unrelated to the disease.

Loss of response (LOR): Observed loss of response (other than efficacy, see above) in patient previously exhibiting response to the treatment. May be defined for each cohort.

Hypersensitivity: Defined medically as a state of altered reactivity in which the body reacts with an exaggerated immune response to what is perceived as a foreign substance. For ABIRISK hypersensitivity can be reported as any of multiple observations as listed in appendix A.

DEFINITIONS FOR TERMS THAT ARE COHORT-SPECIFIC

HEMOPHILIA – SPECIFIC TERMS

Inhibitor: Neutralizing antibody to the coagulation factor.

Bethesda Unit: Amount of antibody that neutralizes 50% of the amount of coagulant activity in normal human plasma (or equivalent testbase).

IBD – SPECIFIC TERMS

MULTIPLE SCLEROSIS (MS) – SPECIFIC TERMS

Relapse: Acute exacerbation, clinically significant worsening of symptoms lasting for more than 24 hours.

Remission: Recovery between relapses.

Relapsing-remitting MS (RRMS): Pattern of symptoms in which relapses are followed by complete, or almost complete, remissions.

Primary progressive MS (PPMS): Pattern of symptoms in which disease progresses without remissions from onset of the disease.

Secondary progressive MS (SPMS): Pattern of symptoms in which disease progresses without remission but where the patient has from disease onset first had a period of RRMS.

Expanded Disability Status Scale (EDSS): Scoring system used for classifying and standardizing neurological functions in MS.

Multiple Sclerosis Severity Score (MSSS): A way to rate disease severity that relates scores on the EDSS to the distribution of disability in patients with comparable disease durations.

Interferon beta (IFN-β) treatment: First line treatment for RRMS**.**

Natalizumab (Tysabri): Second line treatment in MS.

Lesions or plaques: Areas of demyelination in the central nervous system.

RA – SPECIFIC TERMS

Definitions for terms from WP2

Samples

ADA positive sample: Serum, DNA, RNA or PBMC from patients identified in WP1 to be positive for anti-drug antibodies following Biopharmaceutical treatment

ADA negative sample: Serum, DNA, RNA or PBMC from patients identified in WP1 to be negative for anti-drug antibodies following Biopharmaceutical treatment

Disease controls: Patients age, sex and ethnically matched and with similar disease duration who are not receiving Biopharmaceutical treatment but are untreated or being treated with conventional therapies (steroids, NSAIDs, methatrexate, azathioprine, cyclophosphamide….etc).

Healthy controls: Serum, DNA, RNA or PBMC collected from healthy individuals age, sex and ethnically matched to the patient samples and who are not receiving Biopharmaceutical or other treatment.

Assays

SOP: standard operating procedure: Method approved by WP2 leaders for collecting, isolating, freezing, transporting and storing serum, peripheral blood mononuclear cells, or RNA or DNA collected from patients and healthy donors; or any other written procedure for performing a method in a similar way.

CBA: cytometric bead array/Luminex: Flow cytometry based assay for analyzing multiple cytokine specificities in serum or tissue culture supernatants

FACS: Flow cytometry based analysis and isolation of PBMC phenotypes.

NGS: Next generation sequencing technology. Technology that quantitatively monitors T cell clonal responses.

MAPPs: MHC-associated Peptide Proteomics: Technology that derives peptides from antigen presenting cells and can be used to identify potential CD4+T cell epitopes**.**

Agretope: Peptide bound to HLA molecules of antigen presenting cells.

DEFINITIONS FOR TERMS FROM WP3

Assays

T cell assay: Assay that is used to evaluate the T cell response and generally the antigen-specific T cell response.

Predictive T cell assay: T cell assay performed with naïve donors or normal donors with the attempt to predict the immunogenicity of the Biopharmaceutical.

DC maturation assay: Assay that measures the differentiation of immature DC into mature DC.

MAPPS: MHC-associated Peptide Proteomics: Technology based on the identification of peptides bound to HLA molecules purified from antigen presenting cells by mass spectrometry.

Artificial lymph node assay: Assay using long-term 3-dimensional (3D) matrix perfusion culture of primary immune cells to evaluate immunological functions mimicking immune reactions that occur within a lymph node.

Affinity (HLA): describes the capacity of a peptide to bind to HLA molecule. It is expressed as IC_{50} (concentration leading to 50% inhibition of the maximal signal) or relative activity (ratio of the IC50 with respect to a reference peptide)

Avidity (T cell): describes the capacity of a T cell to recognize the antigen. Generally it is measured by a dose-range of the corresponding T cell epitope and is expressed as ED50 (effective dose leading to 50% maximal stimulation)

Cell Populations

Dendritic cells (DCs)

mDCs: Myeloid dendritic cells, resemble monocytes; type-1: CD1c+, type-2: CD141+; efficient antigen presenting cells

pDCs: Plasmacytoid dendritic cells, resemble plasma cells; CD303+, produce IFNα to fight viral infections

moDCs: Monocyte-derived dendritic cells; DCs which are derived from CD14+ blood monocytes

HP-DCs: Hematopoietic-derived dendritic cells; DCs which are derived from CD34+ hematopoietic precursor cells

Naive T cell: T cell that has not been activated by the antigen.

Memory T cell: T cell that has previously been activated by the antigen.

Dendritic cell (DC): Antigen-presenting cell involved in the initiation of the T cell response by presenting T cell epitopes and providing appropriate signals of activation.

Immature dendritic cell: Dendritic cell with increased capacity of antigen processing and reduced antigen presentation and T cell priming. Retained phenotypes (human): CD83low, CD86low, CD209.

Mature dendritic cell: Dendritic cell with increased capacity of antigen presentation and T cell priming. Retained phenotypes (human): CD83+, CD86+, CD209low.

Monocyte-derived dendritic cell: Dendritic cell produced in vitro by differentiation of blood monocytes.

Epitope recognition

T cell epitope: Peptide recognized by a T cell when associated with the appropriate HLA molecule

Agretope: Peptide bound to HLA molecules of antigen presenting cells.

Core region: Part of an agretope that contributes directly to the binding to HLA molecule. It is generally of 9 amino acids

Flanking regions: Parts of an agretope that are external to the core region and prolong it at both sides

Anchor residue: Residues that interact with the HLA molecule

Promiscuous peptide: Peptide with a broad specificity for binding to HLA molecules

Immunodominant epitope: (as initially defined by Sercarz): Epitope involved in the T cell response raised against the native antigen such as the whole BIOPHARMACEUTICAL molecule.

Subdominant epitope: Epitope that does not necessarily participate in the T cell response raised against the native antigen but that elicits T cells able to recognize the native antigen.

Cryptic epitope: Epitope that does not participate to the T cell response raised against the native antigen and that elicits T cells that do not recognize the native antigen.

Immunoprevalence: Refers to the frequency of responders to a T cell epitope

Major/minor epitopes: A major epitope is an epitope that participates in a given subject to a large proportion of the T cell response to the native antigen in contrast to a minor epitope

Product Quality Attributes

Aggregate: agglomeration or cluster formation of the Biopharmaceutical drug substance.

APPENDIX A – LIST OF HYPERSENSITIVITY TERMS

None documented	Circumoral oedema	Infusion site urticaria
Administration site pain	Coagulopathy	Injection site hypersensitivity
Administration site rash	Decreased exposure/TK	Injection site urticaria
Administration site reaction	Documented hypersensitivity to administered drug	Laryngeal oedema
Allergic oedema	Drug hypersensitivity	Laryngotracheal oedema
Anaphylactic reaction	Eye oedema	Lip oedema
Anaphylactic shock	Eye swelling	Lip swelling
Anaphylactoid reaction	Eyelid oedema	Mortality
Anaphylactoid shock	Face oedema	Oedema mouth
Angioedema	Fixed eruption	Oropharyngeal swelling
Application site hypersensitivity	Hypersensitivity	Periorbital oedema
Asthma	Infusion site hypersensitivity	Pruritus allergic
Bronchospasm	Infusion site rash	Pruritus generalised
Circulatory collapse	Infusion site reaction	Rash generalised

IMMEDIATE ADVERSE REACTIONS	
LOCALIZED	
	Injection site reactions (pruritus, oedema, erytema, pain)
SYSTEMIC	
SKIN and MUCOSAE	Generalized pruritus
	Urticaria and/or Angioedema
	Angioedema (lip, tongue, pariorbital, laryngeal)
	Rash
RESPIRATORY	Bronchospasm/dyspnea
	Wheezing,
	Throat constriction
CIRCULATORY	
	Hypotension
	Loss of consciunness, shock
	Tachycardia
OTHERS	
	Fever
	Shivers
	Back pain
DELAYED ADVERSE REACTIONS	
LOCALIZED	
	Injection site reactions (pruritus, erythema, infiltrating plaques)
SYSTEMIC	
	Generalized maculopapular exanthema
	Lichenoid exanthema
	Granulomatous exanthema
	Psoriasiform eruption
	Erithema multiforme
	Steven-Jonhson syndrome

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