Considerations for Immunogenicity Assessment at Various Clinical Phases

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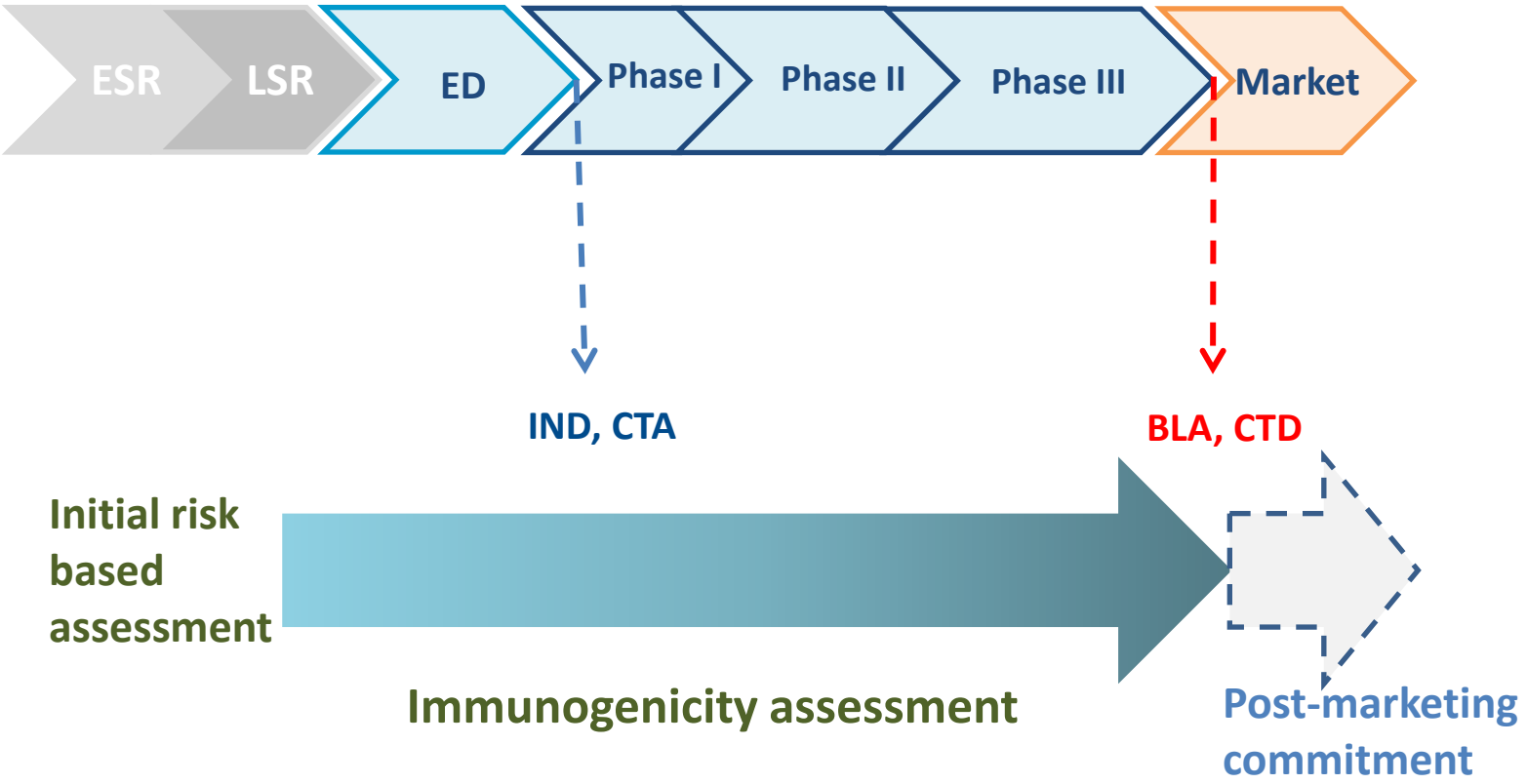
Immunogenicity Assessment Is An Integral Part of Biotherapeutic Development



Anti-drug antibodies (ADAs) are defined as presence of host antibodies directed towards the biotherapeutic in the circulation.

Outline

- Immunogenicity assessment at various clinical stages
  - FIH study: risk-based strategies for immunogenicity assessment
  - Bioanalytical strategy: a tiered approach
  - Phase II study and beyond: refine immunogenicity assessment strategy based on evolved clinical data
- Case studies of immunogenicity monitoring plan in various clinical phases
  - Case study#1: Immunogenicity monitoring of a bispecific mAb in a Phase I study
  - Case Study#2: Updated immunogenicity assessment plan to align with the modified Phase III development plan
- Summary
- Acknowledgements

Immunogenicity Risk Assessment

How Likely Is an Antibody Response?

Less likely

More likely

How Human is the Drug?
Human-**Humanized**-Chimeric-Mouse

Homology of Drug to Endogenous Counterpart
High – Partial **--** Low

Dosing/Dose Regimen Plan
Frequency: Single-Acute**–Chronic–**Intermittent
How much Drug: Very High/High/Average/Low

Patient Immune Status (disease + concomitant medication)
Suppressed – Normal - Activated

Impact of Drug on Immune System
Immunosuppressant – Immune Stimulator

Route of Administration of Drug
Oral - i.v. – i.p. – **s.c.** - Inhaled

Clearance of Drug
Fast – Slow

Adapted from Koren et al 2008

Immunogenicity Risk Assessment

How Serious Could ADA Response Be?

Less serious

Is there an Endogenous Version of the Drug?
No - Yes

Endogenous Counterpart of Drug is
Redundant – Unique

Homology of Drug to Endogenous Counterpart
Low – Partial - High

Consequence of Cross blocking ADA Would Be?
Tolerizeable – Manageable – Fatal

Can you dose over ADA?
No MTD – Low MTD

Disease Treated
Life Threatening – Non Life Threatening

Other Options
Alternate treatment available – Only Therapy

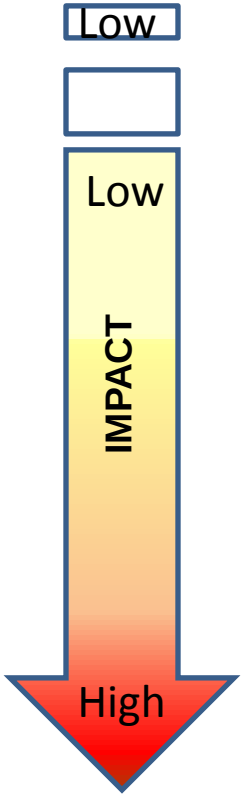
Can Crosslinking ADA Alter the Impact of Drug?
No – Yes (Reverses Antagonist/Blocking to Activating)

More serious

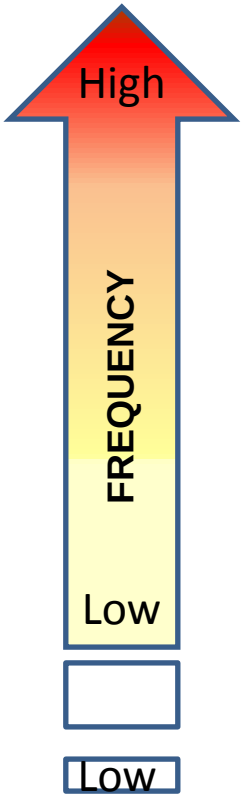
Adapted from Koren et al 2008

Immunogenicity: Consequences

Clinical Sequelae



- Binding ADA
- PK-altering ADA
- Neutralizing ADA
- Allergic ADA
- Cross-reactive neutralizing ADA

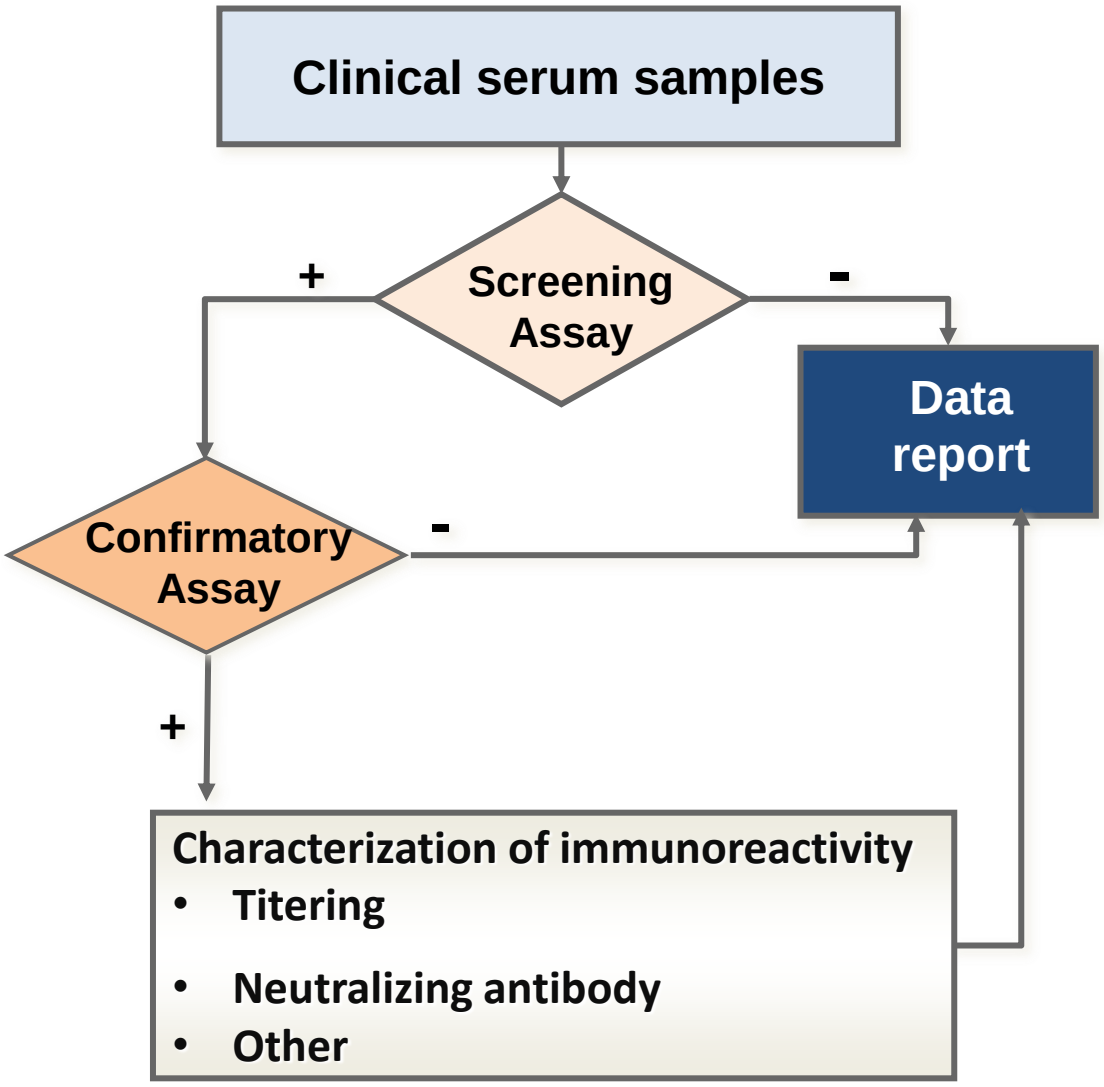


Interpreting Immunogenicity Data in Context

Status	ADA	PK/PD	Safety	Efficacy	Interpretation
Optimal	Yes /No*	No	No	No	ADA not detected*, no apparent safety & efficacy concerns with respect to immunogenicity ADA detected but no clinically relevant effect on PK/PD/S/E
Acceptable	Yes	Yes	No	No	ADA present but minimal effect on PK/PD No clinically significant S or E concerns regarding immunogenicity
Tolerable [Benefit > Risk]	Yes	Yes	No	Yes	ADA present and has effect on PK/PD No efficacy impact or impact can be managed with dose adjustments or changes in frequency Safety concerns regarding immunogenicity are none or minimal & can be managed with premedication or symptomatic treatment
	Yes	Yes	Yes	No	
No Go [Risk > Benefit]	Yes	Yes/No	Yes/No	Yes/No	ADA present and confers limits on efficacy ADA present and confers limits on safety

* Assay method could be questioned if no ADA responses detected

Using A Tiered Approach for Immunogenicity Assessment



For a typical antibody program in Phase I, II, III

For a typical antibody program in Phase III and beyond

Key References

- Healthy Authority Guidance
  - FDA Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products (2014)
  - FDA Draft Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Product (2016)
  - EMA Guidance on Immunogenicity Assessment of Therapeutic Proteins (2017)
- Industrial whitepapers and papers
  - Recommendations on risk-Based strategies for detection and characterization of antibodies against biotechnology products. E. Koren, et al. 2008. J. Immunol. Methods.
  - Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. G. Shankar, et al. 2008. J. Pharm Biomed Anal.
  - Recommendations for the design, optimization and qualification of cell-based assays used for the detection of neutralizing antibody responses elicited to biological therapeutics. S. Gupta, et al. 2007. J Immunol Methods.
  - Risk based approach to immunogenicity concerns of therapeutic protein products. Rosenberg & Worobec 2004 & 2005. BioPharm International
  - Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. Shankar G, et al. 2014. AAPS J.

Case Study#1

Monitoring immunogenicity of a bispecific monoclonal antibody anti-A/B in a Phase I study

More Rigorous Immunogenicity Monitoring Plan In The Phase I Study

Risk Based Assessment: medium

- Risk Factors: new modality; chronic treatments; SC dosing; targeting autoimmune diseases

Analytical strategy

- Assay format: bridging ELISA
- Screen, titer, confirm, characterization (domain mapping)

High immunogenicity observed in the repeated-dose cynomolgus monkey toxicology study

- ADAs detected in 97% (31 of 32) anti-A/B treated cynos
- ADA responses were predominantly towards the anti-B Fab
- High ADA signals correlate with loss of PK and PD
- Safety findings observed in some cynos with high ADA signals
    - consistent with ADA-related effects and *not* direct toxicological effects of anti-A/B

Include multiple interim analysis for closely monitoring immunogenicity in the Phase I study

- Immunogenicity in cyno monkeys generally not considered predictive of clinical incidence
- Combination of high incidence (97%) and high responses (1.54-6.96) was unexpected
- Limited clinical experience with bispecific mAbs

Case Study#2

Updated immunogenicity assessment strategy to align with the modified Phase III development plan

Modified Immunogenicity Assessment Strategy To Align with The Updated Phase III Development Plan

Drug: anti-X, a humanized mAb

Overall low ADA incidences (<6.3%) observed in the complete Phase I & II studies

- No obvious evidence of ADA impact on drug exposure, efficacy and safety

Original analytical strategy to support Phase III study

- Assay format - bridging ELISA
- Tiered approach -screen, titer, confirm
- Characterization - neutralizing antibody (NAb) analysis

Additional analytical work implemented to support the modified Phase III development plan

- Identification of a host cell protein (HCP) in drug materials triggered a modification of Phase III study
  - Tiered approach to monitor antibodies to HCP besides ADAs
- Applied in-study CPF instead of validation CPF for data analysis

Monitoring Both Antibodies to HCP and Drug in The Modified Phase III Studies

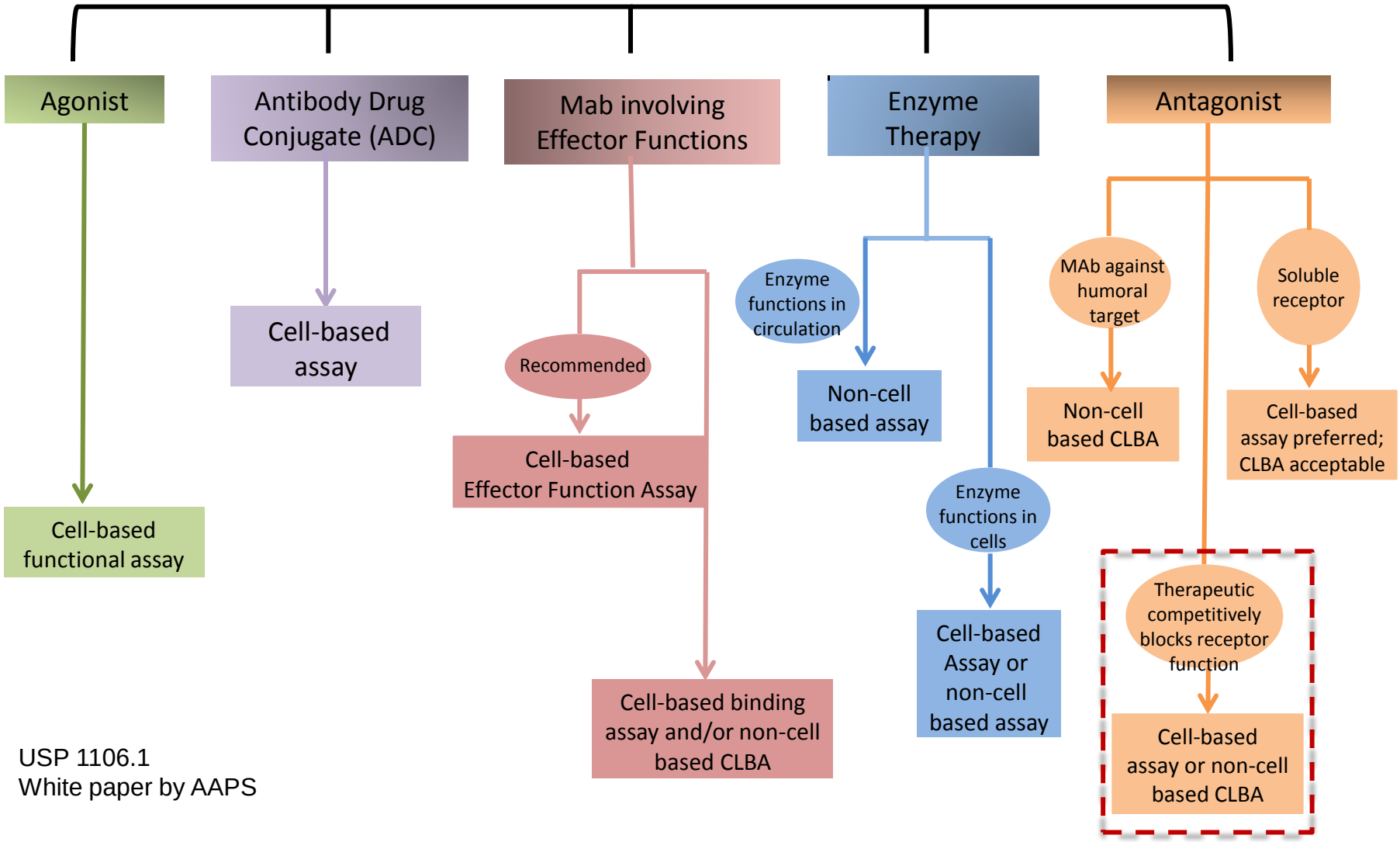
- Anti-X is produced in Chinese Hamster Ovary (CHO) cells. A process-related CHO derived protein impurity has been identified as CHO phospholipase B-like 2 (PLBL2) protein.
- High levels of PLBL2 (34-328ng/mL) detected in clinical materials used in the completed phase II studies.
- Anti-PLBL2 antibody was measured in the Phase II studies and high incidences (up to 98%) were observed, with no clinical sequelae.
- Process improvement was made to reduce PLBL2 levels in the Phase III materials (0.2-0.4ng/mL)
- Immunogenicity assessment strategy in Phase III studies was modified
  - Antibodies to anti-X and PLBL2 protein were monitored

Immunogenicity Results in Phase II & III Studies

Study Phase	PLBL2 levels in drug materials (ng/mg)	Anti-X Dose (mg/dose, Q4W)	Total PLBL2 exposure (ug/dose)	Anti-PLBL2 antibody incidence	ADA incidence
IIa	34-137	250	8.5-34.3	98%	2%
IIa	34-137	125 250 500	4.3-17.1 8.5-34.3 17.0-68.5	90%	1%
IIb	242-328	37.5 125 250	9.1-12.3 30.3-41.0 60.5-82.0	74%	6%
III	0.2-0.4	37.5 125	0.0075-0.015 0.025-0.05	18%	14%

- Lack of correlation between ADA and anti-PLBL2 antibody responses
- Decreased PLBL2 exposure led to significantly decreased anti-PLBL2 Ab positive incidence in the Phase III study

Guidance for NAb Assay Format Selection



- USP 1106.1
- White paper by AAPS

NAb Results Of Phase III Studies

- Assay format
  - Competitive ligand binding ELISA, using drug for capture and target conjugate for detection
  - Used study baseline samples for cutpoint determination
- Phase III NAb results
  - NAbs detected in 13 of 2052 anti-X treated subjects
    - all treatment-induced NAbs
  - NAb positive patients also had higher ADA responses
- Presence of NAbs had no apparent impact on safety
- Patients with higher NAb signals appeared to have lower drug exposure as well as lower than expected efficacy

Clinical impact of ADAs and anti-PLBL2 Antibodies

- No apparent safety signals attributed to presence of ADAs (NAbs) and higher levels of anti-PLBL2 antibodies.
- No apparent impact on the average or distribution of drug exposure and pharmacodynamics responses
  - Except for patients with higher NAb responses
- No consistent trends to suggest impact of positive ADAs and anti-PLBL2 antibodies on overall trial efficacy
  - Except impact on efficacy in patients with higher NAb responses

Summary

- Immunogenicity assessment is an integral part of drug development, and it is a key element of product safety and quality.
- Prediction of immunogenicity of biotherapeutics is challenging and must be assessed in the representative population for every indication being considered.
- Fit for purpose methods and “tiered” strategies are used to assess immunogenicity. These strategies are often modified or evolved based on various considerations including:
  - new modalities, changed CDP
  - evolved strategy by incorporating clinical data
- Immunogenicity data must be assessed in the context of other clinical readouts PK, PD, safety, & efficacy.

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