BiSpekDAb™

Engineered Bispecific Antibodies for the Management of Pulmonary inflammation

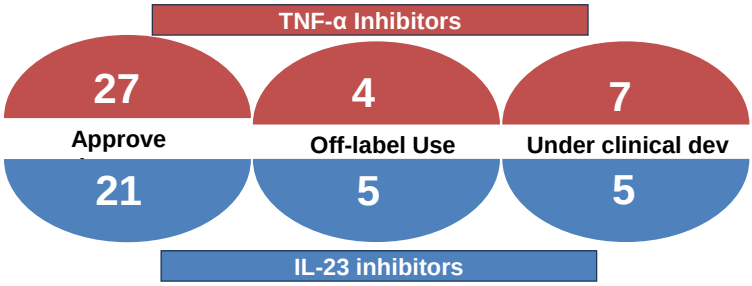
Techno-Commercial Proposal

Prof. Abhay H. Pande,
Department of Biotechnology,
National Institute of Pharmaceutical Education and Research (NIPER)
Sec-67, S.A.S. Nagar (Mohali)-160062 India
(apande@niper.ac.in)

Overview of BiSpekDAb™ and its potential for the treatment and management of inflammatory conditions

Chronic inflammation is at the heart of the initiation / progression of many serious diseases and is going to be a major burden on the national and global healthcare. TNF-α and IL-23 are responsible for the initiation & propagation of a large number of chronic inflammatory diseases. Targeting these two pro-inflammatory cytokines (mediated pathways) is a successfully proven strategy to address multiple chronic inflammatory conditions (see below).

Ankylosing spondylitis; Androgen Independent Prostatic Cancer; **Asthma**; Autoimmune pregnancy complications; Axial spondylarthritis; Behcet uveitis; Blau syndrome; Bone marrow Neoplasms; Chronic granulomatous disease; Crohn disease; Erythrodermic psoriasis; Familial antiphospholipid syndrome; Hidradenitis suppurativa; Irritable bowel syndrome; Juvenile arthritis; Kaposi Sarcoma; Medulloblastoma; Mucocutaneous lymph node syndrome; Multicentric reticulonitiocytosis; Multiple Myeloma; Non-radiographic axical spondylarthritis; Paediatric Crohn disease; Paediatric Ulcer colitis; Pemphigus; Plaque psoriasis; Polyarticular juvenile idiopathic arthritis; Polyendocrinopathies; Psoriasis vulgaris; Psoriatic arthritis; Pustular vulgaris; Pyoderma gangrenosum; Rheumatoid arthritis; Salivary gland adenoma; Sarcoidosis; Systemic lupus erythematosus; **Stroke**; Ulcer colitis; Wegener granulomatosis



Ankylopoietica spondylitis; Amyotrophic Lateral Sclerosis; **Asthma**; Atopic dermatitis; B-Cell Lymphoma; Crohn Disease; Erythrodermic psoriasis; Ichthyosis; Juvenile arthritis; Lymphoid Leukemia; Metastatic castration-resistant prostate cancer; Neoplasms; Pediatric Crohn's disease; Pediatric Ulcer colitis; Pityriasis pilaris; Plaque psoriasis; Pleomorphic perianal fistula; Pustulosis of Palms and Soles; Palmoplantar Keratoderma; Pleomorphic Salivary Gland Adenoma; Psoriasis; Psoriasis vulgaris; Psoriatic Arthritis; Pustular psoriasis; Pyoderma gangrenosum; Pouchitis; Scalp dermatoses; Systemic Scleroderma; Type 1 Diabetes Mellitus; Ulcer colitis; Wound & Injuries

https://synapse.patsnap.com/drug-list?query_id=a3045160-3ce7-4cda-b061-a9c2ed118c8c: ; https://doi.org/10.1183/09031936.00063510 ; https://synapse.patsnap.com/drug-list?query_id=ebbbdd07-49b4-4988-87c6-064289087215; https://doi.org/10.1111/j.1365-2222.2005.02407.x ; https://doi.org/10.1080/14737175.2020.1727742

Current market of TNF-α blockers: **SIX** TNF-α targeting biologics (Adalimumab, Infliximab, Golimumab, Etanercept, Certolizumab pegol, & Ozoralizumab) are already in clinical use and as on date, many more TNF-α blockers are being developed (for >35 diseases; 63 different clinical trials are currently going on). Consequently, the market size of TNF-α is predicted to reach USD 47.32 bn, at a CGAR of 3.59% for 2024-2029.

Current market of IL-23 blockers: **FOUR** IL-23 targeting biologics (Ustekinumab, Guselkumab, Tildrakizumab, Risankizumab) are in clinical use and as on June 2023, 35 companies were developing twenty-four IL-23 Inhibitors for 36 diseases (67 trials are ongoing). The market size of IL-23 blockers is 24.3 bn in 2023 and is expected to grow at 12% CGAR for 2024-2032.

While the available TNF-α and IL-23 blockers are effective, they attenuates only one of several arms of inflammation by targeting only one cytokine (either TNF-α or IL-23). ***This limits their overall effectiveness***!!!! Thus, there is an urgent need to develop more effective agent(s) for the treatment & management of chronic inflammatory conditions.

New Research: Recent scientific data suggest that targeting more than one cytokines, by administrating one or more drugs, is more effective than targeting only one cytokine in controlling chronic inflammatory disease progression and associated symptom management.

Problem statement:

TNF-α and IL-23 targeting biologics have a HUGE market size. However, due to their mono-specific nature, they are found to be partially effective in the treatment and management of many chronic inflammatory diseases. There is an urgent need to develop a drug agent that can target both TNF-α and IL-23. Such dual acting drug cab attenuate several arms of inflammation and can be much more effective than currently available TNF-α and IL-23 targeting biologics.

Solution: BiSpekDAb™

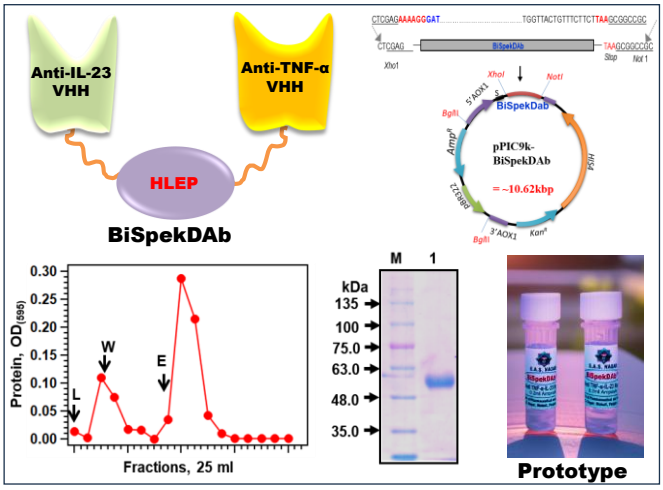
BiSpekDAb™ are engineered bispecific antibodies that target both IL-23 & TNF-α. They comprise of anti-IL23 domain antibody and anti-TNFα domain antibody linked to a half-life extension partner *via* a flexible peptide linker. BiSpekDAb™ attenuate inflammation in animal models of inflammatory conditions (pulmonary inflammation, stroke, and others) by regulating IL-23 & TNF-α signalling pathway.

Development of BiSpekDAb™

1. ***Designing and engineering of BiSpekDAb™ variants***: Using protein engineering approaches, we have engineered **TWO** novel BiSpekDAb variants (FTO completed by PSCST, Punjab).

2. ***Clone development***: High-yield clones (*Pichia pastoris*) capable of producing BiSpekDAb™ variants are developed.

3. ***Production process development***: A simple-n-cost effective process (lab-scale) to produce BiSpekDAb™ variants is developed. This process is amenable for the development of process for the industrial scale production of BiSpekDAb™.



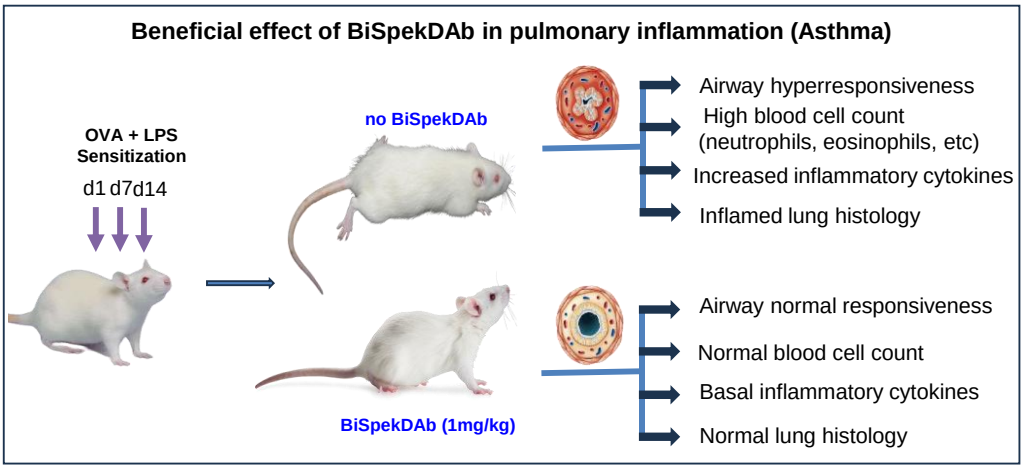
4. ***In vitro studies***: Functional characterization of BiSpekDAb^{TM} variants has been completed using non-cellular and cellular assays.

5. ***Efficacy study in animal models of chronic inflammation***: The efficacy of BiSpekDAb^{TM} variants has already been demonstrated in following models of chronic inflammatory conditions: Pulmonary inflammation (severe asthma) and stroke (in the lab of Prof. S. S. Sharma, Dept. of Pharmacology Toxicology, NIPER SAS Nagar).

Summary of studies already performed:

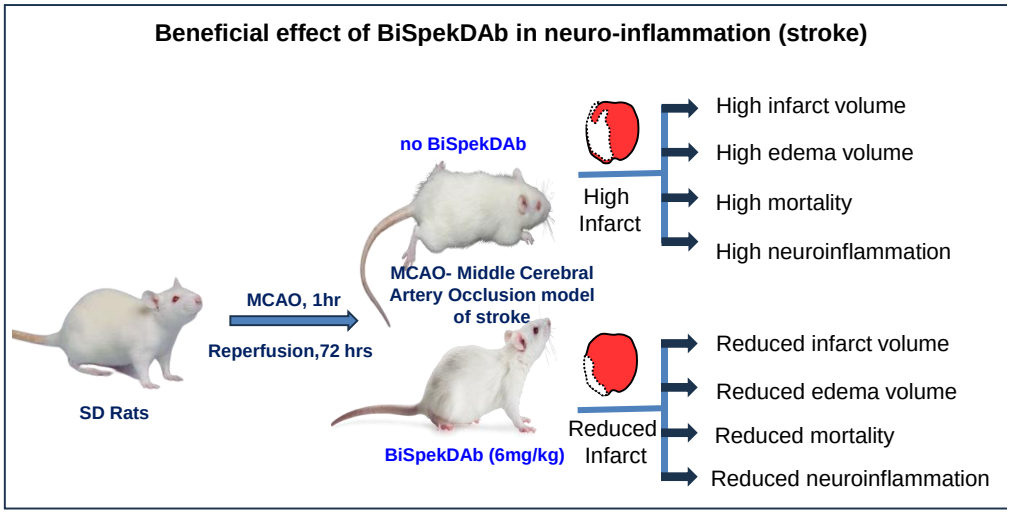
a) Pulmonary inflammation: Pulmonary inflammation includes multiple respiratory disorders such as COPD and severe asthma. 06 different biologics (Omalizumab, Benralizumab, Mepolizumab, Reslizumab, Dupilumab, Tezepelumab) are approved for the treatment of severe asthma. However, these treatments are inadequate.

A BiSpekDAb^{TM} variant-1 (having albumin-based half-life extension partner) effectively attenuated airway hyperresponsiveness and pulmonary inflammation in OVA/LPS-induced asthma in rats by regulating IL-23/TNF-α signaling pathway. Compared to dexamethasone (a first-line glucocorticoid drug for asthma), BiSpekDAb^{TM} showed NO side effects.



b) **Stroke**: A large proportion of stroke survivors have long-lasting, debilitating neurological impairments, yet NO efficacious medical treatment options are available. Targeting TNF-α is being pursued as a promising approach in the management of long-term disabling effects of stroke (Phase 2b study is going on; DOI: 10.1177/23969873241249248)

In a preliminary evaluation, BiSpekDAb^{TM} variant-2 (comprising of blood-brain-barrier crossing as well as half-life improving component) prevented neurological deficit in middle cerebral artery occlusion (MCAO) model of stroke in SD rats. Considering a dire need for the development of treatment for stroke, BiSpekDAb^{TM} can be a game changer candidate.



c) ***Systemic Inflammation***: Beneficial effects of BiSpekDAb variants are being studied in LPS-induced systemic inflammation in mice.

d) ***Arthritis***: Beneficial effects of BiSpekDAb variants are being studied in collagen-induced arthritis in rats.

Our Publications:

Pande et al PolyBodies: Next generation of clinical antibodies. **Drug Discovery Today** (**in press**).

Sandeep et al Generation and partial characterization of a bispecific domain antibody targeting IL-23 and TNF-α (**Communicated**).

Gala et al A novel bispecific single domain antibody alleviates airway hyperresponsiveness and pulmonary inflammation in ovalbumin and lipopolysaccharide induced asthma by regulating IL-23 and TNF-α signaling pathway in rat (**Communicated**)

Shinde et al (2024) Polyvalency - an emerging trend in the development of clinical antibodies **Drug Discovery Today**, 29(1):103846

Sandeep et al (2023) Engineered polyspecific antibodies: A new frontier in the field of immunotherapeutics. **Immunology**, 171:464–496.

Sandeep el al (2023) Polyspecificity - an emerging trend in the development of clinical antibodies. **Molecular Immunology**. 155; 175-183.

Indian Patent application # 202211075699. Tumour necrosis factor alpha-neutralizing domain antibody and method of generation thereof.

PCT/IB2023/063215. Tumour necrosis factor alpha-neutralizing domain antibody and method of generation thereof.

Indian Patent application # 202411012808. Polyvalent tumour necrosis factor-alpha blocking domain antibodies and method of generation thereof

Indian Patent Application # 202411059121. Bispecific domain antibody (BiSpekDAb) and method of generation thereof.

Market Opportunity:

There is a growing need for the development of more effective treatment(s) for chronic inflammatory conditions. The anti-inflammatory biologics market size is projected to grow from USD 93.32 bn in 2023 to USD 139.80 bn by 2030 (at a CAGR of 5.9%). Considering the current market success of TNF-α and IL-23 targeting biologics, there is a very-high chance that BiSpekDAb^{TM} variants can turn out to be potential block-busters in the treatment of multiple inflammatory conditions in coming years!!!

So, there is a HUGE market potential for BiSpekDAb^{TM} as they attenuate two arms of inflammation by targeting two cytokine (TNF-α and IL-23).

Development Plan: Long term (2025-2035)

Long-term (2025-2035) and immediate short-term (2025-2027) plans for the development of BiSpekDAb^{TM} is given as **Annexure 1**

Financial Projections:

- Cost of non-GLP studies is tabulated in **Annexure 2**

- Further cost will require in-depth discussion with the partner company

Risk Assessment:

No idea at this stage

Why BiSpekDAb is ideal for chronic asthma ?

Severe asthma is a multifaceted chronic pulmonary inflammatory disorder which has affected around 300 million people worldwide. It is a complex and chronic inflammatory disorder that often does not respond adequately to existing therapies, including corticosteroids and other asthma controllers. While six biologics—Omalizumab, Benralizumab, Mepolizumab, Reslizumab, Dupilumab, and Tezepelumab—are available, they primarily target single inflammatory pathways and may not provide complete relief due to the multifaceted nature of the disease. BiSpekDAb offers a novel solution by simultaneously inhibiting both IL-23 and TNF-α, two pivotal regulatory cytokines involved in asthma inflammation. This innovative approach positions BiSpekDAb as a potentially more effective treatment option for patients struggling with severe asthma. Choosing BiSpekDAb over approved biologics for asthma is a strategic decision based on its innovative approach to treatment. Here mentioned are three key reasons to consider BiSpekDAb over other biologics:

1. Higher Efficacy: BiSpekDAb uniquely targets both IL-23 and TNF-α, two critical cytokines involved in asthma inflammation, offering a dual-action approach that enhances efficacy compared to existing monospecific biologics, which target single pathways.

2. Cost-Effectiveness: BiSpekDAb is produced using a Pichia pastoris expression system, which significantly reduces production costs compared to the mammalian systems used for other biologics. This allows for a more affordable treatment option without compromising quality.

3. Affordability: Once developed, BiSpekDAb will be the first indigenous biologic available in India, making it accessible and affordable for patients who currently face high costs with imported biologic therapies.

In summary, BiSpekDAb not only promises enhanced therapeutic outcomes but also addresses economic barriers, making it a compelling choice for managing severe asthma effectively.

Annexure 1
BiSpekDAb Development Plan -1 (Long term, 2025-2035)

Developmental Stages	Time-line	Milestones
Stage 1: Discovery & Early Development (Already Done) Engineering antibodies, clone development, lab-scale production process development, *in vitro* testing and efficacy assessment in animal models of chronic inflammation is completed. Prototype of product and proof-of-concept is ready.	2017-2025	Prototype, process of production & PoC READY
Stage 2: Non-GLP studies-1 i) Scale-up of production process (5-10 Lts) ii) Development of stable formulation of BiSpekDAb and stability studies iii) Toxicology studies of BiSpekDAb formulation iv) Safety pharmacology studies of BiSpekDAb formulation v) PK studies of BiSpekDAb formulation	2025-2027	
Stage 3: Non-GLP studies-2 i) Re-validation of stage-2 studies in higher animals ii) Efficacy studies (dose, route etc) of BiSpekDAb formulation in relevant animal model ii) Re-validation of efficacy of BiSpekDAb formulation in relevant animal model		
Stage 4: GLP studies i) GLP-studies for IND application filing ii) IND application filing & iii) Rebuttal		
Stage 5: Manufacturing process for clinical studies i) Preparation of BiSpekDAb batch in GMP facility for clinical studies		
Stage 6: Clinical studies i) Phase I Clinical Trials ii) Phase II Clinical Trials iii) Phase III Clinical Trials		
Stage 7: Regulatory Review and Approval i) NDA / BLA filing ii) Rebuttal iii) Product labelling and marketing approvals iv) Post approval preparation and preparation of product launch		
Stage 8: Commercialization and Post-Market Activities i) Product launch ii) Expansion and Scaling iii) Post-Market Surveillance & Lifecycle Management	---	

Annexure 2

Development Plan-2 (Jan 2025 - Dec 2027)

(Stage 2: Non-GLP studies-1)

Target: to generate data for Stage 3 and 4 studies!

	Experiments	Deliverables	Time-line	Cost
1	**Production**: i) Clone optimization; ii) Process optimization (5 lts fermenter)	- high-yield clone; - optimized process; - data for pilot scale-up (50-100 lts); data for stage-5 experiments	**03 - 18 Mo**	
2	**Formulation & Stability studies**: (as per NDCT-2019 rules) i) Formulation ii) stability studies iii) Data of final formulation	- 2 final formulations; - stability data; - analytical data of formulation; - data for further pre-clinical/clinical studies as well as for scale-up of formulation	**03 - 18 Mo**	
3	**Toxicological studies**: (as per NDCT-2019 rules) i) *Systemic Toxicity studies* (Single dose / dose ranging toxicity studies; *Repeated-dose systemic toxicity studies* (14/28/90/180 days); ii) *Immunogenicity / Hypersensitivity* studies iii) *Local toxicity studies* with proposed route of application? iv) *Genotoxicity studies* v) *Reproductive toxicology studies* (Male fertility, other studies)	- toxicological profile of formulation - therapeutic index of formulation - data for Stage-3/4 studies	**09 - 33 Mo**	
4	**Safety Pharmacological studies**: (as per NDCT-2019 rules) i) Cardiovascular system ii) Central nervous system iii) Respiratory system	- safety profile of formulation - data for Stage-3 experiments	**12 - 18 Mo**	
5	**Pharmacokinetic studies**: i) All ADME parameters	- Pharmacokinetic data / metabolic profile of formulation - data for Stage-3/4/6	**12 - 18 Mo**	
6	**Administrative cost**			

*Tentative, based on the estimates received.

Funding:

1. Partner company shall fund 100% of these studies, or
2. Partner company & NIPER SAS Nagar together shall arrange funding from various schemes of GoI (ex, BIRAC, ICMR, DST, Others).

BiSpekDAb™: Engineered Bispecific Antibodies for the Management of Multiple Inflammatory Conditions

1. Field: Chronic inflammatory diseases are significant burden on the global health. Recent scientific data suggest that targeting more than one cytokine (by one or more drugs) is more effective than targeting only one cytokine in controlling chronic inflammatory disease progression and associated symptom management.

2. Problem: TNF-α & IL-23 are key 'culprit' cytokines that are responsible for numerous inflammatory conditions. 06 TNF-α targeting biologics are approved and many more are being developed for *>35 diseases*. The market size of TNF-blockers is expected to reach USD 47.32 bn (CGAR of 3.59% for 2024-2029). Similarly, 04 IL-23 targeting biologics are approved and >35 companies are developing 24 IL-23 Inhibitors for *36 diseases*. Market size of IL-23 blockers is 24.3 billion in 2023 and will grow at 12% CGAR, 2024-2032. While, the available TNFα and IL23 blockers are effective, they target only one cytokine (either TNFα or IL-23) and this limit their overall effectiveness. Thus, there is an urgent need to develop more effective agent(s) for the treatment and management of chronic inflammatory conditions.

3. Need of the hour: Considering the success of TNF-α/IL-23 blocking biologics and their tremendous market size, there is an urgent need to develop biologic(s) that can target both IL-23 & TNF-α.

4. Our solution: BiSpekDAb™: Engineered bispecific antibodies that target both IL-23 & TNF-α.

PATENT STATUS:

Applied

TRL STATUS: TRL3/4

BiSpekDAb™

SPECIFICATIONS OF TECHNOLOGY:

1. **Dual Action Mode**: Novel engineered biologics that can target two different cytokines

2. **Unique structural design**: Permits good structural stability

3. **Simple-n-cost effective production platform**: High yield clone (*P pastoris*) and simple production process

4. **Superior efficacy**: Target TWO pro-inflammatory cytokines (IL-23 & TNF-α) and effectively ameliorate inflammation by regulating IL-23/TNF-α signaling pathways

5. **Protected intellectual property**: Indian patent filed; Freedom-to-operate (FTO) analysis ensures no infringement on existing products.

6. **Made In India !!!**

Please Contact:

Dr. Abhay H. Pande,

Professor (Department of Biotechnology)
National Institute of Pharmaceutical Edu. Res. (NIPER)
Sector-67, S.A.S. Nagar, Mohali-160062, Punjab (India)
Telephone: 0172-2214682-85, Extn: 2068
E-mail: apande@niper.ac.in;
IPR cell: iprcell@niper.ac.in;
Technical cell: technicalcell@niper.ac.in

SCAN QR TO SEE THE LAB TECHNOLOGIES

SWOT-Analysis

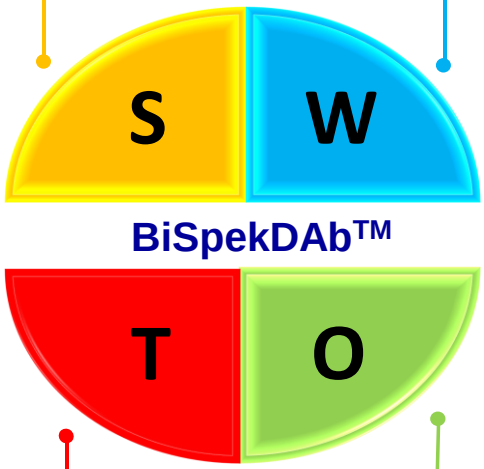
BiSpekDAb™

STRENGTHS

- Anti-inflammatory activity
- Inhibit TWO cytokines
- Improved Pharmacokinetic properties ($t_{1/2}$)
- Industrial feasible protein production technology

WEAKNESS

- *Pichia* production system
- Detailed toxicity, safety and efficacy studies NOT completed yet



THREATS

- IND filing and clinical studies may take substantial time
- Competitors may GO ahead

OPPORTUNITIES

- Novel Bispecific antibody for numerous anti-inflammatory conditions
- Made in India

Business Model Canvas for BiSpekDAb™

<table>
<tr>
<td>Problem:

- Chronic inflammation is responsible for the initiation / progression of many diseases

- TNF-α & IL-23 participate in the initiation / progression of many chronic inflammatory conditions

- 06 anti-TNF-α and 04 anti-IL23 biologics are approved for the treatment of a variety of inflammatory conditions

Shortcomings:

- due to their mono-specific nature, they are partially effective in the treatment and management of numerous diseases

- A dire need to develop more efficacious treatment</td>
<td>Solution:

- Targeting more than one cytokines, by administering one or more drugs, is more effective than targeting only one cytokine in controlling chronic inflammatory disease progression and associated symptom management

- BiSpekDAb™ are engineered bispecific antibodies that block both IL23 & TNFα and manage chronic inflammatory conditions more effectively</td>
<td>Unique Value Prop:

Enhanced Efficacy (by regulating 2 inflammatory pathways)

Reduced Adverse Reaction (potential for lower doses & fewer side effects compared to existing treatments)

Cost-Effective (potentially lower production costs, more accessible and more affordable for Indian patients; Made in India)

Versatility (potential applicability to a range of inflammatory and autoimmune diseases)</td>
<td>Unfair Advantage:

Dual-targeting approach: (1st in the market for its kind) for more comprehensive disease management (better efficacy then existing drugs)

Reduced Adverse Reaction: Potential for lower doses and reduced side effects

Versatility: Potential applicability for the treatment and management of multiple chronic inflammatory conditions (~50)

Affordable-n-accessible: Potential low cost and made in India</td>
<td>Customer Segments:

Disease segments: Multiple chronic inflammatory conditions (~50)

Partners:

National and international Start-ups & Pharmaceutical companies for co-development</td>
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<td>Existing Alternatives:

- Two different TNF-α & IL-23 targeting drugs under clinical assessment

- Bispecific agents that can block both IL23 & TNFα are under pre-clinical and clinical development</td>
<td>Key Metrics:

- Efficacy in multiple pre-clinical models

- Cost of GLP mode proof</td>
<td>High-level Concept:

- Unique design features of BiSpekDAb™ make them potential candidates for the treatment and management of multiple chronic inflammatory conditions</td>
<td>Channels:

National & international
- Start-ups
- Pharmaceutical companies</td>
<td>Early Adopters:

National & international
- Start-ups</td>
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<tr>
<td colspan="3">Cost Structure:
- Cost of non-GLP studies is tabulated in Annexure 2
- Further cost will require in-depth discussion with the partner company</td>
<td colspan="2">Revenue Streams:
- Funding from government/non-government research grants</td>
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