Disease-Modifying Immunotherapies for Autoimmune and Allergic diseases
Apitope is developing highly specific disease-modifying immunotherapies to treat life threatening autoimmune diseases

- Abnormal immune response can cause chronic and life threatening conditions e.g. MS, Graves’ disease, uveitis, type 1 diabetes, IBD
- Current therapies do not reinstate tolerance and instead treat symptoms or globally suppress immune system with potential for side effects including increased risk of infections and cancer/immune diseases
- Ideal therapeutic:
  - will re-instate normal immune balance / tolerance
  - avoid global immune suppression
  - treat the underlying cause of the disease
Senior management & leadership

Dr Keith Martin
Chief Executive Officer
KetoCytonyx Inc., BTG plc., BASF Pharma (Knoll)/Boots Pharmaceuticals
Bath University, Nottingham University; Princeton University

2 products to market
(Meridia in US. Zoleptil in UK)
10 candidates into clinical development

Dr Lotta Jansson
Research Director
Astra Zeneca
Uppsala & Lund universities

Dr Hayley French
Commercial Director
General Counsel
Novartis,
CAMR, UCL Ventures
City law firms

Luc Lammens
Finance & HR Director
Movetis (IPO of 100M€)
Janssen Pharmaceutica et al.

Prof David Wraith
CSO, Founder, Chair Scientific Advisory Board, Consultant
Professor, University of Bristol
Medical Research Council @ Mill Hill, London Stanford University; Cambridge University
>130 peer reviewed papers

Dr Christina Carnegie MB BS FPPM
Chief Medical Officer; Consultant
ImmunoScience Inc, Recro Pharma, Auxilium Pharmaceuticals Inc
Medical Director Abbott UK
King’s College Hospital Medical School
9 clinical development programmes licensed
Apitope presents significant investment opportunity

- **Established leader in discovery and development of antigen specific immunotherapeutic peptides, Apitopes®, focused on autoimmune disease**
  - Apitopes® = Antigen Processing Independent epiTOPES
  - located in Belgium and UK
  - experienced management team with strong scientific and commercial track record

- **Proprietary Apitope® discovery platform delivers therapies into development across a broad range of high value autoimmune disorders**
  - very high selectivity in modifying only the malfunctioning part of immune system
  - minimal side effects due to high specificity
  - safe and well tolerated in clinical trials; no treatment related SAEs to date
  - scalable manufacturing – chemical process, readily synthesized with low cost of goods
  - strong portfolio of IP: Platform to 2022; Peptides composition of matter to 2027 – 2034

- **Extensive clinical and development portfolio of product candidates**
  - 3 in clinical/preclinical development phase in attractive end markets
  - 4 in late discovery phase
  - grant funding for Graves’ disease and uveitis programmes

- **Validation through partners on specific assets:** Merck Serono, FP7

- **Opportunity for significant revenues in ultra orphan indication and targeted clinical programme**
  - Modest funding of Factor VIII programme through development to commercialisation with potential peak sales of $1 billion
## Apitope History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td><strong>Company founded in Bristol</strong></td>
</tr>
<tr>
<td>2002-2006</td>
<td>Angel investor, (£1M) Wyvern &amp; Wellcome Trust (£1M) funding</td>
</tr>
<tr>
<td>2006</td>
<td>Approval for First in Man study of ATX-1467 for MS</td>
</tr>
<tr>
<td>2007</td>
<td>Completed first clinical trial on time and budget</td>
</tr>
<tr>
<td>2008</td>
<td><strong>Series A €10M led by Vesalius Biocapital &amp; LRM; Parent created in Belgium</strong></td>
</tr>
<tr>
<td>2008</td>
<td>Fast Forward (venture arm of US MS Society) commits up to $1M</td>
</tr>
<tr>
<td>2009</td>
<td><strong>Merck Serono Licence Agreement €150M + milestones in addition to industry standard royalties</strong></td>
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<tr>
<td>2012</td>
<td>IWT (Flemish Govt.) €1.2M grant: Graves’ disease and uveitis discovery</td>
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<tr>
<td>2013</td>
<td><strong>Positive efficacy data from second ATX-1467 clinical trial in MS reported</strong></td>
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<tr>
<td>2013</td>
<td><strong>FP7 (European Commission Framework 7) €6M grant: Graves’ disease development</strong></td>
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<tr>
<td>2014</td>
<td>ATX-1467 Phase II clinical trial initiated by Merck Serono</td>
</tr>
<tr>
<td>2015</td>
<td><strong>Series B financing €12 million led by Wales Life Sciences Fund (Arthurian)</strong></td>
</tr>
</tbody>
</table>
Effective tolerance induction may require high dose of peptide antigen: this can be given safely following dose escalation

Dose escalation results in incremental changes in gene expression

Tolerance correlates with expression of genes related to IL-10 secretion (potential surrogate markers in clinical trials)

Tolerance correlates with expression of negative co-stimulatory molecules (potential surrogate markers in clinical trials)
Potentially self-antigen reactive cells are present in all healthy people. Activity of these T helper (Th) cells is controlled by T regulatory (Treg) cells. The result is an immune system that has a fine balance between potentially dangerous Th cells and the Treg cells that suppress them creating an immunological tolerance towards self or foreign antigens.
**Apitopes restore the normal immune balance and modify disease**

**Protein Processing by Dendritic Cells for Antigen Presentation via MHC II Combined with Danger Signals Leads to Imbalance of Immune System and to Tissue Damage**

- **Mature dendritic cell** carries danger signals
- **T helper cell activation**
- **Autoimmune disease affecting brain tissue**
- **Cells capable of causing tissue damage**

**Peptide Binding to MHC on Surface of Immature Dendritic Cells for Antigen Presentation via MHC II Increases Treg to Restore Immune Balance and Protects Tissues from Damage**

- **Immature dendritic cell**
  - Empty MHC receptors on cell surface
  - No Danger signals
- **T regulatory cell activation**
- **Brain Tissue Protected by Regulatory T Cells**
- **Natural Regulatory (CD25, FoxP3) and Induced Suppressor Cells**
# Status of Product Pipeline

<table>
<thead>
<tr>
<th>Project</th>
<th>Indication</th>
<th>Commercialisation</th>
<th>Discovery</th>
<th>Preclinical Development</th>
<th>Phase I FIM/Pop in Patients</th>
<th>Phase II</th>
<th>Market Size US$</th>
<th>Estimated Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATX-MS-1467</td>
<td>Multiple Sclerosis</td>
<td>Merck Serono</td>
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<td></td>
<td></td>
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<td>9.7 - 13.1B</td>
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<td>Multiple Sclerosis</td>
<td>Merck Serono</td>
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<tr>
<td>ATX-MS3</td>
<td>Multiple Sclerosis</td>
<td>Merck Serono</td>
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<tr>
<td>ATX-F8-117</td>
<td>Factor VIII inhibition</td>
<td>Apitope</td>
<td></td>
<td></td>
<td></td>
<td>2016/17</td>
<td>3.7 B</td>
<td>2020</td>
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<tr>
<td>ATX-GD-59</td>
<td>Hyperthyroidism (Graves’ disease)</td>
<td>SEVENTH FRAMEWORK PROGRAMME</td>
<td></td>
<td></td>
<td></td>
<td>2016/17</td>
<td>640 – 800 M*</td>
<td>2024</td>
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<tr>
<td>ATX-UV1</td>
<td>Uveitis</td>
<td>Partner TBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 – 350 M*</td>
<td>2026</td>
</tr>
<tr>
<td>ATX-UV2</td>
<td>Uveitis</td>
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</tbody>
</table>

Apitope funded programmes building value to key inflexion points

*no premium priced products available
# ATX-MS-1467 for Multiple Sclerosis

## Indication
- Relapsing Multiple Sclerosis
- Synthetic soluble copies of four peptide fragments of human myelin basic protein (MBP), a key antigen for Multiple Sclerosis

## Market Opportunity
- Significant unmet needs due to poor efficacy and high side effects

## Commercialisation Strategy
- Global partnership with Merck Serono: €150 M + milestones plus royalties
- On market by 2023

## Development Status
- Efficacy in MS models and immune system both in vivo & in vitro
- Superior efficacy compared to Copaxone in standard in vivo disease model
- Toxicology: well tolerated in multiple studies
- Phase IA safety trial in secondary progressive MS: safe & well tolerated with preliminary evidence of efficacy
- Phase IB safety trial in relapsing Multiple Sclerosis yielded further promising positive efficacy data: reduction in new lesions in brain measured by MRI
- 49 patients in total treated in UK & Russia with no treatment related SAEs and no side effects identified; main AE was mild not dose related injection site reactions that resolved in 2 hours
- Phase II confirmation study anticipated completed 2015 and Phase II dose ranging expected initiation 2015/6
- All development costs paid by Merck Serono
ATX-MS-1467: superior efficacy to glatiramer acetate (Copaxone) in mouse model of Multiple Sclerosis & similar preliminary efficacy in the clinic

Mean number of new or persisting gadolinium (GD) enhancing lesions in relapsing MS patients:

> significantly reduced by 78% following ATX-MS-1467

> remains suppressed at Week 20

*** P<0.001 vs. Week 0; * P<0.05 vs. Week 0
Patients (n=21) from cohort 1 (ITT) with ID administration
## ATX-F8-117 Treatment for Factor VIII Inhibitors

### Indication
- Factor VIII – an essential protein in blood clotting used to treat Haemophilia A (HA)
- Factor VIII Inhibitors develop in ~30% of patients and result in poor clotting leading to joint & brain damage, death

### Current Treatments
- **Immune Tolerance Induction (ITI)** – very high doses of FVIII (daily or 3x week) by catheter - extremely expensive, unpredictable efficacy and poor tolerability. ITI fails in around 30-40% of treated patients.
- Around 60% of patients in Western world do not receive ITI because of cost.
- High doses of expensive by-passing agents used to control bleeds.
- 141 centres in US and 409 in EU

### Market Opportunity
- HA is a significant market of US$3.7 B p.a.
- HA is a genetic disease affecting 1:5,000-10,000 males
- 20,000 severe HA patients in EU and US
- **1,300 severe inhibitor patients treatment in US and 5 major EU markets cost $570 M annually**
- Average annual cost to treat an Inhibitor patient: $572K in US and $292K in EU

### Commercialisation Strategy
- Marketed by Apitope
- Approved by 2020

Source: Reportlinker.com; Global Data (2014)
### Product

- ATX-F8-117 has been developed to significantly change the morbidity and quality of life of Haemophilia A (HA) patients
- Prophylactic treatment with ATX-F8-117 of patients at risk to develop inhibitors will significantly reduce if not eliminate the need for by-passing agents used to treat FVIII intolerant haemophiliacs with inhibitors

### Apitope USP

Compared to standard immune tolerance induction with full-length FVIII concentrates, tolerance induction with ATX-F8-117 is designed to:

- **Be faster in converting sero-positive inhibitor patients into sero-negative ones**
- **Have an improved safety profile due to a catheter-free administration** and therefore a lower risk of bleeding complications and infections
- Suppress inhibitor antibody formation in a highly specific manner
- Be less burdensome for patients and caregivers due to less frequent and intradermal administration
- **Be more cost-effective since it replaces expensive high doses of FVIII and may reduce the need for by-passing agents**

### Development Status

- Patents filed for prevention and treatment; **Orphan applications in 2014**
- Preclinical development initiated Q1, 2014
- Aim to obtain **Market Authorisation in first indication** by 2020 and commercialise in EU
ATX-F8-117 prevents anti-FVIII antibody formation by 96% in DR2tg Mice
ATX-F8-117 therapeutic treatment decreases total anti-FVIII IgG plasma levels in DR2tg mice
### Clinical Costs and Timelines Summary

<table>
<thead>
<tr>
<th>Event Description</th>
<th>2015</th>
<th>2020</th>
<th>2026</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First approval EU – Adult (16+) ITI fails</strong></td>
<td></td>
<td></td>
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<tr>
<td>• First In Man Protocol</td>
<td></td>
<td></td>
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<tr>
<td>• Phase II Protocol</td>
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<tr>
<td>• PIII adaptive design Protocol</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Marketing Authorisation Application &amp; sales force</td>
<td></td>
<td></td>
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<tr>
<td><strong>First approval US – Adult (16+) ITI fails</strong></td>
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<td></td>
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<tr>
<td>• PIII using doses from Phase II in EU</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Marketing Authorisation Application</td>
<td></td>
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<tr>
<td><strong>EU approval 4 – 16 year olds ITI fails</strong></td>
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<tr>
<td>• Phase II dose ranging in paediatrics</td>
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<td></td>
<td></td>
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<tr>
<td>• PIII using doses from Phase II in EU</td>
<td></td>
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<td></td>
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<tr>
<td>• Marketing Authorisation Application</td>
<td></td>
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<tr>
<td><strong>US approval 4 – 16 year olds ITI fails</strong></td>
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<td></td>
</tr>
<tr>
<td>• PIII using doses from Phase II paediatric dose ranging</td>
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<tr>
<td>• Marketing Authorisation Application</td>
<td></td>
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<tr>
<td><strong>EU approval &lt;4 year olds ITI fails</strong></td>
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<tr>
<td>• PIII using doses TBC</td>
<td></td>
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<tr>
<td>• Marketing Authorisation Application</td>
<td></td>
<td></td>
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<td><strong>US approval &lt;4 year olds ITI fails</strong></td>
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<tr>
<td>• PIII using doses TBC</td>
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<tr>
<td>• Marketing Authorisation Application</td>
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<tr>
<td><strong>EU/US approval first line therapy in inhibitor patient all ages</strong></td>
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<tr>
<td>• PIII using doses from Phase II in EU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Marketing Authorisation Application</td>
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</tbody>
</table>

Costs reflect CRO and patient costs; internal costs are not included.
ATX-GD-459 for Graves’ Disease (hyperthyroidism)

Indication
- Overstimulation of the thyroid gland resulting in over-production of thyroxine hormone and enlargement of gland (goitre)
- 60-90% of Hyperthyroidism caused by Graves Disease

Current Treatments
- No cure for Graves Disease
- Treatments target the underlying symptoms e.g. antithyroid drugs, thyroxine and/or removal of thyroid gland
- Issues: poor efficacy
- Drugs in development – Rituximab, Actemra

Market Opportunity
- 2.6 M (N.America), 2.4 M (Europe) – affects up to 2% of women
- 30-50% Graves opthalmopathy (5% sight loss)
- Paediatric Graves’ Disease affects 6,000 US and 6,000 EU

Commercialisation Strategy
- Partner following completion of First in Man clinical trial in Graves’ disease patients

Development Status
- ATX-GD-459 is in pre-clinical development
- Phase I trial in patients to start early Q1, 2016
- FP7 funded development programme
ATX-GD-459 treatment reduces anti-TSHR antibodies in AdV-TSHR immunised DR3tg mice

**ATX-GD-459 dosing**

-2  -1  0  1  2  3  4  5  

Ad-TSHR  Ad-TSHR  Termination

**W0**

PBS, LacZ  PBS, TSHR  P-ATX459, TSHR

**W2**

PBS, LacZ  PBS, TSHR  P-ATX459, TSHR

**W5**

PBS, LacZ  PBS, TSHR  P-ATX459, TSHR

ATX-GD-459 dosing results in significant reduction of TSHR antibodies at W5, with 83% and 81% decreases compared to control groups.
### ATX-UV1 and ATX-UV2 for Uveitis

| **Indication** | • Autoimmune inflammation of the uvea tract (iris, ciliary body and choroid) in the eye  
|               | • Several sub-types  
|               | • Causes 10-15% of blindness |
| **Current Treatments** | • Steroids  
|               | • Issues: Severe cases not responsive to steroids |
| **Market Opportunity** | • Total uveitis Market Size: Incidence: 500,000 in US and EU  
|               | • Market value: estimated to be US$1.6 B by 2017 but currently up to US$350 M (limited data)  
|               | • Bird shot retinopathy is an orphan indication with 5,000 patients; blind within 5 years of diagnosis |
| **Commercialisation Strategy** | • Partner following completion of First in Man clinical trial in uveitis patients |
| **Development Status** | • Antigen target UV1 Epitopes identified: four  
|               | • Antigen target UV2 Epitopes identified: seven  
|               | • Product candidate nomination Q1, 2016, clinical trial starts early 2017 |
Consistent pre-clinical data across disease areas: clinical findings positive

<table>
<thead>
<tr>
<th>Programme</th>
<th>Tolerance data – suppression of T cell proliferation</th>
<th>Relevant disease model data</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis ATX-MS-1467</td>
<td>~60%</td>
<td>&gt;90% inhibition of EAE both prophylactic and therapeutic dosing</td>
<td>78% reduction in new Gd lesions by MRI in Phase I</td>
</tr>
<tr>
<td>FVIII Intolerance ATX-F8-117</td>
<td>~70%</td>
<td>&gt;90% inhibition of neutralising anti-FVIII antibody formation</td>
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<tr>
<td>Graves’ Disease ATX-GD-459</td>
<td>~65%</td>
<td>86% inhibition of anti-TSHR IgG antibody formation</td>
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<tr>
<td>Uveitis ATX-UV-xxx</td>
<td>In progress</td>
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<tr>
<td>Q4</td>
<td>H1</td>
<td>H2</td>
<td>H1</td>
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<tr>
<td></td>
<td>Close Series B financing</td>
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</tbody>
</table>

**Factor VIII:**
- Orphan designation (EU)
- Orphan designation (USA)
- CTA for first clinical trial filed
- First patient first visit

**Factor VIII:**
- Initial clinical data from Phase I on HA patients (Q4)
- Initiate Phase II/III
- Initial Phase II/III data available (H2)
- First Marketing Authorisation Application filed in EU (H2)
- First Marketing Authorisation in EU (H2)

**Graves’**
- CTA for first clinical trial approved (Q1)
- First patient first visit
- Initial clinical data from Phase I on GD patients
- Partner takes licence
- Partner initiates Phase II

**Uveitis:**
- Product Candidate designated
- First patient first visit (H1)
- Initial clinical data (H2)
- Partner takes licence

**Multiple Sclerosis:**
- Initial clinical data in Phase IIA for ATX-1467
Pipeline Products: Current IP Status
To date, the Company has already established 6 distinct patent families with over 100 patents filed around its technology

<table>
<thead>
<tr>
<th>Project</th>
<th>Indication</th>
<th>Commercialisation</th>
<th>Key Patent priority dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATX-1467</td>
<td>Multiple Sclerosis</td>
<td></td>
<td>2002 (granted; includes platform)</td>
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<tr>
<td></td>
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<td>2007 (Granted)</td>
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<tr>
<td>ATX-MS2</td>
<td>Multiple Sclerosis</td>
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<td>2012</td>
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<tr>
<td>ATX-MS3</td>
<td>Multiple Sclerosis</td>
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<td>2012</td>
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<tr>
<td>ATX-F8-117</td>
<td>Factor VIII inhibition</td>
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<td>2008 (Granted); 2009; 2012</td>
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<td>ATX-GD-459</td>
<td>Hyperthyroidism</td>
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<td>2013 2014</td>
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<td>ATX-UV1</td>
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<tr>
<td>ATX-UV2</td>
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<td>TBC</td>
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</table>


Summary

- Apitope is the leader in developing disease-modifying immunotherapies for treating life threatening autoimmune diseases that is differentiated from other players

- Proprietary Apitope® discovery platform applicable to autoimmune (our focus) and allergic disorders (opportunity for broad partnership)

- Strong clinical and development portfolio of product candidates

- Validated with big pharma partners and large grants

- Experienced management team with strong scientific and commercial track record

- **Significant opportunity** - funding through to launch ultra orphan indication with high (£500k to 1,000k) potential sales in relatively short time frame