
Bioxyne
Investor Presentation
July 16th 2012

HI-164OV – Executive Summary

Clinical:

- **First-in-class** oral therapeutic vaccine for reduction of number and severity of COPD exacerbations
- **Two separate Phase 2a and a Phase 2b** safety and efficacy randomized trials completed
- 320-patient, multi-center, placebo controlled, double-masked Phase 2b trial recently completed. HI-164OV did not differ from placebo under ITT and PP analyses.
- However, Phase 2b trial post-hoc analysis demonstrated **significant improvements** in primary and secondary outcomes (p=<0.05) in the **under 65 years** patient sub-group.

Regulatory:

- **Well depicted development program** based on regulatory guidance
- Clear strategy for the removal of asset from FDA clinical hold

CMC:

- **Drug substance stable** up to 12 months at 2-8 degrees Celsius
- Drug product produced at IDT Australia, international contract manufacturers currently under assessment

IP:

- **Robust IP estate** with key issued patent families valid through 2029

Commercial:

- **Significant opportunity** in a market with high unmet clinical need.
- Base case estimate **$500M peak year sales**

Approved product would represent paradigm shift in COPD therapeutics.

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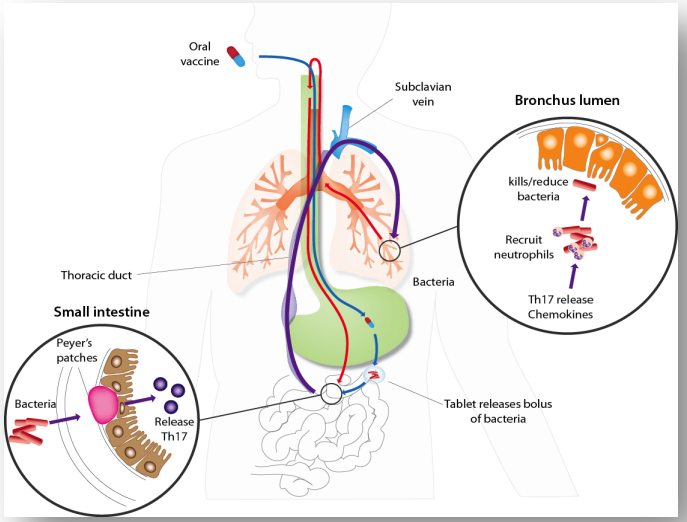
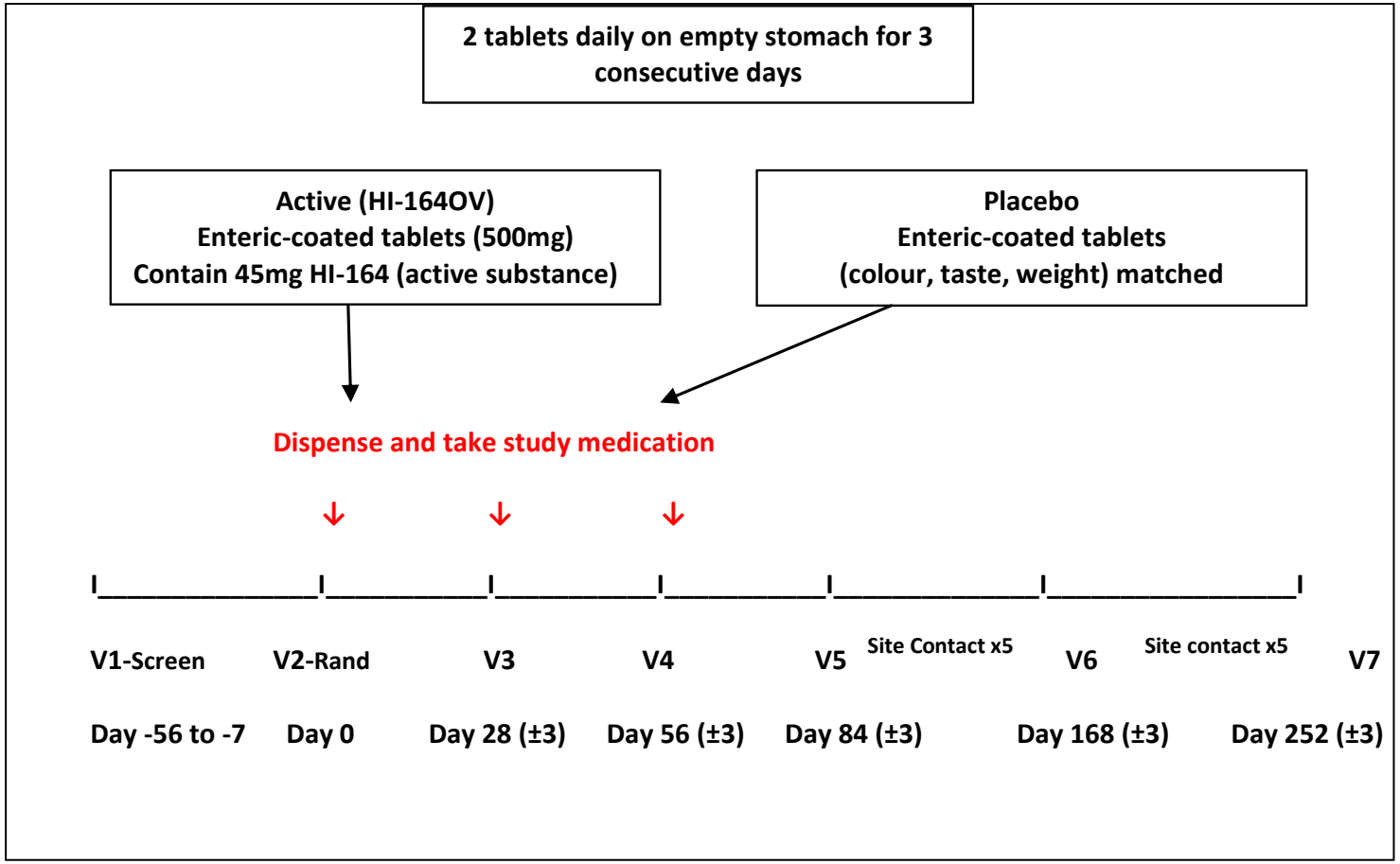
CLINICAL

HI-164 OV has a well established mechanism of action

- The oral therapeutic vaccine is an **enteric-coated tablet** containing active substance which is killed non-typeable *Hemophilus influenzae* bacteria (NTHi).
- Tablet bypasses the stomach and disintegrates in the duodenum releasing the killed bacteria which are taken up by intestinal Peyer's patches lymphoid tissue **generating an NTHi-specific immune response.**
- NTHi-specific lymphocytes then **'home' to various mucosal tissues including the lung bronchial tissue.**
- In the lung the specific T lymphocytes are re-activated by exposure to live NTHi which colonize the airways and release cytokines such as IL-17 which activates airway epithelial cells thus releasing more cytokines and these and IFNg directly recruit and **activate polymorphonuclear phagocytic cells which then phagocytose and kill bacteria.**
- By this means **bacterial flare-ups are reduced** resulting in reduction of inflammation and reduction of severity of bronchitis exacerbation



HI-164 OV – Phase 2b study design



Source: Bioxyne team analysis.

HI-164 OV – Phase 2b key findings

Phase 2b clinical study (n=320) : Did not meet 1° or 2° outcome measures
However post-hoc subgroup analysis of age group under 65 years showed

- **Significant (p <0.05) improvements in primary and secondary outcomes**
- **Placebo-like safety**

Statistical significance for primary and secondary endpoints on ITT and PP bases not achieved

Trial achieved statistically significant improvement in primary and secondary outcomes for patients < 65 years (p < 0.05)

< 65 years age group, HI-164 OV reduced number of exacerbations, and extended time to such exacerbations …

Additionally < 65 years group saw hospitalization number and duration of hospitalization were reduced …

… as well as courses of corticosteroid required for exacerbations.

Excellent safety/tolerability

Source: Bioxyne data on file.

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HI-164 OV – Key Phase 2b efficacy results in <65 year subgroup

Significant (p <0.05) improvements in primary and secondary outcomes in the < 65 years patient subgroup*

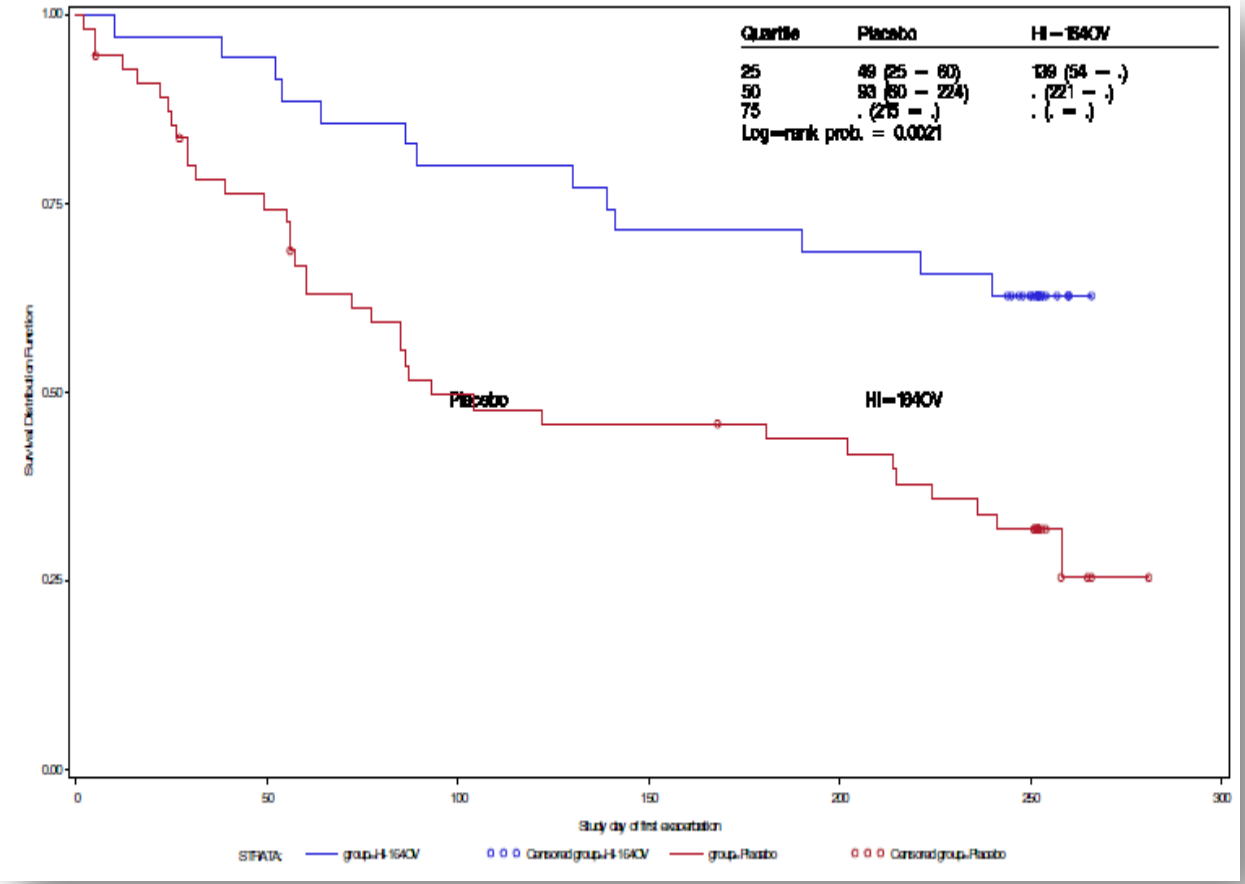
HI-H005 | Analysis in patients ≤ 64 years (N=35 Active, 56 Placebo)

Outcome metric	Events (or patients): Active/Placebo	% protection	P value
Time to first primary exacerbation (days) See K-M plot	first quartile 49/139	65	**0.0021**
Counts of acute primary exacerbations	21/72 events; (13/37 patients)	71	**0.0017**
No. courses of corticosteroid for exacerbations (mean / patient)	0.6/1.6	63	**0.038**
Days of corticosteroid use (mean days)	5.9/19.3	69	**0.0231**
Separate hospital admission count for all causes	12/37 events; (6/22 patients)	68	**0.0287**
Duration of hospitalizations for all causes (mean days)	1.63/4.02	59	**0.0326**
Separate hospital admissions for exacerbations	7/22 events; (5/12 patients)	68	0.0856
Duration of hospitalizations for exacerbations (mean days)	1.03/2.95	65	NS

Source: Bioxyne data on file.

* <65 years subgroup is a post-hoc analysis of study data

HI-164 OV – Key Phase 2b efficacy results



Source: Bioxyne data on file.

- ***Post hoc*** **analysis showed early and sustained separation of the KM curves in the < 65 years subgroup for time to first exacerbation. This subgroup analysis was not protocol specified.**
- **ITT and PP populations showed no difference for primary and secondary endpoints.**

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Phase 2a study (HI-H002) data (n=38 patients)

Outcome measure	HI-164OV (18)	Placebo (20)	% protection (p value)
Number of acute episodes per subject			
Total	1.22	1.45	16 (0.55)
Antibiotic-treated	0.83	1.15	28 (0.33)
Corticosteroid-treated	0.28	0.75	63 (0.05)
Proportion of subjects with episodes			
Total	0..72	0.65	0 (NS)
Corticosteroid-treated	0.22	0.55	56 (0.07)
Antibiotic treatment per subject			
Courses	1.00	2.4	56 (0.03)
Total days	7.6	27.2	72 (0.01)
≥ 3 antibiotic courses	0.11	0.55	80 (0.01)
Duration of episodes, mean days (range)	14.3 (3-81)	22.7 (4-74)	37 (0.01)
Hospitalizations for respiratory causes (admissions/subjects admitted)	1/1	11/7	90/86(0.04)

Source: Bioxyne data on file.

- **Efficacy data (post-hoc analysis of exacerbations requiring corticosteroids or hospitalization) from this Phase 2a study led to the choice of primary outcome measure for the Phase 2b study (study HI-H005).**
- **Safety: there was no clear indication of any differences between the treatment groups in the proportion of patients with one or more adverse events in any system organ class.**

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HI-164 OV – US Development Timeline

Drug substance (transfer from Pharmasynth to Lonza)

- Potency assay transfer, optimisation, qualification
- Transfer other specification assays
- Transfer of manufacture documentation and materials
- Scale-up to production
- GMP documentation preparation
- Engineering batch
- cGMP batches (3rd quarter 2013)

GLP Animal toxicology study – perform in last quarter 2013

Drug product (transfer from IDT Australia to international)

- International manufacturing site to be selected
- Process transfer
- GMP tablet batches (4th quarter 2013)

FDA: submit GLP toxicity, CMC and 005 study safety data 1st quarter 2014

Bioxyne has understanding of regulatory requirements in US and EU with strategy for moving forward in these jurisdictions

Source: Bioxyne team estimates.

REGULATORY

HI-164OV – Regulatory Engagement

Australia: Australian clinical studies with HI164-OV have been conducted under the TGA Clinical Trial Notification scheme (CTN) where ethics committees reviewed and approved the studies. Signed approvals were sent to the TGA together with a copy of the study protocol and TGA gave approval for studies to commence. All serious adverse events were notified to the TGA.

USA: The product is currently on clinical hold with the FDA and the following actions have been requested:

- An acceptable safety profile of a repeat-dose rat toxicology study. (protocol was submitted to FDA for review on August 19, 2011 (BB-IND No. 13,760, Serial # 0013), the Division responded with recommendations (September 27, 2011 FDA correspondence),
- Comparability of drug substance and drug product lots used in repeat-dose rat toxicology study and clinical studies HI-H005 and HI-H006. (Processes have been modified and updated to appropriate standards. Drug substance manufacture is being transferred to Lonza biotec for scale-up. Lot produced for study HI-006 will also be used for animal toxicology study.
- Improved safety data collection. (FDA requirements have been addressed in the recently completed HI-H005 study in Australia. An acceptable safety profile of HI-164OV in this study has now been demonstrated).

CHEMISTRY, MANUFACTURING, AND CONTROLS

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HI-164OV – Chemistry, Manufacturing, and Controls (CMC)

- HI-164OV is an enteric-coated tablet containing 45mg of drug substance. Drug substance is lyophilised inactivated whole cells of the bacterial species non-typeable Haemophilus influenzae strain 164 (NTHi164)
- Properties
  - Stable for appearance and potency for up to 12 months at 2-8 degrees C
  - Stable up to 1 months under accelerated conditions (25 degrees C/60% RH.
- The manufacturing process is production of drug substance by fermentation, inactivation of bacteria with formaldehyde, washing and lyophilisation. Drug substance is then combined with excipients in a tablet core which is then enteric-coated.
- HI-164OV's clinical dosage form is a tablet.
- HI-164OV is provided as 6 tablets per cycle (2 tablets per day for 3 consecutive days). Three lots of tablets are provided in total for the 3 dosing cycles based 1 month apart.
- For phase 2, the drug substance producer was Pharmasynth Ltd, and manufacturer of final tablet product was IDT Australia.

  Bioxyne is in the process of transferring drug substance manufacture to Lonza. An international drug product manufacturer is being sought.

INTELLECTUAL PROPERTY

HI-164OV – Intellectual Property

- Bioxyne is protecting HI-164OV with a multifaceted patent strategy aimed at protecting all aspects of the use of oral immunotherapy with *H. influenzae* in COPD and severe allergic asthma.
- Patents have been applied to protect the means of selection of suitable *H.influenzae* strains, the specific isolate NTHI-164, the use of HI-164OV in preventing exacerbations in COPD and the use of HI-164OV in the treatment of allergic asthma.
- One of Bioxyne's key patent relating to the NTHI-164 Isolate is based on International Patent Application No. PCT/IB2009/007303.
- Applications based on this aforementioned international application are likely to expire in about 2029, if the applications are maintained.
- All of the patents and patent applications listed in the attached Schedule (except where indicated) are currently pending and in force, although some are subject to the payment of periodic renewal fees.
- Under confidentiality, the full assembly of the IP estate will be divulged. Conversations with retained counsel to Bioxyne can be arranged.

HI-164OV – Intellectual Property

Ref	Patent Sponsor/ Company	Title	US Patent or US Publication No.	Type of Patent	Inventors
PT011	Hunter Immunology Ltd	Non Typeable Haemophilus influenzae vaccines and their uses	US20110206765 (Pub No.)	Utility	Dunkley,M., & Clancy,R.
PT008	Hunter Immunology Ltd	Composition and methods for treatment of Candidiasis	US7655248	Utility	Clancy, R., Pand, G., & Shokrallah E.
PT006	Hunter Immunology Ltd	Use of a mutant form of EtxB or CtxB to deliver an agent to a target cell wherein the mutant has GM-1 Binding activity	US7422752	Utility	Hirst, T.
PT004	Hunter Immunology Ltd	Treatment of prophylaxis of asthma	US20100150967 (Pub No.)	Utility	Dunkley, M.,, Clancy,R., Cripps ,A.,Otzyck,D.
PT001	Hunter Immunology Ltd	Oral killed vaccines and method for providing same	US7858073	Utility	Clancy,R., Pang, P., & Comans P
PT007	Hunter Immunology Ltd	Compositions and methods for treatment of mucosal infections	US20040057965 (Pub No.)	Utility	Dunkley,M., & Clancy,R.
PT0012	Hunter Immunology Ltd	Otitis Media Treatment and vaccines	Filed not published	Australian Provisional	Clancy, R.

Source: Bioxyne data on file.

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COMMERCIAL

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HI-164OV – Forecast assumptions based on 2 possible scenarios

- The commercial model has been developed with 2 scenarios.
- The first being a targeted therapeutic for the under 65 year age group.
- The assumptions driving the model include a penetration rate of 60% of moderate to severe COPD patients, this representing a conservative uptake when compared to vaccination for the influenza virus.
- The pricing model is for $US 450 per annual course of treatment in Europe and North America based upon feedback from pharmaceutical company executives, with a decreased pricing model in place for the developing countries.
- The market opportunity identified for this sub group of COPD patients is conservatively estimated to be US$ 500M peak year per year.
- When all the moderate to severe COPD sufferers are included in the financial model, and similar pricing and penetration numbers applied, this market opportunity increases to $US 1,400 M peak year sales.
- Under confidentiality, full assumptions associated with product forecasts will be shared.


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