Crohn’s Disease and MAP
Everything Old is New Again

Patrick L. McLean
August 16, 2015
Financial Disclosure


- CEO and acting Chairman of Giaconda Ltd., AU developer of an earlier formulation of RHB-104 and royalty beneficiary.
Disclaimer and Forward Looking Statements

This presentation does not constitute an offer or invitation to sell or issue, or any solicitation of an offer to subscribe for or acquire any of the Company’s securities or to participate in any investment in the Company. No representation or warranty is made to the accuracy or completeness of this presentation. You must make your own investigation and assessment of the matters contained herein. In particular, no representation or warranty is given, and the Company has no responsibility, as to the achievement or reasonableness of any forecasts, estimates, or statements as to prospects contained or referred to in this presentation.

Statements in this presentation that are not historical facts (including statements containing "believes," "anticipates," "plans," "expects," "may," "will," "would," "intends," "estimates" and similar expressions) are forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. These statements are not guarantees of future performance, are based on current expectations of future events and are subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements, including risks that we will not have sufficient working capital, that there will be delays in obtaining, or we will be unable to obtain, FDA or other regulatory approvals for our products, unable to establish collaborations, or that our products will not be commercially viable, among other risks. Additional information about the risk factors that may affect the realization of forward-looking statements is set forth in the Company’s filings with Securities and Exchange Commission, including the Company's Annual Report on Form 20-F filed on February 26, 2015. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. You should not place undue reliance on forward-looking statements as a prediction of actual results.

All forward-looking statements included in this presentation are made only as of the date of this presentation. We assume no obligation to update any written or oral forward-looking statement made by us or on our behalf as a result of new information, future events or other factors.
Where There is Inflammation, Look For Infection

- **Crohn’s disease (CD)**
  - Pathologic response to altered gut microbiota

- **RHB-104**
  - Combination antibiotic targeting *Mycobacterium avium paratuberculosis*
    - a putative cause of CD

- **Paradigm shift not unlike *H. pylori* and peptic ulcer disease**
Crohn’s Disease

- Devastating illness
- No cure
- Cause unknown
- > 1.2 million patients: N America and Europe †
- Well characterized
  - Severe abdominal pain, diarrhea, bleeding, bowel obstruction, and a variety of systemic symptoms
  - Granuloma formation

† Global data report
Current CD Therapy

- Not curative
- Focus on modulation of inflammation
  - Simply turn down the volume
Early Antibiotic Trials

- Longstanding belief CD is Johnes-like †.
- 15 Anti-TB trials in 1980’s † †.
- Some used single and others up to 4 drugs.
- *M. tuberculosis* and MAP: different antibiotic sensitivities.
- No effective Anti-Tuberculosis combination works in MAP.
- Specific Anti-MAP drugs emerged for HIV MAC epidemic.

† Dalziel T. BMJ 1913; II:1068
† † Greenstein RJ. Lancet. Infect Dis 2003; 3:507-14
Early Anti-MAP Studies

- Gui *et al.*, 1997 – 68% remission
  - Rifabutin / Clarithromycin or Azithromycin

- Douglass *et al.*, 2000 – 20/28 responded
  - Rifabutin / Clarithromycin / Clofazimine

- Shafran *et al.*, 2002 – 21/29 responded
  - Rifabutin / Clarithromycin

- Borody *et al.*, 2002 – 8/12 responded
  - Rifabutin / Clarithromycin / Clofazimine
Rationale for Triple Antibiotic Therapy for MAP

• **Mycobacterial infections in humans are complex**
  – Mycobacteria survive and persist within host macrophages as parasites

• **Effective anti-mycobacterial agents require intracellular penetration**

• **ATS/IDSA and WHO advise triple antibiotic therapy for non-tuberculosis mycobacterial disease**
Anti-MAP Therapy in Crohn’s patients – Phase II Results†

Deep colonic ulcers before anti-MAP therapy

Healing, with scarring, after 20 months on anti-MAP therapy

Extensive pseudo-polyps before anti-MAP therapy

Recovered mucosa after 20 months on anti-MAP therapy

Anti-MAP Case Study †

- 63 year old male with severe CD
  - Colonoscopy - edema, exudates, cobble stoning and ulcers
  - Refused infliximab
  - Treated with Anti-MAP therapy
    Mucosal healing and eradication of MAP

Anti-MAP Case Study †

Borody et al. 2007 - Open Label Phase II Subset Analysis†

CD patients with high CDAI (n=22)

* p<0.0001, compared with pre-treatment values

Mean CDAI Score

Treatment Period

David has been on AMAT and in remission since 1996
Rationale for RHB-104 Triple Antibiotic Treatment of CD

- Rifabutin, clarithromycin, and clofazimine active against *Mycobacterium avium complex* (MAC)
  - *M. avium paratuberculosis* (MAP) is a subspecies of MAC
  - All active intracellularly

- Current CD therapies have some anti-MAP activity

- Previous clinical experience
  - All clinical efficacy studies in CD have included “all comers”
  - RHB-104 is intended for all CD patients
MAP US First Phase III Study Dose Escalation - Ongoing

Individual Capsule Components of RHB-104:

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>95mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>45mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td>10mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weekly Dose Escalation</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active &amp; Placebo Arms</td>
<td>1 capsule bid</td>
<td>2 capsules bid</td>
<td>3 capsules bid</td>
<td>4 capsules bid</td>
<td>5 capsules bid</td>
</tr>
</tbody>
</table>

Target dose in Active Arm:
- Clarithromycin - 950 mg
- Rifabutin - 450 mg
- Clofazimine - 100 mg
To determine whether the % of patients who experience at least one relapse of Crohn’s Disease between weeks 16-52 given proven remission at week 16, was significantly different between those treated with anti-paratuberculosis therapy (APT) or placebo.

Pfizer Study Showed Strong Signs of Efficacy

Original Study Relapse Endpoint
Skewed denominator at week 16

213 Patients (100%)

Active Arm: 102 Active + prednisolone
- Remission: 66% (67/102) \( p = .017 \)
- Relapse: 39% (26/67) \( p = .054 \)

Placebo: 111 Placebo + prednisolone
- Remission: 50% (55/111)
- Relapse: 56% (31/55)

Patients not in remission excluded from study

16 Weeks
- Remission: 66% (67/102) \( p = .017 \)
- Relapse: 39% (26/67) \( p = .054 \)

52 Weeks
- Remission: 50% (55/111)
- Relapse: 56% (31/55)

104 Weeks
- Remission: 43% (12/28)
- Relapse: 43% (12/28)

† Phase III study conducted by Pharmacia for Australian approval and published by Selby et al (2007), Gastroenterology 132:2313-2319.; Reanalysis published by Behr and Hanley (2008), Lancet Infectious Diseases 8:344. including all subjects randomized at the beginning of the study, disregarding any occurrence following randomization.
Pfizer Study Showed Strong Signs of Efficacy

Original Study Relapse Endpoint †
Skewed denominator at week 16

Remission Endpoint Reanalysis ††
Randomized denominator at time 0

<table>
<thead>
<tr>
<th></th>
<th>Active Arm</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>213 Patients</td>
<td>(100%)</td>
<td>213 Patients</td>
</tr>
<tr>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
</tr>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>+ prednisolone</td>
<td>+ prednisolone</td>
</tr>
<tr>
<td></td>
<td>102</td>
<td>111</td>
</tr>
<tr>
<td>Patients not in remission excluded from study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Remission: 66% (67/102) p = .017
Relapse: 39% (26/67) p = .054
Relapse: 24% (10/41) p = .14

Remission: 50% (55/111)
Relapse: 56% (31/55)

16 Weeks

Remission Endpoint Reanalysis

<table>
<thead>
<tr>
<th></th>
<th>Active Arm</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>213 Patients</td>
<td>(100%)</td>
<td>213 Patients</td>
</tr>
<tr>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
</tr>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>+ prednisolone</td>
<td>+ prednisolone</td>
</tr>
<tr>
<td></td>
<td>102</td>
<td>111</td>
</tr>
</tbody>
</table>

Remission: 66% (67/102) p = .017
Relapse: 40% (41/102) p = .003
Relapse: 30% (31/102) p = .005

16 Weeks

† Phase III study conducted by Pharmacia for Australian approval and published by Selby et al (2007), Gastroenterology 132:2313-2319.; †† Reanalysis published by Behr and Hanley (2008), Lancet Infectious Diseases 8:344. including all subjects randomized at the beginning of the study, Disregarding any occurrence following randomization
Pfizer Study Data Could Have Compared Favorably to Remicade®

Remission Endpoint Reanalysis (from Pfizer PIII Australian study)

Remicade® ACCENT I†

Response at 2 Weeks

59% (113/192)

Remission At 30 Weeks

39% (44/113) All subjects = 23% (44/192)

Remission At 54 Weeks

28% (31/113) All subjects = 16% (31/192)

Separate trials; Theoretical comparison

213 Patients (100%)

Active Arm

Placebo + prednisolone

102 Active + prednisolone

66% (67/102)

p = .017

50% (55/111)

111 Placebo + prednisolone

40% (41/102)

p = .003

22% (24/111)

30% (31/102)

p = .005

14% (16/111)

Remission at 16 Weeks

Remission at 52 Weeks

Remission at 104 Weeks

† Hanauer et al, (2002), The Lancet 359: 1541-1549. study similar to the reanalysis conducted by Behr and Hanley
RHB-104 MAP US First Phase III Study - Ongoing

- Multi-center, randomized, double-blind, placebo-controlled, parallel group study
- 270 moderate to severe CD subjects randomized 1:1
- CDAI score of ≥220 and ≤450 at baseline
- Add-on to 5-ASA, immunomodulators, steroids, selective biologics
- Up to 120 sites in US, Canada, Israel, Australia, New Zealand, and selected EU countries
- Primary endpoint
  - Remission at 26 weeks
- Lead investigator – Prof. David Graham MD
- Clinicaltrials.gov search Crohn’s disease, Anti-MAP, RHB-104
Additional Study Endpoints

• Secondary and exploratory endpoints include:
  – Maintenance of remission through week 52
  – Time and duration of remission/response
  – CRP and fecal calprotectin

• Efficacy outcome measures in relation to MAP
• Health related quality of life using IBDQ and SF 36
• Steroid discontinuation
• Safety
• Population PK
• CDEIS
• Validation of MAP assay
Conclusions

- *H. pylori* was strongly associated with ulcers
- Eradicating *H. pylori* is proven to treat ulcers
  - *H. pylori* association is causal
- MAP and CD are strongly associated
- If anti-MAP therapy treats CD and eradicates MAP, we will have proven the association is causal
Questions?