

Protocol #1310-1263

Recombinant DNA Advisory Committee (RAC)

December 5, 2013

Presenters:

- Dr. William J. Sandborn, MD (Study PI)
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- Dr. Bernard Coulie MD PhD
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- Dr. Pieter Rottiers PhD
Vice President R&D, ActoGeniX
- Dr. Lothar Steidler PhD
Vice President Technology, ActoGeniX

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Responses to Questions from RAC reviewers

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Please note that at time of IND submission to FDA, all reports will be available and can be shared with any of the RAC-OBA personnel upon request under confidentiality

AG014 – Rationale

Mucosal delivery and neutralization

Evidence for improved efficacy/safety

- TNF-alpha expressed mainly in gut of IBD patients
- Evidence that administered *L. lactis* is present in inflamed gut tissue
- Active delivery of anti-TNF-alpha at the site of inflammation
- No systemic exposure to anti-TNF-alpha
 - No evidence for immunogenicity
 - No risk for systemic opportunistic infections
 - Overall improved safety profile

Summary Overview of AG014

- Active principle: anti-TNF-alpha Fab (certolizumab) locally secreted by *L. lactis*
- *L. lactis* resistant to bile and other noxious conditions in the GI tract (trehalose accumulation)
- Current capsule formulation designed to release *L. lactis* in terminal ileum
- Pharmacodynamic (PD) studies with surrogate strain demonstrated efficacy in different colitis mouse models
- Pharmacokinetic (PK) studies demonstrated exposure in ileum & colon
- Repeat Dose Toxicity (RDT) studies demonstrated no treatment related toxicity
- Safety pharmacology in animal models demonstrated no bacteremia/sepsis or shedding of the expression cassette

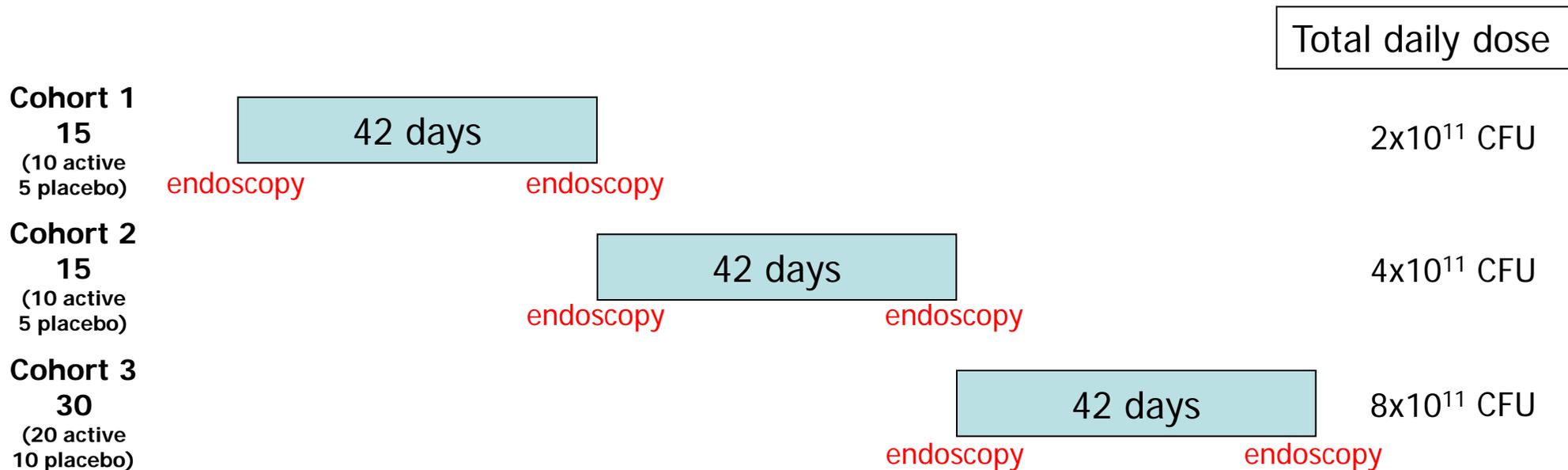
Summary Overview of AG014

Clinical development:

- A single-center, open-label Phase 1 study to assess safety, medical endoscopic sampling methodology and to characterize the PK of AG014 in Healthy Subjects (Europe)
- A Phase 2a, randomized, multi-center, double-blind, placebo-controlled, sequential dose escalation study to assess the safety, tolerability, PK and PD of AG014 administered orally in subjects with Moderate to Severe Active Ulcerative Colitis (UC)
- Exploratory efficacy data will also be collected
- Pre-IND meeting with CBER/FDA on June 13th, 2013

AG014 – Phase 2a study design

AG014 – Phase 2a study design



DSMB safety/tolerability assessment

From one Cohort to the Next: Upon 42 day treatment completion of all 15 subjects

→ If OK, dose escalation to the next level (in addition to timely monitoring of adverse events)

Staggered approach: in each cohort, every single subject of the first 6 subjects will be dosed for 7 days consecutively before the next subject can be dosed

Phase 2A Q&A (1/2)

*To Full Study
Design*

- Inclusion/Exclusion criteria
 - No inclusion of teens (≥ 18)
 - Mayo Clinical Score 6-12: interferes with QoL, accepted to define UC pts for studies evaluating biologicals
 - Surgery: ileocollectomy and pouch procedures to treat active disease carry high morbidity and high complication rates
- Stopping rule
 - Clinical sepsis determined by one positive blood culture/ PCR attributable to sAGX0354: study stop
 - Symptoms suggesting clinically significant bacteremia attributable to sAGX0354 as determined by 3 consecutive blood cultures: stop treatment for the subject
- Concomitant medication
 - Prednisone, or equivalent glucocorticoid (≤ 20 mg/day) is acceptable as follows:
 - a. Minimum dosing period of 4 weeks prior to screening, AND
 - b. Stable dose for 2 weeks prior to screening, AND
 - c. Expected to remain on a constant dose during this study
 - Stable dose steroids will not confound the analysis, steroids routinely co-administered with systemic TNF blockers: side effect data will be interpretable during analysis
 - Oral MMX-budesonide not excluded: 6 mg of MMX-budesonide equivalent to 20mg prednisone.

Phase 2A Q&A (2/2)

- No combination therapy with systemic anti-TNF-alpha
 - AG014 developed as stand alone therapy: safe and effective alternative to systemically administered anti-TNF-alpha
 - Systemic treatment with certolizumab (Cimzia) is confounding variable in assessment of safety and tolerability of AG014
- Outcome clinical trial evaluating Cimzia for IBD – December 2013:
 - Full data set will not be public
 - Except for mode of action, AG014 has different product profile (formulation, drug substance, oral administration, dosing frequency, local delivery, PK profile etc.).
- Other protocol considerations
 - Protocol will be adapted to include serum pregnancy testing only
 - No psychological support, follow up or cross group controlled component is planned (early phase, small sample size and relatively short treatment)
 - Evaluation on impact of home environment in this early phase study is not planned.
 - Blood, colon biopsy and fecal samples will be collected to analyze levels of a broad range of biomarkers

Informed Consent Form

- Upon completion of the study and in line with the regulatory requirements, anonymized information pertaining to the communication on the outcome of the study will be made publicly available in the form of
 1. A summary on the relevant Clinical Trials Registers & related websites such as www.clinicaltrials.gov and/or EudraCT Register <https://www.clinicaltrialsregister.eu>
 2. Information pertaining to the notification of the End Of study to NIH-RAC.

Safety – Past experience

AG011 and AG013- Safety Summary

AG011 (moderate to severe UC)

- Generally safe and well tolerated
- Most frequently reported event: worsening UC
- SAEs in 3 (7.5%) AG011 treated and 2 (10.0%) placebo treated subjects (AG011: all 3 experienced worsening of UC, placebo: 1 worsening of UC with secondary anemia and 1 thrombocytopenia post-treatment)
- No clinically relevant changes in laboratory results
- No systemic exposure of hIL-10 or immunogenicity towards hIL-10

AG013 (oral mucoitis in head&neck cancer patients receiving triple chemo)

- Generally safe and well tolerated
- AE profile of AG013 similar to that of placebo
- Most frequently reported events in the phase 1b: nausea, oral pain, fatigue, diarrhea and mucosal inflammation
- 4 subjects experienced SAEs (none attributed to IMP) in phase 1b: (2 febrile neutropenia, 1 nausea, abdominal pain, dehydration and 1 pyrexia)
- No sepsis from AG013 bacteria
- No clinically relevant changes in laboratory results
- No systemic exposure to live AG013 bacteria nor to hTFF1

Worsening of colitis - Conclusions

- Trend towards increased number of reported AEs “worsening of colitis” in AG011 vs placebo-treated group
 - 50% of these AEs in the AG011 group are classified as unlikely or not related to study medication
 - There is no dose-dependency
- Worsening of colitis cannot be substantiated by
 - Increase in endoscopic colitis scores or,
 - Increase in histological colitis scores

AG011 and AG013- Safety Summary

AG011 (moderate to severe UC)

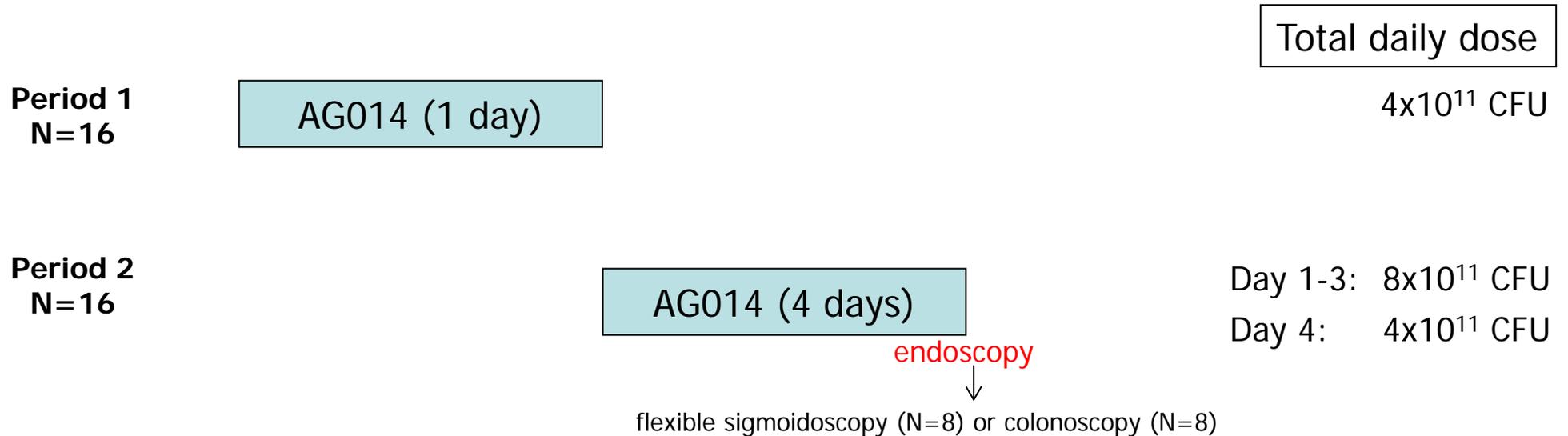
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Phase 1 Healthy Volunteers

AG014 – Phase 1 study design



Period 1:

- safety and PK of AG014 orally administered once
- measure time of capsule disintegration (serum marker)
- define intersubject variability and range for PK

Period 2:

- safety and PK of AG014 orally administered for 4 days
- impact of bowel preparation for endoscopy on the PK profile of AG014

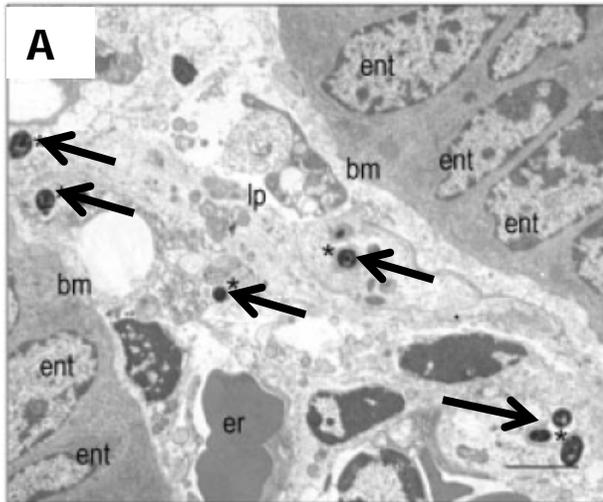
Preclinical & Product characteristics

Overview Q&A

- Efficacy was demonstrated with surrogate *L. Lactis* anti-mTNF-alpha strain
 - No humanized colitis model available
- Non-GLP RDT study demonstrated no treatment related toxicity
 - Colitis model using surrogate *L. lactis* secreting anti-mTNF-alpha acknowledged by FDA & EMA
 - Non-GLP status is acknowledged by FDA & EMA
 - All preclinical (PK, PD and RDT) studies were conducted following the GLP-considerations as much as possible
 - Final report of RDT study will be overseen by QA unit/person
- Safety pharmacology data available
 - No evidence for shedding of expression cassette
 - No evidence for sepsis/bacteremia after IV administration
- *L. lactis* certolizumab displays full biological activity
- MoA: mucosal delivery and neutralization
 - Evidence that *L. lactis* get trapped and reside in inflamed gut tissue
 - Active delivery of anti-TNF-alpha at the site of inflammation
 - Reducing gut inflammation may control circulating TNF-alpha

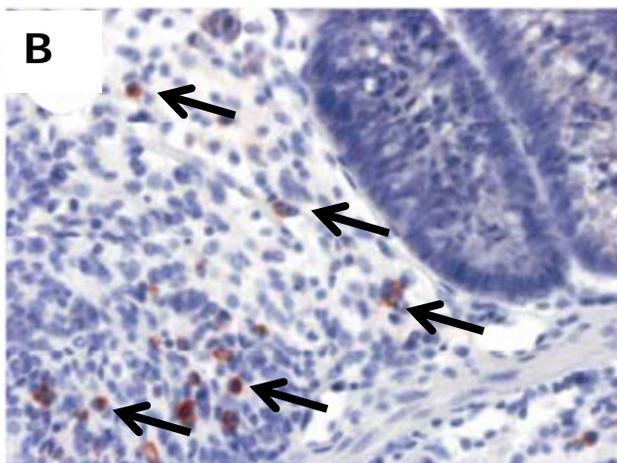
AG014 – Mucosal delivery and neutralization

Inflamed gut mucosa (mice)



(A) *L. lactis* get trapped and reside in inflamed gut tissue

L. lactis (arrow) in a strip of lamina propria (lp) between 2 crypts (ent: enterocytes, bm: basement membrane, er: erythrocytes)



(B) Active delivery of protein at the site of inflammation

Anti-TNF-alpha (arrow) associated with the surface of lamina propria cells, especially in eroded zones of the mucosa with dominant inflammatory infiltrate

Containment of GM *L. lactis*

- All spillage should be decontaminated with detergent or bleach
- Decontamination acts independently and in surplus of the inherent environmental containment system