A study of the cytokine-cytomonocys MIA model

A. A collaged induced arthritis model in cyorhinogous monkey was employed to demonstrate the potential immunogenic effects of ALX-0761 on the development of arthritis.

- At the end of the arcalimation period, the animals were stratified on the following study groups based on body weight: ALX-0761 was administrated prophylactically by two different routes: IL-17a and IL-12 were injected at the same time, 3 times weekly, starting on the 8th day of the first immunization. All groups consisted of 10 individuals.

- The cyorhinogous monkeys were immunized twice with bovine collagen type II in presence of Freund's complete adjuvant to induce an arthritic disease mimicking human RA.

- As passive control, isocontrol (IV administration, 30mg/kg) was included in the study.

- Immunoassays to exclude systemic infection. Only data of adequately exposed animals (i.e., within 3-fold exposure of that predicted based on single-dose) are reported in the present, i.e., in all the two-cytomonocys treated groups and in the isocontrol/treatment group. The vehicle was comprised of Emulsol.

B. ALX-0761: A Nanobody that targets both IL-17A and F

- The therapeutic effect of ALX-0761 on arthritic arthritis was evaluated by the measurement of arthritic score of the joints. Key-examination scores of the affected joints, general condition score, anacrine-protein (CPR) concentrations and body weight. In addition, total body weight (IL-17A and IL-12) and exploratory pharmacodynamic biomarkers (IL-6, -15, TNF-α and MMP-3) were evaluated.

- ARX-0761 and the arthritic score of the arthritic animals total. the sum of the swelling scores of the 64 individual joints (as depicted in grams), with a maximal score of 230 per animal.

- A risk developed in vehicle-treated rats and variably developed in IL-17a-treated rats with ALX-0761 treatment.

Methods and Results: I: X-ray scores A and B

- X-ray Images of the depicted joints of the hands and feet were taken with an X-ray TV system.

- KL score represents the total number of band scores per animal in which narrowing of joint space was not seen on the radiographic surface. The maximal score is 48.

- In the vehicle group, progressive joint space narrowing (KL-score A) and bone erosion (KL-score B) scores were observed over time.

- Statistically significant decreases were detected on day 56 in IL-64A group 3.8 mg/kg ALX-0761 (p<0.0001) and p<0.001 respectively, compared with the vehicle group.

- In the vehicle group, IL-64A group, and vehicle 3.8 mg/kg ALX-0761, the IL-17a, IL-12, and IL-64A levels were significantly higher compared with the vehicle 3.8 mg/kg IL-17a, IL-12 and vehicle group.

- IL-64A and IL-12 levels were recognized in all IL-6, IL-15, IL-17A as well as MMP-3 levels within the disease the IL-6 was significant, IL-15, IL-17A treatment with those findings were not statistically significant.

Methods and Results: II: General condition score, CRP, and body weight

- The general condition score evaluates the mobility and body position of the animals on a scale of zero to 28, with 28 indicating normal weight and of display of an abnormal behavior.

- CRP was measured in serum with a latex turbidimetric immunoassay.

- The mean value was determined throughout the study using an electronic balance.

- In the vehicle group, the general condition worsened from day 20 onwards. Overall, the differences in mean values between the maximal condition index observed was three on a scale of five. Count, body weight dropped in this group. Likely due to muscle wasting and IL-64A levels increase, reflection of the ongoing inflammation during establishment of the disease.

- Towards ALX-0761 administration alleviated the general condition index score compared to non-treated animals but did not achieve statistical significance in either of the two doses. Similarly, the change in body weight did not achieve statistical significance in the ALX-0761 treated group and the average levels of CRP were lower in ALX-0761 treated groups but did not reach statistical significance.

Conclusions

- IL-64A and 3 mg/kg IL-12 resulted in a significant decrease in CRP levels and body weight compared to vehicle group, suggesting that IL-6, IL-15, IL-17A, IL-12 treatment with those findings were not statistically significant.

- IL-64A significantly improved KL score in the vehicle and the arthritic animals. The x-ray score and the arthritic score. A beneficial effect on the general condition score, x-ray score A, CRP levels and body weight support these findings although no statistical differences could be determined.

- A trend towards reduction of IL-6, IL-15, IL-17A, and IL-12 was observed at varying times in the ALX-0761-treated groups.

- No dose-dependency could be established for ALX-0761 suggesting that targeting IL-6 was barely during both regimens.

Preclinical Study of ALX-0761, a Nanobody® Neutralizing Both IL-17A and F in Cynomolgous Monkey Collagen Induced Arthritis Model

Katrien Vanheusden1, Laurent Delattre2, Alex Henneryck2, Alain Vicari3, Roland Grenninglöf4, Sofie Poelmans5, Heidi Wouters3 and Thomas Stöhr1

1Abylnx NV, 2Calypso Biotech, 3EMO Serono

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