# CLINICAL STUDY REPORT

# Addendum 17.2 Efficacy Summary Follow-up

## A Randomized, Placebo-Controlled, Phase IIb Dose-Finding Study of CYT003-QbG10, a TLR9-Agonist, in Patients with Moderate to Severe Allergic Asthma not Sufficiently Controlled on Current Standard Therapy (GINA Steps 3+4)

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|---|---|
| Trial Number: | **CYT003-QbG10 12** |
| EudraCT number: | 2012-003070-39 |
| Study Dates: | FPFV: 14 Oct 2012 LPLV on Day of Premature<br>Screening: 14 Oct 2012 Study Termination: 14 Apr 2014<br>1st injection: 28 May 2013 |
| Investigational Product: | CYT003-QbG10 (CYT003) |
| Indication Studied: | Persistent Allergic Asthma |
| Development Phase: | Phase IIb |
| Study Design: | Randomized, placebo-controlled, parallel-group, multicenter, dose-finding, efficacy, pharmacodynamic and safety study |
| Sponsor: | Cytos Biotechnology AG, Wagistrasse 25<br>CH-8952 Schlieren, Switzerland |
| Legal representative in EU: | Clinical Technology Center (International) Limited,<br>Granta Park, Great Abington, Cambridge<br>Cambridgeshire CB21 6GQ, United Kingdom |
| Principal Investigator: | PD Dr. Thomas Casale<br>American Academy of Allergy Asthma and Immunology<br>University of South Florida<br>12901 Bruce B Downs Blvd, MDC19, Tampa, FL 33612<br>USA |
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| Biostatistics: | Tony Wu, Ph.D. Lead Biostatistician, Biostatistics, PPD |
| Authors: | J. Willers, A. Hammann, L. Trokan, M. Zimmermann, J. Klisic, P. Martin, C. Lassen<br>Cytos Biotechnology AG, CH-8952 Schlieren, Switzerland |
| GCP Statement: | This study was performed in compliance with the ICH-GCP |
| Version Number: | Final |
| Release Date: | 11-Aug-2014 |
| Replaces Version of: | - - - - - - |

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# 3 Investigational Plan

The study consisted of 3 distinct phases, i.e., Screening/Run-in, Treatment, and Follow-up phases, involving a total of 15 ambulatory visits per patient (Figure 9.1-1), from screening visit to end of study.

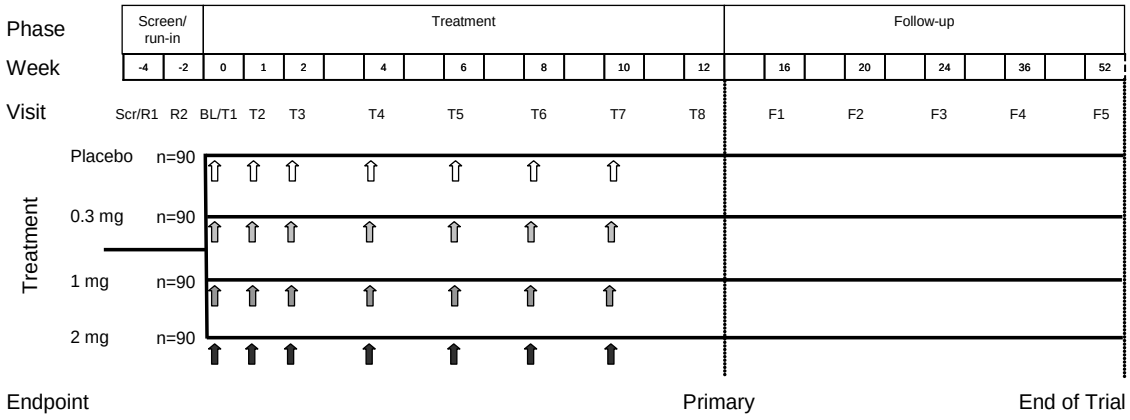


**Figure 3-1 Study Overview**

Injections of CYT003 (0.3, 1.0 or 2.0 mg) versus placebo, weekly for the first 3 weeks, were given at baseline visit (BL/T1) and at weeks 1, 2, 4, 6, 8, and 10. Visit Windows were ±3 for Visit R2 and Visit T4 to T8, ±1 for Visits T2 and T3, and ±7 for Visits F1 to F5 Scr = screening visit, R1-R2 = run-in visits, BL = baseline visit, T1-T8 = treatment visits, F1-F5 = follow-up visits

**Follow-up Phase** was planned as a 9-month phase with on-site visits at months 4, 5, 6, 9 and 12. Each patient was followed with standard “step-up” or “step-down” in therapy as indicated by the clinical status and according to local current medical practice. The study was prematurely terminated mid of April 2014 when most of the patients had finished the 6-months follow-up visit (i.e. Visit F3).

# 4 Asthma Control Questionnaire (ACQ)

The ACQ scores during follow-up between week 12 and week 24 do not reveal any significant changes between the active treatment groups and placebo.

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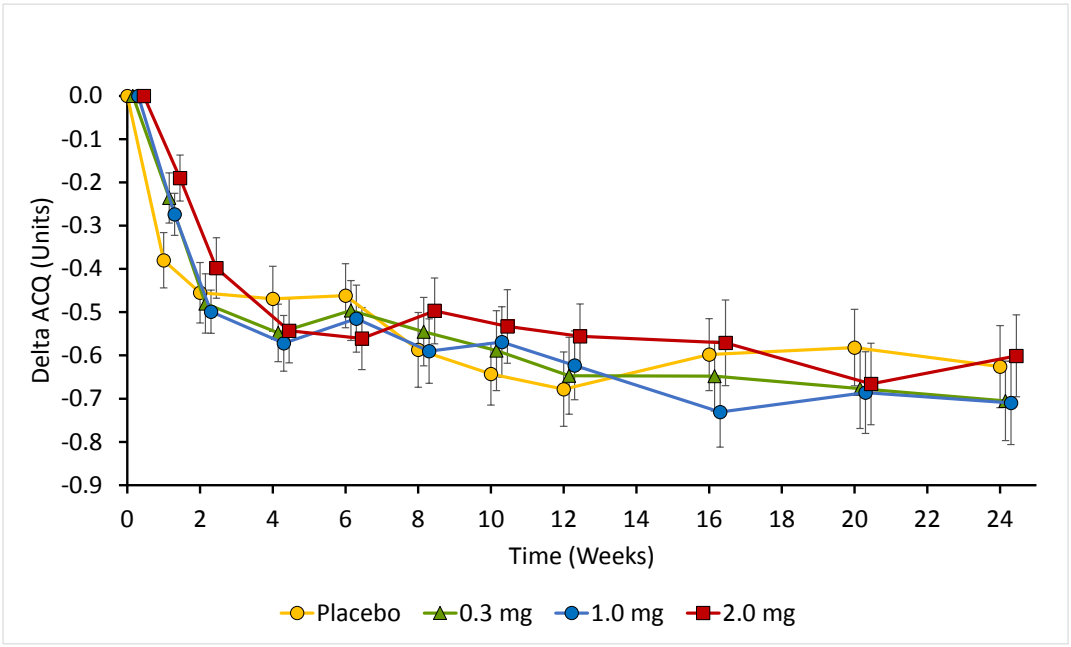


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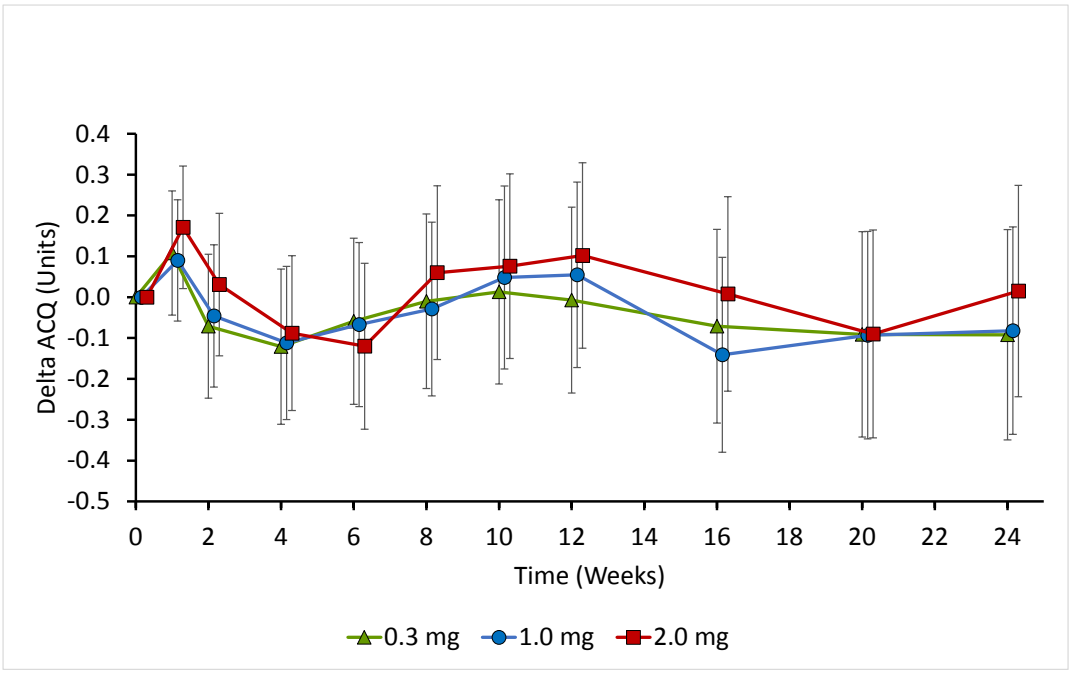


**Figure 4-1 ACQ Score – Change from Baseline at all Time Points**

Panel A: The curves represent the mean (±SEM) of the change in ACQ at each time point over 6 months. Only observed values of the FAS are considered. ACQ scores could vary from 0 to 6. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: The curves represent the LS mean and 95% CI of the change in ACQ at each time point over 6 months, where the active treatment groups are compared to placebo of the FAS population without LOCF. [Source: Table 14.2.4.1 up to Month 6]

ACQ scores below 1.5 indicate that the asthma is at least “partially controlled”. Since an ACQ score of 1.5 or higher was a prominent criteria for inclusion, every patient who reported lower scores at a later time point experienced an improvement in asthma. The figure below presents the percentage of patients whose asthma is partially controlled during 6 months.

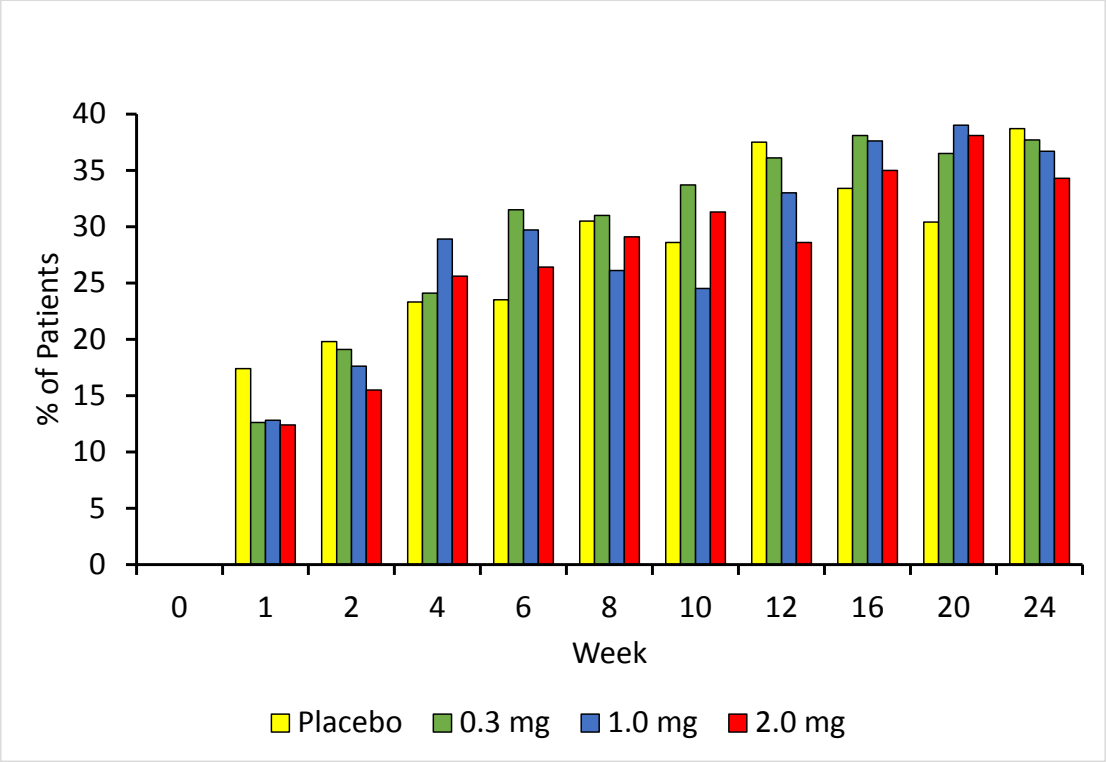


**Figure 4-2 ACQ Score – % of Patients with ACQ < 1.5**

The columns represent the percentage of patients with at least "partially controlled" asthma at each time point up to 6 months. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.4.3 up to Month 6]]

Patients with different cultural background may answer the questionnaire differently. In order to take such potential cultural differences into consideration a subgroup analysis was performed where the participating countries are grouped into three regions. A drop of ACQ scores is seen in all regions and in all treatment groups. No significant differences can be observed.

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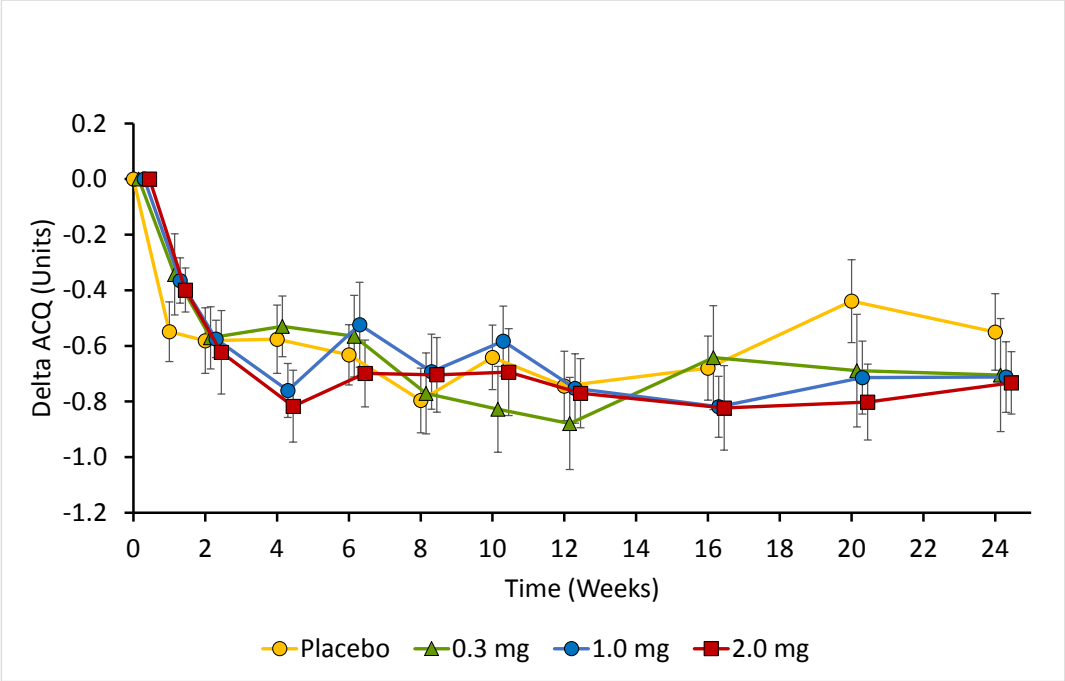
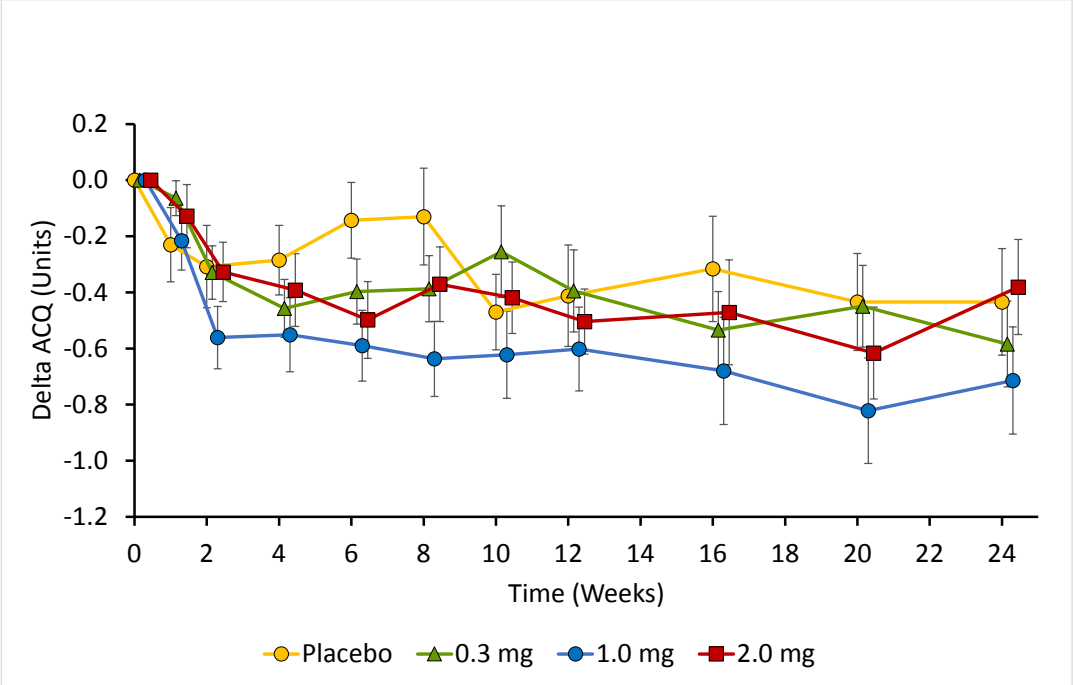

0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
Delta ACQ (Units)
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Weeks)
Placebo
0.3 mg
1.0 mg
2.0 mg

B


0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
Delta ACQ (Units)
0
2
4
6
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14
16
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22
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Time (Weeks)
Placebo
0.3 mg
1.0 mg
2.0 mg

C

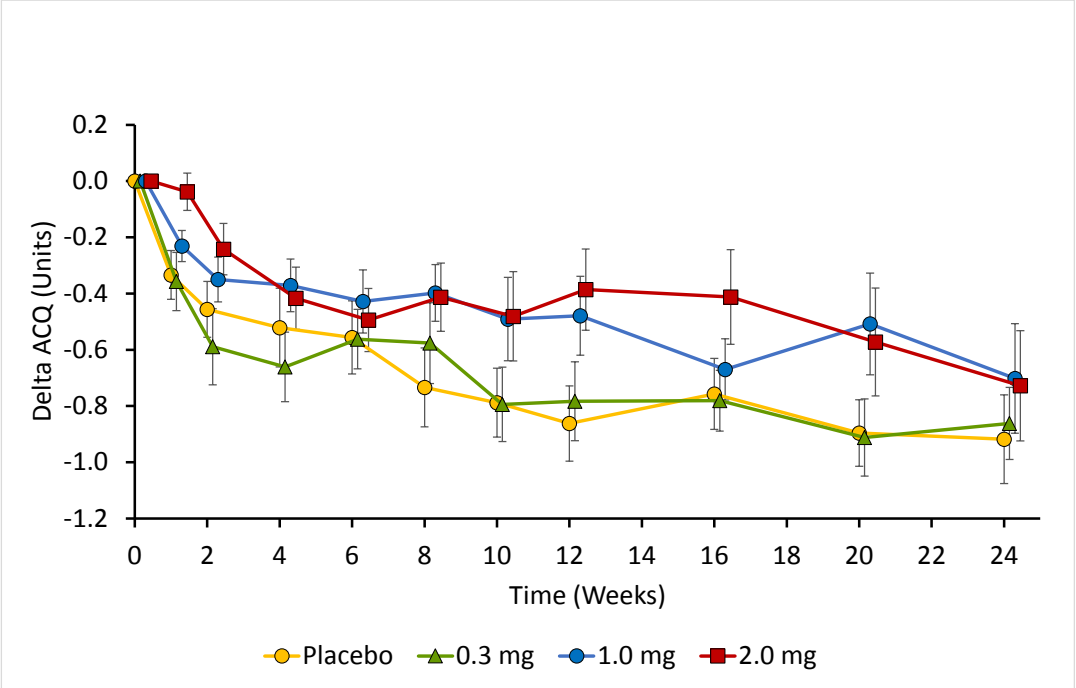


**Figure 4-3 ACQ – Change from Baseline – per Study Region**

Panel A: Patient subgroup from study region A (USA). The curves represent the mean (±SEM) of the change in ACQ score at each time point over 6 months. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: Patient subgroup from study region B (Germany, Israel, Czech Republic, Hungary). The curves represent the mean (±SEM) of the change in ACQ score at each time point over 6 months. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel C: Patient subgroup from study region C (Ukraine, Russia, Poland). The curves represent the mean (±SEM) of the change in ACQ score at each time point over 6 months. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10. [Source: Table 14.2.13.1 up to Month 6]]

# 5 Forced Expiratory Volume in One Second (FEV1)

As part of the ACQ, the forced expiratory volume in one second (FEV1) has been analyzed separately as well. After initial increase over the first 4 weeks in all treatment groups the volumes dropped again and continued with no clear trend between 0mL and 100mL volume improvement until months 6.

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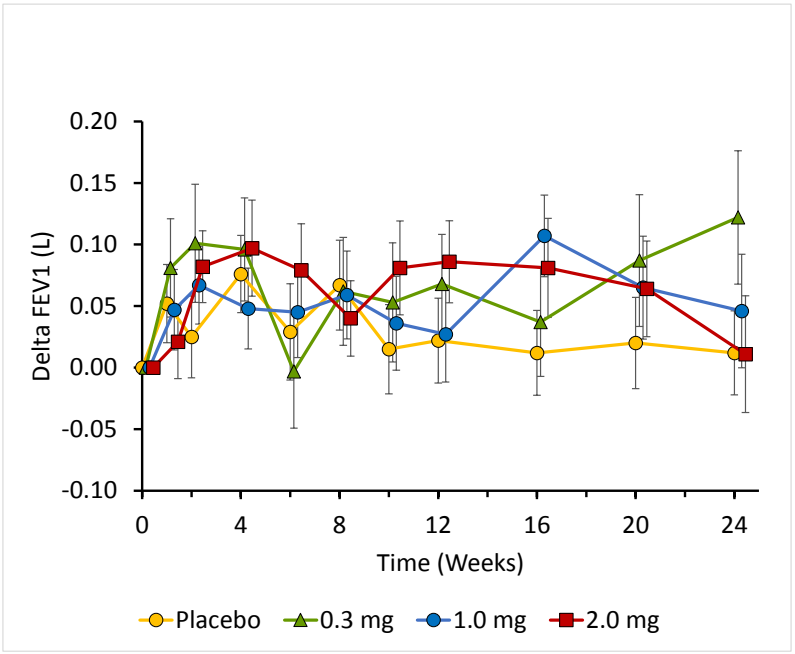


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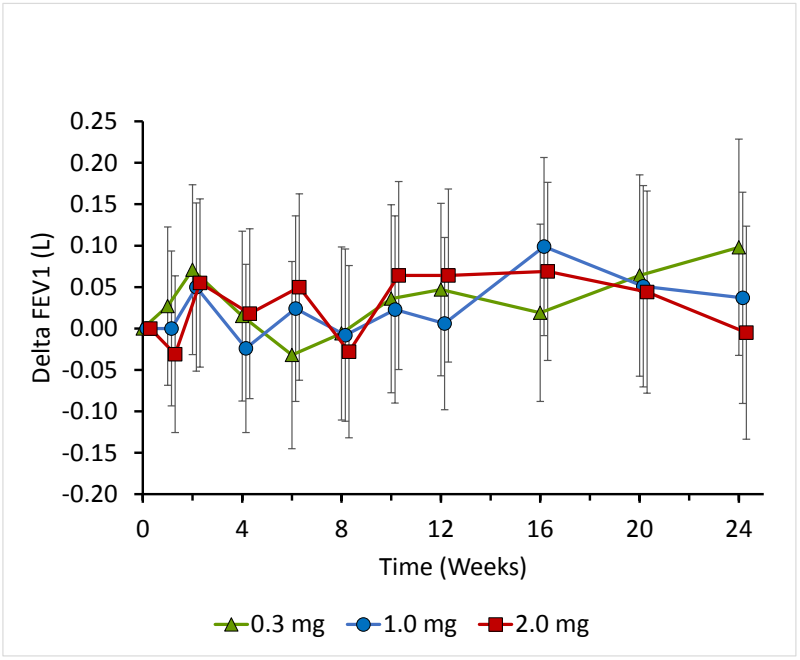


**Figure 5-1 FEV1 – Change from Baseline at all Time Points**

Panel A: The curves represent the mean (±SEM) of the change in FEV1 (in liter) at each time point over 6 months. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: The curves represent the LS mean and 95% CI of the change in FEV1 (in liter) at each time point over 6 months, where the active treatment groups are compared to placebo of the FAS population without LOCF. [Source: Table 14.2.5.1 up to Month 6]]

When looking at FEV1 in % predicted the same picture can be observed as for absolute values in liter.

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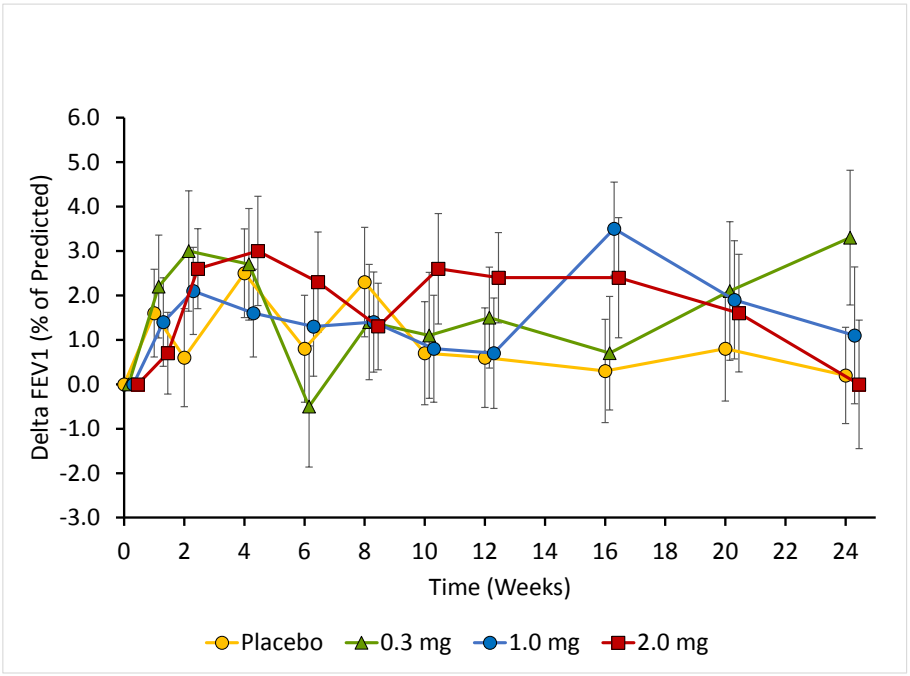


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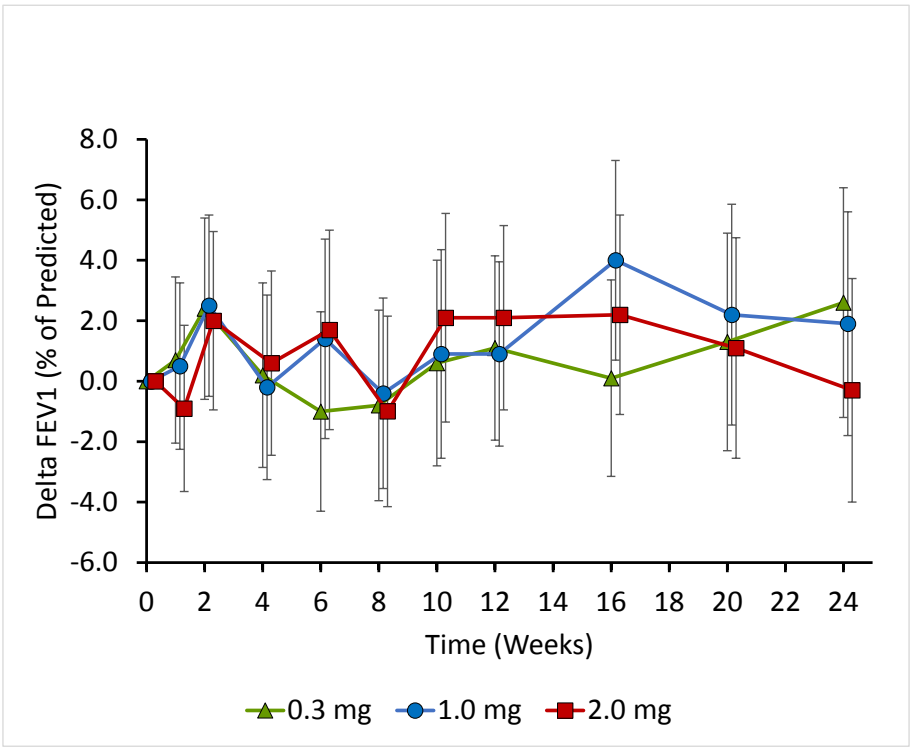


**Figure 5-2 FEV1 (% of Predicted) – Change from Baseline**

Panel A: The curves represent the mean (±SEM) of the change in FEV1 (in % predicted) at each time point over 6 months. Only observed values of the FAS are considered. Study drug injections were given at baseline visit and at weeks 1, 2, 4, 6, 8, 10.

Panel B: The curves represent the LS mean and 95% CI of the change in FEV1 (in % predicted) at each time point over 6 months, where the active treatment groups are compared to placebo of the FAS population without LOCF. [Source: Table 14.2.5.3 up to Month 6]]

# 6 Conclusion

The primary efficacy outcome parameter (change from baseline in ACQ score) revealed a strong placebo effect. Compared to the ACQ the treatment effect on FEV1 as secondary outcome parameter was less dominant. Again, a positive response was seen for active and placebo treated patients within the first weeks, then the FEV1 values returned more or less to baseline values. This picture was similar for all other investigated secondary outcome parameters, such as MiniAQLQ, eosinophils, FeNO. It has to be taken into consideration that during the follow-up phase of the study (from week 12 onwards) the patients could step-up or step-down with their standard controller medication and could change the use of LABA according to their medical need.