



Omalizumab in patients with allergic (IgE-mediated) asthma and IgE/bodyweight combinations above those in the initially approved dosing table

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ARTICLE INFO

Article history:

Received 8 November 2013

Received in revised form

6 March 2014

Accepted 10 March 2014

Available online 18 March 2014

Keywords:

Omalizumab

PK/PD

IgE

Bodyweight

ABSTRACT

Background: When first approved in the European Union (EU), the omalizumab dosing table had upper bodyweight and IgE limits of 150 kg and 700 IU/mL, respectively. In this study, we assessed the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of omalizumab in patients with IgE/bodyweight combinations above those in the original dosing table.

Methods: A multicentre, open-label, parallel-group study assessed the safety, PK and PD of omalizumab in 32 patients with mild-to-moderate allergic (IgE-mediated) asthma. Patients received two subcutaneous injections of omalizumab at one of three dosage levels (450, 525, or 600 mg), chosen according to baseline IgE (300–2000 IU/mL) and bodyweight (40–150 kg), with a 14-day interval between injections.

Results: Overall, 69 adverse events (AEs), none of them serious, were reported by 26 (81.3%) patients. Analysis of laboratory measurements, vital signs and ECG data revealed no adverse findings of clinical relevance. The PK profile was consistent with previous data for lower doses. Mean maximum decrease of free IgE from screening was $\geq 99\%$ for all three doses, and mean free IgE concentrations remained < 25 ng/mL for at least 2 weeks after the second dose. The reductions in free IgE were consistent with levels previously associated with clinical improvements.

Conclusions: The safety and PK/PD findings from this study are consistent with previous data, and supported the extension of the omalizumab dosing table to include those patients with higher IgE/bodyweight combinations.

Clinical trial registry and registration number: clinicaltrials.gov (NCT00546143).

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1. Introduction

Omalizumab is a humanised, monoclonal anti-immunoglobulin E (IgE) antibody, given by subcutaneous (s.c.) injection, that

specifically targets and binds free IgE, reducing levels of free IgE, while also inhibiting the binding of IgE to the high-affinity IgE receptor [1]. In the European Union (EU), omalizumab is approved as add-on therapy for the treatment of patients (age ≥ 6 years) with severe persistent allergic (IgE-mediated) asthma that remains uncontrolled despite treatment with high-dose inhaled corticosteroid (ICS) and a long-acting β_2 -agonist (LABA) [2]. The efficacy and safety of omalizumab in the treatment of severe allergic asthma have been established through an extensive clinical trial programme [3–6]. The original omalizumab dosing strategy was designed to achieve a target average free IgE level of 25 ng/mL (10.4 IU/mL; 1 IU/mL = 2.4 ng/mL), and was shown to result in free IgE levels < 50 ng/mL (20.8 IU/mL) in more than 95% of patients [7].

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¹ Study was undertaken while Dr. Kornmann was at this address.

Such reductions are associated with improved clinical outcomes [7].

The appropriate omalizumab dosage and dosing and schedule are determined by the patient's bodyweight (kg) and baseline total IgE levels (IU/mL). When initially approved, omalizumab was indicated for patients with a bodyweight of >20–150 kg and an IgE level of ≥ 30 –700 IU/mL, and the highest dose was 375 mg s.c. every two weeks. However, clinical data from the INNOVATE (Phase III pivotal trial of omalizumab) and TENOR studies indicated that up to one-third of patients, or more, had baseline IgE/bodyweight combinations that fell above those in the dosing table, e.g. >600 IU/mL/>60 kg, >500 IU/mL/>70 kg and >300 IU/mL/>90 kg. These patients would require higher omalizumab doses than 375 mg every two weeks [5,8,9].

This study is one of two studies (the other being a recently published allergen bronchoprovocation study [10]) that were carried out according to an European Medicines Agency (EMA) post-approval commitment to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of omalizumab in asthma patients with baseline IgE/bodyweight combinations above those in the original dosing table. Following evaluation of these studies by EMA, the omalizumab dosing table was expanded to include patients with an IgE level up to 1500 IU/mL, and omalizumab doses up to 600 mg every two weeks [2].

2. Methods

2.1. Study design and patients

This was a multicentre, open-label, multi-dose study in patients with mild-to-moderate allergic asthma. Non-smoking male or female (negative pregnancy test required) patients, 18–55 years old with baseline bodyweight ranging from 40 to 150 kg and serum IgE levels of 300–2000 IU/mL, were enrolled in the study. Patients were eligible for inclusion if they had been diagnosed with allergic asthma ≥ 1 year before screening, and were receiving treatment consistent with GINA step 2 or 3 (mild or moderate persistent asthma) [11].

Key exclusion criteria included: a history of anaphylaxis; lung disease other than mild-to-moderate allergic asthma; a smoking history of ≥ 10 pack-years or use of inhaled tobacco products within the last 12 months; oral corticosteroid (OCS) or investigational small molecule drug use within the last 3 months; monoclonal antibody use in the previous 6 months; exacerbation requiring either an emergency room visit within 6 weeks prior to or during screening; intubation and mechanical ventilation in the previous 12 months; or respiratory tract infection within the 4 weeks prior to the first dose.

The study was designed, implemented and reported in accordance with Good Clinical Practice, local regulations, and the ethical principles of the Declaration of Helsinki. This study is registered on clinicaltrials.gov (NCT00546143).

2.2. Treatment

Patients were randomised to one of three omalizumab dose groups (2×450 mg, 2×525 mg or 2×600 mg) according to their baseline IgE level and bodyweight (Table 1). Each patient received two doses of omalizumab by subcutaneous injection; the first dose on Day 1 and the second on Day 15. The doses were selected based on the following criteria; the original dosing algorithm of ≥ 0.016 mg omalizumab per kg bodyweight, per IU/mL baseline IgE, per 4 weeks was applied [12,13]. If the resulting dose would have required more than 4 individual injections, the dose was restricted

Table 1

Omalizumab dosage, in mg, based on bodyweight and serum total IgE levels.

Bodyweight (kg)	Baseline IgE (IU/mL)		
	Omalizumab 2×450 mg ($n = 12$)	Omalizumab 2×525 mg ($n = 8$)	Omalizumab 2×600 mg ($n = 12$)
>125–150	n/a	>300–400	>400–2000
>90–125	>300–400	>400–500	>500–2000
>80–90	>500–600	>600–700	>700–2000
>70–80	>500–700	>700–800	>800–2000
>60–70	>600–800	>800–900	>900–2000
>50–60	>700–900	>900–1000	>1000–2000
>40–50	>900–1100	>1100–1300	>1300–2000

The first dose of omalizumab was administered on Day 1 and the second dose on Day 15.

IgE = Immunoglobulin E; n/a = not applicable.

to 600 mg as the maximum dose per injection is 150 mg [2]. The first condition was met for the 2×450 mg and 2×525 mg dose groups. The second condition applied to the 2×600 mg dose group.

Patients were permitted to continue with existing medications for the treatment of asthma if their asthma had been stable for ≥ 3 months before screening.

2.3. Study assessments and data analysis

Safety assessments were conducted for vital signs, standard clinical laboratory evaluations, anti-omalizumab antibodies, adverse events (AEs) and serious AEs (SAEs). The safety population comprised all patients who received at least one dose of omalizumab and had at least one post-baseline safety assessment. Descriptive statistics for the safety population were provided by treatment group.

Serum samples for PK and PD evaluations were collected pre-dose, at 12 h post-dose on Day 1, and thereafter on Day 2 (24 h post-dose), and on Days 3, 4, 6, 8, 11, 15 (pre-second dose), 16 (24 h after second dose), and on Days 17, 18, 20, 22, 25, 29, 36, 43, 57, 71, 85 and 99.

Total omalizumab concentrations in serum were measured by a specific and validated ELISA method, as described previously [10]. The following PK parameters were derived from the concentration–time profiles of omalizumab between Day 1 and Day 99 (the two doses were not separated for the PK analysis): area under the serum concentration–time curve AUC_{last} (AUC up to the last quantifiable concentration), AUC_{inf} (AUC extrapolated to infinity), C_{max} (maximum concentration after the second dose), T_{max} (the time to C_{max}), $T_{1/2}$ (terminal half-life), and CL/F (apparent total body clearance). PK parameters were determined by non-compartmental methods with WinNonlin™ Professional (Version 5.2, Pharsight, Palo Alto, California, USA).

Serum levels of free IgE and total IgE (i.e. the sum of free and bound IgE) were determined by specific immunoassays, as described previously [10]. PD parameters were determined after both the first and the second omalizumab dose. For free serum IgE, C_{min} (the minimum concentration), T_{min} (time to C_{min}), and the maximum percent decrease from screening were determined. For total IgE, C_{max} , T_{max} and the maximum percent increase from screening were determined.

In the PK/PD analyses, only patients with evaluable PK/PD data were included. Descriptive statistics for PK and PD parameters per treatment group included median and range for T_{max} and T_{min} , respectively, and arithmetic mean and standard deviation for all other parameters.

3. Results

3.1. Patient demographics and baseline characteristics

Overall, 32 patients were enrolled and 31 completed the study. Two patients (both in the 600 mg group) were not included in the PK analysis (one was lost to follow-up and one did not receive the complete second dose, i.e. only 500 mg instead of 600 mg). Patient demographics and baseline characteristics are shown in Table 2.

3.2. Safety

Table 3 shows the most frequently reported AEs (occurring in two or more patients). Overall, 26/32 (81.3%) patients reported 69 AEs, 10 of which (6 patients) were considered by the investigators to be omalizumab-related. Most of the AEs reported in this study were related to the underlying disease and to patients' general health. Two asthma exacerbations (one on study day 3 and one on study day 73, each of moderate severity) were observed in one subject in the 600 mg dose group. Three events of bronchitis were distinct from these asthma exacerbations and observed in three different subjects (two subjects from the 450 mg dose group and one subject from the 600 mg dose group). The AEs suspected by the investigator to be treatment related were: headache and haematoma under the toenails (in the 450 mg dose group); diarrhoea, nausea, vomiting, headache, and pruritus (in the 525 mg dose group); and headache, abdominal pain, and sore throat (in the 600 mg dose group). Most AEs were considered to be mild or moderate, transient, and not dose-related. One AE (pain in the right calf) was reported as severe, but not omalizumab-related. There were no deaths or SAEs reported during the study, no unexpected AEs, and no patients discontinued the study because of an AE.

Laboratory measurements, levels of anti-omalizumab antibodies, vital signs, ECG recordings and spirometric results did not reveal any clinically relevant adverse findings or trends that were potentially related to omalizumab treatment.

3.3. Pharmacokinetics

After the first dose, serum omalizumab concentrations slowly increased and reached peak values 2–10 days after administration, regardless of dosage. Following the second dose on Day 15, omalizumab concentrations increased further and reached overall peak values a couple of days later (Fig. 1a). The mean terminal half-life of omalizumab was around 20 days (range of means for the three dose groups: 18–22 days; Table 4). The mean apparent CL/F of omalizumab was 6.9–9.2 mL/h. Omalizumab total exposure as assessed

Table 2
Patient demographics and baseline characteristics by treatment group.

		Omalizumab 2 × 450 mg (n = 12)	Omalizumab 2 × 525 mg (n = 8)	Omalizumab 2 × 600 mg (n = 12)	Overall (n = 32)
Age, years	Mean	34.9	33.1	37.3	35.4
	(range)	(22–46)	(18–50)	(21–52)	(18–52)
Male	n (%)	6 (50.0)	5 (62.5)	9 (75.0)	20 (62.5)
Caucasian	n (%)	11 (91.7)	7 (87.5)	11 (91.7)	29 (90.6)
Bodyweight, kg	Mean	84.6	80.5	84.0	83.0
	(range)	(62–105.5)	(50–98)	(68.6–95.5)	(50–105.5)
Total IgE at screening,	Mean (SD)				
	IU/mL	503 (143)	670 (202)	989 (205)	727 (280)
	ng/mL	1207 (343)	1608 (485)	2374 (492)	1745 (672)

1 IU/mL of IgE is equivalent to 2.4 ng/mL.

The first dose of omalizumab was administered on Day 1 and the second dose on Day 15.

IgE = immunoglobulin E; SD = standard deviation.

Table 3

Overall and most frequently reported AEs, experienced by at least two patients.

	Omalizumab 2 × 450 mg (n = 12)	Omalizumab 2 × 525 mg (n = 8)	Omalizumab 2 × 600 mg (n = 12)	Overall (n = 32)
Patients with AEs, n (%)	11 (91.7)	7 (87.5)	8 (66.7)	26 (81.3)
Headache	5 (41.7)	3 (37.5)	3 (25.0)	11 (34.4)
Nasopharyngitis	1 (8.3)	2 (25.0)	4 (33.3)	7 (21.9)
Bronchitis	2 (16.7)	0 (0.0)	1 (8.3)	3 (9.4)
Abdominal pain	1 (8.3)	0 (0.0)	1 (8.3)	2 (6.3)
Gastroenteritis	2 (16.7)	0 (0.0)	0 (0.0)	2 (6.3)
Back pain	1 (8.3)	1 (12.5)	0 (0.0)	2 (6.3)
Pain in extremity	1 (8.3)	0 (0.0)	1 (8.3)	2 (6.3)
Dysmenorrhoea	1 (8.3)	0 (0.0)	1 (8.3)	2 (6.3)
Pharyngolaryngeal pain	1 (8.3)	0 (0.0)	1 (8.3)	2 (6.3)

The first dose of omalizumab was administered on Day 1 and the second dose on Day 15.

AE = adverse event.

by AUC_{inf} was in the same range for the three dose groups. The mean exposure after the 2 × 600 mg doses was slightly lower than after 2 × 525 mg doses, but in proportion to the 2 × 450 mg doses. Similarly, the peak exposure as expressed by mean C_{max} was highest after the 2 × 525 mg doses, whereas the increase in C_{max} following 2 × 600 mg was in approximate proportion to the increase in dose from 2 × 450 mg (Table 4).

3.4. Pharmacodynamic analysis

In all three dose groups, omalizumab reduced the level of free IgE by ≥99% after the first dose (Fig. 1b). The mean (SD) C_{min} of free IgE was 11.85 (2.40), 11.79 (2.73) and 16.56 (3.66) ng/mL for the 450 mg, 525 mg and 600 mg dose groups, respectively, and was reached between 2 and 3 days (median T_{min}). IgE levels then increased slightly until pre-second dose on Day 15 in all three groups. Following the second dose, IgE levels declined for a second time; the second mean (SD) C_{min} was 12.09 (2.30), 12.18 (2.65) and 16.26 (5.09) ng/mL for the 450, 525, and 600 mg dose groups, respectively, and occurred between 4 and 5 days (median T_{min}) after the second dose. The maximum percentage decrease of IgE from screening was similar between the three groups, and between the first and second doses (range of means: 99.0–99.3%). Mean free IgE levels remained <25 ng/mL for at least 2 weeks after the second dose.

Total IgE levels increased in all three dose groups up to 14 days after the first dose, and continued to increase after the second dose, reaching a peak between 21 and 28 days (median T_{max}) after the second dose (data not shown). Total IgE levels were still elevated on study day 99 in all dose groups. C_{max} of total IgE increased in a dose-dependent manner. Mean (SD) C_{max} after the second dose was 4511 (1378), 5243 (1621) and 6058 (1368) ng/mL for the 2 × 450 mg, 2 × 525 mg and 2 × 600 mg dose groups, respectively, reflecting both the increase of the omalizumab dose and the parallel increase of baseline IgE values (Table 1). The mean maximum percentage increase in total IgE from screening was 281, 242 and 159%, respectively.

4. Discussion

This clinical study was primarily designed to meet an EMA post-approval commitment regarding the safety and tolerability, PK and PD of omalizumab in patients with mild-to-moderate asthma with baseline IgE/bodyweight combinations above those defined in the initially approved dosing table. It was expected that safety, tolerability, PK and PD data from the present clinical study would be consistent with existing or modelled data; and, if efficacy could be confirmed in a separate study, that this would allow for an

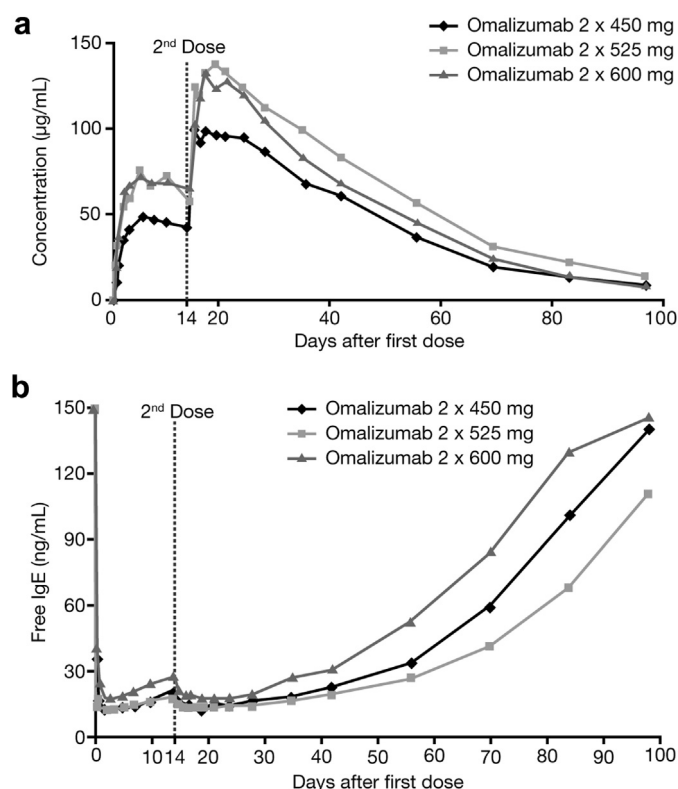


Fig. 1. Arithmetic mean concentration–time profiles of serum omalizumab (a), and free IgE (b) following a first dose on Day 1 and a second dose on Day 15. All individual values of free IgE were above the upper limit of quantification (150 ng/mL) and were therefore set to 150 ng/mL, resulting in a mean (SD) value of 150 (0.0) ng/mL for all pre-dose assessments on Day 1.

extension of the initially approved dosing table, enabling an extended range of asthma patients to receive omalizumab. The rationale for this request was that a substantial number of patients had IgE levels above those in the initial dosing table (INNOVATE [5] and TENOR [9]). Consequently, it was hypothesised that patients with higher IgE levels (>700 IU/mL at baseline) would benefit from the extension of the initially approved dosing table if their IgE was suppressed to a level previously shown to be correlated with clinical efficacy.

Patients with mild-to-moderate allergic asthma with increased IgE levels were selected, but the conclusions drawn from the PD response were used for a dosing table expansion for uncontrolled severe allergic asthma patients, in accordance with the omalizumab label.

Table 4
Pharmacokinetic parameters of omalizumab following a first dose on Day 1 and a second dose on Day 15.

PK parameter	Omalizumab 2 × 450 mg (n = 12)	Omalizumab 2 × 525 mg (n = 8)	Omalizumab 2 × 600 mg (n = 10)
AUC _{last} , day, µg/mL	4347 (843)	6228 (1535)	5692 (1744)
AUC _{inf} , day, µg/mL	4602 (944)	6666 (1570)	5946 (1910)
C _{max} , µg/mL	121.9 (53.2)	161.2 (30.4)	148.1 (38)
T _{max} , day	20.0 (15.0–24.1)	19.0 (15.0–24.0)	17.0 (15.0–21.0)
T _{1/2} , day	19.9 (2.7)	21.6 (2.9)	17.6 (3.8)
CL/F, mL/h	8.49 (1.84)	6.90 (1.64)	9.18 (2.77)

Values are median (range) for T_{max}, and arithmetic mean (SD) for all other parameters.

AUC = area under the serum concentration–time curve; AUC_{last} = AUC up to the last quantifiable concentration; AUC_{inf} = AUC extrapolated to infinity; CL/F = apparent total body clearance; C_{max} = maximum concentration; SD = standard deviation; T_{1/2} = terminal half-life; T_{max} = time to C_{max}.

As observed after the administration of lower doses of omalizumab [12], serum omalizumab concentrations slowly increased to reach maximum concentrations a few days after administration, i.e. 3–6 days (median values) after the second dose. Thereafter, omalizumab was eliminated with a mean T_{1/2} around 20 days. This half-life is similar to values seen previously in subjects with IgE values between 30 and 300 IU/mL after a single omalizumab dose of 150 mg or 300 mg (mean T_{1/2} was 22–23 h) [14]. A mean apparent clearance of omalizumab of 2.4 mL/kg/day was reported for asthma patients [2]. For a patient with a bodyweight of 80 or 85 kg (within the range of mean bodyweight in our study; Table 2), this translates into a CL/F value of 192 mL/day and 204 mL/day, respectively, or 8.0 mL/h and 8.5 mL/h, respectively. These values are within the range of mean values reported in our study (Table 4).

Overall, the PK and PD profiles of omalizumab were consistent with existing data [2,12]. Omalizumab concentrations increased after the first and second doses, reaching overall peak values after the second dose. All omalizumab doses reduced free IgE concentrations by at least 99.0%, a magnitude of reduction that has been associated with improvements in clinical symptoms [15]. Mean free IgE levels remained <25 ng/mL for at least 2 weeks after administration of the second dose. These data suggest that patients with IgE levels higher than 700 IU/mL might be effectively treated with omalizumab.

The inclusion criteria in this study allowed to enrol patients with baseline IgE levels up to 2000 IU/mL (Table 1). In the final extended dosing table approved in the EU, the upper limit of baseline IgE is 1500 IU/mL for patients with a bodyweight up to 50 kg, and decreases bodyweight-dependent in steps for bodyweights between 50 and 150 kg [2]. This ensures that doses for all bodyweight–baseline IgE combinations adhere to the original dosing algorithm of ≥ 0.016 mg omalizumab per kg bodyweight, per IU/mL baseline IgE, per 4 weeks. Patients exposed to omalizumab dosed according to this algorithm showed reductions of free IgE to the range of 10–20 ng/mL, a level which was previously linked to clinical efficacy in asthma endpoints [12].

Omalizumab was well tolerated during this study; the safety findings were consistent with the known safety profile of omalizumab at lower doses [4]. However, this was a short-term study of only two doses, whereas real-world use of omalizumab is typically long-term. This study was not designed to assess efficacy. A further limitation of the study was the small number of patients assessed; this may explain the variations observed in PK and PD values. The results of this study were similar to a corresponding efficacy study, which demonstrated that patients with higher baseline IgE levels treated with omalizumab for 16 weeks experienced a significant reduction in early-phase allergic response compared with patients receiving placebo [10]. The safety and PK/PD findings from this study are consistent with previous trial data and support the extension of the initially approved omalizumab dosing table to patients with baseline IgE levels >700 IU/mL.

Conflict of interest

O.K. has, within the last five years, received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Novartis, Meda Pharma, for consulting from Pfizer, Novartis, for conducting clinical studies from Almirall, AstraZeneca, Bayer, Boehringer Ingelheim, Cephalon, Chiesi, GlaxoSmithKline, Mundipharma, Novartis. H.W. has received speaker fees and consultancy fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Chiesi, and Merck; Pulmonary Research Institute was funded by Novartis to conduct the study. R.F. is an employee of PAREXEL International GmbH; PAREXEL was funded by Novartis to conduct the study. N.K.'s institution (Fraunhofer Society) was paid by Novartis to contribute

to the study (contract research). V.E. and G.K. are employees of Novartis and own stock in Novartis. There are no other financial disclosures/conflicts of interest.

Acknowledgements

This study was undertaken while Oliver Kornmann was based at Mainz University Hospital, Mainz, Germany.

The authors would like to thank all participating patients and members of the study group. Clara Munzu (former employee at Novartis Pharma AG) was the Clinical Trial Leader for this study. Stephan Koehne-Voss (Novartis Pharma AG) reviewed the statistical methodology for accuracy.

Editorial support was provided by Helen Attisha, PhD (CircleScience), funded by Novartis Pharma AG, Basel, Switzerland. Gerald Dodson (Novartis Pharma AG) also assisted in the preparation of the manuscript.

All authors had full access to the data, and were involved in the interpretation and discussion of the results, the decision to submit to a journal, and in the preparation of the manuscript.

The data from this trial were presented in part as an abstract at the European Respiratory Society Annual Congress (ERS), 18–22 September 2010, Barcelona, Spain [Kornmann O et al., *Eur Respir J* 2010; 36(Suppl. 54):717s].

This study was sponsored by Novartis Pharma AG, Basel, Switzerland, whose employees designed the study, collected, analysed and interpreted the data, wrote the clinical study report and made the decision to submit the paper to a journal.

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