Clinical and pharmacoeconomic aspects of omalizumab: a 4-year follow-up

Francesco Menzella, Nicola Facciolongo, Roberto Piro, Debora Formisano, Alberto Roggeri, Anna Simonazzi, Claudia Castagnetti, Cristiano Carbonelli and Luigi Zucchi

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Abstract:

Objectives: The aim of this study was to assess the stability of the effectiveness of omalizumab as add-on treatment in 11 patients with severe persistent allergic asthma followed for 4 years. Secondary outcomes were safety and economic impact, in terms of use of healthcare resources.

Methods: This retrospective study was designed to analyse a series of patients with severe allergic asthma treated with omalizumab. Patients were initially enrolled as part of the CIGE025A2425 international multicentre clinical trial. At the end (week 32), 11 responsive patients went on to complete the study and continued omalizumab treatment until June 2010. The monitoring visits coincided with the timescales planned for administering the drug and for the follow up. To estimate the economic impact, the PRE–POST treatment comparison was obtained by comparing the annual pretreatment costs with an annual average of the 4-year posttreatment period costs

Results: After 4 years, 81.8% of patients showed a good/excellent Global Evaluation of Treatment Effectiveness scale score and 81.2% showed an excellent increase (>1.5) in the Asthma Quality of Life Questionnaire score. The average forced expiratory volume in one second (FEV_1) at 4 years was 75.3% compared with the predicted normal value for each patient, with a net increase ($p = 0.009$) compared with baseline FEV_1 values (58.6%). The frequency of serious exacerbations dropped by 94.7% compared with the pretreatment period, while mild–moderate exacerbations fell by 41.8%. A reduction in costs was observed for hospital admissions (97.3%), visits to emergency department (ED) (97.5%) and mild–moderate exacerbations (84%). The average cost reduction of concomitant drugs remained at 36%.

Conclusions: This study confirms the effectiveness and reliability of omalizumab over the long term, while providing an excellent safety profile. The additional cost due the use of omalizumab was offset by the medium- and long-term savings associated with the reduction in hospital admissions and access to ED.

Keywords: asthma, efficacy, omalizumab, quality of life

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Background

Asthma is a chronic illness that is characterized by a morbidity and mortality that significantly impacts upon socio-economic resources [National Heart, Lung, and Blood Institute, 2002]. Inhaled corticosteroids (ICSs) are recognized as the most effective class of drugs and are recommended by international guidelines as first-line treatment [Frois *et al*. 2009]. Unfortunately, often ICSs are not sufficient in preventing exacerbations, hospitalizations and sometimes deaths, and thus combination therapy with a bronchodilator is often necessary [Global Initiative for Asthma, 2006]. This combined treatment option allows improvement in symptoms and lung function and reduced exacerbations, and in addition, it is usually well tolerated and makes it possible to reduce the dose of ICSs [Global Initiative for Asthma, 2009].

Patients with severe asthma have inadequate control of their disease, despite the multidrug optimal therapy they follow, and represent the patient subpopulation that consumes the majority of healthcare resources [National Heart, Lung,

and Blood Institute, 2002; Loddenkemper *et al.* 2003]. Drugs which provide improved control of this disease are urgently required. Omalizumab is the first biologic drug available for the treatment of severe asthma [Humbert *et al.* 2005]. A number of clinical trials have been performed with the aim of assessing the effectiveness and safety of omalizumab. Results from these trials have shown that this molecule was able to significantly improve control of asthma and quality of life (QoL), with an excellent safety profile [Humbert *et al.* 2005; Rodrigo *et al.* 2011; Walker *et al.* 2006]. Real-life data have led to the same conclusions, while the cost-effectiveness assessment varied according to the analytical methods [Oba and Salzman, 2004; Wu *et al.* 2007; Campbell *et al.* 2010] and the country-specific setting. With regard to its long-term effectiveness, few studies are available and have limited case histories [Pace *et al.* 2010; Nopp *et al.* 2010]. The aim of this study was to evaluate the long-term stability (4-year follow up) of the effectiveness of omalizumab as add-on treatment in patients with severe persistent allergic asthma, to evaluate the safety profile and to analyse the economic savings in terms of use of healthcare resources.

Methods

Study design

This retrospective study was designed to analyse a series of patients with severe allergic asthma treated with omalizumab. Patients were initially enrolled as part of the CIGE025A2425 international multicentre, open-label, parallel-group clinical trial (November 2005/September 2008) (Table 1).

The primary objective was to evaluate the persistency of the response to the treatment with omalizumab administered for 32 weeks as add-on therapy to optimized asthma therapy, in patients who have inadequate asthma control, despite treatment according to Step IV of GINA 2002. All patients signed the informed consent and were enrolled between November 2005 and June 2006.

At the end of the 32-week period, 11 responsive patients went on to complete the study and continued omalizumab treatment until June 2010. The monitoring visits coincided with the timescales planned for administering the drug (every 2 or 4 weeks) and for the follow up, as indicated by Italian Drug Agency (AIFA).

This study was approved by local ethics committee (Protocol Number 2011/0006211/03-01-2011).

End points

The primary end point was to evaluate the persistency of benefit provided by omalizumab as add-on treatment beyond 32 weeks and up to 4 years from the start of the treatment, compared with the same parameters assessed during the 12 months prior to initial drug administration.

Secondary end points were as follows:

- safety and tolerability during the follow-up period;
- economic impact of treatment in terms of the use of healthcare resources, number of exacerbations and potential reduction in drug consumption

Evaluation of effectiveness

The Global Evaluation of Treatment Effectiveness scale (GETE) was used to evaluate the effectiveness of omalizumab at both 32 weeks and at 4 years after initial drug administration [Global Initiative for Asthma, 2009; Lloyd *et al.* 2007]. This evaluation was performed independently by both investigator and patient using the same five-point scale. A good or excellent response was used to define a patient who has responded to treatment. The evaluation of QoL was conducted through the Juniper Asthma-Related QoL Questionnaire (AQLQ) [Juniper *et al.* 1993].

The AQLQ is composed of 32 questions which cover four domains: activity limitation, symptoms, environmental stimuli and emotional function. Patients recall their experiences during the previous 2 weeks and score a number of asthma-related problems on a seven-point scale from 1 (maximum impairment) to 7 (no impairment). We used an overall summary index, which is the mean of the responses to the 32 items (total score). This questionnaire was found to be valid, reproducible and responsive to change over time and a change in the score of 0.5 or more points has been determined to be the minimal clinically important difference.

Serious or mild exacerbations during the 12 months preceding the study were documented, along with those at 32 weeks and at 4 years, together with any hospital admissions

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
• Written informed consent provided
• Men or women of any race
• 12–75 years of age
• Body weight ≥20 kg and ≤150 kg and with a total serum immunoglobulin E (IgE) level ≥30 to ≤700 IU/ml
• Diagnosis of allergic asthma ≥1 year duration at screening and a history consistent with Global Initiative for Asthma (GINA) step 4 clinical features
• Positive skin prick test to at least one perennial allergen, positive radioallergosorbent test (RAST) if total IgE levels ≤76 IU
• Demonstrating ≥12% increase in forced expiratory volume in one second (FEV_1) within 30 minutes of taking salbutamol
• FEV_1 ≥40% and ≤80% of the predicted normal value for the patient (performed between November 2005 and June 2006)
• Receiving a high dose of the inhaled corticosteroid ≥800 µg beclomethasone dipropionate (BDP) or equivalent and regular inhaled long-acting beta agonists (LABAs) for at least 3 months before screening and >1000 µg BDP + LABAs for at least 4 weeks
• Patients who have suffered multiple (i.e. at least two) independent documented severe asthma exacerbations while receiving high doses of inhaled corticosteroid (ICS) (≥800 µg BDP or equivalent) and regular inhaled LABAs requiring treatment with systemic corticosteroids
• Evidence of poor asthma control (asthma symptoms, nighttime awakenings, use of rescue medication)
Exclusion criteria
• Women who are pregnant or who are breast-feeding
• Patients who do not adhere to protocol medication washouts
• Patient on unacceptable medications
• Patients with significant underlying medical conditions that could have an impact on the interpretation of results should be excluded (e.g. infection, haematological disease, malignancy, renal, hepatic, coronary heart disease or other cardiovascular disease, endocrinologic or gastrointestinal disease) within the previous 3 months
• Unable to perform spirometry and peak flow measurements or complete a patient diary or note book or complete questionnaires on paper and over the telephone
• Previously randomization into this or any other omalizumab study or otherwise receiving omalizumab

or emergency department (ED) visits. Serious exacerbations were classified as those which required systemic steroids, hospitalization or visits to ED. Mild to moderate exacerbations of asthma were classified as those which required treatment at home or in the physician's office.

Lung function was evaluated by measurement of initial forced expiratory volume in one second (FEV_1) and then FEV_1 values at 32 weeks and at 4 years.

Cost analysis

In order to estimate the economic impact on the use of health services (hospital admissions, visits to ED, exacerbations and drugs), a monetary value was assigned to each event recorded in both the 12 months prior to the beginning of the study and in the follow-up period.

More specifically:

- For admissions, the average value of the diagnosis-related group (DRG) 96 and 97 (bronchitis and asthma with and without complications) was considered; in the event of admissions for respiratory insufficiency, the DRG 87 [Ministero della Sanità, 2006] was used.
- The economic cost for a visit to ED was obtained by calculating the fees charged [Ministero della Sanità, 1996] for each individual routine service conducted during the stay in ED (general checkup, pulmonary checkup, blood gas analysis, blood chemistry tests and chest X-ray).
- Moderate exacerbations were evaluated based on the fees charged [Ministero della Sanità, 1996] for the individual services generally used (e.g. specialist checkup and

Table 2. Baseline clinical characteristics.

Characteristics		Baseline values (n = 11)
Age (years), mean ± SD		47.5 ± 9.64
		range (33–67)
Gender, *n* (%)	Males	7 (63.6)
	Females	4 (36.4)
Weight (kg), mean ± SD		81.6 ± 12.1
		range (52–109)
Smoking history, *n* (%)	Nonsmoker	8 (72.7)
	Previous smoker	3 (27.3)

weekly treatment with oral steroids, long-acting beta agonists [LABAs] and antibiotics). No cost was attributed to mild exacerbations.

– The daily cost for each class of drugs was obtained from information available on drug price for the public and the national effective use of these drugs during the period January–August 2010. In particular, for the class of LABA, formoterol and salmeterol were considered; for anticholinergics, tiotropium; for ICSs, beclomethasone dipropionate, budesonide and fluticasone propionate; for antileukotrienes, montelukast and zafirlukast; for oral steroids, prednisone and methylprednisolone; for antibiotics, penicillins, cephalosporins, macrolides and fluoroquinolones, assuming an average treatment duration of 6 days (except 3 days for azithromycin). The cost of fixed combinations was not included as, in the case that the patient had used a fixed combination instead of a free combination LABAs + ICSs, the daily cost could have been slightly underestimated.
– The PRE–POST treatment comparison was obtained by comparing the annual pretreatment costs with an annual average of the 4-year posttreatment period costs.

Statistical analysis

Data are summarized by the primary measures of central tendency and dispersion, in addition to frequencies and percentages. The *t*-test and Wilcoxon test for paired data were used to verify the significance of trends observed from the main parameters of lung function and QoL indicators. A value of $p < 0.05$ was considered statistically significant. Data were analysed using SPSS v.15.0 (Chicago, IL, USA).

Results

Baseline

A total of 11 white patients were examined in the present study and their demographic characteristics and smoking status are presented in Table 2.

All patients were affected by severe allergic asthma which was not controlled by optimized asthma therapy and daily symptoms leading to a significant impairment in QoL, represented by the low AQLQ score at baseline (median 2.8; range 1.2–3.6). The median value of baseline IgEs (ImmunoCap-Phadia, Sweden) was 256 IU/l (range 31–687.6). The dosage of omalizumab was calculated using dosage tables, the monthly average being 437.5 mg (range 150–750 mg). Seven patients (63.6%) received the drug every 2 weeks and four patients (36.4%) every 4 weeks. During the 12-month period preceding the treatment, all patients had at least one mild–moderate exacerbation, seven (63.6%) at least one hospitalization and four (36.3%) at least one emergency visit to ED (without subsequent hospitalization). Approximately half of patients (45%) had between four and five exacerbations and an average number of visits to ED of 2.5 (range 1–4).

The average value of the baseline FEV_1 was 58.6% (range 42–75) (Table 3).

All patients used ICS and LABA inhalers at the maximum dose, eight patients (72.7%) antileukotrienes, 10 patients (90.9%) oral steroids, one patient (9.1%) theophylline, five patients (45.5%) anticholinergics and eight patients (72.7%) short-acting bronchodilators (Table 4).

Evaluation of effectiveness

Follow up at 32 weeks. Eight patients (72.7%) showed a good/excellent GETE and three patients

Table 3. Effectiveness of omalizumab treatment.

Outcomes	Baseline	32-week effectiveness	4-year effectiveness
Percentage with good or excellent GETE rating		72.7%	81.8%
AQLQ (median, range)	2.8 (1.21–3.6)	4.6 (2.9–5.1)	5.6 (2.25–6.7)
Percentage improving in AQLQ total score >0.5		72.7%	100 %
FEV_1 % (average, range)	58.6 (42–75)	78.1% (40–100) (p = 0.006)	75.4% (39–109) (p = 0.009)
IgE total (median, range)	256 IU/l (31–687.6)	285 IU/ml (49.3–676.4) (p = 0.131)	287 IU/ml (57.6–656.3) (p = 0.131)
Severe exacerbation, n (Δ%) *	19	2 (–89.5%)	1 (–94.7%)
Mild + moderate, n (Δ%) *	55	16 (–70.9%)	32 (–41.8%)

*The Δ% shows the percent variation from baseline
AQLQ, Asthma Quality of Life Questionnaire; FEV_1, forced expiratory volume in one second; GETE, Global Evaluation of Treatment Effectiveness; IgE, Immunoglobulin E.

(27.3%) showed a moderate GETE (Table 3). The median value of AQLQ was 4.60 points. Eight patients (72.7%) showed an increase in the total AQLQ score (>0.5 points). Two patients (25%) showed a moderate increase (>1.0 points) and six patients (75%) showed an excellent increase (>1.5 points) in AQLQ score. Overall, the average increase was by 1.4 points (Table 3).

At the intermediary check, two hospital admissions were recorded, with a drop compared with the pretreatment period of 89.5%. The number of mild–moderate exacerbations was reduced by 70.9% (n = 16) compared with the previous 12 months. The average FEV_1 at 32 weeks was 78.1% (range 40–100%) (p = 0.006). All patients continued to use ICSs and LABAs, 45.5% antileukotrienes (n = 5), 9.1% oral steroids (n = 1), none theophylline, 18.2% anticholinergics (n = 2), 63.6% short-acting bronchodilators (SABAs; n = 7); see Table 4.

Follow up at 4 years. Nine patients (81.8%) showed a good/excellent GETE and two showed (18.2%) a moderate rating (Table 3). The median value of AQLQ was 5.6 points.

Two patients (18.8%) showed a moderate increase in the total AQLQ score (>1 point) while nine (81.2%) showed an excellent increase (>1.5). The average increase was 2.6 points compared with the baseline value (Table 3).

At the final check, there was only a single visit to ED (–94.7%) and no hospital admissions were observed, compared with the pre-treatment period. The frequency of mild–moderate exacerbations also decreased by 41.8% (Table 3).

The average FEV_1 at 4 years was 75.4% (range 39–109), significantly increased from baseline (p = 0.009), with only a slight reduction compared with the 32-week time point.

All patients continued to use LABAs, 10 patients (90.9%) ICS, two patients (18.2%) anticholinergics, and three patients (27.3%) SABAs. No patients were treated with antileukotrienes, oral steroids or theophylline (Table 4).

Laboratory tests

At 4 years, the median value of total IgEs was 287 IU/ml, with a negligible increase (p = 0.131) compared with the pretreatment value (256 IU/ml); see Table 3. No change in levels of blood count, creatinine or liver function parameters were observed.

Adverse events

No patient showed any systemic or local side effects related to omalizumab treatment over the entire follow-up period.

Economic impact

During the follow-up period, the reduction in hospital admissions was 97.3%, the reduction in costs related to ED visits was 97.5% and the

Table 4. Drug therapy before and after omalizumab treatment.

	Basal		32-week effectiveness		4-year effectiveness	
Drug	Patients (*n*)	% §	Patients (*n*)	% §	Patients (*n*)	% §
LABA	11	100.0%	11	100.0%	11	100.0%
ICS	11	100.0%	11	100.0%	10	90.9%
Antileukotrienes	8	72.7%	5	45.5%	0	0%
Theophylline	1	9.1%	0	0%	0	0%
Anticholinergics	5	45.5%	2	18.2%	2	18.2%
Oral steroids	10	90.9%	1	9.1%	0	0%
SABA	8	72.7%	7	63.6%	3	27.3%

§The percentage is calculated from total number of patients (*n* = 11).
ICS, inhaled corticosteroid; LABA, long-acting beta agonist; SABA, short-acting beta agonist.

Table 5. The cost of treatment and drug therapy before and after omalizumab.

	Cost previous year (€)	Average cost following year (€)	Absolute difference and percentage	
Hospitalization cost	2.158	59	–2.099	–97.30%
ED cost	73	2	–71	–97.50%
Exacerbations cost	211	34	–177	–84%
Total drugs cost	1.585	1.021	–564	–36%
LABA				0%
ICS				–4%
Antileukotrienes				–61%
Theophylline				–92%
Anticholinergics				–55%
Oral steroids				–87%
SABA				–33%
Total costs	4.027	1.116	–2.911	–72%

Calculations based on the average cost per patient
ED, emergency department; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; SABA, short-acting beta agonist.

reduction in the cost due to mild-moderate exacerbations was 84% (Table 5).

With regard to the consumption of drugs, there was an average reduction of 36% compared with the year preceding the use of omalizumab, there were no substantial variations relating to the use of LABAs + ICSs, the consumption of antileukotrienes reduced by 61%, that of anticholinergics by 55%, SABAs by 33%, theophylline by 92% and oral steroids by 87% (Table 5).

The average annual cost of omalizumab was €12,850 per patient. When the reduction in healthcare costs was considered, the annual cost of omalizumab was reduced by 27% (median –22%, range –83% to +7%) resulting in a net cost of €9880 per patient. The analysis did not consider the savings associated with the reduction of complications and long-term comorbidity associated with oral steroids.

Discussion

For patients with severe uncontrolled allergic asthma despite optimal therapy, the monoclonal anti-IgE antibody is a safe and effective add-on treatment which, in suitable patients [Rodrigo *et al.* 2011], allows them to obtain better control of their asthma with an excellent safety profile [Humbert *et al.* 2005; Walker *et al.* 2006], but with an increase in direct costs.

Within the European Union, the annual cost of asthma treatment is approximately €17.7 Billions, associated with an estimated loss of working capacity of €9.8 billion, with the majority of costs attributed to patients with poorly controlled asthma [Loddenkemper *et al*. 2003].

The purpose of the present study was to evaluate the long-term effectiveness of omalizumab in addition to evaluating data available from previous published studies to determine the economic impact of this treatment, assessing the impact upon health services, exacerbations and use of other drugs.

The limitations of this study are determined primarily by the small amount of case histories, initially selected based on the restrictive criteria of an international clinical trial, by the origin and ethnicity of the patients, all whites of Italian origin treated in a single centre. Such factors may represent bias to be taken into consideration when interpreting the results.

The main findings from baseline evaluation of parameters revealed an inadequate control of the disease, which resulted in poor QoL. Furthermore, the majority of patients were treated with traditional drugs at maximum dosage, including chronic use of systemic steroids with their known medium and long-term side effects. The frequent use of health services and emergency visits resulted in high costs for the national health service (NHS) and directly impacted upon working activity. Overall, findings from the present study show a superior effectiveness of omalizumab compared with previous published studies regarding exacerbations and QoL, with some improvement in the control parameters at 4 years compared to the 32 initial weeks [Humbert *et al*. 2005, 2008; Brusselle *et al*. 2009; Cazzola *et al*. 2010].

These data not only show an effectiveness that remains stable over time, but also which progressively improves over time in the majority of patients. This is supported by evidence from the absence of hospital admissions following the intermediate clinical visits. The two hospitalizations (which in both cases occurred within the first 16 weeks of treatment) may be explained by the fact that the effectiveness of the drug was not yet fully optimized, as they did not occur in the remaining follow-up period. The effectiveness of omalizumab during the follow-up period is further demonstrated by the significantly reduced use of asthma medications such as oral steroids, leukotriene modifiers and SABAs.

Another important finding is the marked improvement of spirometric values. The difference between our findings and those observed from other studies [Humbert *et al*. 2005, 2008; Cazzola *et al*. 2010] may be due to various factors, but we believe that the selection criteria of patients according to CIGE025A2425 (i.e. FEV_1 reversibility test +12%) would have provided ample capacity of improvement in these patients.

The evaluation of QoL using AQLQ showed a clear increase even at the first check, which further improved up to the end of the study, when the majority of patients showed an excellent increase in their scores.

In addition to the reduction in the cost of healthcare resources, decreasing the use of drugs has also allowed significant cost savings.

The concern of NHSs related to the cost of omalizumab could have led the national health authorities to restrict access to the treatment. In order to assess a new therapeutic strategy, especially in the case of biologic treatments, it is fundamental to evaluate its benefits in terms of real-life effectiveness and QoL improvement beyond the overall financial cost implications. From this wider perspective, any incremental therapeutic cost represents an investment in the patients' health improvement as demonstrated in this real-life study and in other cost-effectiveness evaluations. Several positive cost-effectiveness evaluations have been conducted in recent years, each demonstrating very different results, possibly due to the variations in methods used for calculating the clinical–economic data and differences in reimbursement policies [Wu *et al*. 2007; Brown *et al*. 2007; Dewilde *et al*. 2006].

Our findings show a marked decrease in the use of healthcare services, with an almost complete reduction in the costs of ED visits and hospital admissions and a 36% reduction in the cost of other treatments. On average, these avoidable costs would offset 27% of the annual cost of omalizumab. The net cost per exacerbation (excluding mild exacerbations) avoided using omalizumab is €2273 and may be an acceptable value to avoid a worsening of the patients' health status. These additional costs must be compared with the level of effectiveness and the patients

QoL achieved at the same time of treatment. In this regard, there is evidence available showing that the cost-effectiveness profile of omalizumab is often considered positive according to national and international parameters [Oba and Salzman, 2004; Brown *et al.* 2007; Dewilde *et al.* 2006]. These figures provide justification for the use of omalizumab in healthcare resources.

It must also be noted that our economic analysis was conservative as it did not take into consideration the following elements:

- the costs avoided from complications caused by systemic steroid use (cataracts, steroid-induced diabetes, osteoporosis, etc.) and the long-term cost avoided due to an improvement of health status;
- the cost of omalizumab and other treatments, as the full (not discounted) price was used and hospitals can purchase the drug at a lower cost;
- the social costs, as our evaluation did not include the impact of omalizumab on working activity considering that the average age of patients is 47.5 years.

Conclusions

The overall evaluation has confirmed the effectiveness of omalizumab with evidence of persistency in long-term results, which even tend to improve over time in all of the parameters considered, as shown by few studies about long-term treatment [Pace *et al.* 2011]. We would like to remind the reader, however, that patients were initially selected as part of a clinical trial; because of that, the inclusion criteria are therefore more restrictive than those contained in the data sheet of the drug. This initial selection bias, however, could help identify people who may be more responsive to omalizumab in the long run; of course, to remove this bias would require studies with larger series. The safety profile was also shown to be optimal, as no patient showed any systemic or local side effects. A slight increase in total IgE was observed; it was lower than that found by other authors [Hamilton *et al.* 2005]. Concerning this matter, it is well known that patients treated with omalizumab may exhibit a reduction of serum free IgE levels with increased total IgE due to the formation of IgE anti-IgE small immune complexes, which have a longer half-life than free IgE [Hamilton *et al.* 2005; Hayashi *et al.* 2006]. However, this condition does not have any pathological significance, and it has not been detected in all studies; for example, a paediatric study showed a decrease of total IgE after omalizumab treatment [Steiss *et al.* 2008].

The estimated increase in direct costs is therefore significantly offset by the medium- and long-term savings made by healthcare services. These savings are also independent of quantifying the improvement in work and school performance, the probable reduction in comorbidity and long-term complications linked to the chronic use of systemic steroids and the significant improvement in QoL.

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Conflict of interest statement

Francesco Menzella and Luigi Zucchi participated in the clinical trial and contracted research for Novartis.

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