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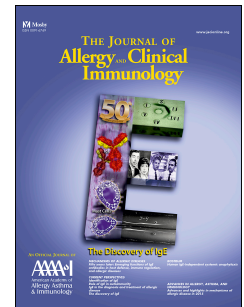
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**Omalizumab is effective in cold urticaria - results of a randomized, placebo
controlled trial**

Martin Metz, M.D.¹, Andrea Schütz, M.D.¹, Karsten Weller, M.D.¹, Marina Gorczyza,
M.D.¹, Sebastian Zimmer, M.D.², Petra Staubach, M.D.², Hans F. Merk, M.D.³,
Marcus Maurer, M.D.¹

¹Dept. of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Germany

²Dept. of Dermatology, University Medical Center Mainz, Mainz, Germany

³Dept. of Dermatology and Allergy, RWTH Aachen University, Aachen, Germany

Corresponding author:

Marcus Maurer, MD

Dept. of Dermatology and Allergy

Charité – Universitätsmedizin Berlin

Charitéplatz 1

D-10117 Berlin, Germany

Phone: +49-30-450-518 043

Fax: +49-30-450-518 972

Email: marcus.maurer@charite.de

22 Short summary

23 We report the results of a randomized, controlled study that shows that omalizumab
24 reduces individual temperatures required to induce symptoms (critical temperature
25 thresholds) and is well tolerated in cold urticaria patients unresponsive to
26 antihistamines.

To the editor:

Cold urticaria, a common and dangerous form of chronic inducible urticaria, is characterized by itchy wheals, angioedema, or both that typically occur within minutes at cold-exposed skin and mucosal sites.¹ Cold urticaria accounts for one third of all cases of physical urticaria and it is the most dangerous urticaria disease with potential loss of consciousness and death due to extensive cold contact.² Up to 72% of cold urticaria patients experience systemic reactions after extensive cold contact.² The underlying cause of cold urticaria is as of yet largely unknown. However, at least in some patients, IgE has been shown to be a relevant factor.³ As the trigger of cold urticaria, i.e. cold exposure, is difficult if not impossible to avoid in everyday life, effective symptomatic treatment is needed. In many patients, antihistamine treatment, even with higher than standard doses, is not sufficient to control the occurrence of cold urticaria signs and symptoms.^{4, 5} Several case reports suggest that patients with cold urticaria can benefit from treatment with omalizumab, a humanized anti-IgE antibody.^{6, 7} Here, we report the results of an investigator-initiated multicenter phase 2 trial evaluating the efficacy and safety of two different doses of omalizumab as compared to placebo in patients with cold urticaria refractory to antihistamine treatment.

Results

31 cold urticaria patients were recruited at three study centers, and all patients were included in the primary endpoint and safety analysis (For details on study procedures see supplementary material and Fig E1). The planned number of patients to be included was 60, but an independent blinded interim analysis was performed for ethical reasons after half of all planned patients had been included. Cold urticaria is a potentially life threatening disease and placebo treatment of patients does not

provide protection from cold-induced systemic reactions including anaphylactic shock. As the interim analysis showed marked clinical and statistical superiority of omalizumab compared to placebo, the study was terminated. The baseline, demographic and clinical characteristics were comparable in all groups (Table E1). Mean changes from baseline in the individual temperatures required to induce symptoms (i.e. critical temperature thresholds) at week ten (primary endpoint) were markedly and significantly higher (Fig 1A) both in the group receiving 150 mg omalizumab ($-10.6^{\circ}\text{C} \pm 2.4$, $p=0.001$) and 300 mg omalizumab ($-10.4^{\circ}\text{C} \pm 3.1$, $p=0.013$), compared with placebo ($-0.3^{\circ}\text{C} \pm 1.1$) (Fig 1A). The treatment with omalizumab resulted in a rapid reduction of critical temperature thresholds with first improvements seen as early as four weeks after the first treatment (Fig 1B). In the follow up period after the last injection, critical temperature thresholds in the omalizumab groups increased and did not show differences to those in the placebo group six weeks after the last injections. No significant difference between 150 mg and 300 mg omalizumab was observed at any time during the study (Fig 1A, B). Individual critical temperature thresholds can differ considerably. Therefore, we additionally assessed the critical temperature thresholds in every patient at baseline and ten weeks later (Fig 1C). Patients with low and high baseline critical temperature thresholds showed similar responses to omalizumab treatment. Furthermore, the rate of patients responding to treatment is an important parameter of treatment efficacy. The responder analysis showed significant differences between the groups ($p=0.012$, Chi-Squared Test). The rate of cold urticaria patients with complete response at week 10 after placebo treatment was 0/12 (0%), whereas 4/10 (40%) showed complete response to 150 mg omalizumab and 4/9 (44%) to omalizumab 300 mg (Fig 1C). No response at all was observed in 9/12 (75%) of patients treated with placebo, 1/10 (10%) of omalizumab 150 mg, and 2/9 (22%) of omalizumab 300 mg

treated patients (Fig 1C). The frequency of adverse events was similar across all groups, and no serious adverse event occurred in any of the treatment groups (Table E2).

Here, we show that omalizumab is effective in cold urticaria with effect sizes that are comparable to those in chronic spontaneous urticaria patients treated with omalizumab. Furthermore, the rate of complete responders, i.e. patients with no symptoms at all, is comparable in clinical trials of omalizumab in chronic spontaneous urticaria (34-40%)⁸ and our studies in cold urticaria (44%), indicating overall similar efficacy of omalizumab in patients with CSU and cold urticaria refractory to antihistamine treatment.

Interestingly, omalizumab was found to be similarly effective in both doses, 150 mg and 300 mg, with no statistical differences between the two treatment groups. This is in contrast to chronic spontaneous urticaria, where also both doses have been reported to be effective, but 300 mg omalizumab has been shown to be more effective in the reduction of symptoms than 150 mg omalizumab.⁸ In chronic spontaneous urticaria, efficacy of omalizumab appears to be largely independent of the levels of total IgE. This has led to the licensing of a fixed dose (300mg) for treatment in chronic spontaneous urticaria irrespective of the levels of total IgE. Whether this may be different in cold urticaria, and thus whether non-responders to omalizumab may have different levels of IgE as responders, we cannot answer here. In a comparison of responders and partial or non-responders (Table E3), more atopic patients were seen in the group of complete responders (5 of 8 vs 1 of 11, respectively; $p=0.04$). The numbers of patients in this comparison is, however, too low to draw a final conclusion. Future clinical trials with more patients will have to be performed to answer this and to show whether 150mg omalizumab is, in contrast to chronic spontaneous urticaria, the optimal dose. Interestingly, the efficacy of

omalizumab in cold urticaria was found to be similar irrespective of the critical temperature thresholds at baseline, indicating that disease severity is not a predictor of treatment response.

It is as of yet unknown why omalizumab has these strong effects on disease activity in cold urticaria. The relevance of IgE in is still controversially discussed and the pathophysiologic role of IgE in chronic inducible urticaria in general is largely unknown. Experiments using passive serum transfer have suggested that a soluble transferable factor, presumably IgE, might be involved, in some patients, in the pathogenesis of physical urticaria forms such as symptomatic dermographism, solar urticaria, and cold urticaria.^{3, 9, 10} The marked efficacy of anti-IgE treatment seen here argues in favor of a pathogenetic role for IgE in cold urticaria. This could be a specific IgE, which is directed against a skin-derived protein that becomes accessible upon stimulation by cold. Future investigations need to be carried out to better characterize the role of IgE in cold urticaria pathogenesis and the mechanism of action of omalizumab in cold urticaria. Also, additional controlled trials are needed to test if omalizumab is similarly effective in other chronic inducible urticaria types such as solar, heat or pressure urticaria - diseases that all have been described in case reports to be effectively treated by omalizumab.

In conclusion, omalizumab in doses of 150 mg and 300 mg resulted in a high rate of complete and partial responders in patients with cold urticaria and a pronounced overall reduction of disease activity. The results of the studies show that cold urticaria patients unresponsive to antihistamine treatment can benefit from a well-tolerated and effective treatment with omalizumab.

Martin Metz, M.D.¹

Andrea Schütz, M.D.¹

Karsten Weller, M.D.¹

Marina Gorczyza, M.D.¹

133 Sebastian Zimmer, M.D.²

134 Petra Staubach, M.D.²

135 Hans F. Merk, M.D.³

136 Marcus Maurer, M.D.¹

137

138 ¹Dept. of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Germany

139 ²Dept. of Dermatology, University Medical Center Mainz, Mainz, Germany

140 ³Dept. of Dermatology and Allergy, RWTH Aachen University, Aachen, Germany

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Keywords

Inducible urticaria, omalizumab, cold urticaria, IgE

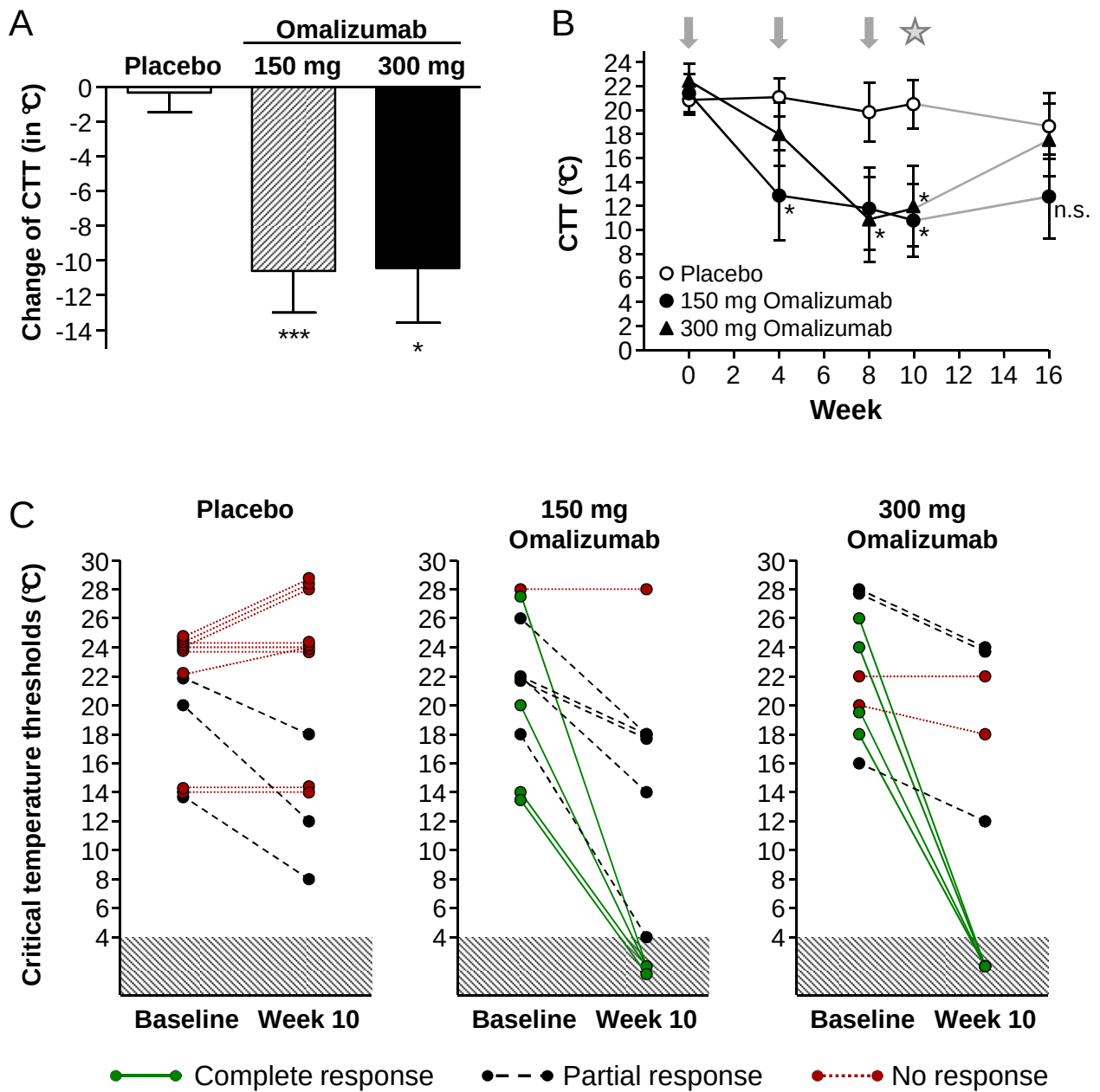
Figure legend**Figure 1. Omalizumab is effective in cold urticaria.**

Critical temperature thresholds (CTT) were assessed using TempTest® and mean reduction of CTT from baseline at the primary endpoint at week ten (**A**) and mean absolute values at every investigated time point is shown (**B**). Omalizumab 150 mg, omalizumab 300 mg, or placebo were injected subcutaneously three times every four weeks (indicated by an arrow). The star indicates the primary endpoint readout two weeks after the last injection. Individual provocation thresholds before and after treatment are shown in **C**. Individual CTT before and after treatment, CTT were assessed using TempTest®

*= $p<0.05$, **= $p<0.01$, ***= $p<0.005$, n.s.=not significant.

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Figure

Supplementary Material

Methods

We performed an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of two doses of omalizumab over 16 weeks in adult patients with antihistamine-refractory cold urticaria (CUTEX trial). The trial was conducted in university hospitals in Berlin, Mainz and Aachen, all in Germany. The study protocol was approved by all relevant ethics committees and the German regulatory authority for monoclonal antibodies (Paul Ehrlich Institut) and was conducted in accordance with the Declaration of Helsinki. The study has been registered with EudraCT (2011-003746-41) and with ClinicalTrials.gov (NCT 01580592). Participants were recruited from Jul 1, 2012 to Dec 31, 2014.

Patients

All patients were and had to be between 18 and 75 years old with a history of at least 6 months of ColdU refractory to antihistamine treatment. Exclusion criteria included treatment with systemic steroids, cyclosporine, methotrexate, dapsone, or other immunosuppressives within the previous 4 weeks, the use of any antihistamine or leukotriene antagonist four days prior to visit 1, a history of malignancies within five years before the screening visit, a known hypersensitivity to omalizumab, previous treatment with omalizumab, and pregnancy. Before inclusion, all patients provided written informed consent.

Randomization and masking

After a one to two week screening period, patients were randomly assigned to receive omalizumab 150 mg, omalizumab 300 mg, or placebo in a ratio of 1:1:1. No stratification was used. Patients were enrolled by the respective study centers and randomized centrally to the treatment arms using a randomization list provided by the study drug provider (Novartis, Basel, Switzerland), who was not involved in the rest of the trial. Blinding of study medication was achieved by using placebo containing the same ingredients as the omalizumab formulation, excluding omalizumab. There were no visible differences between omalizumab and placebo, however, the viscosity of the two differed. Therefore, a separate and independent unblinded study team, which did not engage in study-specific communication with the blinded study team, was responsible for the preparation and injection of the study drug. Unblinded study team members were not involved in any other parts of the trials.

Procedures

Each patient received three s.c. injections of 150 mg omalizumab, 300 mg Omalizumab, or placebo in 4-week intervals, with the primary readout two weeks after the last injection. This ten week treatment period was followed by a six week follow-up period. At the end of week 0, 4, 8, 10, and 16, patients underwent provocation tests at the study center to assess trigger thresholds. For the determination of critical temperature thresholds, TempTest® 4.0 (Courage + Khazaka Electronics GmbH, Germany) was used, a validated device for standardized and reproducible cold provocation^{E1}.

Outcomes

The primary outcome was the change of the critical temperature threshold, i.e. the temperature at which a patient will start to develop symptoms, from baseline to week ten of the treatment period, as determined by provocation testing using TempTest®. Secondary outcomes included the safety of patients treated with omalizumab, the long-term effects of omalizumab on the reduction of trigger thresholds, and the rate of complete and partial responder to omalizumab. Safety was evaluated by recording and monitoring the frequency of treatment-emergent adverse events and serious adverse events. Long term effects were assessed eight weeks after the last injection. Complete response to treatment was defined as a negative provocation test result for the lowest temperature (4°C), at the end of week ten after the start of treatment. Partial response was defined as an improvement of the critical temperature threshold of at least 4°C.

Statistical analysis

CUTEX is the first clinical trial with the aim to obtain efficacy and safety data for omalizumab in ColdU. Accordingly, a sample size calculation based on previous data was not possible.

Baseline demographic data and clinical characteristics are expressed as frequency (n) and percentages for gender, median and interquartile range (IQR) for age, and mean $\pm$ SD for BMI, provocation thresholds and duration of disease. Continuous variables, i.e. changes from baseline in provocation threshold at week ten (primary endpoint) as well as CTT at different time points during the study course, are expressed as means $\pm$ SEMs. Categorical data (responder rates) are presented as frequencies (n) and percentages.

The primary endpoint was analyzed by one-way ANOVA. In case of a significant result, all three treatment arms were compared without correction for multiple testing

by using the unpaired student's *t*-test. The latter was also applied for the comparison of the CTT at different time points during the study course. In all analyses with the unpaired student's *t*-test, p-values were chosen from the test performed either for 'equal variances assumed' or for 'equal variances not assumed', depending on the Levene's test for equality of variances. The responder distribution at week ten was compared between treatment arms with the chi-squared test. The statistical program used was IBM SPSS Statistics Version 22.

All efficacy analyses were done in the per protocol population, safety analyses were performed in all participants who received at least one dose of study drug.

Role of the funding source

The trial was an investigator-initiated trial funded, in part, by Novartis and by intramural grants. Novartis had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Supplementary reference

- E1. Magerl M, Abajian M, Krause K, Altrichter S, Siebenhaar F, Church MK. An improved Peltier effect-based instrument for critical temperature threshold measurement in cold- and heat-induced urticaria. *J Eur Acad Dermatol Venereol* 2015; 29:2043-5.

Supplementary figure legend**Figure E1. Trial profile****Supplementary Tables****Table E1. Baseline demographic and clinical characteristics of the intention-to-treat population by treatment group.**

Data are n (%) for sex, median (IQR) for age, or mean (SD) for BMI, provocation thresholds at baseline and duration of disease.

CTT, critical temperature threshold

Table E2. Reported adverse events.

Adverse events occurring in 5% or more of patients (i.e. more than one patient) in the placebo or either omalizumab group are listed separately. Data are n or n (%).

Adverse events were classified according to ICD-10 classifications. A patient who reported two or more adverse events within the same organ system was counted only once for that term.

Table E3. Comparison of complete responders and partial or non-responders.

Patients were considered positive for “Atopy” if there was a positive history of allergic diseases, e.g. allergic rhino-conjunctivitis.

Abbreviation: CSU, chronic spontaneous urticaria; CINDU, chronic inducible urticaria

* $p = 0.04$, all other parameters showed no statistically significant differences.

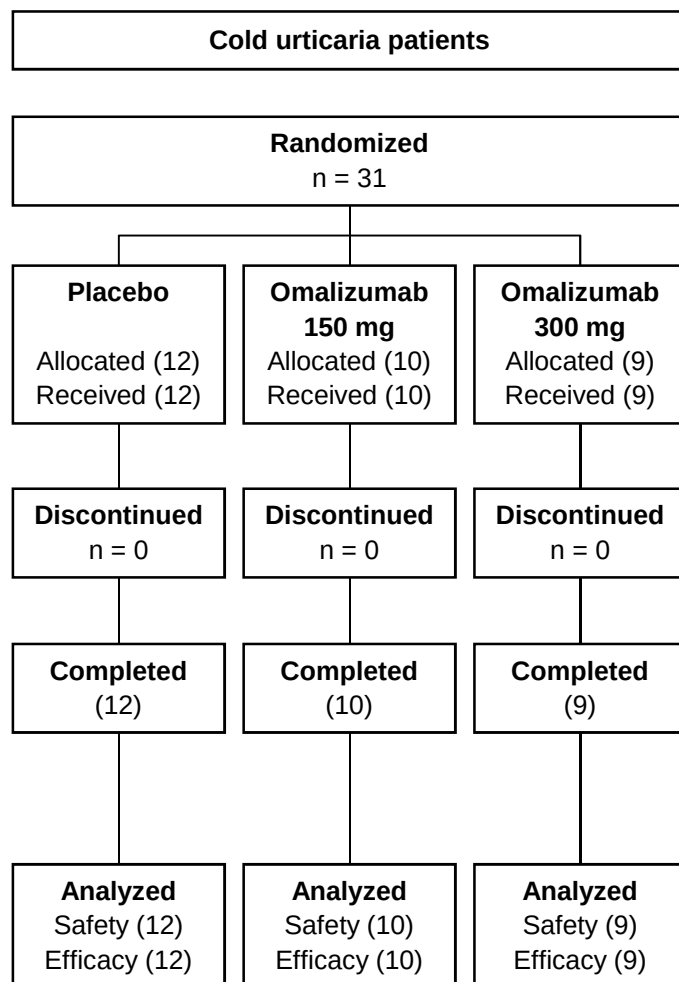


Figure E1

Cold urticaria (ColdU) patients				
	All patients (n=31)	Placebo (n=12)	Omalizumab 150mg (n=10)	Omalizumab 300mg (n=9)
Sex				
Male	8 (26%)	3 (25%)	3 (30%)	2 (22%)
Female	23 (74%)	9 (75%)	7 (70%)	7 (78%)
Age (years)	45 (32-56)	46 (34-50)	32 (28-63)	46 (39-64)
BMI (kg/m²)	27.0 (4.4)	27.0 (4.8)	26.2 (5.1)	27.9 (3.4)
CTT at Baseline (in °C)	21.5 (4.5)	20.8 (4.3)	21.4 (5.1)	22.4 (4.3)
Duration of ColdU (months)	80.8 (86.6)	65.5 (76.1)	103.4 (111.8)	76.2 (72.5)

Table E1

Cold urticaria patients

	Placebo n=12	Omalizumab 150mg; n=10	Omalizumab 300mg; n=9
Total number of adverse events	35	20	18
Total number of serious adverse events	0	0	0
Patients with any adverse event	9 (75%)	7 (70%)	7 (78%)
Patients with any serious adverse event	0	0	0
Discontinuation due to adverse event	0	0	0
AE's observed in more than one patient:			
Upper respiratory tract infection	4 (33%)	2 (20%)	2 (22%)
Other infections	4 (33%)	1 (10%)	1 (11%)
Headache	1 (8%)	2 (20%)	2 (22%)
Local reaction at injection site	0	2 (20%)	0

Table E2

	Non or partial responder (n=11)	Complete responder (n=8)
Atopy	1 (9.1%)	5 (62.5%)*
Food allergy	1 (9.1%)	1 (12.5%)
CSU comorbidity	1 (9.1%)	0 (0%)
Presence of other types of CINDU	1 (9.1%)	0 (0%)
Duration of ColdU (years, mean $\pm$ SEM)	9.5 (2.5)	4.9 (2.3)

Table E3.