Onset of action of loratadine/montelukast in seasonal allergic rhinitis patients exposed to grass pollen

Friedrich Horak¹, Petra Zieglmayer¹, René Zieglmayer², Patrick Lemell²

¹ Medical University of Vienna, ENT Department, Vienna, Austria
² Allergy Center Vienna West, Vienna, Austria

Correspondence to: Prof. Dr. Friedrich Horak, ENT University Clinic, Währinger Gürtel 18–20, 1090 Vienna, Austria; e-mail: f.horak@vcc.at

Key words
- Allergic rhinitis
- CAS 79794-75-5
- CAS 151767-02-1
- Loratadine
- Montelukast
- Nasal congestion
- Vienna Challenge Chamber

Arzneimittelforschung
2010;60(■):■–■
Abstract

Given the impact of allergic rhinitis (AR) on quality of life, it is important that AR medications have rapid onset of symptom relief. The objective of this study was to determine the onset of action of loratadine (CAS 78979-75-5)/montelukast (CAS 151767-02-1) 10 mg/10 mg (L/M) versus placebo in seasonal AR (SAR) subjects. In this single-center, double-blind, cross-over study, subjects with SAR and confirmed sensitivity to grass pollen received single doses of L/M or placebo following exposure to grass pollen in the Vienna Challenge Chamber. Subjects recorded symptoms at 15-min intervals during the first 2 h post dose and at 30-min intervals during the next 2 h. After a 14-day washout, the subjects crossed over to the other treatment. The primary endpoint was onset of action of L/M, defined as the first time point at which the mean change from baseline in total symptom score became and remained significantly different with L/M versus placebo. Secondary endpoints included nasal congestion score and rhinomanometry findings. Onset of action with L/M for total symptom score was 1 h, 45 min ($P < 0.01$ vs placebo). Significant improvements in subject-assessed nasal congestion scores ($P < 0.01$) and rhinomanometry ($P = 0.036$) were noted with L/M as compared with placebo. Overall, L/M was well tolerated. In conclusion, L/M demonstrated rapid onset for broad symptom relief, including nasal congestion, in subjects with SAR.

1. Introduction

Although traditional outpatient studies during peak allergy seasons provide “real-world” conditions suitable for determining the overall efficacy and tolerability of seasonal allergic rhinitis (AR) therapies, the pharmacodynamics of these medications are best studied under the precisely controlled and monitored conditions of allergen challenge chambers (ACCs) [1–3]. Unlike studies performed during the pollen seasons, studies performed in challenge chambers can control for such variables as day-to-day differences in pollen counts/exposure to allergens, patient adherence to medication regimens, and the bias inherent in a trial where subjects must recall symptoms and record them in a diary that is returned to the center [2, 3]. In challenge chamber studies, subjects are under constant supervision of study investigators, ensuring closer monitoring of the timing and recording of their subjective responses (i.e., AR symptom measurements) and adherence to medication [3]. Additionally, investigators can perform more precise objective measures of nasal patency, such as rhinomanometry and weighing of nasal secretions, which are more difficult to incorporate into outpatient studies or for which multicenter and outpatient designs render the data less accurate [3, 4].

Because of their complexity of design, there are a limited number of allergen challenge chambers [3]. The first such chamber, the Vienna Challenge Chamber (VCC) at the University Clinic of Vienna, Austria, was developed in 1985 and rebuilt and renovated in 1992 and 2002 [3]. This system features a monitored, forced-air ventilation system with openings near the ceiling and floor to ensure uniform distribution of the chal-
lenge allergen, smooth surfaces in the chamber that are
constructed of aluminum to prevent allergen accumula-
tion, and a window for constant observation [3]. As
many as 20 subjects can be in the enclosed system at
one time and are exposed to a uniform concentration
of grass pollen (monitored every 5 min), constant hu-
midity (35%) and consistent ambient temperature
(24°C; monitored every 5 s) [5]. These conditions result
in reproducible assessments of study medications [6,
7]. Reproducibility of assessments is an important fac-
tor, particularly in the allergen exposure experimental
model and to study onset of action and efficacy of AR
medications [3, 6–10].

Of the symptoms of AR (eg, sneezing, runny nose,
watery eyes), subjects rank nasal congestion as the most
frequent and bothersome symptom [11, 12]; moreover,
subjects experience decreased work productivity as well
as sleep and emotional disturbance associated with this
symptom [11, 13–15]. Pharmacodynamic studies con-
ducted in ACCs contribute to the characterization of AR
treatment efficacy by providing accurate determinations
and comparisons of the onset and duration of action for
multiple symptom parameters, including nasal conges-
tion. These data may then be used to help guide treat-
ment decisions for patients with AR because the ideal
qualities of an AR medication include efficacy against a
broad range of symptoms; ability to improve patient
quality of life; and lack of the need for comedications
as well as the rapid onset and effective symptom relief
that can be sustained for 24 h [3, 16].

Loratadine (CAS 79794-75-5)/montelukast (CAS 151767-
02-1) (L/M) is a single fixed dose of 10 mg of loratadine
and 10 mg of montelukast in an oral tablet. Both agents
are approved for the treatment of AR symptoms: lorata-
dine is a nonsedating, selective peripheral histamine-1
receptor antagonist and montelukast is a selective cy-
steinyl leukotriene (CysLT1) receptor antagonist. L/M
has 24-h efficacy for the relief of a broad range of nasal
and ocular symptoms and for measurements of nasal
patency [17–19]. In one of these studies, an outpatient
trial evaluating 2 weeks of treatment during the spring
allergy season, L/M treatment significantly reduced the
daytime nasal symptom score (average of the scores for
the individual symptoms of nasal congestion, rhinor-
hea, itching, and sneezing) as well as significantly re-
duced nasal congestion compared to placebo (P < 0.001
and P < 0.05, respectively) [17]. In another study, 2
weeks of treatment with L/M during the spring allergy
season was as effective as pseudoephedrine in relieving
daytime and nighttime nasal congestion and improving
peak nasal inspiratory flow (PNIF) [19]. The efficacy and
pharmacodynamics of L/M in patients with AR exposed
to ragweed pollen also have been evaluated in 2 pre-
vious studies conducted in ACCs [20, 21]. In the first
study, L/M was more effective than phenylephrine in re-
lieving nasal congestion [20]. The second study revealed
that L/M had an onset of action of 1 h and 15 min versus
placebo for the primary parameter of change from base-
line in total symptom scores (TSS) [21]. This paper presents the results of a similarly designed study that investigates the onset of action of L/M compared with placebo in subjects with AR exposed to grass pollen in the VCC.

2. Patients and methods

2.1 Study design

This was a phase III, double-blind, placebo-controlled crossover study conducted at a single center in Vienna, Austria. Prior to enrollment, the subjects were screened at an initial office visit 1 to 14 days before the first treatment visit. At screening, the subjects’ eyes, ears, and upper and lower respiratory tract were examined and a medical history was taken. Those who had not been tested within the past 12 months underwent skin prick or intradermal testing to confirm sensitivity to grass pollen. Eligible participants were randomized at the first treatment visit to receive a single dose of either L/M 10 mg/10 mg or placebo. After a 14-day washout period, subjects were then crossed over to the other arm for treatment visit 2 (L/M → placebo; placebo → L/M). At each treatment visit, subjects entered the VCC and recorded symptoms using a computer-based diary system every 15 min for 2 h before dosing; those not meeting the symptom inclusion criteria during this interval were not randomized.

The subjects were randomized sequentially using numbers generated by the UNIFORM function of the SAS software. Each subject received a single dose of L/M and placebo as determined by the computer-generated random code, with one treatment administered at the first visit and the second treatment administered after a 2-week washout period. Active treatment and placebo tablets were identical in appearance, and the investigator, subjects, and study center staff were blinded to treatment assignment. All subjects provided written informed consent at the screening visit prior to any procedures. The trial protocol and informed consent forms were approved by an independent ethics committee, and the study was conducted in accordance with Good Clinical Practice standards and International Conference on Harmonisation guidelines.

2.2 Study preparations

In this study, the combination, L/M was evaluated in subjects with AR. L/M is a single fixed dose of 10 mg of loratadine and 10 mg of montelukast in an oral tablet. Both agents are approved for the treatment of AR symptoms. Loratadine is a non-sedating, selective peripheral histamine-1 receptor antagonist and montelukast is a selective cysteinyl leukotriene (CysLT1) receptor antagonist. Both the active and placebo tablets were manufactured by Merck Frosst Canada Ltd., Kirkland, Quebec, Canada. Study drug and placebo tablets and clinical trial supplies were distributed by the sponsor, Schering-Plough Research Institute, Kenilworth, NJ (USA).

2.3 Subjects

Eligible participants were aged ≥19 years with a minimum 2-year history of seasonal AR (SAR) and a positive skin prick or intradermal test within the past 12 months confirming hypersensitivity to grass pollen. Additionally, subjects were required to have nasal congestion symptom scores of ≥2, total nasal symptom scores (TNSS) of ≥7, total non-nasal symptom scores (TNNSS) of ≥3, and TSS of ≥10 following exposure to the grass
pollen allergen in the ACC (time point, 0 h) at both treatment
visits. Women had to have had a negative serum pregnancy test
at screening and be using a medically accepted method of birth
control. Subjects who had a respiratory infection within the
2 weeks prior to the predose evaluation, at the first treatment
visit, or at anytime during the treatment phase were excluded.
Those who, in the opinion of the investigator, were dependent
upon nasal, oral, or ocular decongestants; nasal topical antihis-
amines; or nasal steroids were also excluded. Other exclusion
criteria were rhinitis medicamentosa, nasal structural abnorm-
alities significantly impairing air flow, or other clinically signif-
icant medical condition that might interfere with the study or
require treatment.
Prohibited medications generally were those used to treat in-
flammatory respiratory conditions and nasal and ocular allergy
symptoms, such as antihistamines, decongestants (including
pseudoephedrine), cromolyn sodium, corticosteroids of any
kind (except for low-potency topical corticosteroids), antileu-
kotrienes, and nasal and ocular saline. Immunotherapy and
systemic antibiotics, with the exception of a stable dose for pre-
ventive treatment, were also prohibited. Subjects who had been
taking prohibited medications were required to have disconti-
ued their use 3 months to 12 h (depending on the specific med-
ication) before the first treatment visit and not to use them for
the duration of the study.

2.4 Efficacy and safety parameters
After dosing of the study medication, the subjects recorded the
symptoms—including anterior or posterior nasal discharge; na-
sal congestion; sneezing; eye tearing; eye redness; and itching
of the eyes, nose, and ears/nasal cavity—at 15-min intervals for the
first 2 h and then at 30-min intervals for next 2 h. Symptoms
were rated on a scale of 0 (none) to 3 (difficult to tolerate). In
addition, as an objective measure of nasal patency, subjects
underwent anterior rhinomanometry every 30 min beginning
2 h before provocation. Subjects were given preweighed tissues
to use, which also were collected every 30 min starting 2 h prior
to provocation. Tissues were then reweighed to measure nasal
secretions. The study’s primary efficacy endpoint was the onset
of action of L/M, which was defined as the first time point at
which L/M became and consistently remained significantly dif-
ferent from placebo in the change from baseline for TSS. Sec-
dondary endpoints included the individual symptom score for
nasal congestion, rhinomanometry measurements, and nasal
secretion weights.
Safety assessments included vital signs and adverse events
(AEs). AEs included physical or clinical changes and the onset
or worsening of disease in participants during the study irre-
spective of relationship to trial medications. Symptoms arising
as a result of SAR were not considered AEs unless judged by
subjects to be unrelated to their underlying SAR. AEs were rated
as mild, moderate, severe, or life threatening and assessed as
unlikely, possibly, or probably related to the study drug. Severe
AEs (SAEs) were those considered life threatening, requiring
hospitalization, or resulting in a congenital abnormality or
birth defect or significant disability.

2.5 Statistics
Assuming a pooled standard deviation of 3.0, it was determined
that a sample size of approximately 64 subjects would ensure
an 80% power to detect a difference of ≥1.5 points in change
from baseline in TSS between L/M and placebo at the 5% sig-
nificance level. Analysis of variance (ANOVA) was used to de-
tect a carryover effect between treatment visits as well as overall response to treatment. If no significant effect of treatment-by-period interaction was found due to a carry-over effect of study drug, the primary and secondary variables at each time point post dose were analyzed using paired t tests. These paired t tests were used to determine the onset of action which was the first time point post treatment at which a consistent statistically significant difference between L/M and placebo occurred. Efficacy analyses were performed for the intent-to-treat (ITT) population, defined as all randomized participants who received both doses of study drug with available follow-up data. Safety analyses were performed on the group of subjects who had received ≥1 dose of study drug.

3. Results

3.1 Subjects

A total of 74 subjects who completed screening were randomized into the study, with 37 subjects in each treatment arm (L/M → placebo; placebo → L/M). Fig. 1 illustrates the flow of participants through the study. Of the 74 randomized subjects, 71 completed the crossover study and comprised the ITT population. There was no imbalance between treatment arms for subject demographics and other baseline characteristics (Tables 1 and 2). The mean age of study participants was approximately 26 years, and subjects had been experiencing SAR symptoms for an average of approximately 13 years. There were more female subjects (57%) than male, and all participants were Caucasian.

*Fig. 1, Tab. 1+2*

3.2 Efficacy

The primary trial endpoint was time to onset of action of L/M for TSS. At baseline, mean TSS was comparable between treatments: 11.99 for L/M and 12.20 for placebo (P > 0.05). Mean change from baseline in TSS for L/M became significantly superior to placebo 1 h, 45 min after dosing (Fig. 2), at which time point symptom scores had decreased by 31.0% for L/M versus 16.3% for placebo (P < 0.01). Differences between L/M and placebo remained consistently significant from this time point until the end of the 4-h treatment observation period (P < 0.01). Decreases from baseline in mean TSS for subjects taking L/M began as quickly as 30 min post dose, and consistent decreases were seen with L/M from 30 min post dose to the end of the 4-h period. In contrast, decreases with placebo leveled off at approximately 18% to 19% from 2 h after dosing until the end of the observation period. After 4 h, L/M had changed TSS by 48.3% from baseline, compared with 19.0% with placebo (P < 0.01; Fig. 3).

Mean baseline nasal congestion scores were comparable between treatments (2.24 with L/M vs. 2.25 with placebo; P > 0.05). L/M treatment significantly reduced nasal congestion (Fig. 4A). The difference in mean change from baseline for L/M versus placebo became significant 2 h after dosing (onset of action), with decreases of 27.9% with L/M and 12.0% with placebo.
(P < 0.01). This difference remained significant at all subsequent time points. At 4 h post dose, the mean nasal congestion score had decreased 34.5 % with L/M compared with 8.0 % with placebo (P < 0.01).

Rhinomanometry readings paralleled the results for subjective nasal congestion symptom scores (Fig. 4B), improving by 8.9 % with L/M but worsening by 5.9 % with placebo at the 2-h time point; the difference between the groups was significant (P = 0.036).

Nasal secretions were significantly reduced from baseline with L/M treatment (baseline nasal secretion was 2.32 g with L/M group and 2.50 g with placebo). The decrease from baseline for this measure with L/M (0.92 g) became significantly different from the decrease with placebo (0.10 g) at 2 h post dose (P < 0.01) and remained significantly different from this time onward.

The mean decrease from baseline in nasal secretions after 4 h was 1.47 g with L/M compared with 0.31 g with placebo (P < 0.01).

3.3 Safety

Overall, the safety profile of L/M was similar to that of placebo. There were no reported abnormalities or clinically significant changes in vital signs at any study visit. Only 3 subjects (4 %) reported an AE during the study: 2 subjects experienced a mild upper respiratory tract infection, and 1 subject experienced a severe, unrelated fracture of the right knee. All 3 subjects had received placebo but were not crossed over to the L/M arm and discontinued the study. There were no deaths or life-threatening SAEs, and only 1 SAE was reported during the study (severe knee fracture). No AEs or SAEs were considered related to study medication.

4. Discussion

The Allergic Rhinitis and Its Impact on Asthma and the European Academy of Allergy and Clinical Immunology workshop noted that AR medications should take effect quickly, maintain that effect for a long duration (ie, 24 h), and provide relief for a broad range of AR symptoms, including nasal and ocular symptoms [16]. In our study in the VCC, the onset of action of L/M for TSS occurred rapidly (1 h, 45 min. after dosing. L/M treatment resulted in decreases in mean TSS scores at every 15-min measurement interval beginning 15 to 45 min post dosing while, in contrast, decreases in the mean score with placebo for these measures tended to level off between 2 h and 2 h, 30 min.

This study also investigated the effect of L/M on nasal congestion using both a subjective measure (subject-assessed symptom scores) and an objective measure (rhinomanometry). There are several techniques and devices available to objectively quantify nasal obstruction/congestion and airflow resistance, including nasal peak air flow meters, acoustic rhinometry, and rhinoseometry, as well as rhinomanometry which is a well
established objective measure [22]. Rhinomanometry is not appropriate for use in studies requiring at-home monitoring, but it is well suited for allergen challenge studies [22, 23]. In our study, rhinomanometry results corresponded with results for nasal congestion scores, with identical onsets of action for L/M versus placebo (2 h post dose). Our study also incorporated a second objective efficacy parameter in nasal secretion weights, which represent an objective measure of nasal hyperresponsiveness [22]. Time to onset of action for change from baseline with L/M versus placebo for nasal secretions also occurred 2 h after dosing, paralleling the results for nasal congestion symptoms and rhinomanometry measurements.

Overall, our results are consistent with those of 2 previous studies investigating the efficacy and onset of action of L/M in challenge chambers. The first study compared L/M 10 mg/10 mg with phenylephrine (PE) 10 mg and placebo for the treatment of nasal congestion in 379 subjects with SAR exposed to ragweed pollen in an environmental exposure unit (EEU) [20]. Although the primary efficacy endpoint was efficacy in the relief of nasal congestion, defined as the average change from baseline during the first 6 h post dosing in the nasal congestion score, onset of action for both active medications versus placebo was an important secondary endpoint. In that study, onset of action was not based on TSS as in the current study but on nasal congestion score, and the results showed that the onset of action with L/M was 2 h, 20 min [20], somewhat longer than the onset of action found in the current trial of 1 h, 45 min. However, when compared with the onset of action for L/M for nasal congestion scores in our study (2 h), the results are more consistent. In the previous study, L/M also was more effective than PE or placebo for relieving nasal congestion during the early phase (the first 6 h) of the allergic response and in improving total, nasal, and non-nasal symptoms and PNIF [20].

In the second study, onset of action for L/M versus placebo was evaluated in 310 subjects with AR exposed to short-ragweed pollen in an EEU (data on file) [21]. The onset of action for L/M versus placebo for mean change from baseline in TSS of 1 h, 15 min was somewhat shorter than our results [21]. Although that trial shared many common elements with our study in design, unlike our study, it was not a crossover trial and was conducted in the EEU as opposed to the VCC [21]. Unlike the VCC, the EEU utilizes a priming technique to mimic the natural increase in sensitivity to allergens experienced by patients with SAR over the course of an allergy season [3]. Both the VCC and the EEU provide accurate and reproducible results and are considered valid techniques to determine AR medication efficacy and pharmacologic properties [3].

In conclusion, the current study found a rapid onset of action for L/M versus placebo for improving TSS, which includes nasal congestion, rhinorrhea, nasal itching, sneezing, and ocular symptoms. In addition to sub-
ject-assessed nasal congestion symptoms, L/M also im-
proved objective measures of nasal patency. The inci-
dence of AEs in the study was low, and no AEs were
considered related to study medication.

Acknowledgments
Support for this paper was provided by the Schering-Plough/
Merck Pharmaceuticals. The author thanks Christina McMa-

Literature
JM, Rehn D. Pharmacodynamic dose finding of dimetind-
dene in a sustained release formulation. Arzneimittel-
[2] Day JH, Ellis AK, Rafeiro E, Ratz JD, Briscoe MP. Experi-
mental models for the evaluation of treatment of aller-
Krug N, et al. The role of allergen challenge chambers in
the evaluation of anti-allergic medication: an international
Geldmacher H, et al. Validation of an environmental expo-
sure unit for controlled human inhalation studies with
grass pollen in patients with seasonal allergic rhinitis. Clin
[5] Horak F, Stubner UP, Zieglmayer R, Harris AG. Effect of de-
sloratadine versus placebo on nasal airflow and subjective
measures of nasal obstruction in subjects with grass pol-
len-induced allergic rhinitis in an allergen-exposure unit. J
of the effects of desloratadine 5-mg daily and placebo on
nasal airflow and seasonal allergic rhinitis symptoms in-
Perez L, et al. Effects of rupatadine vs. placebo on aller-
gen-induced symptoms in patients exposed to aeroallergi-
gens in the Vienna challenge chamber. Ann Allergy Asthma
of astemizole-D and loratadine-D during prolonged, con-
trolled allergen challenge in the Vienna challenge cham-
transally applied dimethindene maleate solution as spray
in adult volunteers with symptoms of seasonal allergic rh-
nitis in the Vienna challenge chamber. Arzneimittelfor-
and tolerability of intranasally applied dimethindene male-
ate solution versus placebo in the treatment of seasonal
allergic rhinitis. Arzneimittelforschung. 2000;50(12):1099–
105.
and work productivity in allergic rhinitis: findings from a
sufferers. Executive summary: available at:


Fig. 1: Flow of participants through the study.

Fig. 2: Onset of action of loratadine/montelukast (L/M): mean change from baseline in total symptom score across time with L/M versus placebo (n = 71).

Fig. 3: Mean percentage change from baseline in total symptom score (TSS), total nasal symptom score (TNSS), and total non-nasal symptom score (TNNSS) 4 h post dose with loratadine/montelukast (L/M) and placebo (n = 71).
Fig. 4A: Mean change from baseline in nasal congestion score across time with loratadine/montelukast (L/M) versus placebo (N = 71).

Fig. 4B: Mean change from baseline in sum of nasal flow by rhinomanometry across time with loratadine/montelukast (L/M) versus placebo (N = 71).
Table 1: Subject demographics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo → L/M (n = 37)</th>
<th>L/M → Placebo (n = 37)</th>
<th>All subjects (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (years)</td>
<td>26.5</td>
<td>25</td>
<td>25.8</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22 (59)</td>
<td>20 (54)</td>
<td>42 (57)</td>
</tr>
<tr>
<td>Male</td>
<td>15 (41)</td>
<td>17 (46)</td>
<td>32 (43)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>37 (100)</td>
<td>37 (100)</td>
<td>74 (100)</td>
</tr>
<tr>
<td>Duration of AR, mean (years)</td>
<td>12.4</td>
<td>12.9</td>
<td>12.7</td>
</tr>
</tbody>
</table>

Table 2: Baseline characteristics.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>L/M (mean ± SEM)</th>
<th>Placebo (mean ± SEM)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSS</td>
<td>11.99 ± 0.22</td>
<td>12.20 ± 0.23</td>
<td>0.312</td>
</tr>
<tr>
<td>Nasal congestion score</td>
<td>2.24 ± 0.05</td>
<td>2.25 ± 0.05</td>
<td>0.857</td>
</tr>
<tr>
<td>Rhinomanometry</td>
<td>716.3 ± 42.1</td>
<td>705.3 ± 38.3</td>
<td>0.764</td>
</tr>
<tr>
<td>Nasal secretions</td>
<td>2.32 ± 0.25</td>
<td>2.50 ± 0.29</td>
<td>0.435</td>
</tr>
</tbody>
</table>

Hinweis zu den Nutzungsrechten (keine Gültigkeit für Presseinformationen!) · Right of use (not valid for press releases)

Mit der Unterzeichnung der Druckfreigabeerklärung räumt der Autor dem Verlag das ausschließliche zeitlich, räumlich und inhaltlich unbeschränkte Recht zur Veröffentlichung, Vervielfältigung, Verbreitung und öffentlichen Wiedergabe in allen Sprachen und Ländern ein, einschließlich des Rechts zur Speicherung in und Nutzung durch Datenbanken jeder Art (Online, auch Internet, und Offline) sowie der weiteren Vervielfältigung zu gewerblichen Zwecken im Wege des fotomechanischen oder eines anderen Verfahrens.

By signing “Ok to print”, the author grants the publisher the exclusive right – unrestricted with regard to time, territory and contents – of publication, duplication, distribution and public communication in all languages and countries, including the right of storage and use in databases of any kind (online including internet and offline) as well as of the further duplication for commercial purposes by photomechanical reproduction or other techniques.

Nach Erledigung der Korrektur: ☐ zum Druck frei / OK to print
After completing corrections: ☐ neuer Abzug erbeten / new galley proof requested

Datum / Date
Unterschrift / Signature