Combination of Empagliflozin and Linagliptin as Second-Line Therapy in Subjects With Type 2 Diabetes Inadequately Controlled on Metformin

DOI: 10.2337/dc14-2364

OBJECTIVE
To evaluate the efficacy and safety of combinations of empagliflozin/linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin.

RESEARCH DESIGN AND METHODS
Subjects were randomized to a combination of empagliflozin 25 mg/linagliptin 5 mg (n = 137), empagliflozin 10 mg/linagliptin 5 mg (n = 136), empagliflozin 25 mg (n = 141), empagliflozin 10 mg (n = 140), or linagliptin 5 mg (n = 132) as add-on to metformin for 52 weeks. The primary end point was change from baseline in HbA1c at week 24.

RESULTS
At week 24, reductions in HbA1c (mean baseline 7.90–8.02% [62.8–64.1 mmol/mol]) with empagliflozin/linagliptin were superior to those with empagliflozin or linagliptin alone as add-on to metformin; adjusted mean (SE) changes from baseline were −1.19% (0.06) (−13.1 mmol/mol [0.7]) with empagliflozin 25 mg/linagliptin 5 mg, −1.08% (0.06) (−11.8 mmol/mol [0.7]) with empagliflozin 10 mg/linagliptin 5 mg, −0.62% (0.06) (−6.8 mmol/mol [0.7]) with empagliflozin 25 mg, −0.66% (0.06) (−7.2 mmol/mol [0.7]) with empagliflozin 10 mg, and −0.70% (0.06) (−7.6 mmol/mol [0.7]) with linagliptin 5 mg (P < 0.001 for all comparisons). In these groups, respectively, 61.8, 57.8, 32.6, 28.0, and 36.1% of subjects with baseline HbA1c ≥7% (≥53 mmol/mol) had HbA1c <7% (<53 mmol/mol) at week 24. Efficacy was maintained at week 52. The proportion of subjects with adverse events (AEs) over 52 weeks was similar across treatment arms (68.6–73.0%), with no hypoglycemic AEs requiring assistance.

CONCLUSIONS
Combinations of empagliflozin/linagliptin as second-line therapy for 52 weeks significantly reduced HbA1c compared with the individual components and were well tolerated.
Empagliflozin is the recommended first-line pharmacotherapy for patients with type 2 diabetes (1), but most patients will ultimately require additional therapies to maintain glycemic control (2,3). Maintaining intensive glucose control early in the disease process may lead to legacy benefits that persist beyond the period of treatment (4). Therefore, when metformin fails to achieve glycemic control, add-on combination therapy with two oral antidiabetes agents may be beneficial.

Inhibition of the sodium glucose co-transporter 2 (SGLT2), located in the proximal tubule of the kidney, reduces renal glucose reabsorption, thereby increasing urinary glucose excretion and reducing hyperglycemia in patients with type 2 diabetes (5). Since this mechanism is independent of insulin, SGLT2 inhibition is associated with a low risk of hypoglycemia. Additional benefits include weight loss (6) and reduction in blood pressure (7). Empagliflozin is a potent and selective SGLT2 inhibitor (8). In a phase III trial in patients with type 2 diabetes, empagliflozin 10 and 25 mg given as add-on to metformin for 24 weeks were well tolerated, with a low risk of hypoglycemia, and produced clinically relevant reductions in HbA1c, fasting plasma glucose (FPG), weight, and blood pressure versus placebo (9).

Inhibitors of dipeptidyl peptidase-4 (DPP-4) reduce blood glucose in patients with type 2 diabetes by preventing degradation of incretin peptides such as GLP-1, stimulating insulin release and inhibiting glucagon secretion (10). As DPP-4 inhibition leads to a glucose-dependent release of insulin, it is associated with a low risk of hypoglycemia (11). Linagliptin is a potent and selective DPP-4 inhibitor (12). In a phase III trial in patients with type 2 diabetes, linagliptin 5 mg given as add-on to metformin for 24 weeks improved glycomic control without weight gain and was well tolerated, with a low risk of hypoglycemia (13).

Given the complementary mechanisms of action of SGLT2 inhibitors and DPP-4 inhibitors, a combination of empagliflozin and linagliptin as add-on to metformin (triple therapy) may offer particular treatment benefits compared with the addition of either empagliflozin or linagliptin as add-on to metformin (dual therapy). This study evaluated the efficacy and safety of a once daily combination of empagliflozin/linagliptin as add-on to metformin in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS
Study Design
This was a phase III, randomized, double-blind, parallel-group study conducted from August 2011 to September 2013 in 197 centers in 22 countries. The clinical trial protocol was approved by the institutional review boards, independent ethics committees, and competent authorities of the participating centers and complied with the Declaration of Helsinki in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice. All subjects provided written informed consent. The trial was registered with clinicaltrials.gov (NCT01422876).

Inclusion and Exclusion Criteria
The study enrolled subjects aged ≥18 years with BMI ≤45 kg/m² and HbA1c >7 to ≤10.5% (>53 to ≤91 mmol/mol) at screening who had been treated with metformin immediate release (≥1,500 mg/day, maximum tolerated dose, or maximum dose according to local label) at an unchanged dose for ≥12 weeks prior to randomization and were on a diet and exercise regimen.

Exclusion criteria included uncontrolled hyperglycemia (glucose level >240 mg/dL after an overnight fast confirmed by a second measurement during placebo run-in); treatment with any antidiabetes drug except metformin within 12 weeks prior to randomization; estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) equation; acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent; bariatric surgery in the last 2 years; investigational drug intake within 1 month prior to consent; and treatment with antiobesity drugs within 3 months prior to consent.

Treatment and Interventions
After a 2-week placebo run-in period, subjects were randomized (1:1:1:1:1) to receive empagliflozin 25 mg/linagliptin 5 mg as a fixed dose combination (FDC) tablet, empagliflozin 10 mg/linagliptin 5 mg FDC tablet, empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg for 52 weeks as add-on to metformin at an unchanged dose. FDC tablets, empagliflozin tablets, and linagliptin tablets were taken once daily in the morning. Randomization was performed using a third-party interactive voice and web response system and was stratified by HbA1c at screening (<8.5% [<69 mmol/mol]) and ≥8.5% (≥69 mmol/mol), eGFR at screening (≥90 mL/min/1.73 m² and ≤89 mL/min/1.73 m²), and region (Europe, Asia, North America, and South America). Study visits were scheduled at screening, at the start of the placebo run-in, at baseline, and at weeks 6, 12, 18, 24, 32, 40, and 52 of treatment. A follow-up visit occurred 4 weeks after the last dose of study drug for subjects who completed the treatment period or within 7 days after the last administration of study drug for those who discontinued treatment before week 52.

Rescue medication was to be initiated if a subject had blood glucose >240 mg/dL after an overnight fast between weeks 1 and 12, blood glucose >200 mg/dL after an overnight fast between weeks 12 and 24, or blood glucose >180 mg/dL or HbA1c >8% (>63.9 mmol/mol) after an overnight fast between weeks 24 and 52. The initiation, choice, and dosage of rescue medication were at the discretion of the investigator, according to local prescribing information, but use of DPP-4 inhibitors, GLP-1 analogs, and SGLT2 inhibitors was not permitted. In cases of hypoglycemia, rescue medication was to be reduced or discontinued before any reduction in background metformin dose. If hyper- or hypoglycemia could not be controlled, the subject was discontinued from the trial.

End points and assessments
The primary end point was the change from baseline in HbA1c at week 24. Key secondary end points were change from baseline in FPG at week 24, change from baseline in body weight at week 24, and the proportion of subjects with baseline HbA1c ≥7% (≥53 mmol/mol) who had HbA1c <7% (<53 mmol/mol) at week 24. Exploratory end points were as follows: change from baseline in HbA1c at week 24 in subgroups of subjects with HbA1c ≥8.5 and <8.5% at baseline; change from baseline in HbA1c, FPG,
weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) at week 52, and the proportion of subjects with baseline HbA1c ≥7% (≥53 mmol/mol) who had HbA1c <7% (<53 mmol/mol) at week 52.

Safety end points included vital signs, clinical laboratory parameters, and adverse events (AEs). Preferred terms coded according to the Medical Dictionary for Drug Regulatory Activities [MedDRA] version 16.0). AEs included all events with an onset after the first dose and up to 7 days after the last dose of study medication. Confirmed hypoglycemic AEs were defined as AEs with plasma glucose ≤70 mg/dL and/or requiring assistance. Events consistent with urinary tract infection (UTI) events consistent with genital infection, and events consistent with volume depletion (identified from AEs reported spontaneously by the investigator using prospectively defined search categories based on 77, 89, and 8 preferred terms, respectively), hypersensitivity reactions based on 77, 89, and 8 preferred terms, respectively, were analyzed using ANCOVA model described for the primary end point. Categorical changes in HbA1c, at weeks 24 and 52 were analyzed using logistic regression with noncompleters considered failure (NCF) imputation.

Treatment differences in the primary and key secondary end points were tested hierarchically in the following order: HbA1c, FPG, body weight (empagliflozin/linagliptin vs. linagliptin), and the percentage of subjects who reached HbA1c <7%. Within each end point, superiority of empagliflozin 25 mg/linagliptin 5 mg versus the individual components was tested first, followed by the test of empagliflozin 10 mg/linagliptin 5 mg versus the individual components. Every test was at a significance level of 5% (two sided). A test of superiority was confirmatory only if the previous tests were positive. Following this procedure, the family-wise error rate was preserved at 5% (two sided). Safety analyses were descriptive, except for changes in lipid parameters, which were analyzed using ANCOVA.

A sample size of 133 subjects per group was required to provide power of 89% to detect a 0.5% treatment difference in HbA1c between empagliflozin/linagliptin and the individual components, assuming a common SD of 1.05% and using a significance level of 2.5% (one sided).

RESULTS

Subjects

A total of 686 subjects were randomized and treated, of whom 674 comprised the FAS (Supplementary Fig. 1). Baseline characteristics of the FAS were balanced between treatment groups (Table 1).

Efficacy

At week 24, reductions from baseline in HbA1c were significantly greater with empagliflozin/linagliptin compared with empagliflozin 25 mg and compared with linagliptin 5 mg, but not compared with empagliflozin 10 mg (Fig. 1B). In subjects with HbA1c <8.5% (<69 mmol/mol) at baseline (mean baseline 7.53–7.62% [59–60 mmol/mol]), reductions from baseline in HbA1c were significantly greater with empagliflozin/linagliptin compared with the individual components (Supplementary Fig. 2).

In subjects with baseline HbA1c ≥7% (≥53 mmol/mol), significantly more subjects in the empagliflozin/linagliptin groups reached HbA1c <7% (<53 mmol/mol) at week 24 compared with the individual components (Fig. 1C). Reductions from baseline in FPG at week 24 were significantly greater with empagliflozin/linagliptin compared with the individual components (Fig. 1D). Sensitivity analyses of changes from baseline in HbA1c and FPG at week 24 were consistent with the results of the primary analyses (Supplementary Table 1). Reductions from baseline in weight at week 24 were significantly greater with empagliflozin/linagliptin compared with linagliptin but were not significantly different compared with the respective empagliflozin components (Fig. 1E).

Significant reductions in HbA1c with the combination of empagliflozin/linagliptin were sustained at week 52 (Fig. 2A and Supplementary Fig. 3). Greater proportions of subjects with baseline HbA1c ≥7% (≥53 mmol/mol) had HbA1c <7% (<53 mmol/mol) at week 52 with empagliflozin/linagliptin compared with the individual components (Fig. 2B). At week 52, empagliflozin/linagliptin significantly reduced FPG compared with linagliptin 5 mg (Supplementary Table 2). FPG was significantly reduced with empagliflozin 25 mg/linagliptin 5 mg compared with empagliflozin 25 mg, but there was no significant difference in change in FPG with empagliflozin 10 mg/linagliptin 5 mg compared with empagliflozin 10 mg (Supplementary Table 2).

Reductions from baseline in weight at week 52 were significantly greater with empagliflozin/linagliptin compared with linagliptin but were not significantly different compared with the respective empagliflozin components (Fig. 2C). Reductions from baseline in SBP at week 52 were significantly greater with empagliflozin/linagliptin compared with
linagliptin but not compared with the respective empagliflozin components (Fig. 3A). Empagliflozin/linagliptin reduced DBP at week 52; the difference in change from baseline compared with linagliptin 5 mg was of borderline significance (P = 0.05), but differences compared with the empagliflozin components were not statistically significant (Fig. 3B). Reductions in blood pressure in the empagliflozin/linagliptin and empagliflozin groups were not associated with increases in pulse rate; mean (SD) changes from baseline at week 52 were −0.45 bpm (9.15) with empagliflozin 25 mg/linagliptin 5 mg, −0.11 bpm (7.79) with empagliflozin 10 mg/linagliptin 5 mg, 1.24 bpm (8.99) with empagliflozin 25 mg, 0.24 bpm (9.65) with empagliflozin 10 mg, and 1.41 bpm (8.32) with linagliptin 5 mg.

Safety
The proportion of subjects with one or more AE was similar across treatment groups (Table 2). Most events were mild or moderate in intensity. There was one death in the empagliflozin 10 mg/linagliptin 5 mg group (hypertensive heart disease) and one death in the empagliflozin 10 mg group (lung neoplasm and metastatic nonsmall cell lung cancer). No patients discontinued due to hypoglycemia. One subject (on empagliflozin 25 mg) discontinued due to hyperglycemia, and another patient (on empagliflozin 10 mg/linagliptin 5 mg) discontinued due to “lack of efficacy,” which is suggestive of hyperglycemia. Confirmed hypoglycemic AEs were reported in 3.6% of subjects on empagliflozin 25 mg/linagliptin 5 mg, 2.2% on empagliflozin 10 mg/linagliptin 5 mg, 3.5% on empagliflozin 25 mg, 1.4% on empagliflozin 10 mg, and 2.3% on linagliptin 5 mg; no events required assistance. Events consistent with UTI were reported in 10.2% of subjects on empagliflozin 25 mg/linagliptin 5 mg, 9.6% on empagliflozin 10 mg/linagliptin 5 mg, 13.5% on empagliflozin 25 mg, 11.4% on empagliflozin 10 mg, and 15.2% on linagliptin 5 mg; these events were reported in a greater proportion of female than male subjects in every group (Table 2). Most subjects with events consistent with UTI reported only events of mild or moderate intensity. One subject on empagliflozin 10 mg had severe urosepsis that required hospitalization and led to discontinuation of study drug; the subject recovered following treatment with antibiotics. One subject on empagliflozin 25 mg experienced moderate exacerbation of chronic pyelonephritis that did not lead to discontinuation of study drug.

Table 1—Demographics and baseline characteristics

<table>
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<tr>
<th></th>
<th>Empagliflozin 25 mg/linagliptin 5 mg (n = 134)</th>
<th>Empagliflozin 10 mg/linagliptin 5 mg (n = 135)</th>
<th>Empagliflozin 25 mg (n = 140)</th>
<th>Empagliflozin 10 mg (n = 137)</th>
<th>Linagliptin 5 mg (n = 128)</th>
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<td>≤1 years</td>
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<td>&gt;5 to 10 years</td>
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<td>50 (35.7)</td>
<td>39 (28.5)</td>
<td>42 (32.8)</td>
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<tr>
<td>&gt;10 years</td>
<td>32 (23.9)</td>
<td>26 (19.3)</td>
<td>30 (21.4)</td>
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<td>32 (25.0)</td>
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<tr>
<td><strong>HbA1c (%)</strong></td>
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<td>Empagliflozin/linagliptin 5 mg</td>
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<td>7.95 (0.80)</td>
<td>8.02 (0.83)</td>
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<td>64 (10.2)</td>
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Data are mean (SD), unless otherwise stated, in the FAS (subjects treated with one or more doses of study drug who had a baseline and one or more on-treatment HbA1c measurements).
Figure 1—Efficacy parameters at week 24. A: Change from baseline in HbA₁c at week 24 (ANCOVA in FAS using LOCF imputation). B: Change from baseline in HbA₁c at week 24 in subjects with baseline HbA₁c $\geq 8.5\%$ (ANCOVA in FAS [LOCF]). C: Subjects with HbA₁c $\geq 7\%$ ($\geq 53$ mmol/mol) at baseline who reached HbA₁c $\leq 7\%$ ($\leq 53$ mmol/mol) at week 24 (logistic regression analysis). D: Change from baseline in FPG at week 24 (ANCOVA in FAS [LOCF]). E: Change from baseline in body weight at week 24 (ANCOVA in FAS [LOCF]). Data are adjusted mean ± SE or n (%). OR, odds ratio.
on empagliflozin 25 mg/linagliptin 5 mg or linagliptin (Table 2). Two subjects on empagliflozin 25 mg experienced events consistent with genital infection that led to discontinuation of study drug. “Chronic pancreatitis” was reported in one subject on linagliptin 5 mg after approximately 11 months of treatment. The investigator did not consider the
pancreatitis to be related to the study medication and did not discontinue or reduce the study medication. Hypersensitivity reactions were reported in one subject on empagliflozin 25 mg/linagliptin 5 mg (angioedema), one subject on empagliflozin 10 mg/linagliptin 5 mg (urticaria), and one subject on linagliptin 5 mg (angioedema). No subjects experienced worsening of heart failure or were hospitalized due to heart failure.

Changes from baseline in laboratory measurements at week 52 are shown in Supplementary Table 3. Changes from baseline in eGFR observed at week 52 and at follow-up were small in all groups. Mean changes from baseline in hematocrit were 4.2–5.0% in the empagliflozin/linagliptin and empagliflozin groups and 1.3% in the linagliptin group. Mean changes from baseline in uric acid were −45.2 to −63.6 μmol/L in the empagliflozin/linagliptin and empagliflozin groups and 9.5 μmol/L in the linagliptin group. There were no significant differences in lipid measurements (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) with empagliflozin/linagliptin compared with the individual components, except for a greater increase from baseline in HDL cholesterol with empagliflozin 25 mg/linagliptin 5 mg compared with linagliptin 5 mg (Supplementary Table 3). Shifts in urine albumin to creatinine ratio are shown in Supplementary Table 4. A higher proportion of subjects with microalbuminuria at baseline shifted to no albuminuria at the end of treatment with empagliflozin/linagliptin than with the individual components.

CONCLUSIONS
This randomized controlled trial was designed to evaluate the efficacy and safety of a combination of an SGLT2 inhibitor and a DPP-4 inhibitor as add-on to metformin in subjects with type 2 diabetes. The combination of empagliflozin (10 mg or 25 mg) and linagliptin (5 mg) resulted in a significant reduction in HbA1c and FPG compared with the individual components at week 24. As expected, greater reductions from baseline in HbA1c (≥8.5%) were observed with empagliflozin/linagliptin than with the individual components.

Patients who initially achieve glycemic goals with one oral antidiabetes drug frequently require additional agents over time in order to maintain glycemic control due to the progressive nature of type 2 diabetes (1). The combination of empagliflozin and linagliptin added on to metformin offered a sustained reduction in HbA1c, FPG, weight, and blood pressure, which persisted up to week 52.

Reductions in weight and SBP with empagliflozin alone were maintained when empagliflozin was used in combination with linagliptin in this study. In phase III trials, empagliflozin has consistently been associated with weight loss and SBP reduction (9,14–16). The weight loss observed with empagliflozin is due mainly to loss of calories via
Empagliflozin has been reported to reduce eGFR, likely due to hemodynamic changes, which are fully reversed after treatment discontinuation (18,21). In this study, treatment with empagliflozin/linagliptin or its components resulted in little to no change from baseline in eGFR at week 52. Both linagliptin and empagliflozin individually have been reported to result in reductions in albuminuria (21,22), possibly via changes in glomerular structure with linagliptin or functional, hemodynamic changes due to tubulo-glomerular feedback mechanisms with empagliflozin (18,21). Interestingly, in this study, with the limitation of an exploratory analysis based on a small number of subjects, empagliflozin/linagliptin appeared to result in greater proportions of subjects shifting from microalbuminuria to no albuminuria compared with the individual components.

Hypoglycemia is associated with increased morbidity and mortality (23), reduced quality of life (24), and poor glycemic control (25) in patients with type 2 diabetes. Thus the risk of hypoglycemia is an important consideration for the choice of add-on therapy for patients with type 2 diabetes who do not achieve adequate glycemic control with metformin (1). Both empagliflozin and linagliptin are associated with a low risk of hypoglycemia when given as add-on to metformin (9,13,26–29), and a low risk of hypoglycemia was also observed with empagliflozin/linagliptin, with no hypoglycemic events requiring assistance. Overall, in this study, the safety profiles of empagliflozin/linagliptin were similar to the known safety profiles of the individual components.

Strengths of this study include the large number of subjects assessed and the 52-week duration of treatment. Limitations include the lack of a placebo arm, which means that the additive efficacy of empagliflozin/linagliptin compared with the individual components cannot be conclusively assessed, although only small changes from baseline in HbA1c with placebo would be expected.

In conclusion, empagliflozin/linagliptin as add-on to metformin provided greater...
glucose-lowering efficacy than the individual components, with a low risk of hypoglycemia. Empagliflozin/linagliptin was well tolerated, with safety profiles similar to the known safety profiles of empagliflozin and linagliptin. These results suggest that immediate use of triple therapy in patients who have failed on metformin may provide advantages over the traditional staggered treatment approach.

**Acknowledgments.** Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Elizabeth Ng and Wendy Morris (Fleishman-Hillard Group, Ltd.) during the preparation of this article.

**Duality of Interest.** This study was funded by Boehringer Ingelheim and Eli Lilly and Company. R.A.D. has served on scientific advisory boards for Boehringer Ingelheim, AstraZeneca, Janssen, Novo Nordisk, Takeda, and Lexicon; participated in speakers’ bureaus for AstraZeneca and Novo Nordisk; and received grants/research support from AstraZeneca, Janssen, Bristol-Myers Squibb, Takeda, and Xeris. P.S., D.L., R.K., H.J.W., and U.C.B. are employees of Boehringer Ingelheim. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** R.A.D. contributed to the interpretation of data and to the drafting of the manuscript. A.L. contributed to the acquisition and interpretation of data and to the drafting of the manuscript. S.P., D.L., R.K., H.J.W., and U.C.B. contributed to the study design, interpretation of data, and the drafting of the manuscript. All authors approved the final version. All authors had full access to the study data and were responsible for the final decision to submit the manuscript. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and approved the final version. R.A.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


**References.**

12. Thomas L, Eckhardt M, Langkopf E, Tadayon M, Himmelsbach F, Mark M. (R)-8-(3-amino-piperidine-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3-7-dihydropurine-2,6-dione (BI 1356), a novel xanthine-based dipeptidyl peptidase 4 inhibitor, has a superior potency and longer duration of action compared with other dipeptidyl peptidase-4 inhibitors. J Pharmacol Exp Ther 2008;325:175–182