

Original article

Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjunctivitis in Germany

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Abstract

Objectives:

An economic evaluation was conducted to assess the outcomes and costs as well as cost-effectiveness of the following grass-pollen immunotherapies: OA (Oralair; Stallergenes S.A., Antony, France) vs GRZ (Grazax; ALK-Abelló, Hørsholm, Denmark), and ALD (ALK Depot SQ; ALK-Abelló) (immunotherapy agents alongside symptomatic medication) and symptomatic treatment alone for grass pollen allergic rhinoconjunctivitis.

Methods:

The costs and outcomes of 3-year treatment were assessed for a period of 9 years using a Markov model. Treatment efficacy was estimated using an indirect comparison of available clinical trials with placebo as a common comparator. Estimates for immunotherapy discontinuation, occurrence of asthma, health state utilities, drug costs, resource use, and healthcare costs were derived from published sources. The analysis was conducted from the insurer's perspective including public and private health insurance payments and co-payments by insurers. Outcomes were reported as quality-adjusted life years (QALYs) and symptom-free days. The uncertainty around incremental model results was tested by means of extensive deterministic univariate and probabilistic multivariate sensitivity analyses.

Results:

In the base case analysis the model predicted a cost-utility ratio of OA vs symptomatic treatment of €14,728 per QALY; incremental costs were €1356 (95%CI: €1230; €1484) and incremental QALYs 0.092 (95%CI: 0.052; 0.140). OA was the dominant strategy compared to GRZ and ALD, with estimated incremental costs of –€1142 (95%CI: –€1255; –€1038) and –€54 (95%CI: –€188; €85) and incremental QALYs of 0.015 (95%CI: –0.025; 0.056) and 0.027 (95%CI: –0.022; 0.075), respectively. At a willingness-to-pay threshold of €20,000, the probability of OA being the most cost-effective treatment was predicted to be 79%. Univariate sensitivity analyses show that incremental outcomes were moderately sensitive to changes in efficacy estimates. The main study limitation was the requirement of an indirect comparison involving several steps to assess relative treatment effects.

Conclusion:

The analysis suggests OA to be cost-effective compared to GRZ and ALD, and a symptomatic treatment. Sensitivity analyses showed that uncertainty surrounding treatment efficacy estimates affected the model outcomes.

Introduction

Allergic rhinoconjunctivitis (AR) is defined as inflammation of the nasal membranes and upper airways caused by allergens such as grass or tree pollens and house dust mites. The condition is characterized by a combination of the following symptoms: sneezing, nasal congestion, nasal itching, rhinorrhoea,

and watery and itchy eyes^{1,2}. AR is a common disease with a prevalence of ~25% in Germany 2010³. According to the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines, 10–40% of patients suffer from co-existing allergic asthma. A large prospective study presented evidence for an increased risk of asthma in adults with AR^{4,5}.

It has been known for a long time that allergic reactions affect patient's daily living; impairments in work and school performance are common, particularly in AR patients with moderate/severe symptoms, all leading to a significant reduction in quality-of-life (QoL)^{4,6}.

AR is associated with a high economic burden in Germany. The Federal Statistical Office attributed DM 350 million for anti-allergic medication in 1996 ($\pm 75\%$ of the total expenditures for AR). The total costs (direct and indirect) added up to DM 467 million. In 2000, the total costs were exceeding €240 million⁷. Moreover, in a study by Schramm *et al.*⁸, the average annual cost of seasonal AR ranged from €1089 per child/adolescent to €1543 per adult.

The primary approach to AR is the identification and avoidance of the allergens, which is often hardly achievable for pollen. The goal of pharmacotherapy is to prevent or reduce allergy symptoms, both in terms of severity and duration. The most commonly used medications are antihistamines, corticosteroid nasal sprays, and eye drops⁹. Specific immunotherapy (SIT) is considered to be the only potentially causal therapy for AR and is mainly administered by two routes, subcutaneous (SCIT) and sublingual (SLIT). A Cochrane review and meta-analysis of immunotherapy (SLIT vs placebo) has demonstrated evidence of efficacy by reduction in rhinitis symptoms and medication requirements in the first season¹⁰. Furthermore, beneficial and sustained preventive effects with SIT have been shown^{11–14}.

OA (Oralair; Stallergenes S.A., Antony, France) is a sublingual immunotherapy tablet for treatment of seasonal, grass pollen allergic rhinitis. OA's active substance consists of five purified and calibrated pollen extracts that correspond to the epidemiological characteristics of patient exposure in Europe. These grass extracts are: perennial rye (*Lolium perenne*), meadow (*Poa pratensis*), timothy (*Phleum pratense*), cocksfoot (*Dactylis glomerata*), and sweet vernal (*Anthoxanthum odoratum*)¹⁵. A recent trial demonstrated sustained efficacy of co-seasonal treatment over three pollen seasons; long-term follow-up results are currently under investigation¹⁶. Efficacy data from randomized controlled trials (RCTs) for grass allergens has been published for treatment alternatives GRZ (Grazax; ALK-Abelló, Hørsholm, Denmark) (SLIT) and ALD (Alk Depot SQ; ALK-Abelló) (SCIT).

Nowadays, physicians and decision-makers critically appraise the clinical benefits and economic consequences of competing immunotherapeutic strategies to base allocation of healthcare resources. Accordingly, the objective of

the present study was to assess the cost-effectiveness of OA as compared with GRZ and ALD, and symptomatic medication against grass pollen induced AR in Germany.

Methods

Model structure

A Markov model was constructed to evaluate the costs and QoL of patients with AR to grass pollen receiving immunotherapy (Figure 1). Several studies have documented a sustained effect of SIT up to 7 years after ending treatment^{11–14}. Based on this evidence a time horizon of 9 years with a cycle length of 1 year was chosen; the grass pollen season had a length of 3 months¹⁷.

At the start of the analysis, patients initiated either immunotherapy—OA, GRZ, or ALD allowing additional symptomatic medication—or symptomatic treatment alone. After discontinuation of immunotherapy, solely symptomatic treatment was continued. All patients were at risk of developing chronic asthma.

Model inputs

Patient characteristics at baseline

Baseline characteristics of the modelled cohort were consistent with the clinical trial patient population in the conducted meta-analysis (see below). Included patients suffered from moderate/severe seasonal AR to grass pollen and/or conjunctivitis with a positive grass allergen-specific skin prick test and/or raised serum grass allergen-specific IgE. On average, they were 29 years old and free of co-existing chronic asthma at inclusion.

Effect parameters

Estimates for symptom scores during the pollen season were based on a literature review and meta-analysis. Other effect parameters (Table 1) were extracted from published sources.

A systematic review conducted (November 2010) in PubMed and the Cochrane database identified eight RCTs for OA (2), GRZ (4), and ALD (2) that fulfilled all inclusion criteria and presented symptom scores as a primary outcome. Unfortunately, a variety of scoring systems were employed by trial authors to calculate the level of rhinitis symptoms experienced by the patients. Published guidelines from the Cochrane Collaboration for conducting meta-analyses recommend the use of the standard mean difference (SMD) to compare continuous data measured with various instruments¹⁸. The SMD analyzes the difference in means between two treatment groups, immunotherapy and placebo, in units of pooled standard deviation. Other meta-analyses in the

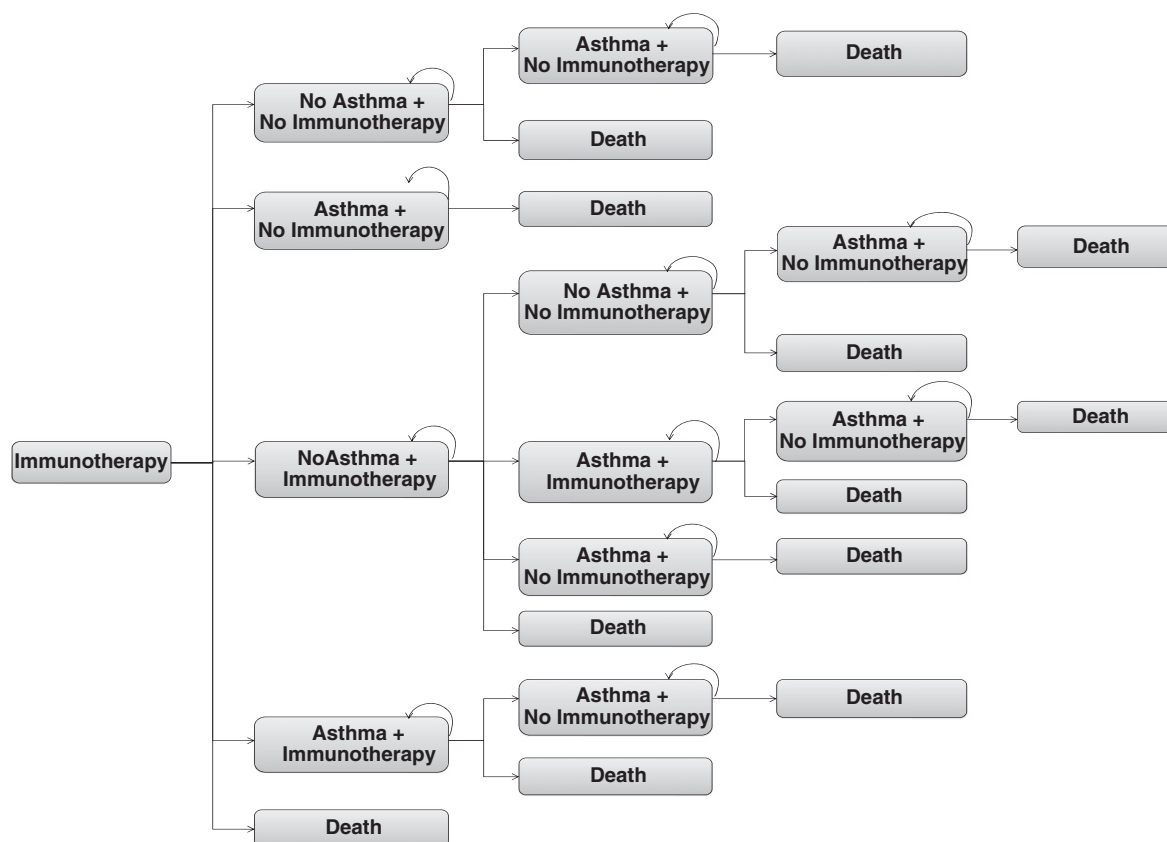


Figure 1. Structure of applied Markov model with a cycle length of one year. Patients enter the model receiving either immunotherapy (Oralair/Grazax/ALK Depot SQ) or only symptomatic treatment (upper two arms).

therapeutic field of AR also applied this method^{10,19}. First, the SMD was calculated with the symptoms scores of each trial, afterwards pooled efficacy per treatment was estimated by means of a fixed effect model. The SMD is not suitable for clinical interpretation; therefore, it was re-expressed in the units of the most common measurement instrument, the Rhinoconjunctivitis Total Symptom Score (RTSS), again following the Cochrane Collaboration guidelines¹⁸. The reader is referred to the supplementary appendix for a more detailed description of the literature review and meta-analysis.

Few included studies reported symptom-free days (SFD) during the pollen season as efficacy outcome besides RTSS^{20–22}. A SFD was defined as a day with complete absence of all symptoms and no use of rescue medication. A combined weighted average has been calculated for immunotherapy treatment as values could not be specified for each comparator separately.

Effects of immunotherapy in terms of symptom scores and SFDs observed after one season were assumed to remain constant and thus extrapolated up to 9 years, based on current results from grass allergen SIT^{11–14}. Patients discontinuing immunotherapy generate costs and outcomes associated with the symptomatic treatment arm.

Discontinuation of SLIT and SCIT compounds were extracted from a paper on prescription renewal rates by Sieber *et al.*²³ Development of asthma^{5,24,25} and mortality^{26,27} were incorporated in the model as well.

Utilities

The Rhinitis Symptom Utility Index (RSUI), a preference-based utility index based on rhinitis symptoms²⁸, was applied as a proxy to estimate utility values for symptom scores during the pollen season. The utility value reflecting a specific symptom score was estimated by proportioning the RTSS of each treatment in symptom severity levels and subsequently applying the formula described in the study by Revicki *et al.*²⁸ Table 1 shows the resulting estimates per comparator. Additionally, patient utility estimates were adjusted for co-existing asthma and patient's age^{29,30}.

Costs

Immunotherapy was administered for 3 years corresponding with recommendations as presented in the product information^{15,31,32}. The analysis was conducted from a health insurer's perspective in accordance with German guidelines. Based on this view, disease-related benefits

Table 1. Overview of clinical effect parameters applied in the model.

Model parameter	Value	Reference
<i>Transformed RTSS per season</i>		
OA	2.21	Meta-analysis
GRZ	2.41	Meta-analysis
ALD	2.28	Meta-analysis
Symptomatic treatment	3.51	Meta-analysis
<i>% SFD per season</i>		
Immunotherapy	38.2%	20–22
Symptomatic treatment	26.1%	20–22
<i>Discontinuation</i>		
Discontinuation SLIT	Year 1 29.0%	23
(OA and GRZ)	Year 2 28.2%	23
Discontinuation SCIT	Year 1 45.0%	23
(ALD)	Year 2 38.2%	23
<i>Asthma</i>		
Risk of asthma on symptomatic treatment	0.46%	5
Relative risk of developing asthma (immunotherapy vs symptomatic treatment)	50.52%	24,25
<i>Mortality</i>		
General population*	0.046%	26
Asthma*	0.069%	27
<i>Utility</i>		
RTSS 2.21 (OA)	0.874	28
RTSS 2.41 (GRZ)	0.861	28
RTSS 2.28 (ALD)	0.869	28
RTSS 3.51 (symptomatic treatment)	0.793	28
Asthma	0.977	29
Age 29–35	0.970	30
Age 36–38	0.960	30

*Probabilities represent mortality at start of the analysis (29 years of age).
OA, Oralair; GRZ, Grazax; ALD, Alk Depot SQ.

covered by both the public and private health insurance are reflected as well as co-payments by insureds. The ex-factory and public prices of all drugs were derived from the Lauer-Taxe April 2011³³. Drug costs were adjusted for patient co-payments, and mandatory rebates for the manufacturer, the distributor, and the pharmacy.

Additionally, costs for symptomatic medication were calculated. The number of loratidine tablets and budesonide puffs used during the season presented by Bachert *et al.*³⁴ were adjusted for an average pollen season's length of 90 days (Table 2).

Besides drug costs, expenses for specialist visits, treatment administration, diagnostics, and asthma were included in the analysis, taking into account that health care costs were remunerated through four available systems: Public insurance (90%)—sub-divided by lumps sums (80%)³⁵, ambulatory setting (15%)³⁶, and visits to a privately licensed doctor (5%)³⁷—and private insurance (10%). Table 2 presents all weighted average costs applied in the model.

Resource use for ALD was based on the number of injections administered by a specialist, corresponding with 24 visits in the first year (up dosing scheme) and nine in the next 2 years. OA and GRZ patients were assumed to consult their doctor once per quarter during

Table 2. Costs (2011) in base case analysis.

Model parameter	Value	Reference
<i>Annual drug cost</i>		
OA	€706.37	15,33
GRZ	€1285.94	30,33
ALD	Year 1 €1018.76	31,33
	Year 2,3 €613.94	31,33
<i>Rescue medication per year</i>		
Loratidine	Immunotherapy €5.14	33,34
	Symptomatic tx €7.54	33,34
Budesonide	Immunotherapy €2.04	33,34
	Symptomatic tx €3.56	33,34
<i>Resource use</i>		
Specialist visit 10 minutes	€13.45	35–37
Specialist visit 30 minutes	€5.81	35–37
Immunotherapy injection	€2.70	35–37
Diagnostic tests	€20.54	35–37
Asthma	€1012.03	8

OA, Oralair; GRZ, Grazax; ALD, Alk Depot SQ.

treatment for optimal adherence³⁸. Furthermore, diagnostic tests to confirm seasonal AR to grass pollen were performed prior to immunotherapy initiation. Based on an allergy survey, 1.9 specialist visits per year were assumed to take place during treatment with symptomatic medication alone⁹.

Lastly, annual direct costs of moderate asthma were fixed as published by Schramm *et al.*⁸.

Model outcomes

Model outcomes were expressed as incremental costs per quality-adjusted life year (QALY) and SFD gained, next to the number needed to treat to prevent one case of asthma. Discount rates were set at 3% a year for both costs and outcomes as per the German IQWiG (Institute for Quality and Efficiency in Health Care) guidelines³⁹.

Sensitivity analyses

Deterministic and probabilistic sensitivity analyses were carried out to determine the influence of uncertainty on the final results. In several univariate and multivariate analyses, values for parameter estimates were varied within the uncertainty distributions that best reflect the nature of each specific parameter. A beta distribution was applied for utility values and transition probabilities. With respect to healthcare costs, pollen season, relative risk estimates, and the symptom score of symptomatic medication, lognormal distributions were applied. Normal distributions were used for treatment efficacy of each immunotherapy (SMD values of meta-analysis). The standard deviation was arbitrarily assumed to vary 15% around mean costs and 10% around mean effects, in case information on variance was not available in the publication.

Table 3. Incremental model results and ICERS.

OA vs	ΔCosts	ΔQALYs	ICER
Symptomatic treatment	€1356	0.092	€14,728
ALD	–€54	0.027	Dominant
GRZ	–€1142	0.015	Dominant
OA vs	ΔCosts	ΔSFDs	
Symptomatic treatment	€1356	49	€28
ALD	–€54	14	Dominant
GRZ	–€1142	0	Cost saving

OA, Oralair; GRZ, Grazax; ALD, Alk Depot SQ.

Within the deterministic univariate sensitivity analyses, the impact on incremental QALYs and costs was determined when each model parameter was varied separately within the limits of its 95% confidence intervals. Results of the analyses are presented using tornado graphs.

In the multivariate probabilistic sensitivity analysis, 1000 simulations were processed to represent the uncertainty of model results by varying the parameters by random draws from their assumed distributions. Based on the simulations, scatterplots and acceptability curves were drawn to estimate the probability of OA being considered cost-effective compared with its comparator treatments at a given willingness-to-pay (WTP) threshold per QALY gained.

Scenario analyses

The main model assumption was that the efficacy observed after one season is sustained until 9 years. To test the impact of the time horizon, costs and outcomes were evaluated after a period of 3 years, as efficacy data of OA is available for this period¹⁶.

In an additional scenario analysis, utility data were based on an alternative literature source. Utilities, derived from the EQ-5D, associated with GRZ (0.976) and symptomatic treatment (0.947) were available from a cost-effectiveness study by Bachert *et al.*³⁴ The utility value for GRZ was assumed to reflect all immunotherapy arms (i.e., OA and ALD).

Results

Base case

Incremental (discounted) QALYs during the 9-year period are estimated at 0.015, 0.027, and 0.092 when OA is compared with GRZ, ALD, and symptomatic treatment, respectively (Table 3). The QALY differences are mainly explained by the higher efficacy of OA in terms of RTSS compared with the other treatment options.

The estimated total costs consist of drug, treatment-related, and asthma costs. For all immunotherapy agents, drug costs are the main component contributing for ~70–85% of the total discounted amount. They range from €70 for symptomatic medication to €1474 for OA, leading to total incremental costs of €1356. OA is slightly more expensive than ALD; however, this is compensated by intensive resource use for the latter, due to administration of SCIT injections by a specialist. High drug acquisition costs account for GRZ as the most expensive treatment option.

The incremental values of OA compared to symptomatic treatment result in a cost-utility ratio of €14,728 per QALY. As a consequence of positive incremental outcomes combined with cost savings, OA is the dominant strategy in comparison to GRZ and ALD (Table 3).

Additionally, immunotherapy with OA results in a lower total number of asthma patients compared to symptomatic treatment. After a time horizon of 9 years, the number needed to treat (NNT) to prevent one case of chronic asthma is 98 patients.

Sensitivity analyses

Figure 2 presents the results of the deterministic univariate sensitivity analyses of OA vs its comparators. The tornado graphs show that in all comparisons incremental outcomes are most sensitive to variations in efficacy values in terms of symptom scores. Incremental QALYs change from –0.026 to 0.056 while varying the relative efficacy GRZ vs OA within the limits of its 95% confidence interval. The parameter has a moderate influence on the results as treatment efficacy values directly affect the overall patient's QoL. The estimated incremental costs are slightly sensitive to changes in transition probabilities of immunotherapy discontinuation.

The results of the probabilistic sensitivity analysis are presented as a scatterplot and an acceptability curve (Figures 3 and 4). Based on the simulations, 95% confidence intervals for incremental outcomes (0.052–0.140) and costs (€1230–€1484) are estimated for the comparison of OA vs symptomatic treatment. For the comparison of OA vs GRZ, 95% confidence intervals for incremental outcomes and costs were estimated at –0.025 to 0.056 and –€1255 to –€1038, respectively. Corresponding values for OA vs ALD are –0.022 to 0.075 for incremental outcomes and –€188 to €85 for incremental costs. The percentage of simulations predicting positive effects is estimated at 75.1%, 85.9%, and 100.0%, when OA is compared to GRZ, ALD, or symptomatic treatment, respectively (Figure 3).

The acceptability curves demonstrate that if society's WTP for drug treatment is below €15,000, symptomatic medication is predicted to be the most cost-effective

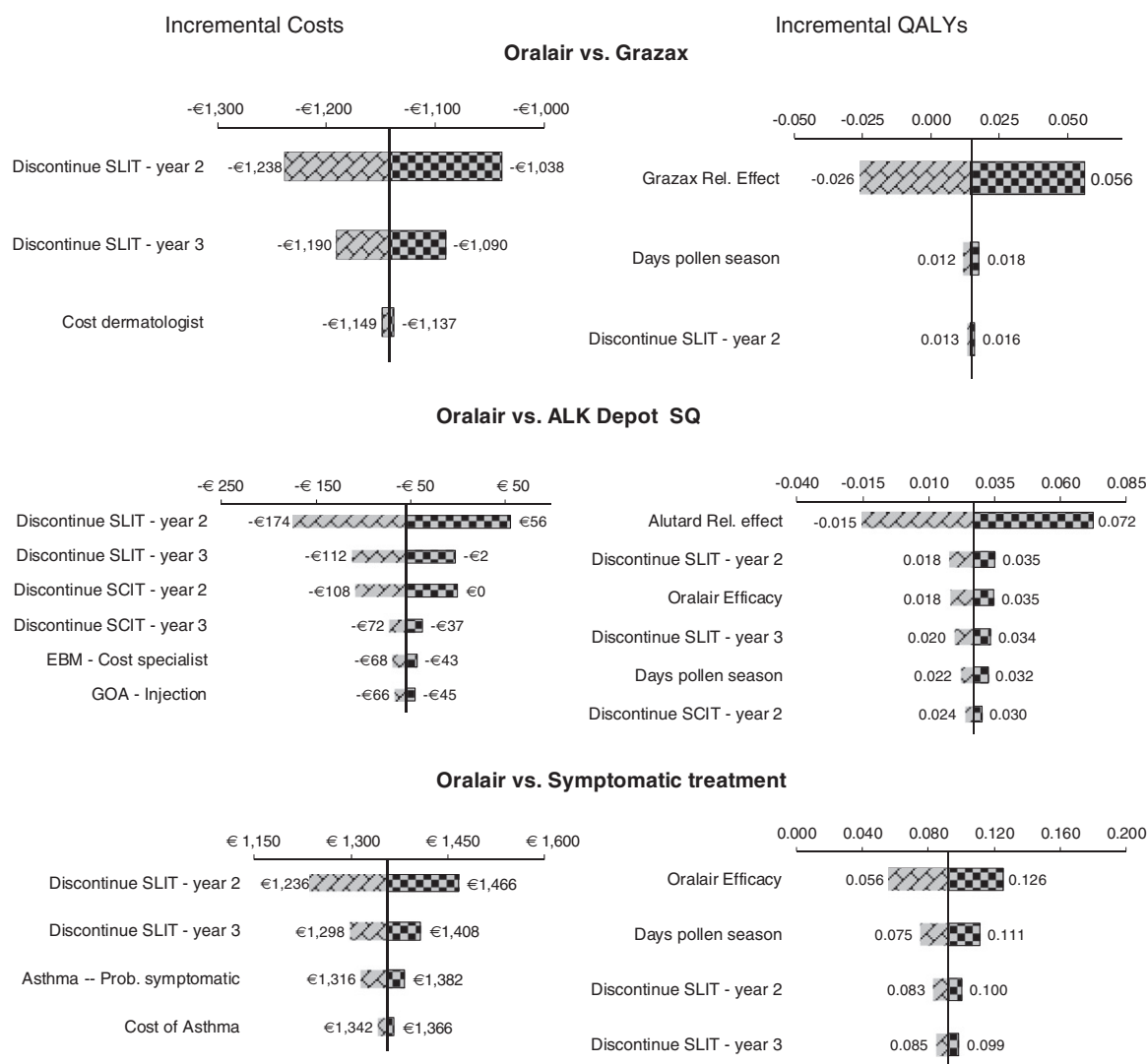


Figure 2. Overview of the results of the univariate sensitivity analyses for all three comparisons: Tornado graphs present the impact on incremental costs (left) and incremental outcomes (right) when changing parameters within their outer limits of their 95% confidence intervals according to their uncertainty distributions (not all parameters are shown in the graphs). SLIT = sublingual immunotherapy; SCIT = subcutaneous immunotherapy.

option; OA becomes the most cost-effective option above this level. At a WTP threshold of €20,000, the probability of OA being the most cost-effective treatment is predicted at 79% (Figure 4).

By reducing the time horizon to 3 years, the cost-utility ratio of OA vs symptomatic medication rises to €33,577 per QALY gained. In an additional scenario analysis this specific ratio is decreased to €10,336, when EQ-5D values from Bachert *et al.*³⁴ were applied. OA remains the dominant strategy in comparison to GRZ and ALD in both scenarios (Table 4).

Discussion

The current economic evaluation was designed to assess the cost-effectiveness of OA in patients with seasonal,

grass allergic rhinoconjunctivitis. Since AR leads to marked impairments in quality-of-life and workability, and affects ~25% of the German population, the need for cost-effective treatment is high. The analysis was conducted from the health insurer's perspective; healthcare costs were calculated through all remuneration systems in order to reflect the situation in Germany as closely as possible.

All base case results showed that point estimates for cost-effectiveness are considered to be generally acceptable in Western countries (<€30,000 per QALY), but there is uncertainty surrounding the model predictions. The univariate sensitivity analyses of all comparisons show that incremental QALYs were especially sensitive to changes in efficacy estimates during the pollen season, since higher symptom scores result in higher patient utilities leading to

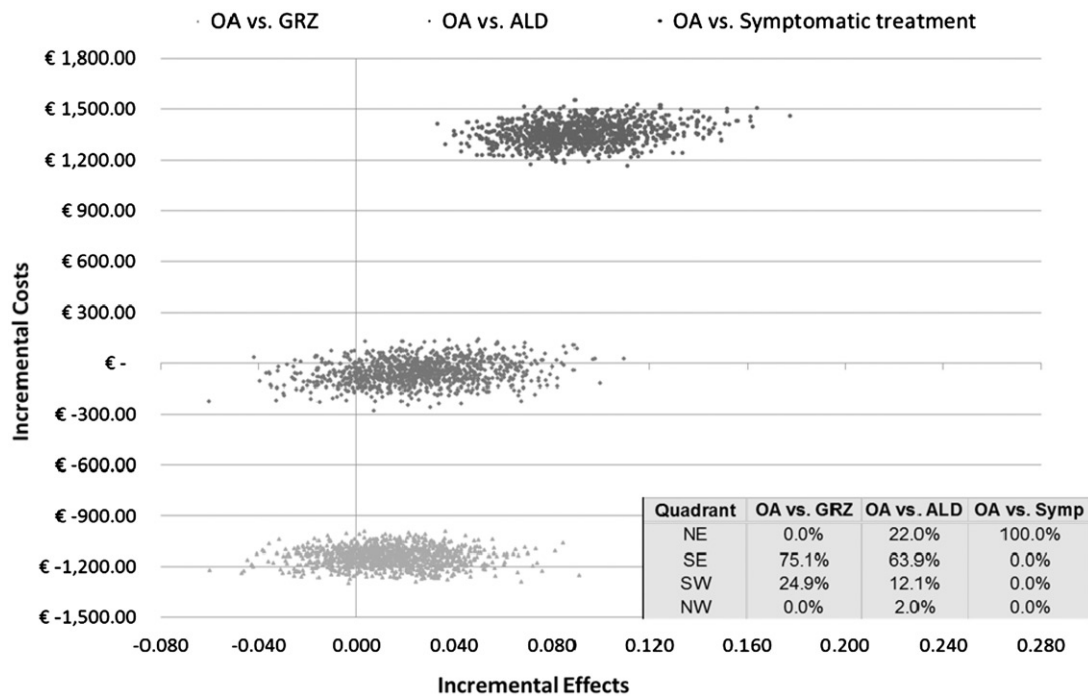


Figure 3. Scatter plots presenting uncertainty surrounding the incremental costs and incremental QALY estimates, generated in the conducted multivariate sensitivity analyses for Oralair versus its comparators. QALY = quality-adjusted life-year.

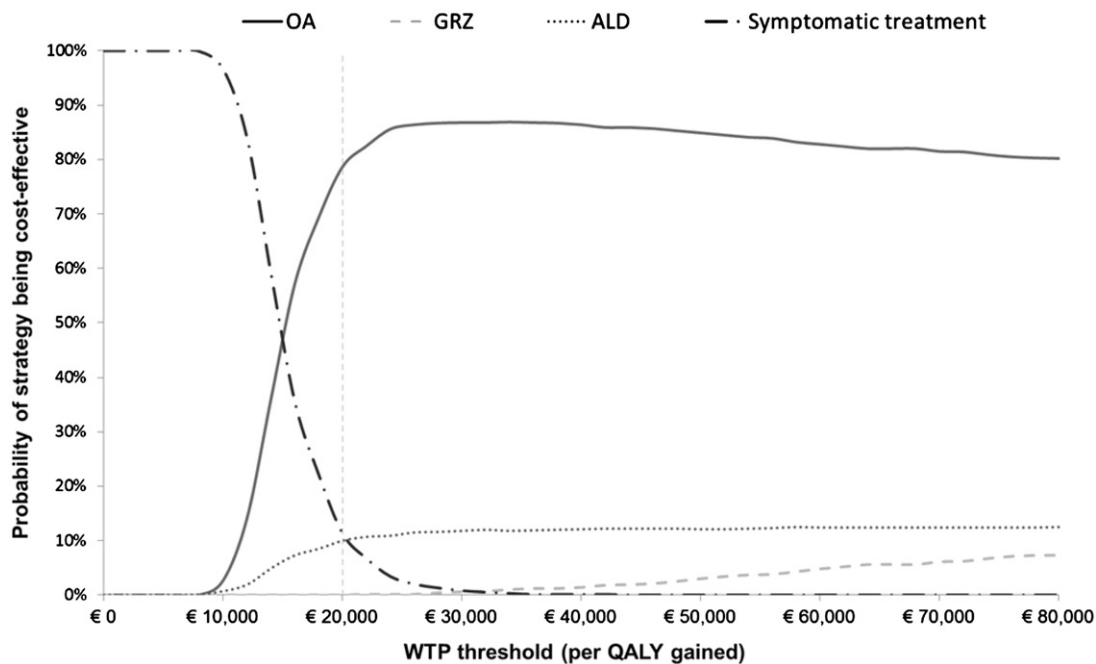


Figure 4. Acceptability curves: estimated probability that a specific treatment strategy is cost-effective given different values of the willingness-to-pay (WTP) threshold. QALY = quality-adjusted life-year.

more QALYs gained over time. Discontinuation rates have some influence on the incremental costs, as immunotherapy treatment is the main cost component.

The evaluation contains several strengths and limitations. To our knowledge, it is the first effort that has been

made to explore relative efficacy and cost-effectiveness of immunotherapy agents on a product level. Other studies addressed SLIT or SCIT as a group²⁹ or conducted a pharmacoeconomic analysis alongside a clinical trial with placebo as only comparator³⁴. Health economic analyses with

Table 4. Results of the conducted scenario analyses.

Scenario	ΔCosts	ΔQALYs	ICER
<i>EQ-5D utilities</i>			
OA vs symptomatic tx	€1356	0.131	€10,336
OA vs ALD	–€54	0.037	Dominant
OA vs GRZ	–€1142	0	Cost saving
<i>Time horizon: 3 years</i>			
OA vs symptomatic tx	€1381	0.042	€33,577
OA vs ALD	–€46	0.008	Dominant
OA vs GRZ	–€1170	0.007	Dominant

OA, Oralair; GRZ, Grazax; ALD, Aik Depot SQ.

GRZ and ALD vs placebo were presented in four publications of two health economic studies, one of each treatment^{34,40–42}. They concluded that ALD was dominant and GRZ had reasonable cost-utility ratios (e.g., €18,263 in Germany for an annual tablet price of €1500).

Ideally, a direct assessment of two or more treatments within a clinical trial is used for comparative efficacy data. A limitation of the current analysis was that an indirect comparison of relevant treatment options was required due to absence of head-to-head trials. All studies used placebo (symptomatic medication) as a common comparator, and had similar inclusion criteria. Combining published efficacy data of multiple trials in one meta-analytical framework reflects the best available evidence to date, although it is acknowledged that the chosen methodology has limitations, such as heterogeneity between studies. Furthermore, the methodology to assess the relative treatment effect involved several steps which may increase the uncertainty around the estimates. Future head-to-head clinical trials comparing immunotherapy agents are encouraged in order to reduce uncertainty around these inputs.

The key model assumption relates to the extrapolation of treatment effect. Study results of the first season were extrapolated up to 9 years. Observations from a number of studies with SIT serve as basis for this assumption, showing sustained efficacy for 6 more years after 3 years of treatment^{11–14}. Other cost-effective analyses on grass allergens projected results over the same time horizon^{34,42}. The exact duration of sustained effect is still under investigation for SLIT products¹⁶. Reducing the time horizon to 3 years, which reflects the maximum duration of treatment, increases the ICER from €14,728 to €33,577, as seen in the scenario analysis.

Next to symptom control, prevention of asthma and new sensitizations are important goals of immunotherapy. An attempt was made to incorporate long-term preventive effects of allergen extracts on development of asthma by applying the relative risk (± 0.5) as calculated from studies by Novembre *et al.*²⁴ and Moller *et al.*²⁵, as data for OA and GRZ are currently unavailable. The analysis results could

be updated upon availability of data of the specific SLIT compounds.

Effects of adverse events have not been considered in the analysis. Side-effects with grass allergen tablets (i.e., OA and GRZ), such as itching, swelling, irritation, inflammation, and burning/tingling sensation of the tongue, are usually mild and reversible, and mostly appear during the first days of treatment^{15,31}. SCIT (i.e., ALD) is also associated with mostly mild and moderate side-effects; however, occasions of severe systemic reaction, possibly leading to anaphylactic shock, have been reported^{32,43}. It is expected that inclusion of adverse events will not significantly influence QoL or healthcare costs and, thus, the final results. Furthermore, hospitalizations are not considered, as they hardly occur in the reflected patient population.

Utility estimates were based on a paper of Revicki *et al.*²⁸ They developed and evaluated the RSUI as an outcome indicator for evaluating cost-effectiveness of treatment strategies for AR. The index was designed to summarize the frequency and severity of common rhinitis-related symptoms. The resulting scores are not directly comparable to utility estimates, due to the fact that the standard gamble technique was not rated on a complete health to death scale. Alternatively, Bachert *et al.*³⁴ directly classified QoL by means of the EQ-5D. Applying the latter as a source for utility inputs did not have considerable impact on the final model results.

Conclusion

In conclusion, the analysis suggests OA to be cost-effective compared to GRZ and ALD, and symptomatic medication. Sensitivity analyses showed that uncertainty surrounding treatment efficacy estimates affected the model outcomes. Research efforts are encouraged in order to retrieve direct evidence on efficacy and tolerability of immunotherapy agents for the treatment of AR.

Transparency

Declaration of funding

The study was funded by Stallergenes GmbH.

Declaration of financial relationships

The authors had complete access to all data and had final control over the content, review, and submission of this manuscript. Kirsten Y. Westerhout and Bram G. Verheggen have disclosed that they are employees of Pharmerit International, a company that was paid by Stallergenes to develop the manuscript. C. H. Schreder has disclosed that he is an employee of Stallergenes GmbH, Kamp-Lintfort, Germany. M. Augustin has disclosed he is a consultant to Stallergenes.

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Appendix: Systematic literature review & Meta-analysis

A systematic review was conducted in PubMed and the Cochrane database to identify randomized controlled trials for OA, GRZ and ALD. The figure below presents an overview of the search results and the number of included RCTs.

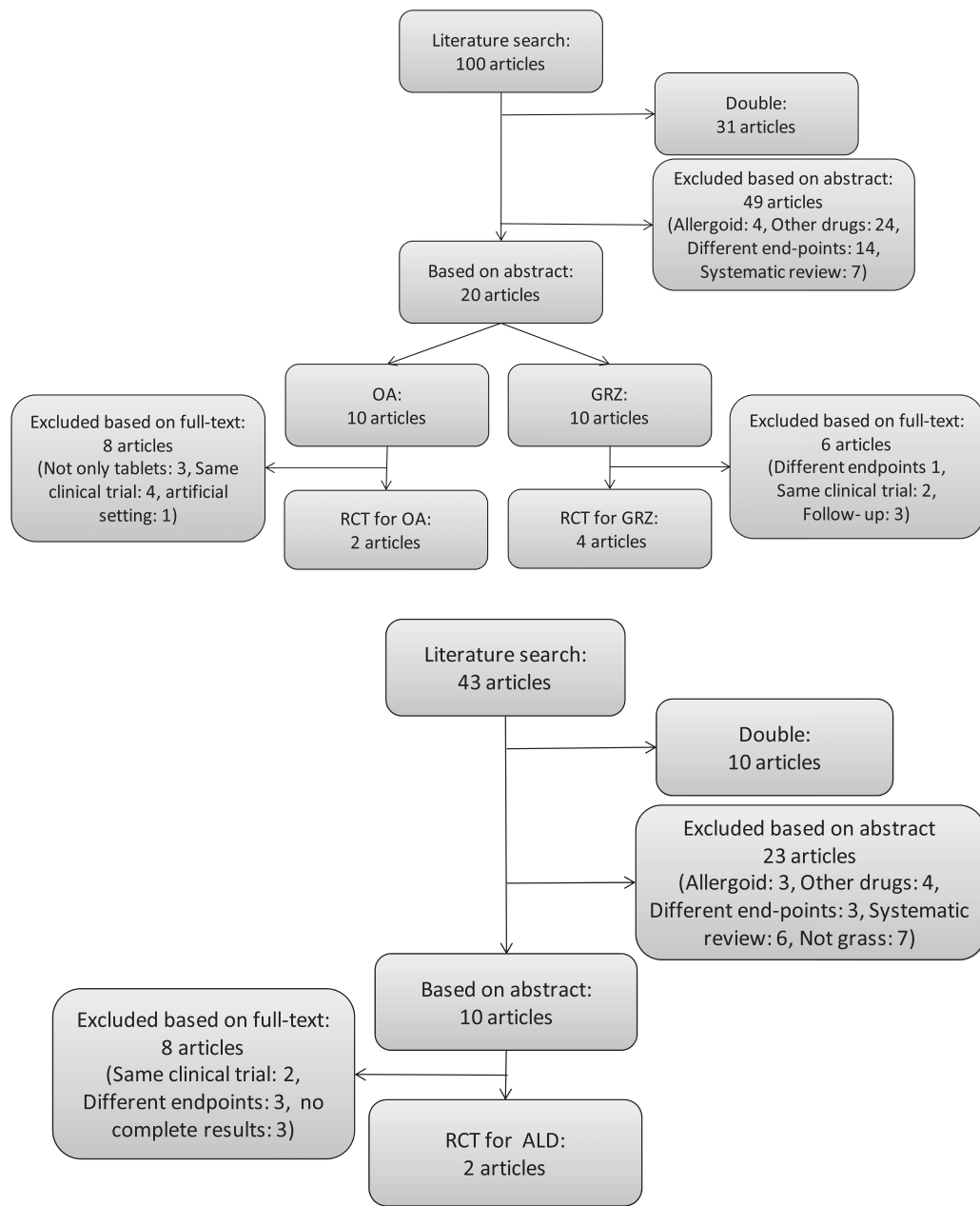


Figure A1. Flowchart of literature searches and results for SLIT (upper) and SCIT (lower). OA, Oralair; GRZ, Grazax; ALD, Alk Depot SQ.

As a next step, efficacy data reported as symptom scores were extracted for the treatment arms of the included studies, along with the corresponding standard deviations and number of patients treated (Table A1).

Table A1. Extracted numbers of patients, symptom scores and standard deviations of the active and placebo treatment arm.

	Active			Placebo		
	N	Mean	SD	N	Mean	SD
OA						
Didier <i>et al.</i> , 2007 ¹	136	3.58	2.976	148	4.93	3.229
Wahn <i>et al.</i> , 2009 ²	131	3.25	2.86	135	4.51	2.93
GRZ						
Durham <i>et al.</i> , 2006 ³	252	2.61	2.10	249	3.06	2.10
Dahl <i>et al.</i> , 2006 ⁴	282	2.36	1.6	286	3.37	2.2
Dahl <i>et al.</i> , 2006 ⁵	61	2.1	1.7	32	3.3	2.2
Bufe <i>et al.</i> , 2009 ⁶	117	2.67	2.38	121	3.17	2.14
ALD						
Walker <i>et al.</i> , 2001 ^{7*}	22	525	1127.6	22	1160	923.6
Frew <i>et al.</i> , 2006 ⁸	187	3.13	3.419	89	4.39	3.019

*Data estimated from median and interquartile range. OA, Oralair; GRZ, Grazax; ALD, Alk Depot SQ.

The symptom scores were measured with the RTSS in the OA and GRZ studies. The scoring system rates 6 symptoms (stuffy nose, runny nose, itchy nose, sneezing, watery eyes and itchy eyes) daily on a 4-point scale, with 0 = none, 1 = mild, 2 = moderate, 3 = severe. As a result, the symptom scores can range from 0–18. ALD applied different scoring systems. Published guidelines for conducting meta-analyses recommend the use of the standard mean difference (SMD) to compare continuous data measured with various instruments⁹.

$$\text{Formula} = \text{SMD} \frac{M_2 - M_1}{\text{SD}_{\text{pooled}}}$$

M_1 = Mean SS Placebo
 M_2 = Mean SS Active
 $\text{SD}_{\text{pooled}}$ = Pooled Standard Deviation

This method was applied to all individual symptom scores of the included RCTs and the resulting SMDs are presented in Table 2. In order to obtain one efficacy value per treatment, a fixed effect model was applied to pool the results^{10,11}.

Table A2. Standard mean differences (SMDs) with intervals for every study separately and per treatment combined.

	Mean SMD	variance	95% CI interval	
Didier <i>et al.</i> , 2007	−0.434	0.014	−0.670	−0.198
Wahn <i>et al.</i> , 2009	−0.435	0.015	−0.678	−0.192
($I^2 = 0\%$) Pooled OA	−0.435	0.086	−0.604	−0.265
Durham <i>et al.</i> , 2006	−0.214	0.008	−0.390	−0.038
Dahl <i>et al.</i> , 1 2006	−0.525	0.007	−0.692	−0.357
Dahl <i>et al.</i> , 2 2006	−0.637	0.050	−1.074	−0.199
Bufe <i>et al.</i> , 2009	−0.221	0.017	−0.476	0.034
($I^2 = 67\%$) Pooled GRZ	−0.365	0.054	−0.471	−0.259
Walker <i>et al.</i> , 2001	−0.561	0.094	−1.164	0.041
Frew <i>et al.</i> , 2006	−0.382	0.017	−0.637	−0.128
($I^2 = 0\%$) Pooled ALD	−0.409	0.120	−0.644	−0.175

OA, Oralair; GRZ, Grazax; ALD, Alk Depot SQ.

Although the SMD may be a parameter of clinical relevance, its use in a health economic model is limited. As a certain value for an SMD cannot be captured within the concept of health states, no quality of life data, costs or transition probabilities can be attached to the SMD. However, a possibility for interpreting the SMD is to re-express it in the units of one or more of the specific measurement instruments, in this case the RTSS. Multiplying a SMD by a typical among-person standard deviation for a particular scale yields an estimate of the difference in mean outcome scores (experimental versus control) on that scale. The standard deviation could be obtained as the pooled standard deviation of baseline scores in the studies⁹.

Specifically, the formula of SMD is used in reverse to obtain the symptom score again. Only this time a “typical standard deviation” (3.01) is used, based on the 2 OA studies. In order to estimate the symptom score for placebo, all placebo means that were measured with the RTSS were averaged (3.51). The results are displayed in Table A3. The final symptom scores were used in for the cost-effectiveness model and can be found in the method section in Table A1.

Table A3. Re-expressing of pooled standard mean differences (SMD) in mean difference & RTSS.

	SMD	Mean Difference	RTSS (range 0–18)
OA	−0.435	−1.31	2.21
GRZ	−0.365	−1.10	2.41
ALD	−0.409	−1.23	2.28
Placebo	—	—	3.51

OA, Oralair; GRZ, Grazax; ALD, Alk Depot SQ.

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