Abstract: Purpose: Apremilast, an oral phosphodiesterase-4 inhibitor, is effective and well tolerated in the treatment of moderate-to-severe psoriasis. The cost-effectiveness of introducing apremilast before biologics was assessed from a UK payer perspective. Materials and methods: A 10-year Markov cohort model was developed to compare alternative treatment sequences: (1) apremilast followed by adalimumab and etanercept and (2) adalimumab followed by etanercept. Non-responders moved to the next treatment line, and patients for whom etanercept therapy failed continued on best supportive care (BSC) in both sequences. Response was defined as a ≥ 75% reduction in Psoriasis Area and Severity Index score (PASI-75) at the end of the trial periods (12–16 weeks). A network meta-analysis provided efficacy inputs. Results: A treatment-extension strategy, apremilast had an incremental cost-effectiveness ratio of £20,593 per quality-adjusted life-year gained versus the comparator sequence. PASI-75 was sustained for 0.73 additional years, and the total time on biologics and BSC was reduced by 0.44 and 1.01 years, respectively. These results were consistent with findings from sensitivity and scenario analyses. Conclusions: Apremilast, an oral treatment option for the treatment of moderate-to-severe plaque psoriasis, is cost-effective from a UK payer perspective when administered before biologics based on assumptions detailed within this analysis.
1. Introduction
Plaque psoriasis is a chronic, systemic, inflammatory disease that affects between 1.3% and 2.6% of the UK population (Parisi, Symmons, Griffiths, & Ashcroft, 2013). Health-related quality of life (HRQoL) surveys in the United Kingdom involving patient-reported outcomes demonstrate that psoriasis has a negative impact on patients’ psychosocial functioning (Anstey, McAteer, Kamath, & Percival, 2012; Lebwohl et al., 2014; Nash, McAteer, Schofield, Penzer, & Gilbert, 2015). Furthermore, the economic burden associated with psoriasis management poses a significant challenge to limited healthcare resources. European studies have estimated that moderate to severe plaque psoriasis is responsible for €5397 to €5690 in annual direct medical costs per patient (Colombo et al., 2008; Schoffski et al., 2007).

The emergence of biologic agents over the past 15 years has improved the treatment of psoriasis, offering effective alternatives for patients who are unresponsive to, or intolerant of, conventional systemic therapies (Sivamani et al., 2013). Biologic therapies, although effective, are associated with adverse events (AEs) such as infusion site reactions and increased risk of infection, and may have limitations such as the injectable mode of administration, regular monitoring required in the summary of product characteristics, and tolerability and safety concerns (Carretero et al., 2015; Gniadecki et al., 2015; Kalbe et al., 2015; Lebwohl et al., 2014; Levin, Gottlieb, & Au, 2014). Furthermore, waning efficacy over time leads to frequent dose escalation, treatment switching, or discontinuation (Warren et al., 2015; Levin, Gottlieb, & Au, 2014; Lebwohl et al., 2014; Yeung et al., 2013; Iskandar et al., 2017). National Institute for Health and Care Excellence (NICE) Clinical Guideline 153 recommends switching to a second biologic following failure of a first-line biologic therapy; however, the optimal sequence of biologics has yet to be determined (Leman & Burden, 2012, National Institute for Health and Care Excellence, 2012a). The annual cost of biologic treatments for psoriasis is expensive and contributed to an overall increase in mean cost per patient of £7774 in the 12 months following initiation of biologic therapy, emphasizing the significant economic burden on the UK National Health Service (NHS) (Cheng & Feldman, 2014; Fonia et al., 2010).

Unmet need is prevalent among patients who experience failure of, or have a contraindication to receiving, conventional systemic therapies prior to biologic therapy who have significant disease burden. Likewise, patients who are not candidates for biologic therapy or may be intolerant of other therapies are in need of treatment alternatives. Under-treatment and suboptimal disease management exacerbate the negative impact on patients’ work, personal, and social lives (Anstey et al., 2012; Nash et al., 2015). Moreover, the high cost of acquiring biologic therapies contributes to the increased economic burden of psoriasis management to the health service (Fonia et al., 2010). In addition to cost, patient preference is an important determinant in treatment choice and supporting preferences may result in better outcomes from treatment through improved adherence and compliance (Eliasson et al., 2017).

Apremilast is an oral phosphodiesterase-4 inhibitor that regulates pro- and anti-inflammatory mediators implicated in psoriasis (Schaffer et al., 2010). The efficacy and safety of apremilast for the treatment of moderate to severe psoriasis was established in two pivotal phase III clinical trials: ESTEEM 1 (NCT01194219) (Papp et al., 2015) and ESTEEM 2 (NCT01232283) (Paul et al., 2015). Data through 3 years for apremilast shows no increase in severity or frequency of AEs including risk of infection with longer-term exposure (Crowley et al., 2017). In the European Union, apremilast is approved for patients whose condition fails to respond to, who have a contraindication to, or who are intolerant of other systemic therapies ('Otezla Summary of Product Characteritics', 2015).
In November 2016 and February 2017, NICE published final guidance recommending apremilast for use in moderate to severe psoriasis and psoriatic arthritis, respectively, on the NHS (National Institute for Health and Care Excellence, 2017, 2016). The Summary of Product Characteristics (SmPC) for apremilast does not specify the requirement for screening at treatment initiation or regular laboratory monitoring for toxicity (‘Otezla Summary of Product Characteristics’, 2015), which may favourably impact patient convenience and reduce NHS resource use leading to potential cost savings.

In order to aid UK decision makers on the efficient allocation of resources given a fixed budget, an assessment of cost-effectiveness is usually required. This study sought to determine the cost-effectiveness of apremilast treatment, placed in sequence prior to tumour necrosis factor-alpha (TNF-α) inhibitors, in patients for whom traditional systemic therapy had failed. As part of the analysis, a systematic literature review and network meta-analysis (NMA) were conducted to provide indirect comparisons because head-to-head comparisons of apremilast with other approved therapies are lacking.

2. Materials and methods

2.1. Systematic literature review and network meta-analysis

2.1.1. Literature review

A systematic literature review of content published through February 2015 was performed to identify reports of all randomized controlled trials (RCTs) relevant for the NMA. The PubMed/ Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov databases were queried using psoriasis- and drug-specific search terms and the interventions of interest (ie, apremilast, adalimumab, etanercept, infliximab, and ustekinumab). (See Table A1 for the detailed search strategy.)

An RCT publication was deemed to meet inclusion criteria if it: (1) had a study population composed of psoriasis patients aged ≥ 18 years (unless outcomes for adult patients were reported as subgroups); (2) included one or more treatments of interest as systemic monotherapy; and (3) reported one or more of the desired efficacy/safety endpoints (ie, PASI outcomes, AEs, and discontinuation) (Table A2). Only English-language publications were retained, and no restrictions were imposed on publication date. Open-label extension studies were eligible only if they were randomized and comparator-controlled. Excluded were non-randomized studies (eg, case reports, case series, and observational studies), single-arm studies, and studies in which different dosages or formulations of the same drug were examined but a comparator was not included. Also excluded were studies without full text and studies that concerned nail psoriasis. Conference abstracts and presentations were omitted.

In addition, the references cited in systematic reviews, meta-analyses, and health technology assessment (HTA) documents were examined to uncover publications that might not have been captured during the searches. To ensure comprehensive and accurate data collection from each study, pertinent data were extracted by two independent reviewers and collated to check for inconsistencies, which were resolved.

2.1.2. NMA methodology

An NMA based on published models was conducted in WinBugs (MRC Biostatistics Unit, Cambridge, UK) using a Bayesian analysis framework. Non-informative prior distributions were used so that model outcomes would be determined only by the clinical trial data. The meta-analysis included the PASI-50, PASI-75, and PASI-90 outcome measures. To make efficient use of the data for this type of measure, a multinomial model with a probit link was used (Dias, Sutton, Ades, & Welton, 2013). The results are presented as the probabilities of achieving PASI-50, PASI-75, and PASI-90.
3. Cost-effectiveness analysis

3.1. Model overview

A Markov state-transition cohort model was developed in Excel 2013 (Microsoft, Redmond, WA, USA) to allow comparison between treatment sequences. This was done because patients with psoriasis are more likely to receive multiple lines of therapy due to AEs or waning efficacy. The model framework was adapted from the University of York Assessment Group model for psoriasis, which was validated by a UK clinician (Woolacott et al., 2006).

In this sequential-treatment model, each treatment line was considered as a mutually exclusive health state. The health states are illustrated in Figure 1. Patients entered the model in a health state dictated by the treatment pathway under investigation. In the apremilast cohort, patients entered the model in the "apremilast trial period" health state, whereas patients in the comparator cohort began with the selected biologic therapy. The biologic treatment sequence used in the base case was determined by expert opinion. For patients not responding to or discontinuing other treatment options, the sequence consisted of adalimumab, followed by etanercept, and then BSC. Patients who had been receiving apremilast as first-line therapy subsequently were transitioned to the biologic-therapy sequence. Patients in the comparator sequence initiated on adalimumab and then transitioned to the next biologic therapy in the sequence (Iskandar et al., 2017).

Response to active therapy was assessed after the respective trial period (ranging from 12−16 weeks) using the PASI-75 response criteria. Patients who achieved this outcome were assumed to remain on the treatment until withdrawal due to either loss of efficacy or another cause according to a comprehensive, long-term withdrawal probability. Non-responders and patients who discontinued during the continued-use period were assumed to progress to subsequent lines of therapy.

The model was based on a cycle length of 28 days because this offered the best compromise for the different durations of the apremilast and biologic trial periods. A time horizon of 10 years was considered in the base case, which is consistent with other published economic evaluations of psoriasis (Pan et al., 2011, Royal College of Physicians (UK). National Clinical Guideline Centre (UK), 2012a; Woolacott et al., 2006).

3.2. Inputs

The mean age and body weight of patients consisted of pooled estimates from apremilast phase III clinical trials (Table 1) (Papp et al., 2015; Paul et al., 2015). Trial period lengths were based on...
economic evaluation and phase III clinical trials (Bansback et al., 2009; Griffiths et al., 2010; Pan et al., 2011). Specifically, the duration was set to 16 weeks for adalimumab and 12 weeks for etanercept. The trial period for apremilast was 16 weeks, which corresponds to the time point used to evaluate treatment response for the primary endpoint in the phase III RCTs (Papp et al., 2015; Paul et al., 2015).

3.2.1. Efficacy estimates

Due to the lack of head-to-head trial data for apremilast versus the comparators routinely used in NHS practice, PASI response rates for all treatments were derived from the NMA results (Table 2). Response rates for patients on BSC were assumed to be similar to those of the placebo group, and treatment response for each therapy was assumed to be constant across cycles, similar to previous cost-effectiveness studies of psoriasis (Bansback et al., 2009; Griffiths et al., 2010; Pan et al., 2011; Woolacott et al., 2006). The model also assumed that withdrawals occurred in the ‘continued use’ health state, where a 20% annual dropout probability was applied for each drug. This assumption was made in other recently published cost-effectiveness analyses (CEA) (Loveman, Turner, Hartwell, Cooper, & Clegg, 2009; Pan et al., 2011; Woolacott et al., 2006). All-cause mortality, based on life tables for England and Wales, was incorporated into all health states (Office for National Statistics).

Both baseline utility and changes in utility were obtained from pooled estimates of apremilast trial data (Table 1). Utility gains from treatment were estimated using the mean difference in EQ-5D scores from baseline for each PASI category (ie, < PASI-50, ≥ PASI-50 to < PASI-75, ≥ PASI-75 to < PASI-90, and ≥ PASI-90).

3.2.2. Costs

Treatment frequency, dosage, and mode of administration were based on product labels and clinical input. Resource use associated with monitoring, routine laboratory tests, physician visits, and administration was obtained from a recent cost-effectiveness study conducted by the National Clinical Guidelines Centre (NCGC) (Table A3) (Royal College of Physicians (UK). National Clinical Guideline Centre (UK), 2012a, 2012b). Apremilast was assumed to require the same number of physician visits as both adalimumab and etanercept. Drug-acquisition costs were quoted from the 2015 British National Formulary (BNF) (Joint Formulary Committee, 2014). Administration costs were obtained from the NCGC study; costs for physician visits reflected NHS reference costs (2012/2013); and monitoring costs were sourced from the NCGC and the literature (NHS Department of Health and Social Care (UK), 2015; Royal College of Physicians (UK). National Clinical Guideline Centre (UK), 2012a; Woolacott et al., 2006). One inpatient day per cycle was assumed for non-responders. Hospitalization costs for non-responders and BSC were obtained from a 2010 study by Fonia et al. (Fonia et al., 2010). The evaluation was undertaken from the NHS and Personal Social Services (PSS) perspective, and therefore included only direct healthcare costs.

3.3. Outcomes

The model outcomes were quality-adjusted life years (QALYs) gained, total costs, and the incremental cost-effectiveness ratio (ICER). Costs and outcomes were discounted at 3.5% per year in accordance with the NICE reference case (National Institute for Health and Care Excellence, 2012a). The amount of time spent on biologics and BSC was assessed in some scenario analyses.

3.4. Sensitivity analyses

Deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were performed to investigate uncertainty in the results. The specific inputs that were varied are listed in Table 1. Posterior distributions from the NMA were used for efficacy data in the PSA.

3.5. Alternative scenarios

Various scenarios were investigated within the analyses, including modifications to the following: position of apremilast within the treatment sequence; time horizon; efficacy decline of second-line
| Parameter                          | Values (mean)                  | Source                                           |
|-----------------------------------|--------------------------------|--------------------------------------------------|
| Patient characteristics           |                                |                                                  |
| Mean age                          | 45.94                          | Pooled apremilast trial data (Papp et al., 2015; Paul et al., 2015) |
| Mean weight                       | 92.63                          | Pooled apremilast trial data (Papp et al., 2015; Paul et al., 2015) |
| Mean baseline utility             | 0.65                           | Pooled apremilast trial data                     |
| Efficacy data                     |                                |                                                  |
| PASI                              | Table 2                        | NMA, Celgene 2015 (Mughal et al., 2016)          |
| Annual long-term drop-out rate    |                                |                                                  |
| Apremilast                        | 20.0% uniform distribution ± 25.0% | Assumption                                      |
| Adalimumab                        | 20.0% uniform distribution ± 25.0% | Turner et al. (Turner, Picot, Cooper, & Loveman, 2009) |
| Etanercept                        | 20.0% uniform distribution ± 25.0% | Pan et al. (Pan et al., 2011)                    |
| Infliximab                        | 20.0% uniform distribution ± 25.0% | Woolacott et al. (Woolacott et al., 2006)        |
| Ustekinumab                       | 20.0% uniform distribution ± 25.0% | Pan et al. (Pan et al., 2011)                    |
| Utilities: mean change in EQ-5D by PASI category |                      |                                                  |
| Category                          | Change in EQ-5D score, mean (95% CI) | Distribution | Source |
| ≥ PASI-90                         | 0.20 (0.12, 0.28)              | Normal                                           | Pooled apremilast trial data |
| ≥ PASI-75 to < PASI-90            | 0.16 (0.11, 0.21)              | Normal                                           |                                |
| ≥ PASI-50 to < PASI-75            | 0.08 (0.03, 0.12)              | Normal                                           |                                |
| < PASI-50                         | 0.02 (−0.02, 0.06)             | Normal                                           |                                |
| Costs                             |                                |                                                  |
| Drug costs                        |                                |                                                  |
| Apremilast (30 mg x 1)            | £9.82                          | Celgene; assumed annual cost of £7150            |
| Adalimumab (40 mg x 1)            | £352.14                        | BNF 2014; adalimumab (Joint Formulary Committee, 2014) |
| Etanercept (25 mg x 1)            | £89.38                         | BNF 2014; etanercept (Joint Formulary Committee, 2014) |
| Infliximab (100 mg x 1)           | £419.63                        | BNF 2014; infliximab (Joint Formulary Committee, 2014) |
### Table 1. (Continued)

| Parameter                                                                 | Values (mean) | Source                                                                                       |
|---------------------------------------------------------------------------|---------------|-----------------------------------------------------------------------------------------------|
| **Ustekinumab (45 mg x 1)**                                               | £2147.00      | BNF 2014; ustekinumab (Joint Formulary Committee, 2014)                                     |
| **Administration costs**                                                 |               |                                                                                               |
| Self-administration for apremilast, adalimumab, and etanercept            | £0.00         | Assumption (apremilast); NCGC 2012, Appendix O (adalimumab, etanercept) (Royal College of Physicians (UK). National Clinical Guideline Centre (UK), 2012a) |
| **Physician visits**                                                     |               |                                                                                               |
| First visit                                                               | £112.46       | NHS reference cost for 2012/2013; service code 330 (dermatology) (NHS Department of Health and Social Care (UK), 2015) |
| Follow-up visit                                                           | £98.85        | NHS reference cost for 2012/2013; service code 330 (dermatology) (NHS Department of Health and Social Care (UK), 2015) |
| **Monitoring costs**                                                     |               |                                                                                               |
| Hepatic function panel                                                   | £0.76         | Woolacott et al. (Woolacott et al., 2006)                                                      |
| PIIINP                                                                    | £26.93        | Woolacott et al. (Woolacott et al., 2006)                                                      |
| Complete blood count                                                     | £3.01         | Woolacott et al. (Woolacott et al., 2006)                                                      |
| GFR                                                                       | £316.05       | NHS reference cost 2012/2013; service code 330 (dermatology); currency code: RA37Z (NHS Department of Health and Social Care (UK), 2015) |
| Urea and electrolytes                                                    | £1.01         | Woolacott et al. (Woolacott et al., 2006)                                                      |
| Liver biopsy                                                              | £596.95       | Woolacott et al. (Woolacott et al., 2006)                                                      |
| Hospitalization cost                                                     | £45.04        | Fonia et al. (Fonia et al., 2010)                                                             |
| BSC costs                                                                 | £348.22, uniform distribution ± 25.0% (£261.17, £435.28) | Fonia et al. (Fonia et al., 2010)                                                             |
| **Other parameters**                                                     |               |                                                                                               |
| Mortality rates                                                          | Published life tables | UK life tables (Office for National Statistics, 2013)                                           |
| Discount rate                                                            |               |                                                                                               |
| Costs                                                                     | 3.5% DSA range (0.0%, 6.0%) | NICE 2013                                                                                      |
| Utilities                                                                | 3.5% DSA range (0.0%, 6.0%) | NICE 2013                                                                                      |

BNF = British National Formulary; BSC = best supportive care; CI = confidence interval; DSA = deterministic sensitivity analyses; EQ-5D = European Quality of Life-5 Dimensions; GFR = glomerular filtration rate; HAQ = Health Assessment Questionnaire; NHS = National Health Service; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PIIINP = type III procollagen peptide.
Table 2. Results of the network meta-analysis: treatment response by PASI categories

| PASI | Placebo | Apremilast 30 mg | Adalimumab 40 mg | Etanercept 25 mg | Infliximab 5 mg/kg | Ustekinumab 45 mg | Ustekinumab 90 mg |
|------|---------|------------------|------------------|-----------------|-------------------|-------------------|-------------------|
| 50   | 0.17 (0.12, 0.22) | 0.54 (0.43, 0.63) | 0.83 (0.75, 0.90) | 0.68 (0.59, 0.77) | 0.95 (0.92, 0.98) | 0.91 (0.87, 0.95) | 0.94 (0.9, 0.96) |
| 75   | 0.06 (0.04, 0.08) | 0.29 (0.21, 0.38) | 0.62 (0.51, 0.72) | 0.43 (0.33, 0.54) | 0.85 (0.78, 0.91) | 0.77 (0.68, 0.84) | 0.81 (0.73, 0.87) |
| 90   | 0.01 (0.01, 0.02) | 0.10 (0.06, 0.15) | 0.35 (0.25, 0.46) | 0.19 (0.13, 0.27) | 0.64 (0.52, 0.74) | 0.51 (0.41, 0.61) | 0.57 (0.46, 0.67) |

Data are expressed as probability (95% credible interval). PASI = Psoriasis Area Severity Index.
biologic therapies after failure of first-line biologics or apremilast; utility estimates; trial duration for apremilast (ie, using 24 weeks instead); assumptions for the apremilast long-term withdrawal probability; resource-use estimates for BSC; and length of treatment sequences. To simulate efficacy decrement for biologics following first-line biologic failure, a 13.7% reduction in PASI response rates (based on Mazzotta, Esposito, Costanzo, & Chimenti, 2009) and an 82% increase in dropout rates (based on Gniadecki, Kragballe, Dam, & Skov, 2011) were incorporated.

4. Results

4.1. Network meta-analysis results
Of the initial 1223 unique articles identified during the systematic literature review, 195 were shortlisted for full-text review after screening abstracts and titles. Twenty-four trials, including three phase III apremilast studies, ultimately were selected for the NMA (Table A4). A random-effects model was chosen for the NMA because the fit was slightly superior to the fixed-effects model and to account for heterogeneity among the studies. The NMA results (Table 2) suggest that PASI outcomes for apremilast 30 mg, administered twice daily, were superior to those of placebo.

4.2. Base-case analysis
The base-case results indicate that placing apremilast ahead of TNF-α inhibitors generates a QALY gain of 0.09 compared with TNF-α inhibitors alone, and increases costs by £1882 during a 10-year period, resulting in an ICER of £20,593/QALY gained (Table 3) (2012b). Use of apremilast shortened the average time spent on biologics by 0.44 years (3.92 vs 4.36 years), and increased the average time spent at PASI-75 by 0.73 (4.58 vs 3.84 years). Moreover, the time in BSC decreased by more than a year in the apremilast sequence (4.50 vs 5.52 years).

Drug-acquisition costs represented 68.56% of total costs for the apremilast sequence, whereas these costs accounted for 61.93% of the total costs in the comparator sequence. Accordingly, BSC costs were higher for the comparator sequence than for apremilast (34.75% vs 27.23%). The share of monitoring and administration costs and hospitalization costs was comparable across sequences (3.76% vs 3.13%, and 0.45% vs 0.20%, respectively).

4.3. Sensitivity analysis
DSA and PSA results indicate that the uncertainty surrounding the model parameters did not affect the base-case conclusions. In the DSA (Figure 2), the ICER for the apremilast sequence was most sensitive to the cost of BSC per cycle (range, £9728/QALY–£31,458/QALY) and was found to be inversely related to this parameter value. Utility gains for PASI-0 to PASI-50 and for PASI-75 to PASI-90 also were key cost-effectiveness drivers. When higher utility gains were assumed for PASI-0 to PASI-50, the apremilast sequence was less favourable than the base case (£28,409/QALY), whereas assuming higher gains for PASI-75 to PASI-90 had the opposite impact (£16,425/QALY). Discount rates for both costs and utilities were among the other influential DSA parameters.

The ICER from the PSA, which was calculated based on 5000 individual simulations (Figure 3), was consistent with the deterministic ICER (£19,570/QALY vs £20,593/QALY). The base-case apremilast sequence was cost-effective in 51% and 91% of scenarios at willingness to pay (WTP) thresholds of £20,000 and £30,000/QALY, respectively (Figure 4). All simulations fell in the northeast quadrant of the cost-effectiveness plane, indicating 100% probability of the apremilast sequence being more effective than the comparator sequence.

4.4. Alternative scenarios
In addition to the sensitivity analyses, various alternative scenarios were tested to understand the implications of alternative treatment sequences, assumptions, and time horizons (Tables 3 and 4, Figure 5). In the vast majority of scenarios, positioning apremilast before biologic treatment was cost-effective at a WTP threshold of £30,000/QALY gained. Of note, the ICER for the apremilast sequence was consistent with the base case when withdrawal rates were reduced and when costs...
Table 3. Base-case results and alternative-parameter value scenarios

|                                | Mean costs | Mean QALYs | Incremental costs | Incremental QALYs | ICER     |
|--------------------------------|------------|------------|-------------------|-------------------|----------|
| **Base-case analysis**a        |            |            |                   |                   |          |
| Apremilast sequence            | £61,520    | 6.33       | £1882             | 0.09              | £20,593  |
| Comparator sequence            | £59,638    | 6.24       |                   |                   |          |
| **1-year time horizon**        |            |            |                   |                   |          |
| Apremilast sequence            | £9,399     | 0.73       | -£581             | -0.02             | Cost saving, but less effective (£37,929) |
| Comparator sequence            | £9,980     | 0.74       |                   |                   |          |
| **5-year time horizon**        |            |            |                   |                   |          |
| Apremilast sequence            | £37,244    | 3.53       | £386              | 0.04              | £10,283  |
| Comparator sequence            | £36,858    | 3.49       |                   |                   |          |
| **40-year time horizon**       |            |            |                   |                   |          |
| Apremilast sequence            | £117,031   | 14.07      | £3,374            | 0.14              | £24,265  |
| Comparator sequence            | £113,657   | 13.93      |                   |                   |          |
| **Decline in efficacy of biologic therapy after failure on first biologic therapy**b | | | | | |
| Apremilast sequence            | £59,048    | 6.26       | £2,374            | 0.11              | £22,399  |
| Comparator sequence            | £56,674    | 6.15       |                   |                   |          |
| **Alternative utility estimates (Woolacott et al.,(Woolacott et al., 2006) utilities)** | | | | | |
| Apremilast sequence            | £61,520    | 6.57       | £1,882            | 0.09              | £20,337  |
| Comparator sequence            | £59,638    | 6.47       |                   |                   |          |
| **Alternative utility estimates (TA350 utilities)(National Institute for Health and Care Excellence, 2015)\textsuperscript{d}** | | | | | |
| Apremilast sequence            | £61,520    | 6.93       | £1,882            | 0.08              | £23,533  |
| Comparator sequence            | £59,638    | 6.85       |                   |                   |          |
| **Trial period for apremilast increased to 24 weeks, consistent with SPC** | | | | | |
| Apremilast sequence            | £61,739    | 6.32       | £2,101            | 0.08              | £26,122  |
| Comparator sequence            | £59,638    | 6.24       |                   |                   |          |
| **Apremilast annual withdrawal probability from clinical trial data (19.5%)** | | | | | |
| Apremilast sequence            | £61,527    | 6.33       | £1,890            | 0.09              | £20,321  |
| Comparator sequence            | £59,638    | 6.24       |                   |                   |          |
| **Resource use for BSC set to value used in previous NICE single-technology appraisals (£5327.71/year)** | | | | | |
| Apremilast sequence            | £64,483    | 6.33       | £1,179            | 0.09              | £12,905  |

(Continued)
associated with BSC resource use were increased. Alternative utility estimates from published literature had equivocal consequences; those from the study by Woolacott et al. (2006) led to a small decrease in the ICER, whereas the higher figures from NICE TA350 (2015) increased the ICER. Although apremilast was cost saving but less effective over a 1-year time horizon, this intervention proved cost-effective over the medium- (5 and 10 years) and long-term (40 years).

Apremilast remained a cost-effective intervention when included in the other proposed treatment sequences (Table 4). The ICER was consistent with the base case when the anti-IL/12/23 ustekinumab was included in the sequence after adalimumab, and with each supplementary biologic appended to the treatment sequence. Inclusion of apremilast before a sequence of four biologics was a dominant strategy. The total time on biologics for patients treated with apremilast decreased as the treatment sequence became longer (–0.25 years for a single-biologic sequence versus –1.07 years for a four-biologic sequence) (Figure 6). Apremilast remained cost-effective when Benepali (biosimilar etanercept) was included in place of Enbrel in an exploratory analysis.

| Comparator sequence | Mean costs | Mean QALYs | Incremental costs | Incremental QALYs | ICER |
|---------------------|------------|------------|------------------|-------------------|------|
| Comparator sequence | £63,303    | 6.24       |                  |                   |      |
| Non-responder cost (£225.00) (Poria et al., 2010) |
| Apremilast sequence | £62,618    | 6.33       | £2512            | 0.09              | £27,485 |
| Comparator sequence | £60,106    | 6.24       |                  |                   |      |
| 50% hospitalization assumed for BSC |
| Apremilast sequence | £57,653    | 6.33       | £2799            | 0.09              | £30,625 |
| Comparator sequence | £54,854    | 6.24       |                  |                   |      |

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; SPC = Summary of Product Characteristics.

aBase-case treatment sequence: apremilast → adalimumab → etanercept → BSC vs adalimumab → etanercept → BSC.
bAssumed a reduction of 13.7% in PASI response rates and an increase of 82% in drop-out rates. (Gniadecki et al., 2011; Mazzotta et al., 2009)
cBaseline = 0.642; < PASI-50 = 0.11; ≥ PASI-50 to < PASI-75 = 0.19; ≥ PASI-75 to < PASI-90 = 0.23; ≥ PASI-90 = 0.26. (National Institute for Health and Care Excellence, 2015)
5. Discussion

Apremilast is an orally administered, novel inhibitor of PDE-4 that does not require pre-screening or routine laboratory monitoring for toxicities within the SmPC. The efficacy and safety of apremilast have been demonstrated in two large phase III RCTs. In addition to demonstrating efficacy on conventional skin outcomes such as PASI used for regulatory purposes in clinical trials, apremilast has shown significant benefits on nail and scalp psoriasis, palmoplantar psoriasis, and HRQoL outcomes such as the DLQI and pruritus (itching) VAS.

The aim of this study was to assess the cost-effectiveness of placing oral apremilast within the current context of the NHS and to provide guidance for efficient resource allocation. Under base-case assumptions, administration of apremilast before the standard sequence of biologic therapies was found to be cost-effective when using the conventional WTP threshold of £30,000/QALY. Moreover, it augmented the duration of PASI-75 and PASI-90 responses, while shortening the time in BSC. Patients on BSC due to failure of conventional systemic therapies or biologic therapy may experience increased burden of disease resulting in emotional distress and negative psychosocial functioning that can lead to a negative impact on work, education, personal relationships and activities of daily living (Anstey et al., 2012; Nash et al., 2015).
### Table 4. Additional scenarios evaluating other possible treatment sequences

|                          | Mean costs | Mean QALYs | Incremental costs | Incremental QALYs | ICER       | Time on biologics (years) | Time on BSC (years) |
|--------------------------|------------|------------|-------------------|-------------------|------------|--------------------------|---------------------|
| **1 Biologic sequence**  |            |            |                   |                   |            |                          |                     |
| APR> ADA> BSC            | £55,057    | 6.17       | £2906             | 0.12              | £24,565    | -0.25                    | -1.21               |
| ADA> BSC                 | £52,152    | 6.05       |                   |                   |            |                          |                     |
| **Alternative 2 biologic treatment sequences** |              |            |                   |                   |            |                          |                     |
| APR> UST> ADA> BSC       | £67,982    | 6.47       | £976              | 0.07              | £14,449    | -0.59                    | -0.87               |
| UST> ADA> BSC            | £67,006    | 6.41       |                   |                   |            |                          |                     |
| **3 Biologics**          |            |            |                   |                   |            |                          |                     |
| APR> ADA> ETA> UST> BSC  | £71,673    | 6.57       | £75               | 0.05              | £1649      | -0.77                    | -0.68               |
| ADA> ETA> UST> BSC       | £71,598    | 6.52       |                   |                   |            |                          |                     |
| **4 Biologics**          |            |            |                   |                   |            |                          |                     |
| APR> ADA> ETA> UST> INF> BSC | £85,437 | 6.73       | -£3067            | 0.01              | Dominant   | -1.07                    | -0.39               |
| ADA> ETA> UST> INF> BSC  | £88,504    | 6.72       |                   |                   |            |                          |                     |
| **Exploratory: base case including extended biologic sequence (includes secukinumab)** | £72,058 | 6.73 | £15 | 0.01 | £2054 | -1.06 | -0.40 |
| **Exploratory: base case including Benepali (etanercept)** | £72,043 | 6.72 | | | |
| APR> ADA> Benepali> BSC  | £60,622    | 6.33       | £2026             | 0.09              | £22,166    | -0.44                    | -1.01               |
| ADA> Benepali> BSC       | £58,596    | 6.24       |                   |                   |            |                          |                     |

**Note:** Efficacy for secukinumab was set as 95.0% for PASI-50, 84.0% for PASI-75, and 62.0% for PASI-90.

ADA = adalimumab; APR = apremilast; BSC = best supportive care; ETA = etanercept; ICER = incremental cost-effectiveness ratio; INF = infliximab; QALY = quality-adjusted life-years; SEK = secukinumab; SPC = Summary of Product Characteristics; UTA = ustekinumab.
Few cost-effectiveness analyses on psoriasis have explored the implications of the intervention within a treatment sequence (National Institute for Health and Care Excellence, 2006, 2008a, 2008b, 2009; Woolacott et al., 2006). The conventional direct comparison of two interventions was considered a limitation by NICE in previous appraisals, particularly because it is common for patients with psoriasis to cycle through various biologic therapies during the course of their disease in routine NHS practice (Levin et al., 2014). In the base-case scenario of the present study, apremilast was placed before adalimumab and etanercept in the treatment sequence, the two most widely used biologics for psoriasis management at the time of the analysis. Adding ustekinumab to the sequence did not change the conclusion of the cost-effectiveness result; neither did placing secukinumab or infliximab as a fifth-line therapy prior to BSC. Apremilast remained cost-effective when Benepali, the licensed biosimilar etanercept, was considered. Placing apremilast before the biologic treatments extended the treatment period and reduced patients’ time on BSC and on injection-based biologic therapies that usually are associated with high monitoring costs and increased risk of serious infection (Kalb et al., 2015; Royal College of Physicians (UK). National Clinical Guideline Centre (UK), 2012b). The apremilast strategy resulted in higher QALYs as a result.

Sensitivity analyses indicated that the model outcomes are dependent on long-term components, particularly the cost of BSC. Increasing the per-cycle resource use for BSC in the scenario analyses to that used in previous NICE single-technology appraisals (ie, TA 103, 134, 146, and 180) effectively improved the ICER to £12,905/QALY, because patients not treated with apremilast
spend more time on BSC. Using an arbitrary assumption of 50% hospitalization rate associated with BSC had the opposite outcome and represented one of only two scenarios where the apremilast sequence was not deemed cost-effective. Likewise, higher non-responder costs served to widen the cost differential, because fewer patients treated with apremilast (as opposed to biologic therapies) attain PASI-75, the treatment-efficacy marker chosen for this study. Nonetheless, the DSA and scenario analyses did not reveal any substantial variations in the model conclusions.

The modelling approach employed in this study is a noteworthy strength. The method was derived from the published York Assessment Group model and was adapted to allow for a treatment sequence approach (Woolacott et al., 2006). This modelling method accurately reflects the natural history and treatment pathways of patients in the United Kingdom with moderate-to-severe plaque psoriasis and allows payers to evaluate the cost-effectiveness of apremilast in a clinically relevant position within the therapy sequence.

Some limitations were apparent in the cost-effectiveness analyses of apremilast. Due to the lack of head-to-head trial data comparing apremilast with each of the comparators, an NMA was conducted to inform the efficacy parameters. The studies included within the NMA showed some heterogeneity that may limit the reliability of the results. Furthermore, no adjustment for baseline risk using methods such as meta-regression was included. This approach was taken to ensure consistency with the majority of previous economic evaluations in psoriasis. Only short-term clinical trial data were incorporated into the analysis – at the detriment of generalizability of prolonged responses – because long-term efficacy data were not available. To compensate, we assumed persistence on the therapy of choice after response assessment and factored in an annual discontinuation rate similar to that of previous modelling studies (Woolacott et al., 2006). The model used PASI score to assess improvements in disease severity which also has inherent limitations. In addition, improvements in psoriasis symptoms unrelated to PASI response, such as scalp and nail psoriasis, and pruritus (itch), were not explicitly included in the model. The model included approved medications available at the time of analysis; recently approved therapeutic options including ixekizumab, brodalumab, guselkumab and dimethyl fumarate were not included in the analysis.

Moreover, the model did not explicitly account for costs of treating or disutility arising from AEs. Fixed treatment sequences, especially in scenario analyses with extensive sequences, may not be entirely consistent with real-world practice, because patients tend to customize future treatment prospects according to their previous response and tolerability issues, which are not likely to be homogeneous throughout a study population. Societal benefits were not factored into the model and the potential disutility of administering injectable therapies was not captured, which can be considered conservative toward apremilast. Apremilast treatment has shown a long-term improvement in work productivity based on clinical trial data. Lastly, future work must focus on accurately estimating the costs of BSC in NHS practice, given its importance as a driver of cost-effectiveness for apremilast in this study and previous analyses involving biologic therapy.

6. Conclusions

Apremilast is a non-biologic, oral treatment option available in the treatment armamentarium for psoriatic disease. Based on the assumptions detailed within this analysis, oral apremilast is a cost-effective solution that may address the unmet need of patients who have suboptimal disease management or who are not suitable for conventional systemic treatments such as methotrexate. The results of this analysis show that the use of apremilast, in a clinically relevant position before biologic therapy, resulted in less time on BSC and injection-based biologic therapy, and was found to be a cost-effective strategy for the NHS compared with biologic therapy alone at a WTP of £30,000/QALY. Results for scenarios in which apremilast is positioned ahead of sequences of more than two biologic therapies were consistent with those for the base case. The choice of treatment pathway sequencing in moderate to severe plaque psoriasis is likely to be driven by patient and physician choice.
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Author details
Anthony Bewley 1
E-mail: anthony.bewley@bartshealth.nhs.uk
Jonathan Barker 2
E-mail: jonathan.barker@kcl.ac.uk
Farhan Mughal 3
E-mail: ayaan.mughal2008@gmail.com
ORCID ID: http://orcid.org/0000-0002-8332-7898
Helene Cawston 4
E-mail: helene.cawston@amaris.com
Vidya Damera 5
E-mail: vidya.damera@inventivhealth.com
James Morris 6
E-mail: james.morris@cogentia.co.uk
Tom Tencer 7
E-mail: tencer@celgene.com

1 Department of Dermatology, Whips Cross University Hospital & The Royal London Hospital, London, Whips Cross Road, E11 1NR, UK.
2 St John’s Institute of Dermatology, Faculty of Life Sciences and Medicine, Kings College London, 9th Floor Tower Wing, Guy’s Hospital, London SE1 9RT, UK.
3 Department of H.E.O.R and Pricing, Celgene Ltd, Hayes, Uxbridge, UB11 1DB, UK.
4 Mapi Group, 27 rue de la Villette, 69003 Lyon, France.
5 Inventiv Health Consulting, 10 Bloomsbury Way, London WC1A 2SL, UK.
6 Cogentia Healthcare Consulting, 16-20 Regent Street, Cambridge CB2 1DB, UK.
7 Department of Global Pricing and Market Access for Immunology and Dermatology, Celgene Corporation, NJ, 556 Morris Avenue, Summit, 07901, USA.

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Appendix

Table A1. Search terms used to identify relevant citations from PubMed, EMBASE, and CENTRAL

| PubMed/Medline | EMBASE | CENTRAL |
|----------------|--------|---------|
| **General search terms** | | |
| “psoriasis”[MeSH Terms] OR “psoriasis”[All Fields] NOT ((“arthrit*” OR “psoriatic”[MeSH Terms] OR (“arthrit*” OR “arthritis”[All Fields]) AND (“psoriatic arthritis”[All Fields] OR “arthritis, psoriatic”[All Fields])) | “psoriasis”[exp NOT “psoriatic arthritis”/exp | MeSH descriptor: [Psoriasis] explode all trees |
| | | |
| **Treatment-specific search terms** | | |
| “TNF-R Fc fusion protein”[Supplementary Concept] OR “TNF-R Fc fusion protein”[All Fields] OR “etanercept”[All Fields] OR “enbrel”[All Fields] OR “adalimumab”[Supplementary Concept] OR “adalimumab”[All Fields] OR “humira”[All Fields] OR “adalimumab”[D2E7][All Fields] OR “infliximab”[Supplementary Concept] OR “infliximab”[All Fields] OR “remicade”[All Fields] OR “ustekinumab”[Supplementary Concept] OR “ustekinumab”[All Fields] OR “stelara”[All Fields] OR “CNTO 1275”[All Fields] OR “centocor”[All Fields] OR “methotrexate”[MeSH Terms] OR “methotrexate”[All Fields] OR “Rheumatrex”[All Fields] OR “apremilast”[Supplementary Concept] OR “apremilast”[All Fields] OR “tofacitinib”[Supplementary Concept] OR “tofacitinib”[All Fields] OR “xeljanz”[All Fields] OR “secukinumab”[Supplementary Concept] OR “secukinumab”[All Fields] OR “ain457”[All Fields] OR “LY2439821”[Supplementary Concept] OR “LY2439821”[All Fields] OR “ixekizumab”[All Fields] OR “broladumab”[Supplementary Concept] OR “broladumab”[All Fields] OR “amg 827”[All Fields] OR “cyclosporine”[MeSH Terms] OR “cyclosporine”[All Fields] OR (“sandimmun”[All Fields] AND “neoral”[All Fields]) OR “sandimmum neoral”[All Fields] OR “acitretin”[MeSH Terms] OR “acitretin”[All Fields] OR “soriatane”[All Fields] OR “dimethyl fumarate”[Supplementary Concept] OR “dimethyl fumarate”[All Fields] OR “fumaderm”[All Fields] | “tnfr-fc fusion protein” OR “etanercept”/exp OR “enbrel”/exp OR “adalimumab”/exp OR “humira”/exp OR “d2e7” OR “infliximab”/exp OR “remicade”/exp OR “ustekinumab”/exp OR “stelara”/exp OR “cNTO 1275”/exp OR “centocor” OR “methotrexate” | |
| | | |
| “methotrexate”/exp OR “rheumatrex”/exp OR “apremilast”/exp OR “tofacitinib”/exp OR “xeljanz”/exp OR “secukinumab”/exp OR “ain457”/exp OR “LY2439821”/exp OR “ixekizumab”/exp OR “broladumab”/exp OR “amg 827”/exp OR “cyclosporine”/exp OR (“sandimmun”/exp AND “neoral”/exp) OR “sandimmun neoral”/exp OR “acitretin”/exp OR “soriatane”/exp OR “dimethyl fumarate”/exp OR “fumaderm”/exp | etanercept OR enbrel OR adalimumab OR humira OR infliximab OR remicade OR ustekinumab OR stelara OR centocor OR methotrexate OR apremilast OR tofacitinib OR xeljanz OR secukinumab OR ixekizumab OR broladumab OR cyclosporine OR sandimmun OR neoral OR acitretin OR soriatane OR dimethyl fumarate OR fumaderm | |

(Continued)
Table A2. Key inclusion and exclusion criteria

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| • Studies of patients ≥ 18 years of age unless outcomes for adult patients were reported as subgroups | • Non-randomized observational studies (eg, case reports, case series, observational studies) |
| • Randomized controlled trials (RCT) of psoriasis that:                          | • Single-arm studies or studies examining different dosages or formulations of the same drug but without a comparator |
|   ▪ included at least one treatment of interest as systemic monotherapy           | • Studies without full-text publications (ie, studies with only conference abstracts or presentations) |
|   ▪ reported one or more of the key efficacy/safety endpoints                      | • Studies that focused on nail psoriasis                                             |
|   ▪ were published in English                                                    |                                                                                     |

Table A3. Monitoring test assumptions

| Treatment    | Cycle 1               | Cycle 2               | Cycle 3               | Continued use            |
|--------------|-----------------------|-----------------------|-----------------------|--------------------------|
| Apremilast   | 1 HFP, 1 CBC, 1 UE   | 1 HFP, 1 CBC, 1 UE   | 1 HFP, 1 CBC, 1 UE   | Annually: 4 HFP, 4 CBC, 4 UE |
| Adalimumab   | 1 HFP, 1 CBC, 1 UE   | 1 HFP, 1 CBC, 1 UE   |                       |                          |
| Etanercept   | 1 HFP, 1 CBC, 1 UE   | 1 HFP, 1 CBC, 1 UE   |                       |                          |
| Infliximab   | 3 HFP, 3 CBC, 3 UE   | 1 HFP, 1 CBC, 1 UE   |                       |                          |
| Ustekinumab  | 1 HFP, 1 CBC, 1 UE   | 1 HFP, 1 CBC, 1 UE   |                       |                          |

CBC = complete blood count; GFR = glomerular filtration rate; HFP = hepatitis function panel; PIINP = type III procollagen peptide; UE = urea and electrolytes.

Note: “/exp” signifies using the “explode” function of EMBASE to apply the search to the major subject headings including its associated subheadings. PubMed automatically explodes its major subject headings denoted with the keyword “[MeSH]”.

Bewley et al., Cogent Medicine (2018), 5: 1495593
https://doi.org/10.1080/2331205X.2018.1495593
Table A4. Summary of the 24 trials used to conduct the indirect comparison

| Study ID or reference          | Treatment arm 1                                      | Treatment arm 2                                      | Treatment arm 3                                      |
|-------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| ACCEPT (Griffiths et al., 2010) | Ustekinumab 45 mg at weeks 0 and 4, then q12w         | Ustekinumab 90 mg at weeks 0 and 4, then q12w         |                                                       |
| Asahina 2010 (Asahina, Nakagawa, Etoh, & Ohitsuiki, 2010) | Placebo                                             | Adalimumab 40 mg eow with 80 mg loading               |                                                       |
| CHAMPION (Revicki et al., 2008; Saurat et al., 2008) | Placebo                                             | Adalimumab 40 mg eow with 80 mg loading               |                                                       |
| Chaudhari 2001 (Chaudhari et al., 2001) | Placebo                                             | Infliximab 5 mg/kg at weeks 0, 2, and 6              |                                                       |
| ESTEEM 1 (Papp et al., 2015)   | Placebo                                             | Apremilast 30 mg bid                                  |                                                       |
| ESTEEM 2 (Paul et al., 2015)   | Placebo                                             | Apremilast 30 mg bid                                  | Etanercept 50 mg qw injection                         |
| LIBERATE                      | Placebo                                             | Apremilast 30 mg bid                                  | Etanercept 50 mg qw injection                         |
| EXPRESS (Reich et al., 2005; Reich et al., 2006) | Placebo                                             | Infliximab 5 mg/kg at weeks 0, 2, and 6              |                                                       |
| EXPRESS II (Feldman et al., 2008; Menter et al., 2007) | Placebo                                             | Infliximab 5 mg/kg at weeks 0, 2, and 6              |                                                       |
| Gordon 2006 (Gordon et al., 2006; Shikiar et al., 2007) | Placebo                                             | Adalimumab 40 mg eow with 80 mg loading               |                                                       |
| Gottlieb 2004 (Feldman et al., 2005; Gottlieb et al., 2004) | Placebo                                             | Infliximab 5 mg/kg at weeks 0, 2, and 6              |                                                       |
| Igarashi 2012 (Igarashi, Kato, Kato, Song, & Nakagawa, 2012) | Placebo                                             | Ustekinumab 45 mg at weeks 0 and 4, then q12w         | Ustekinumab 90 mg at weeks 0 and 4, then q12w         |
| Leonardi 2003 (Leonardi et al., 2003) | Placebo                                             | Etanercept 50 mg biw                                  |                                                       |
| LOTUS (Zhu et al., 2013)       | Placebo                                             | Ustekinumab 45 mg at weeks 0 and 4, then q12w         |                                                       |
| Papp 2005 (Papp et al., 2005)  | Placebo                                             | Etanercept 50 mg biw                                  |                                                       |
| Papp 2012 (Papp et al., 2012; Strand et al., 2013) | Placebo                                             | Apremilast 30 mg bid                                  |                                                       |
| PEARL (Tsiu et al., 2011)      | Placebo                                             | Ustekinumab 45 mg at weeks 0 and 4, then q12w         |                                                       |
| PHOENIX 1 (Lebwohl et al., 2010; Leonardi et al., 2008) | Placebo                                             | Ustekinumab 45 mg at weeks 0 and 4, then q12w         | Ustekinumab 90 mg at weeks 0 and 4, then q12w         |
| PHOENIX 2 (Papp et al., 2008)  | Placebo                                             | Ustekinumab 45 mg at weeks 0 and 4, then q12w         | Ustekinumab 90 mg at weeks 0 and 4, then q12w         |
| REVEAL (Menter et al., 2008; Menter, Gordon, Leonardi, Gu, & Goldblum, 2010; Revicki et al., 2008) | Placebo                                             | Adalimumab 40 mg eow with 80 mg loading               |                                                       |
| Toni 2010 (Tori & Nakagawa, 2010) | Placebo                                             | Infliximab 5 mg/kg at weeks 0, 2, and 6              |                                                       |
| van de Kerkhof 2008 (van de Kerkhof et al., 2008) | Placebo                                             | Etanercept 50 mg qw                                  |                                                       |
| Yang 2012 (Yang et al., 2012)  | Placebo                                             | Infliximab 5 mg/kg at weeks 0, 2, and 6              |                                                       |

bid = twice daily; biw = biweekly (once every 2 weeks); eow = every other week; q12w = once every 12 weeks; qw = once per week.
