Appendix 1: Literature search strategy

Clinical trials:


Real-world trials:


Pharmacoeconomic models:

### Appendix 2. Summary of clinical trials

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<tr>
<td>Tesfaye et al,2013</td>
<td><strong>Design:</strong> Multinational, randomized, double-blind, parallel group trial&lt;br&gt;N: 804&lt;br&gt;&lt;br&gt;<strong>Treatment regimen:</strong>&lt;br&gt;Initial Therapy x 8 weeks: DUL 60 mg/day (n=401) or PRE 300 mg/day (n=403) Responders (≥30% reduction in BPI-24 hour average pain score) at 8-weeks discontinued and non-responders (&lt;30% reduction) continued therapy at higher or combination doses&lt;br&gt;Combination/High-dose: DUL 120 mg/day or DUL 60 mg/day + PRE 300 mg/day or PRE 300/day + DUL 60 mg/day or PRE 600 mg/day&lt;br&gt;&lt;br&gt;<strong>Inclusion criteria:</strong> Outpatients ≥18 years diagnosed with DPNP according to MNSI ≥3 caused by T1DM or T2DM; patients must not have been on DPNP therapy or completed the washout period&lt;br&gt;&lt;br&gt;<strong>Exclusion criteria:</strong> suicidal risk determined by Beck Depression Inventory&lt;br&gt;&lt;br&gt;<strong>Outcomes:</strong>&lt;br&gt;Primary Outcome: BPI-MSF score (24-hour average pain score on 11 point scale)&lt;br&gt;Safety: TEAEs, SAEs, vital signs, body weight, laboratory tests, BDI-II to assess depression and suicidal risk</td>
<td><strong>Baseline Characteristics:</strong> Baseline characteristics between treatment groups were similar&lt;br&gt;&lt;br&gt;<strong>Efficacy:</strong>&lt;br&gt;At 8 weeks:&lt;br&gt;Responders: DUL 164 (40.9%), PRE 116 (28.8%)&lt;br&gt;Non-responders: Combo n=170, Higher-dose n=173&lt;br&gt;&lt;br&gt;<strong>Combination/high-dose therapy period:</strong>&lt;br&gt;BPI reduction: combo -2.35 vs higher-dose -2.16, p=0.370&lt;br&gt;Mean% (SD) change in BPI: combo -39.4% (33.62) vs higher-dose 34.3% (37.89)&lt;br&gt; Achieving ≥50% BPI reduction: combo 86 (52.1%) vs higher-dose 64 (39.3%) p=0.068&lt;br&gt; Achieving ≥50% BPI pain reduction: higher-dose PRE: 46.9% vs higher-dose DUL: 28.4%&lt;br&gt;&lt;br&gt;<strong>Safety:</strong> No significant differences between treatment groups&lt;br&gt;Most common TEAEs in the initial therapy period: dizziness, somnolence, nausea&lt;br&gt;Combination/high-dose period: No TEAEs were reported by more than 3% of patients. 38 patients experienced a SAE and no SAEs occurred in more than 3 patients of either therapy group</td>
<td>No opioid use or other analgesic use reported.</td>
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<td>Raskin et al,2006</td>
<td><strong>Design:</strong> 28-week, open-label, randomized, parallel, multinational study&lt;br&gt;N: 449&lt;br&gt;&lt;br&gt;<strong>Treatment regimen:</strong> DUL 60 mg BID (n=334) vs DUL 120 mg QD (n=115)&lt;br&gt;&lt;br&gt;<strong>Inclusion criteria:</strong> Outpatients ≥18 years diagnosed with DPNP according to MNSI ≥3 caused by T1DM or T2DM&lt;br&gt;&lt;br&gt;<strong>Exclusion criteria:</strong> suicidal risk determined by Beck Depression Inventory&lt;br&gt;&lt;br&gt;<strong>Outcomes:</strong> Safety, tolerability, compliance (number taking 80-120% of study medication), efficacy (BPI, CGI-S)</td>
<td><strong>Baseline Characteristics:</strong> Baseline characteristics between treatment groups were similar&lt;br&gt;&lt;br&gt;<strong>Efficacy:</strong>&lt;br&gt;Improvements in both treatment groups in BPI and CGI-S scoring (p&lt;0.001)&lt;br&gt;&lt;br&gt;<strong>Safety:</strong>&lt;br&gt;Most common reasons for D/C: Nausea (3.1%), dizziness (1.8%), vomiting (1.8%), fatigue (1.1%), somnolence (1.1%)&lt;br&gt;TEAEs: nausea (41%), somnolence (34%), dizziness (19%), headache (15%), dry mouth (15%), increased sweating (13%), vomiting (13%), constipation (11%), insomnia (10%), diarrhea (10%)&lt;br&gt;&lt;br&gt;<strong>Tolerability:</strong> Completing study: 60-BID: 213 (63.8%), 120-QD: 72 (62.6%)&lt;br&gt;&lt;br&gt;<strong>Compliance:</strong> 90% during weeks 2-3, 94% between visits</td>
<td>Both doses are well-tolerated, this study does not speak much to efficacy. No reports on opiate or other analgesic use.</td>
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<tr>
<td>Raskin et al,2005</td>
<td><strong>Design:</strong> 12-weeks, multicenter, parallel, double-blind, randomized, PCB-controlled trial&lt;br&gt;N: 348&lt;br&gt;&lt;br&gt;<strong>Treatment regimen:</strong> DUL 60 mg QD (n=116) vs DUL 60 mg BID (n=116) vs PCB(n=116)</td>
<td><strong>Baseline Characteristics:</strong> Baseline characteristics between treatment groups were similar; 53% female, 53.7 Caucasian, 58.8 mean age, 85% T2DM, 13.8 mean duration of diabetes, 4.3 mean duration of DN&lt;br&gt;&lt;br&gt;<strong>Efficacy:</strong>&lt;br&gt;Change in 11-point Likert scale pain score: 60-QD and 60-BID were both more efficacious than PCB and safe to use for DPNP</td>
<td>60-QD and 60-BID were both more efficacious than PCB and safe to use for DPNP</td>
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Appendix 2. Summary of clinical trials

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| Wernicke et al,
2006 | Inclusion criteria: Patients ≥18 years with pain due to bilateral peripheral neuropathy caused by T1DM or T2DM with pain for at least 6 months with a score ≥3 per MNSI and ≥4 of pain of Likert scale. Exclusion criteria: depression. Outcomes: Likert pain scale. | PCB 43% vs 60-QD 68%, p<0.001; PCB 43% vs 60-BID 64%, P=0.002. Sustained response at endpoint: PCB 39% vs 60-QD 60%, p=0.002; PCB 39% vs 60-BID 57%, p=0.008. Average daily APAP dose: PCB 202.52 mg vs 60-QD 151.88 mg vs 60-BID 121.65 mg (p=0.040 for 60-BID vs PCB). Safety: TEAEs: PCB 49% vs 60-QD 61%, p=0.086; PCB 49% vs 60-BID 63%, p=0.047. Discontinuation due to AE: PCB 3% vs 60-QD 4.3% vs 60-BID 12.1% (p=0.010 for 60-BID vs PCB). | No information on opioid or other analgesic medication use was reported. |
| Raskin et al,
2006 | Design: 52-week extension trial, randomized, open-labeled (total of 65 weeks of treatment with 12-13 weeks of original trial)18 N: 237. Treatment regimen: DUL 60 mg BID (n=161) vs Routine care (n=76). Inclusion criteria: Patients ≥18 years with pain due to bilateral peripheral neuropathy caused by T1DM or T2DM with pain for at least 6 months with a score ≥3 per MNSI and ≥4 of pain of Likert scale. Exclusion criteria: Depression. Outcomes: Safety and efficacy (SF-36, EQ-5D). | Baseline Characteristics: Baseline characteristics between treatment groups were similar; the DUL group had slightly longer duration of diabetes and DN; 38.8% female, 78.5% Caucasian, 60 years mean age, 5.7 mean MNSI score, 9.9 years duration of diabetes, 90% had T2DM. Health Outcomes: SF-36 scores were only broken down by components EQ-5D (se): Routine care: -0.05 (0.03) vs DUL -0.02 (0.02); group difference (95%CI) 0.02 (-0.04, 0.09). Safety: Deaths: Routine care (n=2), DUL (n=2). All deaths were deemed unrelated to study drug or protocol. Serious AEs: One or more serious AE: Routine care 28.9% vs DUL 16.8%, p=0.039. CHF: Routine care 5.3% vs DUL 0.6%. Discontinuation due to AE: Routine care 5.3% vs DUL 10.6%. TEAEs: 93.2% reported at least 1 TEAE. Pain in extremity: Routine care 15.8% vs DUL 6.2%, p=0.029. Peripheral edema: Routine care: 15.8% vs DUL 5.0%, p=0.010. Balance disorder: Routine care: 5.3% vs DUL: 0.6%, p=0.038. Erythema, feeling abnormal, localized infections: Routine care: 3.9% vs DUL 0%, p=0.032. | |
| Wernicke et al,
2006 | Design: 12-week, randomized, multicenter, double-blinded, PCB-controlled Phase III trial N: 334. Treatment regimen: DUL 60 mg QD (n=114) vs DUL 60 mg BID (n=112) vs PCB (n=198). Inclusion criteria: Patients ≥18 years with pain due to bilateral peripheral neuropathy caused by T1DM or T2DM with pain for at least 6 months with a score ≥3 per MNSI and ≥4 of pain of Likert scale. Exclusion criteria: Depression. Outcomes: Efficacy: 24-hour pain score on 11-point Likert scale, amount of APAP use, pain severity for worst pain, night pain, CGI-Severity, BPI, SF-MPQ. | Baseline Characteristics: Baseline characteristics between treatment groups were similar; the 60 BID DUL group had slightly more males and longer duration of DN; 38.9% female, 60.7 mean age, 78.1% Caucasian, 91% T2DM, 10.2 duration of diabetes, 3.8 duration of DN, 5.6 mean MNSI score. Efficacy: Mean change (SD) in 24-hour average pain score: PCB: -1.39 (0.23) vs DUL 60 QD: -2.72 (0.22) vs DUL 60 BID: -2.84 (0.23), p<0.001 compared to PCB for both DUL groups. Median average daily APAP dose during acute therapy phase: | |
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<tr>
<td>Wernicke et al, 2007</td>
<td>Design: 52-week, open label randomized trial</td>
<td><strong>Baseline Characteristics:</strong> Baseline characteristics between treatment groups were similar; (DUL vs Routine care) 58.1 vs 58.5 mean age, 55.3% vs 51% female, 100% vs 99% Caucasian, 83.8% vs 85.4% T2DM, 13.9 vs 13.6 mean duration of diabetes, 4.6 vs 4.0 mean duration of neuropathy, 5.0 vs 5.2 mean MNSI.</td>
<td>No information on APAP or opioid use was reported.</td>
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<td>N: 293</td>
<td>Safety: Discontinuation due to AE; DUL 7.4% vs DUL 60 QD 14.7% vs DUL 60 BI 17.9%, p=0.025 DUL 60 BI vs PCB Serious AE: PCB 4.6% vs DUL 60 BI 4.4% vs DUL 60 BI 1.8%</td>
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<td>Treatment regimen: DUL 60 mg BID (n=197) vs Routine care (n=96)</td>
<td>Health Outcomes: SF-36, DUL was significantly improved in some aspects of this questionnaire.</td>
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<td>Inclusion criteria: Patients ≥18 years with pain due to bilateral peripheral neuropathy caused by T1DM or T2DM with pain for at least 6 months with a score ≥3 per MNSI and ≥4 of pain of Likert scale.</td>
<td>EQ-SD: no significant differences</td>
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<td>Exclusion criteria: Depression</td>
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<td>Outcomes: Safety: Progression of diabetic complications, SAEs, TEAEs, MNSI</td>
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<td>Health Outcomes: SF-36, EQ-SD</td>
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<td>Safety: Deaths (deemed unrelated to study drug); DUL (n=1), Routine care (n=3) &gt;&gt;1 SAE(s) (deemed not study related); DUL 11.2%, Routine care 16.7%</td>
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<td>Discontinuation due to AE; DUL 5.6%, Routine care 3.1%</td>
<td>Most common TEAEs: Fatigue, nausea, hyperhidrosis, asthenia, nasopharyngitis</td>
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<td></td>
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<td>Safety: DUL was significantly improved in some aspects of this questionnaire</td>
<td>EQ-SD: no significant differences</td>
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<td>Tanenberg et al, 2011</td>
<td>Design: 12-week, randomized, open-label; phase 4 non-inferiority trial</td>
<td>Baseline Characteristics: Baseline characteristics between treatment groups were similar; (DUL vs PRE) 60.9 vs 61.9 mean age, 72.5 vs 82.8 Caucasian, 39.9 vs 43.3 female, 12.3 vs 12.5 mean duration of diabetes, 4.8 vs 4.3 mean duration of DPNP, 5.7 vs 5.9 mean MNSI.</td>
<td>No APAP or opioid use was reported at follow-up.</td>
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<td>N: 407</td>
<td>Primary Outcome: Reduction in daily pain severity score at 12 weeks: -2.6 DUL vs -2.1 PRE (established non-inferiority)</td>
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<td>Treatment regimen: PRE 300 mg QD (n=134) vs DUL 60 mg QD+ PRE current dose (n=135) vs DUL 60 mg QD (n=138)</td>
<td>Secondary Outcome: BPI severity ratings were significantly greater with DUL monotherapy vs PRE monotherapy, but not with other BPI pain measures</td>
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<td>Inclusion criteria: Patients ≥18 years with pain due to bilateral peripheral neuropathy caused by T1DM or T2DM with pain for at least 6 months with a score ≥3 per MNSI and ≥4 of pain of Likert scale.</td>
<td>Discontinuation: Significantly more in DUL monotherapy group (27, 19.6%, p=0.04) than PRE monotherapy (14, 10.4%), but not DUL + PRE group (18, 13.3%, p=0.19)</td>
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<td>Exclusion criteria: Mania, bipolar disorder, obsessive compulsive disorder or posttraumatic stress disorder or judged to be at risk for suicide</td>
<td>TEAEs: Nausea, insomnia, hyperhidrosis and decreased appetite occurred significantly more in DUL monotherapy vs PRE monotherapy group</td>
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<td>Outcomes: Efficacy: Reduction in 24-hour pain score at week 12</td>
<td>Efficacy: Mean (SD) BPI average pain score reduction: DUL -2.3 (0.3)</td>
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<td>Safety: TEAEs, discontinuations, vital signs changes, laboratory analyses, HbA1c levels</td>
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<td>Rowbotham et al, 2012</td>
<td>Design: RCT, 8 weeks, phase 2, multinational, double-blind, PCB-controlled trial parallel study</td>
<td><strong>Baseline characteristics:</strong> (DUL) 56.1% male, 60.1 mean age, 6.61 mean baseline 24-hour pain score</td>
<td>No opioid use reported</td>
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<td>N: 280</td>
<td>Efficacy: Mean (SD) BPI average pain score reduction: DUL -2.3 (0.3)</td>
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| **Boyle et al,** 2012  
Design: RCT, 28-day study, double-blind  
N: 83  
**Treatment regimen:** PRE 600 mg daily (n=27) vs DUL 120 mg daily (n=28) vs AMI 75 mg daily (n=28)  
**Inclusion criteria:** Patients ≥18 years with T1DM or T2DM for at least 1 year and neuropathic pain of diabetic origin  
**Outcomes:** LANSS score >12, BPI pain score  
**Baseline Characteristics:** Baseline characteristics between treatment groups were similar; 31.3% female, 65.1 mean age, 14.2 mean duration of diabetes, 86.7% T2DM, 100% Caucasian  
**Efficacy:**  
Baseline characteristics: Baseline characteristics between treatment groups were similar; 31.3% female, 65.1 mean age, 14.2 mean duration of diabetes, 86.7% T2DM, 100% Caucasian  
**Safety:**  
Discontinuation due to an AE: PRE (n=6), DUL (n=3), AMI (n=1)  
No opioid/APAP use reported | | | Other findings are related to sleep |

| **Gao et al,** 2010  
Design: RCT, 12-weeks  
N: 215  
**Treatment regimen:** DUL 60-120 mg QD (n=106 ) vs PCB (n=109)  
**Inclusion criteria:** Patients ≥18 years with pain due to bilateral peripheral neuropathy caused by T1DM or T2DM with pain for at least 6 months with a score ≥3 per MNSI and ≥4 of pain of Likert scale.  
**Outcomes:** BPI average pain score  
**Baseline Characteristics:** Baseline characteristics between treatment groups were similar; percent male / female differed significantly; 60.1 mean age, 61.5% male, 77.2% Caucasian, 88.4% T2DM, 11.3 mean duration of diabetes, 3.7 mean duration of DN, 5.9 mean 24-hour pain severity  
**Efficacy:**  
Baseline characteristics: Baseline characteristics were similar between treatment groups; percent male / female differed significantly; 60.1 mean age, 61.5% male, 77.2% Caucasian, 88.4% T2DM, 11.3 mean duration of diabetes, 3.7 mean duration of DN, 5.9 mean 24-hour pain severity  
**Safety:**  
Rates of serious AES: Not significantly different in DUL and PCB groups  
TEAEs: Occurred more frequently in the DUL group; most common were nausea, somnolence, dizziness, constipation, lethargy and anorexia  
No opioid/APAP use reported | | | |

| **Goldstein et al,** 2005  
Design: RCT, 12-weeks  
N: 457  
**Treatment regimens:** PCB (n=115) vs DUL 20 mg QD (n=115) vs DUL 60 mg QD (n=114) vs DUL 60 mg BID (n=113)  
**Inclusion criteria:** Patients ≥18 years with pain due to bilateral peripheral neuropathy caused by T1DM or T2DM with pain for at least 6 months with a score ≥3 per MNSI and ≥4 of pain of Likert scale.  
**Outcomes:** 24-hour average pain score  
**Baseline Characteristics:** Baseline characteristics were similar between treatment groups; percent male / female differed significantly; 60.1 mean age, 61.5% male, 77.2% Caucasian, 88.4% T2DM, 11.3 mean duration of diabetes, 3.7 mean duration of DN, 5.9 mean 24-hour pain severity  
**Efficacy:**  
24-hour average pain score mean change at follow-up [mean ± SE]:  
PCB: -1.91±0.22 vs DUL 20mg/day -2.36±0.21, DUL 60 mg/day -2.89±0.22, DUL 120 mg/day -2.34±0.23  
No significant differences in 20 mg group, there were significant differences in DUL 60 mg/day group and DUL 120 mg/day group compared to PCB  
Secondary outcomes: BPI average pain severity [mean ± SE]:  | | | |
## Appendix 2. Summary of clinical trials

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| Kaur et al, 2011| **Design:** RCT, cross-over clinical trial, 6 weeks in each treatment with a 2 week washout between treatment  
**N:** 65  
**Treatment regimen:**  
1st allocation: AMI 10, 25 or 50 mg once daily (n=33) vs DUL 20, 40 or 60 mg once daily (n=32)  
2nd allocation: DUL 20, 40 or 60 mg once daily (n=30) vs AMI 10, 25 or 50 mg once daily (n=29)  
**Inclusion criteria:** Patients 18-75 years of age with T2DM and stable glucose-lowering medications, with DPNP for at least 1 month and VAS pain score >50%  
**Outcomes:** Reduction in median pain score from baseline as assessed by visual assessment score from 0-100 points (Pain score reduction >50%=good response, 25-50%=moderate response, <25%=mild response)  
Secondary endpoints: 11-point Likert scale for pain | **Baseline Characteristics:** 52.5 mean age, 53% female, 7 mean duration of diabetes, 18 mean duration of pain  
**Efficacy:**  
**Improvement of pain scores:** Scores were similar in crossover groups and thus, the data were pooled.  
DUL 34 (59%) had a good response, 13 (22%) had moderate improvement, 5 (9%) had mild improvement;  
AMI 32 (55%) had good response, 14 (24%) had moderate improvement, 9 (16%) had mild improvement  
No significant improvement when DUL and AMI were compared on Likert scale  
**Overall improvement of >30%:** DUL 64% vs AMI 62%  
>50% improvement: DUL 59% vs AMI 55% (no significant difference)  
**Safety:**  
**TEAEs:** Events were similar in both groups (111 in AMI, 112 in DUL); Mild TEAEs were higher in DUL group (p<0.02); Moderate to severe TEAEs were higher in the AMI group (51% vs 24%, p<0.01); Most common AEs with DUL were constipation and somnolence.  
**No opioid use reported.** |    |
| Skljarevski et al, 2009 | **Design:** open-label, multi-center, 34 week study  
**N:** 216  
**Treatment regimen:**  
First 8 weeks: DUL 60 mg QD (n=216)  
Non-responders increased dose  
After 8 weeks: DUL 60 mg QD (n=103) vs DUL 120 mg QD (n=69)  
**Inclusion criteria:** Patients ≥18 years with pain due to bilateral peripheral neuropathy caused by T1DM or T2DM with pain for at least 6 months with a score ≥3 per MNSI and ≥4 of pain of Likert scale. | **Baseline Characteristics:** The baseline characteristics were similar between all groups (those with only 8 weeks of treatment, responders, and non-responders); baseline characteristics reported by subgroups  
**Efficacy:**  
115 (53.2%) of enrolled patients experienced a >=30% reduction in pain at the end of week 8 and were entered as maintenance arm.  
**Maintenance arm:** Mean change in the maintenance arm was 0.35; mean pain ratings increased by 1.04±0.24 at week 12 (p<0.001), 0.49±0.20 at week 16 |    |
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<td><strong>Outcome:</strong> Mean change from baseline (week 8) to 26 weeks in BPI 24-hour average pain rating</td>
<td>(p=0.017) relative to week 8 and went back to post-acute baseline level at weeks 24 and 34; secondary endpoints did not differ significantly from the 8-week baseline measure; authors conclude that these findings indicate that DUL has a maintenance effect; 76 (66.7%) patients in the maintenance arm had at least 50% pain reduction relative to week 0.</td>
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<td><strong>Rescue treatment arm:</strong> Pain scores were significantly reduced at all time points (LSM changes) (p&lt;=0.001) and at week 34 (p&lt;=0.05); range of improvement was -1.02±0.24 at week 12 to -1.72±0.27 at week 16; significant improvement relative to week 8 in secondary endpoints; 21 (31.8%) had at least 50% pain reduction from week 8 on the BPI score.</td>
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<tr>
<td><strong>Acute treatment arm:</strong> Pain ratings were significantly reduced at week 8 from week 0 (p&lt;0.001) the mean ± sd change from baseline in BPI score was -2.49±2.37; secondary measurements were also significantly improved.</td>
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<tr>
<td><strong>Safety and Tolerability:</strong> 20 (9.3%) of patients experienced 27 SEAs; the most common reason for discontinuation in the acute and maintenance groups was adverse events (20 (9.3%) and 14 (13.6%) discontinued in the acute and maintenance groups); lack of efficacy was the most common reason for discontinuation in the rescue treatment arm and in those who had dose increase after 8 weeks (24 (34.8%) and 3 (24%), respectively).</td>
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<td><strong>TEAEs:</strong> Of all 216 patients, 139 (64.4%) experienced at least one TEAE. Of those who received 120 mg/day, 39 (48.1%) reported at least 1 TEAE. The most common TEAEs (rate of occurrence &gt;=5%) were nausea, somnolence, hyperhidrosis, dry mouth, anorexia, asthenia, fatigue, headache and diarrhea.</td>
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<tr>
<td><strong>Paracetamol use:</strong> 17 (7.9%) used paracetamol at any time during study; 11 (9.6%) in maintenance arm reported paracetamol use; 6 (8.7%) reported paracetamol use in the 120 mg QD group.</td>
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DPNP (diabetic peripheral neuropathic pain); LANSS (Leeds assessment of neuropathic symptoms and signs); MNSI (Michigan Neuropathy Screening Instrument); T1DM (type 1 diabetes mellitus); T2DM (type 2 diabetes mellitus); BPI (brief pain inventory); CGI-S (clinical global impression of severity scale); TEAEs (Treatment Emergent Adverse Events); DN (diabetic neuropathy); APAP (acetaminophen); SF-36 (short Form health Survey); EQ-5D (EuroQol Questionnaire – 5-dimension); AE (adverse events);
## Appendix 3. Summary of real-world outcomes studies

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<tr>
<td>Chen et al., 2010</td>
<td>Population: Commercially-insured DPNP patients between 18 – 64 years old; opioid-naïve in 90 days pre-index</td>
<td>Bias adjustment: Multivariable regression models</td>
<td>Eli Lilly</td>
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<tr>
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<td>Dates: Initiated therapy between Mar 2005 – Dec 2005; 12 months pre- and 12 months post-index</td>
<td>Main Outcomes: Opioid utilization and healthcare costs</td>
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<td>Comparison: Retrospective cohort of DUL vs SOC N: 234; Database: US administrative claims from Medstat MarketScan</td>
<td>Baseline/Pre-index characteristics: There were no significant differences in baseline characteristics; (DUL vs SOC) 55.0 vs 55.1 mean age, 60.7% vs 53.8% female, $22,035 vs $21,706 mean total healthcare costs</td>
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<tr>
<td>Wu et al., 2011</td>
<td>Population: Commercially-insured DPNP patients between 18 – 64 years old; opioid-naïve in 90 days pre-index</td>
<td>Post-index (unadjusted): Opioid utilization: (DUL vs SOC) % Users: 52.1 vs 84.6, p&lt;0.05; Days on medication: 31.8 ± 64.7 vs 59.0 ± 88.1, p&lt;0.05; No. of Rx dispensed: 2.1 ± 3.2 vs 3.8 ± 4.1, p&lt;0.05; Days before first use: 246 ± 141 vs 125 ± 124, p&lt;0.05; Morphine equivalents: 1,047 ± 2,808 vs 2,862 ± 6,565, p&lt;0.05</td>
<td>Eli Lilly</td>
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<td>Dates: Initiated therapy between Mar 2005 – Dec 2005; 12 months pre- and 12 months post-index</td>
<td>Healthcare costs ($ - 2007): (DUL vs SOC) Mean total all-cause: $18,623 ± $18,106 vs $30,602 ± $36,283, p&lt;0.05; mean pharmacy all-cause: $6,514 ± $9,895 vs $6,353 ± $4,490, p&lt;0.05</td>
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<td>Comparison: Retrospective cohort of DUL vs SOC N: 499</td>
<td>Comparison: Propensity score match</td>
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<td>Main Outcomes: Opioid utilization and healthcare costs</td>
<td>Population: Retrospective cohort of DUL vs SOC; stratified by MPR above or below 0.8 N: 1,281</td>
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<td>Database: US administrative claims from Medstat MarketScan</td>
<td>Baseline/Pre-index characteristics: The SOC group had statistically higher proportion of patients with any inpatient stay, total hospital days, and total healthcare costs in the pre-index period; (DUL vs SOC) 54.6 vs 55.1 mean age, 56.6% vs 53.7% female, 24.6% vs 40.5% any inpatient stay, 2.0 vs 5.0 total hospital days, $22,003 vs $39,209 total healthcare costs</td>
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<tr>
<td>Zhao et al., 2010</td>
<td>Population: Commercially-insured DPNP patients between 18 – 64 years old; concurrent opioid use in 90 days pre-index</td>
<td>Post-index (unadjusted): Opioid Utilization: % Users: 54.0 vs 76.7, p&lt;0.05; Days on medication: 26.9 ± 56.9 vs 51.4 ± 80.0, p&lt;0.05; No. of Rx dispensed: 1.9 ± 3.0 vs 3.6 ± 4.6, p&lt;0.05; Days before first use 240.5 ± 139.9 vs 158.8 ± 140.9, p&lt;0.05; Morphine equivalents: 1,404.4 ± 4,769.2 vs 2,495.5 ± 6,023.9, p&lt;0.05</td>
<td>Eli Lilly</td>
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<td>Dates: Initiated therapy between Mar 2005 – Dec 2005; 12 months pre- and 12 months post-index</td>
<td>Healthcare costs ($ - 2007): Total all-cause costs: $25,466 ± $36,976 vs $37,524 ± $57,327, p&lt;0.05; total pharmacy all-cause costs: $7,044 ± $4,831 vs $6,710 ± $8,431</td>
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<td>Comparison: Retrospective cohort of DUL vs SOC; stratified by MPR above or below 0.8 N: 1,281</td>
<td>Baseline/Pre-index characteristics: There were significant differences between groups on region, any inpatient stay, total healthcare costs, and diabetes related costs; (range of groups) 54.7-56.0 mean age, 52.9%-59.3% female, $29,166-$45,635 mean total healthcare costs</td>
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<td>Main Outcomes: Change in opioid utilization and healthcare costs</td>
<td>Adjusted differences 12-months pre- to 12-months post-index: Opioid Utilization (DUL cont. = Ref): Days on medication: DUL non-cont. -24.4, p&lt;0.05; SOC cont. -23.7, p&lt;0.05; SOC non-cont. -18.5, p&lt;0.05; No. of Rx dispensed: DUL non-cont. -0.8, p&lt;0.05; SOC cont. -1.5, p&lt;0.05; SOC non-cont. -1.0, p&lt;0.05; Morphine equivalents: DUL non-cont. -3.298, p&lt;0.05; SOC cont. -2.850, p&lt;0.05; SOC non-cont. -3.253, p&lt;0.05</td>
<td>Pfizer</td>
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<td>Database: US administrative claims from Medstat MarketScan</td>
<td>Healthcare costs ($ - year not reported): Total all-cause costs: DUL $28,190 ± $30,881, p&lt;0.05; PRE $24,872 vs $30,914, p&lt;0.05; Total pharmacy all-cause costs: DUL $7,371 vs $9,113, p&lt;0.05; PRE $7,044 vs $8,454, p&lt;0.05</td>
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<td>Gore et al., 2011</td>
<td>Population: Commercially-insured DPNP patients between 18 – 64 years old; newly initiated therapy more than one year after diagnosis of DPNP</td>
<td>Baseline/Pre-index characteristics: There were significant differences between groups on the comorbidities cerebrovascular disease, depression, panic disorder, and back and neck pain; (DUL vs PRE) 55.4 vs 56.3 mean age, 9.7% vs 60.9% female</td>
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<td>Dates: Diagnosis of DPNP and initiation of medication on or after Jan 2005</td>
<td>Pre- to Post-index (unadjusted): Pain med utilization (pre vs post): % Users (any opioid): DUL 61.2 vs 63.8; PRE 61.7 vs 63.0; No. Rx dispensed (any opioid): DUL 8.5 vs 9.0, p&lt;0.05; PRE 7.0 vs 7.3, p&lt;0.05; % Users (any NSAID): DUL 33.9 vs 33.4; PRE 33.5 vs 33.7; No. Rx dispensed: DUL 3.7 vs 3.6; PRE 3.8 vs 3.7</td>
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<td>Comparison: Retrospective cohort of DUL vs PRE N: 1,426</td>
<td>Health care costs ($ - year not reported): Total all-cause costs: DUL $28,190 ± $30,881, p&lt;0.05; PRE $24,872 vs $30,914, p&lt;0.05; Total pharmacy all-cause costs: DUL $7,371 vs $9,113, p&lt;0.05; PRE $7,044 vs $8,454, p&lt;0.05</td>
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<td>Main Outcomes: Pain medication treatment patterns and healthcare costs</td>
<td>Bias adjustment: Propensity score matching; Multivariable regression models</td>
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<td>Database: US administrative claims from PharMetrics Patient-Centric Database</td>
<td>Funding: Pfizer</td>
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<td>Reference</td>
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<td>Zhao et al., 2011</td>
<td><strong>Population</strong>: Commercially-insured DPNP patients between 18 – 64 years old; new initiation of DUL or PRE. <strong>Dates</strong>: Initiated therapy in 2006. <strong>Duration</strong>: 12 months pre- and 12 months post-index. <strong>Comparison</strong>: Retrospective cohort of DUL vs PRE. <strong>N</strong>: 2,573. <strong>Main Outcomes</strong>: Adherence and healthcare costs. <strong>Database</strong>: US administrative claims from Thomson Reuter’s MarketScan. <strong>Bias adjustment</strong>: Propensity score stratified.</td>
<td><strong>Baseline/Pre-index characteristics</strong>: Baseline characteristics were similar between treatment groups; 55 mean age, 58% female, $24,800 total mean pre-index costs. <strong>12-month post-index</strong>: <strong>Medication Possession Ratio (DUL vs PRE)</strong>: Mean total days supply: 119.5 vs 52.9, p&lt;0.05; mean MPR: 0.343 vs 0.129, p&lt;0.05; proportion with MPR=0.8: 15.5% vs 0.7%, p&lt;0.05. <strong>Healthcare Costs ($ - year not reported) (DUL vs PRE)</strong>: Total all-cause: $34,146±$35,658 vs $34,897±$40,043; Total DPNP related: $1,720±$8,930 vs $1722±$9,903; Total Non-DPNP related: $17,955±$29,251 vs $19,129±$33,294; Pharmacy all-cause: $14,471±$11,099 vs $14,046±$11,476.</td>
<td>Eli Lilly</td>
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<td>Margolis et al., 2010</td>
<td><strong>Population</strong>: Commercially-insured; newly diagnosed DPNP; 18 – 64 years old; initiation of medication within 60 days of diagnosis. <strong>Dates</strong>: Diagnosis of DPNP between Oct 2005 and Mar 2009; 6 months pre- and 6 months post-index. <strong>Comparison</strong>: Retrospective cohort of DUL vs PRE. <strong>N</strong>: 946. <strong>Main Outcomes</strong>: Differences in healthcare resource utilization; Differences in healthcare costs. <strong>Database</strong>: US administrative claims from Thomson Reuter’s MarketScan. <strong>Bias adjustment</strong>: Propensity score match; Multivariable regression models.</td>
<td><strong>Baseline/Pre-index characteristics</strong>: No statistically significant differences existed between groups pre-index; 53 mean age, 45-48% female, $16,600-$17,000 mean total costs. <strong>Difference 6 month pre- to 6 month post-index (DUL vs PRE)</strong>: <strong>Unadjusted</strong>: % opioid users: 3.8% vs 2.1%, DUL significantly increased from pre-index; Total costs ($ - 2008): $3,344 vs -$1,750; Total DPNP-related $ -1,186 vs $267; Pharmacy costs $695 vs $645, both DUL and PRE significantly increased from pre-index. <strong>Difference-in-difference adjusted marginal effect (DUL = Ref.)</strong>: Probability of opioid use: -0.013; Total costs ($ - 2008) $154; Total DPNP-related $145.</td>
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<td>Burke et al., 2011</td>
<td><strong>Population</strong>: Commercially-insured DPNP patients between 18 – 64 years old; new initiation of DUL or PRE. <strong>Dates</strong>: Initiation of DUL or PRE between Mar 2006 – Dec 2008; 6 months pre and 6 months post-index period. <strong>Comparison</strong>: Retrospective cohort of DUL vs PRE. <strong>Main Outcomes</strong>: All-cause healthcare resource utilization; DPNP specific healthcare resource utilization. <strong>Database</strong>: US administrative claims from PharMetrics Patient-Centric Database. <strong>Bias adjustment</strong>: Multivariable regression models.</td>
<td><strong>Baseline/Pre-index characteristics</strong>: Adherence to index medication and hypertension as a comorbidity were the only significantly different baseline characteristics; 55 mean age, 47-51% female. <strong>Difference 6 month pre- to 6 month post-index</strong>: <strong>Healthcare Costs ($ - 2008) (DUL vs PRE)</strong>: Total all-cause: $1,560 vs $1,411; Total DPNP-related: $ -240 vs $704, PRE significantly increased from pre-index; Pharmacy all-cause: $981 vs $709, both PRE and DUL significantly increased from pre-index; Pharmacy DPNP-related: $641 vs $478, both PRE and DUL significantly increased from pre-index, DUL and PRE significantly different between groups. <strong>Difference-in-difference adjusted mean cost ratio (DUL = Ref.)</strong>: Total all-cause costs: 0.97 (0.75 to 1.26); Total DPNP-related costs: 2.35 (1.01 to 5.46).</td>
<td>Pfizer</td>
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<td>Oladapo et al., 2012</td>
<td><strong>Population</strong>: Texas Medicaid recipients between 30 – 64 years old; receiving an OAD and a neuropathic pain med. <strong>Dates</strong>: June 2003 – Oct 2009; 6 month pre and 12 months post-index. <strong>Comparison</strong>: Retrospective cohort of DUL vs PRE vs GABA vs TCA. <strong>Main Outcomes</strong>: MPR of OAD medications (MPR of DPNP medications was an independent variable). <strong>Database</strong>: Texas Medicaid beneficiaries. <strong>Bias adjustment</strong>: Multivariable logistic regression.</td>
<td><strong>Baseline/Pre-index characteristics</strong>: Baseline characteristics were not listed by treatment group; 47.6% of patients age between 50-59, 72.4% female. <strong>12-month post-index</strong>: <strong>Medication Possession Ratio</strong>: DUL (n=652) 85.6 ± 18.2; PRE (n=860) 69.4 ± 24.9; GABA (n=1,852) 74.3 ± 24.2; TCAs (n=913) 76.0 ± 23.5, DUL was significantly better than all others from pairwise comparison.</td>
<td>None</td>
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### Appendix 3. Summary of real-world outcomes studies

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<td>Johnston et al.(^t) 2013</td>
<td><strong>Population:</strong> Commercially insured DPNP patients; at least 18 years old; new initiation of DUL or PRE  &lt;br&gt; <strong>Dates:</strong> Initiation of DUL or PRE between Jul 2008 – Oct 2010; 12 months pre- and 6 months post-index  &lt;br&gt; <strong>Comparison:</strong> Retrospective cohort of DUL vs PRE  &lt;br&gt; <strong>Main Outcomes:</strong> Potential costs associated with DDI and DCI  &lt;br&gt; <strong>Database:</strong> US administrative claims from the MarketScan Commercial and Medicare Supplemental databases  &lt;br&gt; <strong>Bias adjustment:</strong> Multivariable regression models</td>
<td><strong>Baseline/Pre-index characteristics:</strong> There were multiple significant differences between DUL users and PRE users; 57.8-63.5 mean age, 48.6-54.3% female  &lt;br&gt; <strong>Multivariable adjusted comparisons for costs (cost ratio (95% CI) predicted cost difference):</strong>  &lt;br&gt; DUL with potential DDI/DCI vs DUL without potential DDI/DCI (Ref.): 1.218 (1.077 – 1.377) $3,346 ± $4,797, statistically significant; PRE with potential DDI/DCI vs PRE without potential DDI/DCI (Ref.): 0.830 (0.640 – 1.076) -$3,888 ± $37,536; DUL with potential DDI/DCI vs PRE with potential DDI/DCI (Ref.): 1.341 (1.043 – 1.725) $6,955 ± $39,672, statistically significant</td>
<td>Pfizer</td>
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Numbers are mean, mean ± SD, or mean (95% confidence interval) unless otherwise noted.  
DPNP = diabetic peripheral neuropathic pain; DUL = duloxetine; PRE = pregabalin; SOC = standard of care; MPR = medication possession ratio; OAD = Oral antidiabetic drugs; GABA = gabapentin; TCAs = tricyclic antidepressants; DDI = drug-drug interactions; DCI = drug-condition interactions
### Appendix 4. Summary of pharmacoeconomic studies

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<th>Methods</th>
<th>Results</th>
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| Wu et al. 2006<sup>60</sup> | **Population:** DPNP patients with moderate-to-severe pain who participated in 52-week extension of 12-week RCT  
**Comparison:** DUL vs usual care  
**N:** 233  
**Time horizon:** 50-weeks  
**Methods:** CEA alongside RCT, 52-week extension  
**Perspective:** United States: third-party payer, employer, societal  
**Data sources:** Effectiveness estimates derived from 52-week extension of RCT; costs derived from historical claims analysis and wage information from BLS  
**Assumptions:** Base-case scenario excluded drug costs; productivity losses assumed to be midpoint of reported ranges  
**Outcome/cost measures:** Change in SF-36 BP over study; costs in 2002 US$; Third-party payer – direct medical costs; Employer – direct and indirect medical costs; Society – employer costs plus out-of-pocket costs  
**Sensitivity analyses:** One-way SA; Medicare cost estimates used; Analysis including only patients completing follow up visit; Explored drug cost differences | **Base-case, DUL vs usual care:**  
Incremental cost:  
Payer - $1600 (p=0.30); Employer - $2196 (p=0.10);  
Society - $2754 (p=0.10)  
Incremental effectiveness:  
SF-36 BP increased 6.43 points (p=0.047)  
ICERs (.5/SF-36 point gained):  
Payer, DUL not significantly cost-effective (-$249, p=0.06)  
Employer, DUL dominant (-$342, p=0.04)  
Society, DUL dominant (-$429, p=0.04)  
**Sensitivity analysis:**  
Similar results | **Limitations:** Exclusion of drug costs in base-case analysis  
Did not use QALYs as outcome and appropriate willingness-to-pay threshold for increase in SF-36 BP remains uncertain  
Poor reporting throughout study |
| Beard et al. 2008<sup>61</sup> | **Population:** DPNP patients with moderate-to-severe pain failing “standard analgesic treatments”  
**Comparison:** DUL as 1st, 2nd, 3rd, or 4th line treatment and No DUL regimen; non-DUL therapies used in this order: TCA, GABA, then opioids  
**N:** Costs and effectiveness estimated for 1,000  
**Time horizon:** 6-months  
**Methods:** Decision tree analysis  
**Perspective:** United Kingdom: healthcare payer, i.e. the National Health Service  
**Data sources:** Effectiveness inputs derived from RCTs identified through literature search; costs derived from British National Formulary, Department of Health National Reference Costs  
**Assumptions:** ≥30% improvement in pain score defined adequate response to continue therapy; Treatment switches could occur at 28 days for LOE or at 7 days for intolerable AEs  
**Outcome/cost measures:** Direct medical costs in 2005 UK£; QALYs  
**Sensitivity analyses:** One-way SA; PSA; Alternate 1- and 2-year time horizons, which assumed sustained treatment effects; Use of PRE instead of GABA; Anticonvulsants used 1st line instead of TCA | **Base-case:**  
**Total cost:**  
No DUL £306,148; DUL 1st £271,358; DUL 2nd £229,077; DUL 3rd £210,487; DUL 4th £309,607  
**Total effectiveness:**  
No DUL 363,9; DUL 1st 366,3; DUL 2nd 365,7; DUL 3rd 365,5; DUL 4th 365,5  
**ICERs:**  
No DUL, DUL 3rd, DUL 4th all dominated by DUL 2nd  
DUL 1st vs DUL 2nd £75,036/QALY gained  
**Sensitivity analyses:**  
DUL 2nd dominant in one-way SA  
DUL 2nd 94% probability of being cost-saving vs No DUL in PSA | **Strengths:**  
Considers important question regarding order of treatments used  
**Limitations:**  
Short time horizon may not be adequate for patients to cycle through 4 different therapies and may not be appropriate for chronic disease  
Probabilistic sensitivity analyses did not include all comparators |
| O’Connor et al. 2008<sup>62</sup> | **Population:** DPNP patients with moderate-to-severe pain without cardiac conduction disorders or recent MI  
**Comparison:** PRE, DUL, GABA, and DES  
**N:** N/A  
**Time horizon:** 3-months  
**Methods:** Decision tree analysis  
**Perspective:** United States: third-party payer  
**Data sources:** Effectiveness inputs derived from RCTs identified through literature searches and from FDA reviews; Costs derived from Red Book and Medicare Physician Fee Schedule  
**Results:**  
PRE vs DUL $47,700/QALY gained  
Society, DUL dominant (p=0.06) | **Base-case:**  
**Total cost:**  
DES $320; DUL $424; PRE $525; GABA $748  
**Total effectiveness:**  
DES 0.120; DUL 0.122; PRE 0.119; GABA 0.118  
**ICERs:**  
DUL vs DES $47,700/QALY gained  
PRE dominated by either DUL or DES  
GABA dominated by either DUL or DES | **Strengths:**  
Incorporated data from unpublished trials  
Compared four commonly used first-line medications  
**Limitations:**  
Short time horizon for chronic disease, but patients may switch therapies frequently |
### Appendix 4. Summary of pharmacoeconomic studies

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| Bellows et al. 2012**A**   | **Assumptions:** DES caused 2-fold increase in MI for baseline SAE; risk of SAE assumed to be 0 for DUL, PRE, and GABA; patients discontinuing due to LOE paid for 6 weeks of medication and non-adherent patients paid for 1 month  
**Outcome/cost measures:** Direct medical costs in 2006 US$; QALYs  
**Sensitivity analyses:** One-way SA; PSA; Alternate 1- and 6-month time horizons; Alternate ≥50% reduction in pain score defined adequate response to therapy; Structural SA, including removing adherence from tree | **Sensitivity analyses:** Model most sensitive to probability of pain relief with DUL in one-way SA  
DUL had 50% probability of being cost-effective, DES had 48%, PRE had 2%, and GABA had 0% at a $50,000/QALY WTP in PSA | Did not consider treatment after discontinuation for LOE or AE  
Base-case analysis did not incorporate risk of SAE for DUL, PRE, or GABA |
| Carlos et al. 2012**A**    | **Population:** DPNP patients with moderate-to-severe pain  
**Comparison:** DUL, PRE, and GABA  
**N:** Costs and effectiveness estimated for N=1000  
**Time horizon:** 3-months  
**Methods:** Decision tree analysis  
**Perspective:** Mexico: healthcare payer, i.e., public healthcare system  
**Data sources:** Effectiveness inputs derived from systematic review of published literature; costs derived from "local sources"  
**Assumptions:** Drug costs estimated from adherence rates  
**Outcome/cost measures:** Direct medical costs in 2010 US$; Proportion with good pain relief and QALYs  
**Sensitivity analyses:** PSA | **Base-case:**  
**Incremental cost:** DUL vs PRE -$85,920; DUL vs branded GABA -$80,808;  
**Incremental effectiveness:** Not reported  
**ICERs:** PRE and branded GABA dominated by DUL  
DUL vs generic GABA $8,194/QALY gained  
**Sensitivity analyses:**  
DUL had 61% probability of being cost-effective, generic GABA had 25%, and PRE had 14% at an unreported WTP value | **Strengths:** Included both generic and branded GABA  
**Limitations:** Lack of detail regarding methods and results due to it being abstract presented at a conference with no manuscript available |

*Note: DPNP = diffuse pain nociceptive process, WTP = willingness to pay, RCT = randomized controlled trial, SA = sensitivity analysis, PSA = probabilistic sensitivity analysis, QALY = quality-adjusted life year, LOE = life-threatening event, MI = myocardial infarction, SAE = serious adverse event, DES = desvenlafaxine, DUL = duloxetine, PRE = pramipexole, GABA = gabapentin.*