

Appendix A Search Strategy

A.1 First phase of SLR

Literature databases

Table 1: PubMed Including MEDLINE® Search (searched on 3rd October 2017)

| | |
|------------------|---|
| Database name | Medical Literature Analysis and Retrieval System Online® (MEDLINE®); MEDLINE® In-Process |
| Search interface | Pubmed.com https://www.ncbi.nlm.nih.gov/pubmed/ |
| Search date | 3 rd October 2017 |
| Period covered | 1 st January 1980 to 3 rd October 2017 |
| Search filter | (134, 141) |

| # | Searches | Facets | Results |
|----|--|-----------------|---------|
| 1 | ("diabetes mellitus, type 1" [mesh] OR type I diabet* [tiab] OR t1dm [tiab] OR t1d [tiab] OR insulin dependent diabet* [tiab] OR insulin dependent diabet* [tiab] OR iddm [tiab]) | Type 1 diabetes | 93932 |
| 2 | ("(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR sotagliflozin [tiab] OR LX4211 [tiab] OR LX-4211 [tiab] OR LP802034 [tiab] OR LP-802034 [tiab]) | Sotagliflozin | 23 |
| 3 | ("Sodium-Glucose Transporter 1/antagonists and inhibitors"[mesh] AND "Sodium-Glucose Transporter 2/antagonists and inhibitors"[mesh]) | SGLT1/2 | 60 |
| 4 | (sglt1 inhibit* [tiab] AND sglt2 inhibit* [tiab]) | | 17 |
| 5 | (sodium glucose cotransporter 2 inhibit* [tiab] AND sodium glucose cotransporter 1 inhibit* [tiab]) OR (sodium glucose co-transporter 2 inhibit* [tiab] AND sodium glucose co-transporter 1 inhibit* [tiab]) | | 1 |
| 6 | ("SGLT1/2 Inhibitor" [tiab] OR "sodium glucose co-transporter 1/2 inhibitor" [tiab] OR "sodium glucose cotransporter 1/2 inhibitor" [tiab]) | | 0 |
| 7 | ("Sodium-Glucose Transporter 2/antagonists and inhibitors"[mesh]) | | 897 |
| 8 | (sglt2 inhibit* [tiab]) | | 1155 |
| 9 | (sodium glucose cotransporter 2 inhibit* [tiab] OR sodium glucose co-transporter 2 inhibit* [tiab]) | 707 | |
| 10 | (gliflozin [tiab] OR gliflozins [tiab]) | 37 | |
| 11 | ("empagliflozin" [Supplementary Concept] OR Empagliflozin [tiab] OR Jardiance [tiab] OR BI-10773 [tiab] OR BI10773 [tiab]) | 626 | |
| 12 | ("2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR Dapagliflozin [tiab] OR Farxiga [tiab] OR Forxiga [tiab] OR BMS-512148 [tiab] OR BMS512148 [tiab]) | 620 | |
| 13 | ("ipragliflozin" [Supplementary Concept] OR Ipragliflozin [tiab] OR ASP-1941 [tiab] OR ASP1941 [tiab] OR Suglat [tiab]) | 119 | |
| 14 | ("6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" [Supplementary Concept] OR Tofogliflozin [tiab] OR CSG-452 [tiab] OR CSG452 [tiab] OR Apleway [tiab] OR Deberza [tiab]) | 59 | |
| 15 | ("remogliflozin etabonate" [Supplementary Concept] OR Remogliflozin [tiab] OR BHV-091009 [tiab] OR KGT-1681 [tiab] OR GSK-189075 [tiab] OR BHV091009 [tiab] OR KGT1681 [tiab] OR GSK189075 [tiab]) | 19 | |
| 16 | ("5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-hydroxymethyl-6,8-dioxabicyclo(3.2.1)octane-2,3,4-triol" [Supplementary Concept] OR Ertugliflozin [tiab] OR MK-8835 [tiab] OR PF-04971729 [tiab] OR MK8835 [tiab] OR PF04971729 [tiab]) | 16 | |
| 17 | ("1,5-anhydro-1-(5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl)-1-thiogucitol" [Supplementary Concept] OR Luseogliflozin [tiab] OR TS-071 [tiab] OR TS071 [tiab]) | 68 | |
| 18 | ("sergliflozin" [Supplementary Concept] OR Sergliflozin [tiab] OR GW-869682X [tiab] OR GW869682X [tiab]) | 17 | |
| 19 | ("metformin" [mesh] OR Dimethylbiguanidine [tiab] OR Dimethylguanylguanidine [tiab] OR Glucophage [tiab] OR Metformin [tiab] OR diabex [tiab] OR diabetosan [tiab] OR Fluamine [tiab] OR Flumamine [tiab] OR Glifage [tiab] OR Siofor [tiab] OR Glucoformin [tiab] OR Riomet [tiab]) | Metformin | 16649 |
| 20 | (add-on [tiab] OR second-line [tiab] OR off-label [tiab] OR adjunct [tiab] OR added to [tiab] OR "Off-Label Use"[mesh]) | Second line | 69371 |

| # | Searches | Facets | Results |
|----|---|--------|---------|
| 21 | ("Treatment Failure"[mesh] OR fail*[tiab] OR sub-optimal*[tiab] OR suboptimal*[tiab] OR poorly controlled[tiab] OR poor control [tiab] OR uncontrolled [tiab] OR inadequate control [tiab] OR inadequately[tiab] OR refractory[tiab] OR inadequate response [tiab] OR nonrespon*[tiab] OR non-respon*[tiab] OR incomplete response [tiab] OR insufficient response [tiab] OR partial response[tiab] OR partially responded[tiab] OR non-goal[tiab] OR persistent[tiab] OR residual symptom*[tiab] OR replacement[tiab] OR previously treated [tiab] OR switch*[tiab] OR discontinue*[tiab] OR intensif*[tiab] OR titration[tiab] OR up-titration[tiab] OR escalate*[tiab] OR advanced[tiab] OR step-up therapy[tiab] OR treatment failure[tiab] OR primary failure[tiab] OR Poor glycaemic[tiab] OR Poor glycaemic[tiab] OR Inadequate glycaemic[tiab] OR Inadequate glycaemic[tiab] OR Partial glycaemic[tiab] OR Partial glycaemic[tiab] OR insufficient glycaemic[tiab] OR insufficient glycaemic[tiab]) | | 2033957 |
| 22 | 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 | | 2096879 |
| 23 | 1 AND 22 | | 13496 |
| 24 | ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh: noexp] OR randomly[tiab] OR trial[tj] OR ((RCT[tiab] OR placebo[tiab] OR sham[tiab] OR dummy[tiab] OR single blind*[tiab] OR double blind*[tiab] OR allocated[tiab] OR allocation[tiab] OR triple blind*[tiab] OR treble blind*[tiab] OR random*[tiab]) NOT (medline[sb]))) | RCTs | 1205043 |
| 25 | 23 AND 24 | | 1665 |
| 26 | ("animals"[mesh] NOT "humans"[mesh]) | | 4391246 |
| 27 | 25 NOT 26 | | 1636 |
| 28 | Limit to English and 1980-current | | 1543 |

Table 2: Embase Search via Ovid (searched on 3rd October 2017)

| | |
|------------------|--|
| Database name | Excerpta Medica database® (Embase®) |
| Search interface | Embase.com https://embase.com/ Search via Ovid |
| Search date | 3 rd October 2017 |
| Period covered | 1 st January 1980 to 3 rd October 2017 |
| Search filter | (134, 141) |

| # | Searches | Facets | Results |
|----|--|-----------------|---------|
| 1 | exp *insulin dependent diabetes mellitus/ | | 63440 |
| 2 | (type I diabet\$ or t1dm or t1d or insulin dependent diabet\$ or insulin dependent diabet\$ or iddm).ti,ab. | Type 1 diabetes | 91721 |
| 3 | 1 or 2 | | 108084 |
| 4 | (sotagliflozin or LX4211 or LX-4211 or LP802034 or LP-802034).ti,ab. | Sotagliflozin | 67 |
| 5 | exp *sotagliflozin/ | | 40 |
| 6 | exp *sodium glucose cotransporter 2 inhibitor/ and exp *sodium glucose cotransporter 1/ | | 22 |
| 7 | (sodium glucose cotransporter 2 inhibit\$ and sodium glucose cotransporter 1 inhibit\$).ti,ab. or (sodium glucose co-transporter 2 inhibit\$ and sodium glucose co-transporter 1 inhibit\$).ti,ab. | SGLT1/2 | 1 |
| 8 | ("SGLT1/2 inhibitor" or "sodium glucose co-transporter 1/2 inhibitor" or "sodium glucose cotransporter 1/2 inhibitor").ti,ab. | | 15 |
| 9 | (sglt1 inhibit\$ and sglt2 inhibit\$).ti,ab. | | 40 |
| 10 | exp *sodium glucose cotransporter 2 inhibitor/ | | 3274 |
| 11 | (sglt2 inhibit\$).ti,ab. | | 2018 |
| 12 | (sodium glucose cotransporter 2 inhibit\$ or sodium glucose co-transporter 2 inhibit\$).ti,ab. | SGLT2 | 948 |
| 13 | (gliflozin or gliflozins).ti,ab. | | 76 |
| 14 | (Empagliflozin or Jardiance or BI-10773 or BI10773).ti,ab. | | 1062 |
| 15 | exp *empagliflozin/ | | 713 |

| # | Searches | Facets | Results |
|----|--|-------------|---------|
| 16 | (Dapagliflozin or Farxiga or Forxiga or BMS-512148 or BMS512148).ti,ab. | | 1204 |
| 17 | exp *dapagliflozin/ | | 884 |
| 18 | (Ipragliflozin or ASP-1941 or ASP1941 or Suglat).ti,ab. | | 206 |
| 19 | exp *ipragliflozin/ | | 153 |
| 20 | (Tofogliflozin or CSG-452 or CSG452 or Apleway or Deberza).ti,ab. | | 97 |
| 21 | exp *tofogliflozin/ | | 76 |
| 22 | (Remogliflozin or BHV-091009 or KGT-1681 or GSK-189075 or BHV091009 or KGT1681 or GSK189075).ti,ab. | | 31 |
| 23 | exp *remogliflozin etabonate/ | | 26 |
| 24 | (Ertugliflozin or MK-8835 or PF-04971729 or MK8835 or PF04971729).ti,ab. | | 54 |
| 25 | exp *ertugliflozin/ | | 42 |
| 26 | (Luseogliflozin or TS-071 or TS071).ti,ab. | | 137 |
| 27 | exp *luseogliflozin/ | | 97 |
| 28 | (Sergliflozin or GW-869682X or GW869582X).ti,ab. | | 15 |
| 29 | exp *sergliflozin etabonate/ | | 8 |
| 30 | exp *metformin/ | | 15586 |
| 31 | (Dimethylbiguanidine or Dimethylguanylguanidine or Glucophage or Metformin or diabex or diabetosan or Fluamine or Flumamine or Glifage or Siofor or Glucoformin or Riomet).ti,ab. | Metformin | 26745 |
| 32 | (add-on or second-line or off-label or adjunct or added to).ti,ab. | | 411565 |
| 33 | exp **off label drug use"/ | | 1620 |
| 34 | exp *Drug treatment failure/ or (fail\$ or sub-optimal\$ or suboptimal\$ or poorly controlled or poor control or uncontrolled or inadequate control or inadequately or refractory or inadequate response or nonrespon\$ or non-respon\$ or incomplete response or insufficient response or partial response or partially responded or non-goal or persistent or residual symptom\$ or replacement or previously treated or switch\$ or discontinue\$ or intensif\$ or titration or up-titration or escalate\$ or advanced or step-up therapy or treatment failure or primary failure or Poor glycaemic or Poor glycaemic or Inadequate glycaemic or Inadequate glycaemic or Partial glycaemic or Partial glycaemic or insufficient glycaemic or insufficient glycaemic).ti,ab. | Second line | 2773795 |
| 35 | or/4-34 | | 3133753 |
| 36 | 3 and 35 | | 18469 |
| 37 | ((exp animal/ or nonhuman/) NOT exp human/) | | 6250998 |
| 38 | 36 not 37 | | 16578 |
| 39 | randomized controlled trial/ or **randomized controlled trial (topic)"/ or exp randomization/ or Single blind procedure/ or Double blind procedure/ or Triple blind procedure/ or Crossover procedure/ or Placebo/ | | 819395 |
| 40 | (RCT or placebo or sham or dummy or single blind\$ or double blind\$ or allocated or allocation or triple blind\$ or treble blind\$ or random\$).ti,ab,kw. | RCTs | 1524903 |
| 41 | 39 or 40 | | 1762199 |
| 42 | 38 and 41 | | 2251 |
| 43 | limit 42 to English language | | 2162 |
| 44 | remove duplicates from 43 | | 2106 |
| 45 | limit 44 to (yr="2016 -Current" and conference abstract) | | 139 |
| 46 | limit 44 to (yr="1980 -Current" and (article or article in press or conference paper)) | | 1190 |
| 47 | 45 or 46 | | 1329 |

Table 3: The Cochrane Library (Wiley) (searched on 3rd October 2017)

| | |
|------------------|---|
| Database name | The Cochrane Central Register of Controlled Trials (CENTRAL) |
| Search interface | Cochrane Library https://www.cochranelibrary.com/ |
| Search date | 3 rd October 2017 |
| Period covered | 1 st January 1980 to 3 rd October 2017 |
| Search filter | (134 , 141) |

| # | Searches | Facets | Results |
|-----|--|-----------------|---------|
| #1 | MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees | Type 1 diabetes | 15621 |
| #2 | type I diabet* or t1dm or t1d or insulin dependent diabet* or insulin dependent diabet* or iddm:ti,ab,kw (Word variations have been searched) | | 3800 |
| #3 | #1 or #2 | | 17577 |
| #4 | sotagliflozin or LX4211 or LX-4211 or LP802034 or LP-802034:ti,ab,kw (Word variations have been searched) | Sotagliflozin | 34 |
| #5 | sodium glucose cotransporter 2 inhibit*:ti,ab,kw (Word variations have been searched) | SGLT1/2 | 404 |
| #6 | sodium glucose cotransporter 1 inhibit*:ti,ab,kw (Word variations have been searched) | | 332 |
| #7 | #5 and #6 | | 331 |
| #8 | "SGLT1/2 Inhibitor" or "sodium glucose co-transporter 1/2 inhibitor" or "sodium glucose cotransporter 1/2 inhibitor":ti,ab,kw (Word variations have been searched) | | 0 |
| #9 | sglt1 inhibit* and sgl2 inhibit*:ti,ab,kw (Word variations have been searched) | | 26 |
| #10 | MeSH descriptor: [Sodium-Glucose Transporter 1] explode all trees and with qualifier(s): [Antagonists & inhibitors - AI] | | 8 |
| #11 | MeSH descriptor: [Sodium-Glucose Transporter 2] explode all trees and with qualifier(s): [Antagonists & inhibitors - AI] | | 1 |
| #12 | #10 and #11 | | 6 |
| #13 | MeSH descriptor: [Sodium-Glucose Transporter 2] explode all trees and with qualifier(s): [Antagonists & inhibitors - AI] | | 130 |
| #14 | sglt2 inhibit*:ti,ab,kw (Word variations have been searched) | | 311 |
| #15 | sodium glucose cotransporter 2 inhibit* or sodium glucose co-transporter 2 inhibit*:ti,ab,kw (Word variations have been searched) | | 489 |
| #16 | gliflozin or gliflozins:ti,ab,kw (Word variations have been searched) | | 2 |
| #17 | Empagliflozin or Jardiance or BI-10773 or BI10773:ti,ab,kw (Word variations have been searched) | 269 | |
| #18 | Dapagliflozin or Farxiga or Forxiga or BMS-512148 or BMS512148:ti,ab,kw (Word variations have been searched) | 290 | |
| #19 | Ipragliflozin or ASP-1941 or ASP1941 or Suglat:ti,ab,kw (Word variations have been searched) | 43 | |
| #20 | Tofogliflozin or CSG-452 or CSG452 or Apleway or Deberza:ti,ab,kw (Word variations have been searched) | 11 | |
| #21 | Remogliflozin or BHV-091009 or KGT-1681 or GSK-189075 or BHV091009 or KGT1681 or GSK189075:ti,ab,kw (Word variations have been searched) | 13 | |
| #22 | Ertugliflozin or MK-8835 or PF-04971729 or MK8835 or PF04971729:ti,ab,kw (Word variations have been searched) | 22 | |
| #23 | Luseogliflozin or TS-071 or TS071:ti,ab,kw (Word variations have been searched) | 30 | |
| #24 | Sergliflozin or GW-869682X or GW869582X:ti,ab,kw (Word variations have been searched) | 2 | |
| #25 | Dimethylbiguanidine or Dimethylguanylguanidine or Glucophage or Metformin or diabex or diabetosan or Fluamine or Flumamine or Glifage or Siofor or Glucoformin or Riomet:ti,ab,kw (Word variations have been searched) | Metformin | 5484 |
| #26 | MeSH descriptor: [Metformin] explode all trees | | 2193 |

| # | Searches | Facets | Results |
|-----|---|-------------|---------|
| #27 | add-on or second-line or off-label or adjunct or added to:ti,ab,kw (Word variations have been searched) | Second line | 39354 |
| #28 | MeSH descriptor: [Off-Label Use] explode all trees | | 51 |
| #29 | MeSH descriptor: [Treatment Failure] explode all trees | | 42 |
| #30 | fail * or sub-optimal * or suboptimal * or poorly controlled or poor control or uncontrolled or inadequate control or inadequately or refractory or inadequate response or nonrespon * or non-respon * or incomplete response or insufficient response or partial response or partially responded or non-goal or persistent or residual symptom * or replacement or previously treated or switch * or discontinue * or intensif * or titration or up-titration or escalate * or advanced or step-up therapy or treatment failure or primary failure or Poor glycemc or Poor glycaemic or Inadequate glycemc or Inadequate glycaemic or Partial glycemc or Partial glycaemic or insufficient glycemc or insufficient glycaemic:ti,ab,kw (Word variations have been searched) | | 195975 |
| #31 | #4 or #7 or #8 or #9 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 | | 226174 |
| #32 | #3 and #31 | | 6683 |
| #33 | #32 not (pubmed or embase):an | | 140 |
| #34 | Limit to trials, 1980= current | | 70 |

Clinical trials registries

Table 4: Clinical Trials (US) Search (<https://clinicaltrials.gov>) as searched on 20th November 2017

| | |
|------------------|--|
| Database name | US National Institutes of Health (NIH) Ongoing Trials Register |
| Search interface | www.clinicaltrials.gov |
| Search date | 3 rd October 2017 |

| # | Keywords | Results |
|----|---|---------|
| 1 | Sotagliflozin | 23 |
| 2 | LX4211 | 20 |
| 3 | LX-4211 | 20 |
| 4 | LP802034 | 0 |
| 5 | LP-802034 | 0 |
| 6 | Empagliflozin | 147 |
| 7 | Jardiance | 147 |
| 8 | BI-10773 | 147 |
| 9 | BI10773 | 147 |
| 10 | SGLT2 inhibitor | 83 |
| 11 | sodium glucose cotransporter 2 inhibitor | 84 |
| 12 | sodium glucose co-transporter 2 inhibitor | 84 |
| 13 | Gliflozin(s) | 0 |
| 14 | Dapagliflozin | 184 |
| 15 | Farxiga | 184 |
| 16 | Forxiga | 43 |
| 17 | BMS-512148 | 184 |

Extract EUnetHTA Submission File

| # | Keywords | Results |
|----|-------------------------|---------|
| 18 | BMS512148 | 184 |
| 19 | Ipragliflozin | 29 |
| 20 | ASP-1941 | 48 |
| 21 | ASP1941 | 48 |
| 22 | Suglat | 29 |
| 23 | Tofogliflozin | 5 |
| 24 | CSG-452 | 1 |
| 25 | CSG452 | 1 |
| 26 | Aplway | 0 |
| 27 | Deberza | 4 |
| 28 | Remogliflozin | 2 |
| 29 | BHV-091009 | 0 |
| 30 | BHV091009 | 0 |
| 31 | KGT-1681 | 0 |
| 32 | KGT1681 | 0 |
| 33 | GSK-189075 | 17 |
| 34 | GSK189075 | 17 |
| 35 | Ertugliflozin | 20 |
| 36 | MK-8835 | 20 |
| 37 | MK8835 | 20 |
| 38 | PF-04971729 | 17 |
| 39 | PF04971729 | 17 |
| 40 | Luseogliflozin | 3 |
| 41 | TS-071 | 0 |
| 42 | TS071 | 0 |
| 43 | Sergliflozin | 0 |
| 44 | GW-869682X | 0 |
| 45 | GW86968X | 0 |
| 46 | Metformin | 1865 |
| 47 | Dimethylbiguanidine | 1865 |
| 48 | Dimethylguanylguanidine | 1865 |
| 49 | Glucophage | 1865 |
| 50 | Diabex | 16 |
| 51 | Diabetosan | 0 |
| 52 | Flumine | 0 |
| 53 | Flumamine | 0 |

Extract EUnetHTA Submission File

| # | Keywords | Results |
|----|-------------|---------|
| 54 | Glifage | 14 |
| 55 | Siofor | 12 |
| 56 | Glucoformin | 8 |
| 57 | Riomet | 1865 |

Table 5: Clinical Trials (EU) Search (<https://clinicaltrialsregister.eu>) as searched on 20th November 2017

| | |
|------------------|---|
| Database name | European Union Clinical Trials Register (EU CTR) |
| Search interface | https://clinicaltrialsregister.eu |
| Search date | 20 th November 2017 |

| # | Keywords | Results |
|----|---|---------|
| 1 | Sotagliflozin | 7 |
| 2 | LX4211 | 7 |
| 3 | LX-4211 | 6 |
| 4 | LP802034 | 0 |
| 5 | LP-802034 | 5 |
| 6 | Empagliflozin | 42 |
| 7 | Jardiance | 31 |
| 8 | BI-10773 | 0 |
| 9 | BI10773 | 5 |
| 10 | SGLT2 inhibitor | 17 |
| 11 | sodium glucose cotransporter 2 inhibitor | 3 |
| 12 | sodium glucose co-transporter 2 inhibitor | 5 |
| 13 | Gliflozin(s) | 0 |
| 14 | Dapagliflozin | 69 |
| 15 | Farxiga | 0 |
| 16 | Forxiga | 42 |
| 17 | BMS-512148 | 25 |
| 18 | BMS512148 | 1 |
| 19 | Ipragliflozin | 0 |
| 20 | ASP-1941 | 0 |
| 21 | ASP1941 | 1 |
| 22 | Suglat | 0 |
| 23 | Tofogliflozin | 0 |
| 24 | CSG-452 | 0 |
| 25 | CSG452 | 0 |

Extract EUnetHTA Submission File

| # | Keywords | Results |
|----|-------------------------|---------|
| 26 | Aplway | 0 |
| 27 | Deberza | 0 |
| 28 | Remogliflozin | 0 |
| 29 | BHV-091009 | 0 |
| 30 | BHV091009 | 0 |
| 31 | KGT-1681 | 0 |
| 32 | KGT1681 | 0 |
| 33 | GSK-189075 | 0 |
| 34 | GSK189075 | 4 |
| 35 | Ertugliflozin | 8 |
| 36 | MK-8835 | 8 |
| 37 | MK8835 | 0 |
| 38 | PF-04971729 | 4 |
| 39 | PF04971729 | 0 |
| 40 | Luseogliflozin | 0 |
| 41 | TS-071 | 0 |
| 42 | TS071 | 0 |
| 43 | Sergliflozin | 0 |
| 44 | GW-869682X | 0 |
| 45 | GW86968X | 0 |
| 46 | Metformin | 730 |
| 47 | Dimethylbiguanidine | 0 |
| 48 | Dimethylguanylguanidine | 0 |
| 49 | Glucophage | 87 |
| 50 | Diabex | 0 |
| 51 | Diabetosan | 0 |
| 52 | Flumamine | 0 |
| 53 | Flumamine | 0 |
| 54 | Glifage | 0 |
| 55 | Siofor | 1 |
| 56 | Glucoformin | 0 |
| 57 | Riomet | 0 |

A.2 Second phase of SLR

Literature databases

Table 6: Search facet for the systematic literature review in MEDLINE® (Pubmed.com interface) as run on 5th October 2018

| | |
|------------------|---|
| Database name | Medical Literature Analysis and Retrieval System Online® (MEDLINE®); MEDLINE® In-Process |
| Search interface | Pubmed.com https://www.ncbi.nlm.nih.gov/pubmed/ |
| Search date | 5th October 2018 |
| Period covered | 1st August 2017 to 5th October 2018 |
| Search filter | (134, 141) |

| No | Query | Facet | Hits |
|-----|---|--------------------|-------|
| #1 | Search (("diabetes mellitus, type 1" [mesh] OR type I diabet* [tiab] OR t1dm [tiab] OR t1d [tiab] OR insulin dependent diabet* [tiab] OR insulin dependent diabet* [tiab] OR iddm [tiab])) | T1D | 88671 |
| #2 | Search (("2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR sotagliflozin [tiab] OR LX4211 [tiab] OR LX-4211 [tiab] OR LP802034 [tiab] OR LP-802034 [tiab])) | Sotagliflozin | 36 |
| #3 | Search (("Sodium-Glucose Transporter 1/antagonists and inhibitors"[mesh] AND "Sodium-Glucose Transporter 2/antagonists and inhibitors"[mesh])) | SGLT1/2 inhibitors | 64 |
| #4 | Search ((sglt1 inhibit* [tiab] AND sgl2 inhibit* [tiab])) | | 23 |
| #5 | Search ((sodium glucose cotransporter 2 inhibit* [tiab] AND sodium glucose cotransporter 1 inhibit* [tiab]) OR (sodium glucose co-transporter 2 inhibit* [tiab] AND sodium glucose co-transporter 1 inhibit* [tiab])) | | 1 |
| #6 | Search (("SGLT1/2 Inhibitor" [tiab] OR "sodium glucose co-transporter 1/2 inhibitor" [tiab] OR "sodium glucose cotransporter 1/2 inhibitor" [tiab])) | | 0 |
| #7 | Search (("Sodium-Glucose Transporter 2/antagonists and inhibitors"[mesh])) | SGLT2 inhibitors | 1142 |
| #8 | Search (sglt2 inhibit* [tiab]) | | 1505 |
| #9 | Search ((sodium glucose cotransporter 2 inhibit* [tiab] OR sodium glucose co-transporter 2 inhibit* [tiab])) | | 1003 |
| #10 | Search ((gliflozin [tiab] OR gliflozins [tiab])) | | 60 |
| #11 | Search (("empagliflozin" [Supplementary Concept] OR Empagliflozin [tiab] OR Jardiance [tiab] OR BI-10773 [tiab] OR BI10773 [tiab])) | | 826 |
| #12 | Search (("2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept] OR Dapagliflozin [tiab] OR Farxiga [tiab] OR Forxiga [tiab] OR BMS-512148 [tiab] OR BMS512148 [tiab])) | | 781 |
| #13 | Search (("ipragliflozin" [Supplementary Concept] OR Ipragliflozin [tiab] OR ASP-1941 [tiab] OR ASP1941 [tiab] OR Suglat [tiab])) | | 150 |
| #14 | Search (("6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triole" [Supplementary Concept] OR Tofogliflozin [tiab] OR CSG-452 [tiab] OR CSG452 [tiab] OR Apleway [tiab] OR Deberza [tiab])) | | 77 |
| #15 | Search (("remogliflozin etabonate" [Supplementary Concept] OR Remogliflozin [tiab] OR BHV-091009 [tiab] OR KGT-1681 [tiab] OR GSK-189075 [tiab] OR BHV091009 [tiab] OR KGT1681 [tiab] OR GSK189075 [tiab])) | | 21 |
| #16 | Search (("5-(3-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-hydroxymethyl-6,8-dioxabicyclo(3.2.1)octane-2,3,4-triole" [Supplementary Concept] OR Ertugliflozin [tiab] OR MK-8835 [tiab] OR PF-04971729 [tiab] OR MK8835 [tiab] OR PF04971729 [tiab])) | | 44 |
| #17 | Search (("1,5-anhydro-1-(5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl)-1-thioglucofuranose" [Supplementary Concept] OR Luseogliflozin [tiab] OR TS-071 [tiab] OR TS071 [tiab])) | | 81 |
| #18 | Search (("sergliflozin" [Supplementary Concept] OR Sergliflozin [tiab] OR GW-869682X [tiab] OR GW869682X [tiab])) | | 18 |
| #19 | Search ((metformin* [mesh] OR Dimethylbiguanidine [tiab] OR Dimethylguanylguanidine [tiab] OR Glucophage [tiab] OR Metformin [tiab] OR diabex [tiab] OR diabetosan [tiab] OR Flumamine [tiab] OR Flumamine [tiab] OR Glifage [tiab] OR Siofor [tiab] OR Glucoformin [tiab] OR Riomet [tiab])) | Metformin | 18422 |

| No | Query | Facet | Hits |
|-----|--|---|---------|
| #20 | Search ((add-on [tiab] OR second-line [tiab] OR off-label [tiab] OR adjunct [tiab] OR added to [tiab] OR "Off-Label Use"[mesh])) | | 74336 |
| #21 | Search (("Treatment Failure"[mesh] OR fail*[tiab] OR sub-optimal*[tiab] OR suboptimal*[tiab] OR poorly controlled[tiab] OR poor control [tiab] OR uncontrolled [tiab] OR inadequate control [tiab] OR inadequately[tiab] OR refractory[tiab] OR inadequate response [tiab] OR nonrespon*[tiab] OR non-respon*[tiab] OR incomplete response [tiab] OR insufficient response [tiab] OR partial response[tiab] OR partially responded[tiab] OR non-goal[tiab] OR persistent[tiab] OR residual symptom*[tiab] OR replacement[tiab] OR previously treated [tiab] OR switch*[tiab] OR discontinue*[tiab] OR intensif*[tiab] OR titration[tiab] OR up-titration[tiab] OR escalate*[tiab] OR advanced[tiab] OR step-up therapy[tiab] OR treatment failure[tiab] OR primary failure[tiab] OR Poor glycaemic[tiab] OR Poor glycaemic[tiab] OR Inadequate glycaemic[tiab] OR Inadequate glycaemic[tiab] OR Partial glycaemic[tiab] OR Partial glycaemic[tiab] OR insufficient glycaemic[tiab] OR insufficient glycaemic[tiab])) | Second-line | 2148621 |
| #22 | #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 | Interventions | 2216635 |
| #23 | #1 AND #22 | T1D + intervention | 12381 |
| #24 | Search (((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as topic[mesh: noexp] OR randomly[tiab] OR trial[ti]) OR ((RCT[tiab] OR placebo[tiab] OR sham[tiab] OR dummy[tiab] OR single blind*[tiab] OR double blind*[tiab] OR allocated[tiab] OR allocation[tiab] OR triple blind*[tiab] OR treble blind*[tiab] OR random*[tiab]) NOT (medline[sb]))) | Study design (RCTs) | 1272113 |
| #25 | #23 AND #24 | T1D + intervention + RCTs | 1605 |
| #26 | Search ((animals• [mesh] NOT humans• [mesh])) | Removing animal studies | 4502073 |
| #27 | #25 NOT #26 | | 1581 |
| #28 | #27 Filters: English | Published in English | 1503 |
| #29 | #27 Filters: Publication date from 2017/08/01 to 2018/10/05; English | From 1 st Aug 2017 to 5 th Oct 2018 | 81 |
| #30 | Search (((((pramlintide[Supplementary Concept]) OR Symlin[Title/Abstract]) OR 'Pramlintide acetate'[Title/Abstract]) OR ac137[Title/Abstract]) OR 'ac 137'[Title/Abstract]) OR Pramlintide[Title/Abstract] | Pramlintide | 395 |
| #31 | #1 AND #22 AND #30 | T1D + pramlintide + RCTs | 67 |
| #32 | #31 NOT #26 | Removing animal studies | 67 |
| #33 | #32 Filters: English | Published in English | 67 |
| #34 | #32 Filters: Publication date from 1980/01/01 to 2018/10/05; English | From 1 st Jan 1980 to 5 th Oct 2018 | 67 |
| #35 | #29 OR #34 | Final hits | 147 |

Table 7: Search facet for the systematic literature review in Embase® (Embase.com) as run on 5th October 2018

| | |
|------------------|--|
| Database name | Excerpta Medica database® (Embase®) |
| Search interface | Embase.com https://embase.com/ Search via Ovid |
| Search date | 5 th October 2018 |
| Period covered | 1 st August 2017 to 5 th October 2018 |
| Search filter | (134, 141) |

| No. | Query | Facet | Hits |
|-----|---|---------------|-------|
| #1 | 'insulin dependent diabetes mellitus'/exp/mj | Disease (T1D) | 67677 |
| #2 | type i diabet*:ab,ti OR t1dm:ab,ti OR t1d:ab,ti OR 'insulin dependent diabet*':ab,ti OR 'insulin dependent diabet*':ab,ti OR iddm:ab,ti | | 56270 |

| No. | Query | Facet | Hits |
|-----|--|--------------------|--------|
| #3 | #1 OR #2 | | 128429 |
| #4 | sotagliflozin:ab,ti OR lx4211:ab,ti OR 'lx 4211':ab,ti OR lp802034:ab,ti OR 'lp 802034':ab,ti | Sotagliflozin | 97 |
| #5 | 'sotagliflozin'/exp/mj | | 68 |
| #6 | sodium glucose cotransporter 2 inhibitor'/exp/mj AND 'sodium glucose cotransporter 1 inhibitor'/exp/mj | SGLT1/2 inhibitors | 7 |
| #7 | ('sodium glucose cotransporter 2 inhibit*':ab,ti AND 'sodium glucose cotransporter 1 inhibit*':ab,ti) OR ('sodium glucose co-transporter 2 inhibit*':ab,ti AND 'sodium glucose co-transporter 1 inhibit*':ab,ti) | | 1 |
| #8 | sglt1/2 inhibitor':ab,ti OR 'sodium glucose co-transporter 1/2 inhibitor':ab,ti OR 'sodium glucose cotransporter 1/2 inhibitor':ab,ti | | 20 |
| #9 | sglt1 inhibit*':ab,ti AND 'sglt2 inhibit*':ab,ti | | 44 |
| #10 | 'sodium glucose cotransporter 2 inhibitor'/exp/mj | SGLT2 inhibitors | 4180 |
| #11 | 'sglt2 inhibit*':ab,ti | | 2530 |
| #12 | sodium glucose cotransporter 2 inhibit*':ab,ti OR 'sodium glucose co-transporter 2 inhibit*':ab,ti | | 1255 |
| #13 | gliflozin:ab,ti OR gliflozins:ab,ti | | 101 |
| #14 | empagliflozin:ab,ti OR jardiance:ab,ti OR 'bi-10773':ab,ti OR 'bi10773':ab,ti | | 1376 |
| #15 | 'empagliflozin'/exp/mj | | 897 |
| #16 | dapagliflozin:ab,ti OR farxiga:ab,ti OR forxiga:ab,ti OR 'bms-512148':ab,ti OR 'bms512148':ab,ti | | 1480 |
| #17 | 'dapagliflozin'/exp/mj | | 1076 |
| #18 | ipragliflozin:ab,ti OR 'asp-1941':ab,ti OR 'asp1941':ab,ti OR 'suglat':ab,ti | | 238 |
| #19 | 'ipragliflozin'/exp/mj | | 183 |
| #20 | tofogliflozin:ab,ti OR 'csg-452':ab,ti OR 'csg452':ab,ti OR 'apleway':ab,ti OR 'deberza':ab,ti | | 126 |
| #21 | 'tofogliflozin'/exp/mj | | 93 |
| #22 | remogliflozin:ab,ti OR 'bhv-091009':ab,ti OR 'kgt-1681':ab,ti OR 'gsk-189075':ab,ti OR 'bhv091009':ab,ti OR 'kgt1681':ab,ti OR 'gsk189075':ab,ti | | 30 |
| #23 | 'remogliflozin etabonate'/exp/mj | | 25 |
| #24 | ertugliflozin:ab,ti OR 'mk-8835':ab,ti OR 'pf-04971729':ab,ti OR 'mk8835':ab,ti OR 'pf04971729':ab,ti | | 98 |
| #25 | 'ertugliflozin'/exp/mj | | 86 |
| #26 | luseogliflozin:ab,ti OR 'ts-071':ab,ti OR 'ts071':ab,ti | | 150 |
| #27 | 'luseogliflozin'/exp/mj | | 103 |
| #28 | sergliflozin:ab,ti OR 'gw-869682x':ab,ti OR 'gw869582x':ab,ti | | 15 |
| #29 | 'sergliflozin etabonate'/exp/mj | | 10 |
| #30 | 'metformin'/exp/mj | Metformin | 16285 |
| #31 | dimethylbiguanidine:ab,ti OR dimethylguanylguanidine:ab,ti OR glucophage:ab,ti OR metformin:ab,ti OR diabex:ab,ti OR diabetosan:ab,ti OR fluamine:ab,ti OR flumamine:ab,ti OR glifage:ab,ti OR siofor:ab,ti | | 29094 |
| #32 | 'add on':ab,ti OR 'second-line':ab,ti OR 'off-label':ab,ti OR 'adjunct':ab,ti OR 'added to':ab,ti | Second line | 244893 |
| #33 | 'off label drug use'/exp/mj | | 1765 |

| No. | Query | Facet | Hits |
|-----|--|---|---------|
| #34 | 'drug treatment failure'/exp/mj OR fail*:ab,ti OR 'sub-optimal*':ab,ti OR 'suboptimal*':ab,ti OR 'poorly controlled':ab,ti OR 'poor control':ab,ti OR 'uncontrolled':ab,ti OR 'inadequate control':ab,ti OR 'inadequately':ab,ti OR 'refractory':ab,ti OR 'inadequate response':ab,ti OR 'nonrespon*':ab,ti OR 'non-respon*':ab,ti OR 'incomplete response':ab,ti OR 'insufficient response':ab,ti OR 'partial response':ab,ti OR 'partially responded':ab,ti OR 'non-goal':ab,ti OR 'persistent':ab,ti OR 'residual symptom*':ab,ti OR replacement:ab,ti OR 'previously treated':ab,ti OR switch*:ab,ti OR discontinue*:ab,ti OR intensif*:ab,ti OR titration:ab,ti OR 'up titration':ab,ti OR escalate*:ab,ti OR advanced:ab,ti OR 'step-up therapy':ab,ti OR 'treatment failure':ab,ti OR 'primary failure':ab,ti OR 'poor glycaemic':ab,ti OR 'poor glycaemic':ab,ti OR 'inadequate glycaemic':ab,ti OR 'inadequate glycaemic':ab,ti OR 'partial glycaemic':ab,ti OR 'partial glycaemic':ab,ti OR 'insufficient glycaemic':ab,ti OR 'insufficient glycaemic':ab,ti | | 2917212 |
| #35 | #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 | Interventions | 3132044 |
| #36 | #3 AND #35 | T1D + interventions | 15164 |
| #37 | ('animal'/exp OR 'nonhuman'/exp) NOT 'human'/exp | Removing animal studies | 6493645 |
| #38 | #36 NOT #37 | | 13769 |
| #39 | 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/mj OR 'randomization'/exp OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'triple blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de | Study design (RCTs) | 862764 |
| #40 | rct:ab,ti,kw OR placebo:ab,ti,kw OR sham:ab,ti,kw OR dummy:ab,ti,kw OR 'single blind*':ab,ti,kw OR 'double blind*':ab,ti,kw OR 'allocated':ab,ti,kw OR 'allocation':ab,ti,kw OR 'triple blind*':ab,ti,kw OR 'treble blind*':ab,ti,kw OR 'random*':ab,ti,kw | | 1603188 |
| #41 | #39 OR #40 | | 1845049 |
| #42 | #38 AND #41 | T1D + Interventions + RCTs | 1963 |
| #43 | #38 AND #41 AND [english]/lim | Published in English | 1896 |
| #44 | #38 AND #41 AND [english]/lim AND [1-8-2017]/sd NOT [6-10-2018]/sd | From 1 st Aug 2017 to 5 th Oct 2018 | 229 |
| #45 | #38 AND #41 AND [english]/lim AND [1-8-2017]/sd NOT [5-10-2018]/sd AND [embase]/lim | Source: Embase | 225 |
| #46 | 'pramlintide'/exp/mj OR symlin:ab,ti OR 'pramlintide acetate':ab,ti OR ac137:ab,ti OR 'ac 137':ab,ti OR pramlintide:ab,ti | Pramlintide | 483 |
| #47 | #3 AND #46 | T1D + pramlintide | 168 |
| #48 | #47 NOT #37 | Removing animal studies | 166 |
| #49 | #41 AND #48 | T1D + pramlintide + RCTs | 83 |
| #50 | #41 AND #48 AND [english]/lim | Published in English | 83 |
| #51 | #41 AND #48 AND [english]/lim AND [1-1-1980]/sd NOT [6-10-2018]/sd | From 1 st Jan 1980 to 5 th Oct 2018 | 83 |
| #52 | #41 AND #48 AND [english]/lim AND [1-1-1980]/sd NOT [6-10-2018]/sd AND [embase]/lim | Source: Embase | 79 |
| #53 | #45 OR #52 | Final hits | 302 |

Table 8: Search facet for the systematic literature review in Cochrane database (Cochrane library interface) as run on 5th October 2018

| | |
|------------------|---|
| Database name | The Cochrane Central Register of Controlled Trials (CENTRAL) |
| Search interface | Cochrane Library https://www.cochranelibrary.com/ |
| Search date | 5 th October 2018 |
| Period covered | 1 st August 2017 to 5 th October 2018 |
| Search filter | (134, 141) |

Extract EUnetHTA Submission File

| No. | Query | Facet | Hits |
|-----|---|--------------------|--------|
| #1 | MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees | T1D | 4666 |
| #2 | (type I diabet* or t1dm or t1d or insulin dependent diabet* or insulin dependent diabet* or iddm):ti,ab,kw | | 18040 |
| #3 | #1 or #2 | | 20455 |
| #4 | (sotagliflozin or LX4211 or LX-4211 or LP802034 or LP-802034):ti,ab,kw | Sotagliflozin | 57 |
| #5 | (sodium glucose cotransporter 2 inhibit*):ti,ab,kw | SGLT1/2 inhibitors | 663 |
| #6 | (sodium glucose cotransporter 1 inhibit*):ti,ab,kw | | 517 |
| #7 | #5 and #6 | | 513 |
| #8 | ("SGLT1/2 Inhibitor" or "sodium glucose co-transporter 1/2 inhibitor" or "sodium glucose cotransporter 1/2 inhibitor"):ti,ab,kw | | 0 |
| #9 | (sglt1 inhibit* and sglt2 inhibit*):ti,ab,kw | | 37 |
| #10 | MeSH descriptor: [Sodium-Glucose Transporter 1] explode all trees and with qualifier(s): [Antagonists & inhibitors - AI] | | 8 |
| #11 | MeSH descriptor: [Sodium-Glucose Transporter 2] explode all trees and with qualifier(s): [Antagonists & inhibitors - AI] | | 150 |
| #12 | #10 and #11 | 6 | |
| #13 | MeSH descriptor: [Sodium-Glucose Transporter 2] explode all trees and with qualifier(s): [Antagonists & inhibitors - AI] | SGLT2 inhibitors | 150 |
| #14 | sglt2 inhibit*:ti,ab,kw (Word variations have been searched) | | 460 |
| #15 | sodium glucose cotransporter 2 inhibit* or sodium glucose co-transporter 2 inhibit*:ti,ab,kw (Word variations have been searched) | | 674 |
| #16 | gliflozin or gliflozins:ti,ab,kw (Word variations have been searched) | | 4 |
| #17 | Empagliflozin or Jardiance or BI-10773 or BI10773:ti,ab,kw (Word variations have been searched) | | 493 |
| #18 | Dapagliflozin or Farxiga or Forxiga or BMS-512148 or BMS512148:ti,ab,kw (Word variations have been searched) | | 491 |
| #19 | Ipragliflozin or ASP-1941 or ASP1941 or Suglat:ti,ab,kw (Word variations have been searched) | | 92 |
| #20 | Tofogliflozin or CSG-452 or CSG452 or Apleway or Deberza:ti,ab,kw (Word variations have been searched) | | 23 |
| #21 | Remogliflozin or BHV-091009 or KGT-1681 or GSK-189075 or BHV091009 or KGT1681 or GSK189075:ti,ab,kw (Word variations have been searched) | | 22 |
| #22 | Ertugliflozin or MK-8835 or PF-04971729 or MK8835 or PF04971729:ti,ab,kw (Word variations have been searched) | | 59 |
| #23 | Luseogliflozin or TS-071 or TS071:ti,ab,kw (Word variations have been searched) | | 38 |
| #24 | Sergliflozin or GW-869682X or GW869582X:ti,ab,kw (Word variations have been searched) | 2 | |
| #25 | Dimethylbiguanidine or Dimethylguanylguanidine or Glucophage or Metformin or diabex or diabetosan or Fluamine or Flumamine or Glifage or Siofor or Glucoformin or Riomet:ti,ab,kw (Word variations have been searched) | Metformin | 7314 |
| #26 | MeSH descriptor: [Metformin] explode all trees | | 3294 |
| #27 | (add-on or second-line or off-label or adjunct or added to):ti,ab,kw | Second line | 39064 |
| #28 | MeSH descriptor: [Off-Label Use] explode all trees | | 32 |
| #29 | MeSH descriptor: [Treatment Failure] explode all trees | | 3073 |
| #30 | ((fail* or sub-optimal* or suboptimal* or "poorly controlled" or "poor control" or uncontrolled or "inadequate control" or inadequately or refractory or "inadequate response" or nonrespon* or non-respon* or "incomplete response" or "insufficient response" or "partial response" or "partially responded" or non-goal or persistent or residual symptom* or replacement or "previously treated" or switch* or discontinue* or intensif* or titration or up-titration or escalate* or advanced or "step-up therapy" or "treatment failure" or "primary failure" or "Poor glycemic" or "Poor glycaemic" or "Inadequate glycemic" or "Inadequate glycaemic" or "Partial glycemic" or "Partial glycaemic" or "insufficient glycemic" or "insufficient glycaemic"):ti,ab,kw | | 213706 |

| No. | Query | Facet | Hits |
|-----|---|---|--------|
| #31 | #4 or #7 or #8 or #9 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 | Interventions | 245683 |
| #32 | #3 and #31 | T1D + intervention | 7597 |
| #33 | #32 not (pubmed or embase):an | Removing duplicates from pubmed and embase | 533 |
| #34 | #33 [Limit: in trials] | Limited to trials | 460 |
| #35 | #33 [Limit: in trials, 2017-2018] | From 1 st Aug 2017 to 5 th Oct 2018 | 410 |
| #36 | (pramlintide OR "ac 137" OR ac137 OR "pramlintide acetate" OR symlin):ti,ab,kw | Pramlintide | 115 |
| #37 | #3 AND #36 | T1D + pramlintide | 75 |
| #38 | #37 not (pubmed or embase):an | Removing duplicates from pubmed and embase | 17 |
| #39 | #38 [Limit: in trials] | Limited to trials | 17 |
| #40 | #39 [Limit: in trials, 1980 to 2018] | From 1 st Jan 1980 to 5 th Oct 2018 | 17 |
| #41 | #35 OR #40 | Final | 423 |

Clinical trials registries

Table 9: Search facet for the systematic literature review in US clinical trial registry (<https://clinicaltrials.gov/>) as run on 5th October 2018

| | |
|------------------|--|
| Database name | US National Institutes of Health (NIH) Ongoing Trials Register |
| Search interface | www.clinicaltrials.gov |
| Search date | 5 th October 2018 |

| No. | Keywords | Hits |
|-----|--|--|
| 1 | Sotagliflozin | 18 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 2 | LX4211 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 3 | LX-4211 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 4 | LP802034 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 5 | LP-802034 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 6 | Empagliflozin | 50 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 7 | Jardiance | 50 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 8 | BI-10773 | 50 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 9 | B110773 | 50 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 10 | SGLT2 inhibitor | 37 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 11 | sodium glucose cotransporter 2 inhibitor | 41 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 12 | sodium glucose cotransporter 2 inhibitor | 41 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 13 | Gliflozin(s) | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 14 | Dapagliflozin | 40 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 15 | Farxiga | 40 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 16 | Forxiga | 10 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 17 | BMS-512148 | 40 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 18 | BMS512148 | 40 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 19 | Ipragliflozin | 2 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 20 | ASP-1941 | 1 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 21 | ASP1941 | 1 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 22 | Suglat | 2 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 23 | Tofogliflozin | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 24 | CSG-452 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 25 | CSG452 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 26 | Aplway | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 27 | Deberza | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |

| No. | Keywords | Hits |
|-----|-------------------------|---|
| 28 | Remogliflozin | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 29 | BHV-091009 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 30 | BHV091009 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 31 | KGT-1681 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 32 | KGT1681 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 33 | GSK-189075 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 34 | GSK189075 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 35 | Ertugliflozin | 1 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 36 | MK-8835 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 37 | MK8835 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 38 | PF-04971729 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 39 | PF04971729 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 40 | Luseogliflozin | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 41 | TS-071 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 42 | TS071 | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 43 | Sergliflozin | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 44 | GW-869682X | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 45 | GW86968X | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 46 | Metformin | 192 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 47 | Dimethylbiguanidine | 192 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 48 | Dimethylguanylguanidine | 192 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 49 | Glucophage | 192 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 50 | Diabex | 1 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 51 | Diabetosan | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 52 | Fluamine | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 53 | Flumamine | 0 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 54 | Glifage | 2 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 55 | Siofor | 2 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 56 | Glucoformin | 4 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 57 | Riomet | 192 [Filters: First posted from 01/08/2017 to 05/10/2018] |
| 58 | Pramlintide | 47 |
| 59 | ac 137 | 47 |
| 60 | ac137 | 47 |
| 61 | Pramlintide acetate | 47 |
| 62 | symlin | 47 |

Table 10: Search facet for the systematic literature review in EU clinical trial registry (<https://www.clinicaltrialsregister.eu/>) as run on 5th October 2018

| | |
|------------------|---|
| Database name | European Union Clinical Trials Register (EU CTR) |
| Search interface | https://clinicaltrialsregister.eu |
| Search date | 5 th October 2018 |

| No. | Keywords | Hits |
|-----|--|--|
| 1 | Sotagliflozin | 11 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 2 | LX4211 | 7 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 3 | LX-4211 | 6 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 4 | LP802034 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 5 | LP-802034 | 5 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 6 | Empagliflozin | 16 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 7 | Jardiance | 15 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 8 | BI-10773 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 9 | BI10773 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 10 | SGLT2 inhibitor | 5 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 11 | sodium glucose cotransporter 2 inhibitor | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |

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| No. | Keywords | Hits |
|-----|---|--|
| 12 | sodium glucose co-transporter 2 inhibitor | 2 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 13 | Gliflozin(s) | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 14 | Dapagliflozin | 11 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 15 | Farxiga | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 16 | Forxiga | 9 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 17 | BMS-512148 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 18 | BMS512148 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 19 | lpragliflozin | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 20 | ASP-1941 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 21 | ASP1941 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 22 | Suglat | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 23 | Tofogliflozin | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 24 | CSG-452 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 25 | CSG452 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 26 | Aplway | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 27 | Deberza | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 28 | Remogliflozin | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 29 | BHV-091009 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 30 | BHV091009 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 31 | KGT-1681 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 32 | KGT1681 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 33 | GSK-189075 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 34 | GSK189075 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 35 | Ertugliflozin | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 36 | MK-8835 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 37 | MK8835 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 38 | PF-04971729 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 39 | PF04971729 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 40 | Luseogliflozin | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 41 | TS-071 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 42 | TS071 | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 43 | Sergliflozin | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 44 | GW-869682X | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 45 | GW86968X | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 46 | Metformin | 36 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 47 | Dimethylbiguanidine | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 48 | Dimethylguanylguanidine | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 49 | Glucophage | 2 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 50 | Diabex | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 51 | Diabetosan | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 52 | Fluamine | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 53 | Flumamine | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 54 | Glifage | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 55 | Siofor | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 56 | Glucoformin | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 57 | Riomet | 0 [Filters: Date range: 01-08-2017 to 05-10-2018] |
| 58 | Pramlintide | 2 |
| 59 | ac 137 | 1 |
| 60 | ac137 | 0 |
| 61 | Pramlintide acetate | 0 |
| 62 | symlin | 0 |

Table 11: Search facet for the systematic literature review in WHO ICTRP clinical trial registry (<http://apps.who.int/trialsearch/>) as run on 7th October 2018

| | |
|------------------|---|
| Database name | The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) |
| Search interface | http://apps.who.int/trialsearch/ |
| Search date | 7 th October 2018 |

| No. | Keywords | Hits |
|-----|---|------|
| 1 | Sotagliflozin | 38 |
| 2 | LX4211 | 29 |
| 3 | LX-4211 | 6 |
| 4 | LP802034 | 0 |
| 5 | LP-802034 | 5 |
| 6 | Empagliflozin | 215 |
| 7 | Jardiance | 46 |
| 8 | BI-10773 | 72 |
| 9 | BI10773 | 7 |
| 10 | SGLT2 inhibitor | 120 |
| 11 | sodium glucose cotransporter 2 inhibitor | 5 |
| 12 | sodium glucose co-transporter 2 inhibitor | 8 |
| 13 | Gliflozin(s) | 0 |
| 14 | Dapagliflozin | 356 |
| 15 | Farxiga | 5 |
| 16 | Forxiga | 50 |
| 17 | BMS-512148 | 29 |
| 18 | BMS512148 | 1 |
| 19 | Ipragliflozin | 63 |
| 20 | ASP-1941 | 1 |
| 21 | ASP1941 | 40 |
| 22 | Suglat | 4 |
| 23 | Tofogliflozin | 38 |
| 24 | CSG-452 | 0 |
| 25 | CSG452 | 10 |
| 26 | Aplway | 0 |
| 27 | Deberza | 0 |
| 28 | Remogliflozin | 5 |
| 29 | BHV-091009 | 0 |
| 30 | BHV091009 | 0 |
| 31 | KGT-1681 | 0 |
| 32 | KGT1681 | 0 |
| 33 | GSK-189075 | 1 |
| 34 | GSK189075 | 20 |
| 35 | Ertugliflozin | 23 |
| 36 | MK-8835 | 20 |
| 37 | MK8835 | 0 |
| 38 | PF-04971729 | 18 |
| 39 | PF04971729 | 1 |
| 40 | Luseogliflozin | 31 |
| 41 | TS-071 | 14 |
| 42 | TS071 | 0 |
| 43 | Sergliflozin | 0 |
| 44 | GW-869682X | 0 |
| 45 | GW86968X | 0 |
| 46 | Metformin | 2874 |
| 47 | Dimethylbiguanidine | 2874 |
| 48 | Dimethylguanylguanidine | 2874 |

| No. | Keywords | Hits |
|-----|---------------------|------|
| 49 | Glucophage | 148 |
| 50 | Diabex | 8 |
| 51 | Diabetosan | 0 |
| 52 | Fluamine | 0 |
| 53 | Flumamine | 0 |
| 54 | Glifage | 2 |
| 55 | Siofor | 2 |
| 56 | Glucoformin | 0 |
| 57 | Riomet | 0 |
| 58 | Pramlintide | 46 |
| 59 | ac 137 | 0 |
| 60 | ac137 | 0 |
| 61 | Pramlintide acetate | 21 |
| 62 | symlin | 11 |

Appendix B List of included/excluded evidence

B.1 Included trials

Table 12: Included trials

| Author/Year | Trial Acronym | Title | Study Design | Clinical Trial Number | Clinical Trial Phase | CSR Number | Study N |
|---|---------------|---|--------------|-----------------------|----------------------|------------|---------|
| Garg SK et al. 2017 | InTandem3 | Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes | RCT | NCT02531035 | 3 | LX4211.321 | 1405 |
| Danne T et al. 2018 | InTandem2 | HbA _{1c} and Hypoglycemia Reductions at 24 and 52 Weeks With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: The European inTandem2 Study. | RCT | NCT02421510 | 3 | LX4211.310 | 782 |
| Buse JB et al. 2018 | InTandem1 | Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study. | RCT | NCT02384941 | 3 | LX4211.309 | 793 |
| Dandona P et al. 2018 | DEPICT-1 | Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes: The DEPICT-1 52-Week Study | RCT | NCT02268214 | 3 | NA | 833 |
| Mathieu et al. 2018 | DEPICT-2 | Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial | RCT | NCT02460978 | 3 | NA | 815 |
| Rosenstock 2018 | EASE-2 | Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials | RCT | NCT02414958 | 3 | NA | 730 |
| Rosenstock 2018 | EASE-3 | Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials | RCT | NCT02580591 | 3 | NA | 977 |
| Lund SS et al. 2009 Lund SS et al. 2008 [#] | NA | Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized study Effect of adjunct metformin treatment on levels of plasma lipids in patients with type 1 diabetes | RCT | NCT00118937 | 4 | NA | 100 |
| Jacobsen IB et al. 2009 | NA | The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control. | RCT | NA | NA | NA | 24 |
| Petrie JR et al. 2017 | REMOVAL | Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes: a double-blind, randomised, placebo-controlled trial | RCT | NCT01483560 | 3 | NA | 428 |
| Zawada et. al. 2018 | NA | Metformin added to intensive insulin therapy improves metabolic control in patients with type 1 diabetes and excess body fat | RCT | NCT01889706 | NA | NA | 114 |
| Meyer et al. 2002 | NA | The Benefits of Metformin Therapy During Continuous Subcutaneous Insulin Infusion Treatment of Type 1 Diabetic patients. | RCT | NA | NA | NA | 62 |

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| | | | | | | | |
|------------------------|----|--|-----|-------------|----|----|-----|
| Pitocco et al. 2012 | NA | Metformin improves endothelial function in type 1 diabetic subjects: a pilot, placebo-controlled randomized study | RCT | NA | NA | NA | 42 |
| Burchardt et. al. 2013 | NA | Metformin added to intensive insulin therapy reduces plasma levels of glycated but not oxidized low-density lipoprotein in young patients with type 1 diabetes and obesity in comparison with insulin alone: a pilot study | RCT | NA | NA | NA | 68 |
| Ratner et al. 2004 | NA | Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: A 1-year, randomized controlled trial | RCT | NA | NA | NA | 651 |
| Edelman ST et al. 2006 | NA | A Double-Blind, Placebo-Controlled Trial Assessing Pramlintide Treatment in the Setting of Intensive Insulin Therapy in Type 1 Diabetes | RCT | NCT00107107 | NA | NA | 296 |
| Fineman et. al. 1999 | NA | Pramlintide therapy in addition to insulin in type I diabetes: effect on metabolic control after 6 months | RCT | NA | NA | NA | 568 |

as Lund SS et al. 2008 and 2009 come from the same trial, and the secondary publication reported additional outcomes, we captured both trials. Only cholesterol outcome Recorded in Lund 2009. End point was 52 weeks while others were 24 in Lund 2008

B.2 Excluded trials

Table 13: Excluded studies at full-text screening with reasons for exclusion (first phase of the review)

| First Author | Year | Title | Exclusion Reason |
|--------------------------|------|---|-----------------------|
| Astellas Pharma Inc. | 2016 | Phase III Study of ASP1941 Double-blind, Parallel-group Study in Combination With Insulin in Patients With Type 1 Diabetes Mellitus | Duplicate Publication |
| Burchardt P. et al | 2016 | Metformin added to insulin reduces plasma levels of glycated-LDL but not oxLDL in young patients with type 1 diabetes and concomitant obesity in comparison to insulin alone - pilot study. | Wrong Intervention |
| Buse J.B. et al | 2017 | Twenty-four-week efficacy and safety of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes (InTandem1). | Duplicate Publication |
| Danne T. et al | 2017 | 24-week efficacy and safety of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes (InTandem2). | Duplicate Publication |
| de Boer I.H. et al | 2014 | Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. | Wrong Population |
| Feldt-Rasmussen B. | 1994 | The development of nephropathy in insulin-dependent diabetes mellitus is associated with poor glycemic control. | Wrong Intervention |
| Giugliano D. et al | 1993 | Metformin for obese, insulin-treated diabetic patients: improvement in glycaemic control and reduction of metabolic risk factors. | Wrong Population |
| Gubitosi-Klug R.A. et al | 2016 | Intensive diabetes treatment and cardiovascular outcomes in type1 diabetes: The DCCT/EDIC study 30-year follow-up. | Wrong Population |
| Hotta N. et al | 1993 | Diabetic neuropathy: effects of intensified glycaemic control with multiple insulin injections. | Wrong Population |
| Khan A.S. et al | 2006 | The effect of metformin on blood glucose control in overweight patients with Type 1 diabetes. | Wrong Population |
| Kosaka K. et al | 1993 | Clinical Evaluation of a New Oral Hypoglycemic Drug CS-045 in Patients with Non-Insulin Dependent Diabetes Mellitus Poorly Controlled by Sulfonylureas: a Double-Blind, Placebo-Controlled Study | Wrong Population |
| Kosaka K. et al | 1993 | Clinical Evaluation of a New Oral Hypoglycemic Drug CS-045 in Patients with Non-Insulin Dependent Diabetes Mellitus Poorly Controlled by Diet Alone: a Double-Blind, Placebo-Controlled Study | Wrong Intervention |
| Langkilde A. | 2015 | Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes (DEPICT 2) | Duplicate Publication |
| Meyer L. et al | 2002 | The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients. | Wrong Population |
| Misra A. | 1994 | Long term complications of IDDM and intensified insulin treatment. | Wrong Population |

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| First Author | Year | Title | Exclusion Reason |
|--------------------------|------|--|-----------------------|
| Mondick J. et al | 2017 | Population pharmacokinetic-pharmacodynamic analysis to characterise the effect of empagliflozin on renal glucose threshold in patients with type 1 diabetes. | Wrong Population |
| Pitocco D. et al | 2013 | Metformin improves endothelial function in type 1 diabetic subjects: a pilot, placebo-controlled randomized study. | Wrong Population |
| Shimada A. et al | 2011 | Pioglitazone may accelerate disease course of slowly progressive type 1 diabetes. | Wrong Population |
| Tervonen T. et al | 1993 | Long-term control of diabetes mellitus and periodontitis | Wrong Population |
| Xu W. | 2016 | The Effects of Metformin on Glycemic Control and Insulin Sensitivity in Adolescents With T1DM | Wrong Population |
| Ziaee A. et al | 2017 | Comparison of adjunctive therapy with metformin and acarbose in patients with Type-1 diabetes mellitus. | Wrong Population |
| Unknown | 2016 | Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. | Wrong Population |
| Unknown | 2015 | A Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Dapagliflozin as an Add-on to Insulin Therapy in Subjects With Type 1 Diabetes Mellitus - Study Two | Duplicate Publication |
| Unknown | 2016 | A Double-blind, Placebo Controlled, Cross-over Renal Mechanistic Trial to Assess the Effect of Adding Empagliflozin Versus Placebo on Renal Hyperfiltration in Patients With Type 1 Diabetes on a Background of the Angiotensin Converting Enzyme Inhibitor (ACEi) Ramipril: BETWEEN Study | Wrong Population |
| Unknown | 2016 | Phase III Study of ASP1941 Double-blind, Parallel-group Study in Combination With Insulin in Patients With Type 1 Diabetes Mellitus | Duplicate Publication |
| Unknown | 2015 | A Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Dapagliflozin as an Add-on to Insulin Therapy in Subjects with Type 1 Diabetes Mellitus - Study Two | Duplicate Publication |
| Unknown | 2013 | A Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Dapagliflozin as an Add-on to Insulin Therapy in Subjects with Type 1 Diabetes Mellitus | Duplicate Publication |
| Unknown | 2015 | A Phase III, randomised, double blind, placebo-controlled, parallel group, efficacy, safety and tolerability trial of once daily, oral doses of Empagliflozin as Adjunctive to insulin therapy over 52 weeks in patients with Type 1 diabetes mellitus (EASE-2) | Wrong Population |
| Unknown | 2016 | Empagliflozin and ACEi Effects on Hyperfiltration in Type 1 Diabetes (BETWEEN Study) | Wrong Population |
| Unknown | 2016 | A Study of ASP1941 in Combination With Insulin in Patients With Type 1 Diabetes Mellitus | Duplicate Publication |
| Unknown | 2011 | 00-18 A.3 Full title of the trial: REducing with MetfOrmin Vascular Adverse Lesions in T1DM (The REMOVAL study) | Wrong Study Design |
| Unknown ⁽¹⁴²⁾ | 2008 | METFORMIN VS PLACEBO IN NEWLY DIAGNOSED TYPE 1 DIABETES MELLITUS: A RANDOMIZED CLINICAL TRIAL | Wrong Population |
| Unknown | 2010 | Effectiveness of Glucophage® SR as an adjunct to insulin in improving glycaemic control, without increasing the episodes of hypoglycaemia, in non-overweight patients with type-1 Diabetes. A.3.2 Name or abbreviated title of the trial where available: Glucophage-SR an adjunct to insulin in non-overweight type-1 Diabetics | Wrong Study Design |

Table 14: Excluded studies at full-text screening with reasons for exclusion (second phase of the review)

| Study name | Year | Title | Exclusion reason |
|---------------|------|---|------------------------------|
| Dandona 2018 | 2018 | Pooled data analysis of composite endpoints from the DEPICT-1 and DEPICT-2 studies using dapagliflozin compared to placebo added to adjustable insulin in type 1 diabetes | Pooled data only |
| Brock 2018 | 2018 | Liraglutide treatment fails to show neuronal repair or neuroprotective effects in patients with type 1 diabetes and diabetic symmetric polyneuropathy | Intervention/Comparator |
| Lüdemann 2018 | 2018 | Pooled analysis of the duration of type 1 diabetes in dapagliflozin vs placebo on adjustable insulin therapy from DEPICT 1 and 2: Effects on glycaemia, weight and insulin dosage | Pooled data only |
| Biester 2018 | 2018 | DAPADream: Improvement of time in range after SGLT2-add-on medication in youth and young adults with type 1 diabetes during | Treatment duration <16 weeks |

| Study name | Year | Title | Exclusion reason |
|----------------|------|--|--|
| | | unannounced meals under full closed loop CSII | |
| Lapuerta 2018 | 2018 | Patients with type 1 diabetes value increased glucose stability and associate it with improved well-being: Exit interviews from Sotagliflozin Phase 3 study | Study design |
| Pettus 2018 | 2018 | Sotagliflozin in combination with optimised insulin therapy reduced HbA _{1c} levels with a decreased daily insulin requirement after 52 weeks in adults with type 1 diabetes | Pooled data only |
| Hals 2018 | 2018 | Favourable effects of insulin treatment for latent autoimmune diabetes in adults do not outweigh autoimmunity-induced decline in insulin release during 21 months of intervention | No SGA disease |
| Henry 2018 | 2018 | Sotagliflozin further improves percentage of patients achieving HbA _{1c} goal without weight gain in adults with type 1 diabetes after insulin therapy optimisation | Pooled data only |
| Danne 2018 | 2018 | inTandem1 and inTandem2: Increased time in range with sotagliflozin as adjunct therapy to insulin in adults with type 1 diabetes by 24-week continuous glucose monitoring | Pooled data only |
| Sherwood 2018 | 2018 | Pilot study of closed-loop glycemic control with the bionic pancreas in cystic fibrosis-related diabetes | Study design |
| Mkrtumyan 2018 | 2018 | Efficacy and safety of Subetta add-on therapy in type 1 diabetes mellitus: The results of a multicenter, double-blind, placebo-controlled, randomized clinical trial | Intervention/Comparator |
| Parkinson 2018 | 2018 | Dose-response and exposure-response (HbA _{1c}) of dapagliflozin in T1DM patients | Pooled data only |
| Pettus 2018 | 2018 | Sotagliflozin in combination with optimized insulin therapy reduced HbA _{1c} levels with a decreased daily insulin requirement after 52 weeks in adults with T1D | Pooled data only |
| Wiromrat 2018 | 2018 | Serum uromodulin (SUMOD) inversely correlates with aortic stiffness in type 1 diabetes (T1D) youth | Intervention/Comparator |
| Nadeau 2018 | 2018 | Metformin improves insulin resistance (IR) and vascular health in youth with type 1 diabetes (T1D) | No SGA age |
| Danne 2018 | 2018 | Increased time-in-range with sotagliflozin as adjunct therapy to insulin in adults with type 1 diabetes as demonstrated by 24-week continuous glucose monitoring (intandem1, intandem2) | Pooled data only |
| Mathieu 2018 | 2018 | Glucose variables in T1D studies with dapagliflozin-pooled analysis of continuous glucose monitoring data from depict-1 and 2 | Pooled data only |
| Johansen 2018 | 2018 | Protocol for Meal-time Administration of Exenatide for Glycaemic Control in Type 1 Diabetes Cases (The MAG1C trial): A randomised, double-blinded, placebo-controlled trial | Intervention/Comparator |
| Mondick 2018 | 2018 | Population Pharmacokineticâ€” Pharmacodynamic Analysis to Characterize the Effect of Empagliflozin on Renal Glucose Threshold in Patients With Type 1 Diabetes Mellitus | Treatment duration <16 weeks |
| Gogtay 2018 | 2018 | Effects of sotagliflozin added to insulin in type 1 diabetes | Review/editorial |
| Melmer 2018 | 2018 | Short-term effects of dapagliflozin on insulin sensitivity, postprandial glucose excursion and ketogenesis in type 1 diabetes mellitus: A randomized, placebo-controlled, double blind, cross-over pilot study | Treatment duration <16 weeks |
| DubÃ© 2018 | 2018 | Beyond glycaemic control: A cross-over, double-blinded, 24-week intervention with liraglutide in type 1 diabetes | Intervention/Comparator |
| Nadeau 2018 | 2018 | Metformin improves vascular haemodynamic function in youth with type 1 diabetes | No SGA age |
| Garg 2017 | 2017 | Effects of sotagliflozin added to insulin in patients with type 1 diabetes | Records identified as duplicate of records included in original SLR: |
| Baker 2017 | 2017 | A 12-week dose-ranging study of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes, (inTandem4; NCT02459899) | Treatment duration <16 weeks |
| Hansen 2017 | 2017 | Autonomic regulation may modify the weight reducing effect of liraglutide in overweight patients with type 1 diabetes | Intervention/Comparator |
| Buse 2017 | 2017 | 24-week efficacy and safety of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes (inTandem1) | Records identified as duplicate of records included in original SLR: |
| Danne 2017 | 2017 | 24-week efficacy and safety of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes (inTandem2) | Records identified as duplicate of records included in original SLR: |
| Bode 2017 | 2017 | Efficacy and safety of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct to insulin in young adults with poorly controlled type 1 | Treatment duration <16 weeks |

| Study name | Year | Title | Exclusion reason |
|-----------------|------|--|------------------------------|
| | | diabetes (JDRF Study) | |
| Mondick 2017 | 2017 | Population pharmacokinetic-pharmacodynamic analysis to characterise the effect of empagliflozin on renal glucose threshold in patients with type 1 diabetes | Treatment duration <16 weeks |
| Hals 2017 | 2017 | A randomised clinical trial testing for optimal beta cell preserving treatment in Latent Autoimmune Diabetes in Adults (LADA) | Intervention/Comparator |
| Katikaneni 2017 | 2017 | Pramlintide vs. Exenatide: Acute and chronic use in adolescents with type 1 diabetes | Children only |
| Herrmann 2016 | 2016 | Impact of Disease Duration on the Effects of Pramlintide in Type 1 Diabetes: A Post Hoc Analysis of Three Clinical Trials | Pooled data only |
| Hinshaw 2016 | 2016 | Effect of pramlintide on postprandial glucose fluxes in type 1 diabetes | Treatment duration <16 weeks |
| Dejgaard 2016 | 2016 | Cardiovascular effects of liraglutide in patients with type 1 diabetes | Intervention/Comparator |
| Kuhadiya 2016 | 2016 | Dapagliflozin as additional treatment to liraglutide and insulin in patients with type 1 diabetes: A randomized clinical trial of 12 weeks | Intervention/Comparator |
| Dube 2016 | 2016 | Crossover, double-blind, unicentric, 52-week trial of liraglutide in type 1 diabetes | Intervention/Comparator |
| Frandsen 2016 | 2016 | The effect of glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RA) on postprandial glucagon secretion independent of the gastric emptying rate | Intervention/Comparator |
| Testa 2016 | 2016 | Patient-centered outcomes and sociodemographic predictors of diabetes treatment effectiveness | Pooled data only |
| Ghanim 2016 | 2016 | Dapagliflozin induces ketosis in patients with type 1 diabetes | Treatment duration <16 weeks |
| Ismail 2016 | 2016 | A biphasic OGTT curve as an indicator of risk for type 1 diabetes (T1D) | Treatment duration <16 weeks |
| Hinshaw 2015 | 2015 | Glucagon inhibition and delay in gastric emptying improves glucose tolerance in type 1 diabetes: A triple tracer mixed meal study | Treatment duration <16 weeks |
| Riddle 2015 | 2015 | Fixed ratio dosing of pramlintide with regular insulin before a standard meal in patients with type 1 diabetes | Treatment duration <16 weeks |
| Renukuntla 2014 | 2014 | Role of Glucagon-like peptide-1 analogue versus Amylin as an adjuvant therapy in type 1 diabetes in a closed loop setting with ePID algorithm | Treatment duration <16 weeks |
| Fang 2013 | 2013 | Study reanalysis using a mechanism-based pharmacokinetic/pharmacodynamic model of pramlintide in subjects with type 1 diabetes | Treatment duration <16 weeks |
| Weinzimer 2012 | 2012 | Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes | Treatment duration <16 weeks |
| Asmar 2010 | 2010 | Do the actions of glucagon-like peptide-1 on gastric emptying, appetite, and food intake involve release of amylin in humans? | Treatment duration <16 weeks |
| King 2010 | 2010 | Comparison of the post-meal glucose response to different insulin bolus waveforms in insulin pump- and pre-meal pramlintide-treated type 1 diabetes patients | Intervention/Comparator |
| Amiel 2005 | 2005 | The effect of pramlintide on hormonal, metabolic or symptomatic responses to insulin-induced hypoglycaemia in patients with type 1 diabetes | Treatment duration <16 weeks |
| Weyer 2005 | 2005 | Properties of pramlintide and insulin upon mixing | Treatment duration <16 weeks |
| Ceriello 2005 | 2005 | Effects of pramlintide on postprandial glucose excursions and measures of oxidative stress in patients with type 1 diabetes | Treatment duration <16 weeks |
| Kovatchev 2004 | 2004 | Numerical Estimation of HbA _{1c} from Routine Self-Monitoring Data in People with Type 1 and Type 2 Diabetes Mellitus | Intervention/Comparator |
| Weyer 2003 | 2003 | Pramlintide Reduces Postprandial Glucose Excursions When Added to Regular Insulin or Insulin Lispro in Subjects With Type 1 Diabetes: A dose-timing study | Treatment duration <16 weeks |
| Levetan 2003 | 2003 | Impact of pramlintide on glucose fluctuations and postprandial glucose, glucagon, and triglyceride excursions among patients with type 1 diabetes intensively treated with insulin pumps | Treatment duration <16 weeks |
| Fineman 2002 | 2002 | The human amylin analog, pramlintide, corrects postprandial hyperglucagonemia in patients with type 1 diabetes | Treatment duration <16 weeks |
| Chagan 2002 | 2002 | Pramlintide - A novel agent in the treatment of type 1 and 2 diabetes mellitus | Review/editorial |
| Whitehouse 2002 | 2002 | A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes | Study design |
| Sansom 2000 | 2000 | Pramlintide, an amylin analog, selectively delays gastric emptying: Potential role of vagal inhibition | Study design |

Extract EUnetHTA Submission File

| Study name | Year | Title | Exclusion reason |
|---------------|----------|---|--|
| Nyholm 1999 | 1999 | The amylin analog pramlintide improves glycemic control and reduces postprandial glucagon concentrations in patients with type 1 diabetes mellitus | Treatment duration <16 weeks |
| Kong 1998 | 1998 | The effect of single doses of pramlintide on gastric emptying of two meals in men with IDDM | Treatment duration <16 weeks |
| Thompson 1997 | 1997 | Effects of 4 weeks` administration of pramlintide, a human amylin analogue, on glycaemia control in patients with IDDM: Effects on plasma glucose profiles and serum fructosamine concentrations | Treatment duration <16 weeks |
| Kong 1997 | 1997 | Infusion of pramlintide, a human amylin analogue, delays gastric emptying in men with IDDM | Treatment duration <16 weeks |
| Nyholm 1996 | 1996 | Acute effects of the human amylin analog AC137 on basal and insulin-stimulated euglycemic and hypoglycemic fuel metabolism in patients with insulin-dependent diabetes mellitus | Treatment duration <16 weeks |
| Dandona 2017 | 2017 Nov | Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. | Records identified as duplicate of records included in original SLR: |
| Petrie 2017 | 2017 Aug | Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (95): a double-blind, randomised, placebo-controlled trial. | Records identified as duplicate of records included in original SLR: |
| Heptulla 2009 | 2009 May | Twenty-four-hour simultaneous subcutaneous Basal-bolus administration of insulin and amylin in adolescents with type 1 diabetes decreases postprandial hyperglycemia. | Treatment duration <16 weeks |
| NCT01269008, | | Closed Loop System With Pramlintide Versus Exenatide | Study design |
| NCT00923715, | | Exenatide (Byetta) Versus Pramlintide (Symlin): role in Post-Prandial Hyperglycemia | No SGA age |
| NCT00505882, | | Efficacy of Pramlintide on Prevention of Weight Gain Early Onset of Type 1 Diabetes | Clinical trial registry with limited information |
| NCT02421510, | | Efficacy, Safety, and Tolerability Study of Sotagliflozin as Adjunct Therapy in Adult Patients With Type 1 Diabetes Mellitus Who Have Inadequate Glycemic Control With Insulin Therapy | Clinical trial registry with limited information |
| NCT02384941, | | Efficacy, Safety, and Tolerability Study of Sotagliflozin as Adjunct Therapy in Adult Patients With Type 1 Diabetes Mellitus Who Have Inadequate Glycemic Control With Insulin Therapy | Clinical trial registry with limited information |
| NCT00776607, | | Randomized Controlled Trial of Insulin Versus Tablets for Latent Autoimmune Diabetes in Adults (LADA) | Clinical trial registry with limited information |
| NCT01706211, | | A Study to Evaluate the Efficacy and Safety of BRL 49653C in Non-insulin Dependent Diabetes | Disease |
| NCT01592279, | | GLP-1 Analogue Treatment in Uncontrolled Type 1 Diabetic Patients | Intervention/Comparator |
| NCT02582814, | | The Safety and Efficacy of Dapagliflozin Therapy in Combination With Insulin in Japanese Subjects With Type 1 Diabetes Mellitus (T1DM) | Clinical trial registry with limited information |
| NCT02383940, | | Efficacy and Safety of Sotagliflozin in Young Adult Patients With Type 1 Diabetes Mellitus and Elevated Hemoglobin A1C | Treatment duration <16 weeks |
| NCT03556033, | | Effect of Dapagliflozin on IAH in T1DM | Clinical trial registry with limited information |
| NCT01269047, | | Use of Exenatide and Pramlintide to Decrease Post-prandial Hyperglycemia | No SGA age |
| NCT01813929, | | Effect of Metformin on Vascular and Mitochondrial Function in Type 1 Diabetes | Treatment duration <16 weeks |
| NCT02765347, | | The Effects of Metformin on Glycemic Control and Insulin Sensitivity in Adolescents With T1DM | Clinical trial registry with limited information |
| NCT02580591, | | Empagliflozin as Adjunctive to Insulin Therapy Over 26 Weeks in Patients With T1DM (EASE-3) | Clinical trial registry with limited information |
| NCT03017352, | | Meal-time Administration of Exenatide for Glycaemic Control in Type 1 Diabetic Cases | Intervention/Comparator |
| NCT00145379, | | The Effect of Metformin in Overweight Patients With Dysregulated Type 1 Diabetes Mellitus | Clinical trial registry with limited information |
| NCT02408705, | | Investigating the Effect of Liraglutide on the Endogenous Glucose Production During in Tye 1 Diabetes Subjects | Intervention/Comparator |
| NCT01434862, | | Pramlintide Combined With Model Predictive Control Algorithm | Clinical trial registry with limited information |
| NCT00489645, | | Effect of Hyperglycemia on Gastric Emptying Interactions With Pramlintide | Clinical trial registry with limited information |
| NCT00206297, | | The Effect of Prolonged Pramlintide Infusion in Pediatric Diabetes | Clinical trial registry with limited information |

| Study name | Year | Title | Exclusion reason |
|--------------|------|--|--|
| NCT02814123, | | Effect of Basal-Bolus Closed-Loop Co-Administration of Insulin and Pramlintide on Improving the Glycemic Control in Type 1 Diabetes | Treatment duration <16 weeks |
| NCT02351232, | | The Lira Pump Trial | Intervention/Comparator |
| NCT03547427, | | Glucagon Counterregulation in Type 1 Diabetes | Treatment duration <16 weeks |
| NCT02460978, | | Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes | Clinical trial registry with limited information |
| NCT01483560, | | REducing With MetfOrmin Vascular Adverse Lesions in Type 1 Diabetes (95) | Clinical trial registry with limited information |
| NCT02407899, | | Protective Effects of Saxagliptin (And Vitamin D3) on ÅŸ Cell Function in Patients With Adult-onset Latent Autoimmune Diabetes | Intervention/Comparator |
| NCT01722227, | | Anti-diabetic Effects of Liraglutide in Adolescents and Young Subjects With Type 1 Diabetes | Intervention/Comparator |
| NCT02702011, | | Empa Add on to Insulin in Japanese Patient With Type 1 Diabetes Mellitus | Treatment duration <16 weeks |
| NCT02284009, | | Albiglutide Versus Placebo in Insulin-treated Subjects With New-onset Type 1 Diabetes Mellitus | Intervention/Comparator |
| NCT02045290, | | Insulin Clamp Ancillary Study for Assessment of Insulin Resistance | Clinical trial registry with limited information |
| NCT03513874, | | Metformin Plus Insulin on Non-obese Autoimmune Diabetes | Clinical trial registry with limited information |
| NCT01140438, | | Treatment of Latent Autoimmune Diabetes of the Adult | Clinical trial registry with limited information |
| NCT01722240, | | Liraglutide in Type 1 Diabetes | Intervention/Comparator |
| NCT01559025, | | Evaluation of Vildagliptin (GalvusÅ®) as add-on to Insulin in New-onset Type 1 Diabetes Mellitus | Intervention/Comparator |
| NCT02897219, | | A Study of ASP1941 in Combination With Insulin in Patients With Type 1 Diabetes Mellitus | Clinical trial registry with limited information |
| NCT02529449, | | Pharmacodynamics, Pharmacokinetics, and Safety of ASP1941 in Patients With Type 1 Diabetes Mellitus | Clinical trial registry with limited information |
| NCT02414958, | | Empagliflozin as Adjunctive to InSulin thErapy Over 52 Weeks in Patients With Type 1 Diabetes Mellitus (EASE-2)Empagliflozin as Adjunctive to InSulin thErapy Over 52 Weeks in Patients With Type 1 Diabetes Mellitus (EASE-2) | Clinical trial registry with limited information |

