SUPPLEMENTAL ONLINE MATERIAL

Table S1. Approved and banned top selling metformin FDCs in India.

Figure S1. Excerpt from World Health Organization Guidelines for Registration of Fixed-dose Combination Medicinal Products - Annex 5. WHO Technical Report Series, No. 929. Geneva, World Health Organization, 2005.

Figure S2. Description and example of electronic search strategy in PubMed conducted 01 April 2016

Figure S3. Flowchart of search strategy and results of literature searches conducted on published trials of five FDCs

Figure S4. Description of clinical trial inclusion criteria

Table S2. Results from the literature search for metformin FDCs in patients with Type 2 diabetes from published clinical trials

Figure S5. Flowchart of search strategy and results of the clinical trial database searches conducted on unpublished trials of five FDCs

Table S3. Details of unpublished trials on metformin FDCs conducted on Type 2 diabetes patients

Table S4. Trials listed on USA and India clinical trials registries for metformin FDC clinical trials conducted on patients with Type 2 diabetes

Table S1. Approved and banned top selling metformin FDCs in India

Fifty-two metformin FDCs have been approved by CDSCO over 20 years from February 1996 through to September 2016.[1] Of these 52, 12 were approvals for the 5 top sellers and of the different dosages for the 5 top-sellers, 10 were banned in March 2016 by the government.[2]

Approved[1]	Banned[2]
3 approvals for Glimpiride + Metformin: Glimepiride 1mg/2mg + Metformin SR 500mg; 13/11/2002 Glimpiride 1mg/2mg + Metformin SR 1000mg; 08/06/2007 Glimepiride IP 0.5 mg + Metformin Hydrochloride ER 500 mg uncoated bilayered tablets (additional strength); 20/01/2014	**None**
1 approval for Glimepiride + Pioglitazone + Metformin: Glimepiride (1mg/2mg) + Pioglitazone (15mg) + Metformin (500mg E.R) uncoated Tablet, as 3rd line treatment of type-II diabetes mellitus when diet, exercise and the single agents and second line therapy with two drugs do nto result in adequate glycemic control; 16/08/2005	**7 banned** S.O. 802 Glimepiride 1/2/1/2mg Pioglitazone 7.5/7.5/7.5/7.5mg Metformin 1000/1000/500/500mg S.O. 806 Glimepiride 1/2/3mg Pioglitazone 15/15/15mg Metformin 1000/1000/1000mg S.O. 807 Glimepiride 1/2mg Pioglitazone 15/15mg Metformin 850/850mg S.O. 808 Glimepiride 2mg Pioglitazone 7.5mg Metformin 850mg S.O. 809 Glimepiride 1mg Pioglitazone 7.5mg Metformin 850mg S.O. 815 Glimepiride Pioglitazone Metformin S.O. 823 Glimepiride 3mg Pioglitazone 15mg Metformin (SR) 500mg

[1] http://cdsco.nic.in/writereaddata/latesapproved%20FDC%20list%20till%2030%20june%202017.pdf.
[2] http://www.cdsco.nic.in/writereaddata/GSR705E.pdf

2 approvals for Glipizide + Metformin: Glipizide 2.5mg/5mg + Metformin 250mg/500mg tablet, for non insulin dependent diabetes mellitus; 20/03/1998 Metformin 500mg CR + Glipizide 5mg CR Tablet, [indication not stated]; 17/12/2003	**1 banned** S.O. 816 Glipizide 2.5mg Metformin 400 mg
5 approvals for Glibenclamide + Metformin: Glibenclamide 2.5mg+Metformin 400mg Film coated Tablets, non insulin dependent diabites mallitus patients poorly controled with sulphonyluren or biguanide alone; 30/11/1995 Glibenclamide IP 2.5mg + Metformin IP 400mg film coated tablets, For the management of type II diabetes mellitus when single drug therapy, diet and exercise do not result in adequate glycemic control; 06/02/1996 Glibenclamide 5mg+ Metformin 500mg Tablets, non insulin dependent diabites mallitus patients poorly controlled with sulphonyluren or biguanide alone; 26/11/96 Glibenclamide 2.5mg/5mg+Metformin 500mg/500mg SR tablet, non insulin dependent diabites mallitus patients poorly controled with sulphonyluren or biguanide alone; 20/08/2004 Glibeneclamide 5mg + Metformin SR 850mg tablet (additional strength), non insulin dependent diabites mallitus patients poorly controled with sulphonyluren or biguanide alone; 15/02/07	**None**
1 approval for Gliclazide + Metformin: Gliclazide M.R. (30mg/60mg/80mg) + Metformin HCl (500mg/500mg/500mg) ER Tablet, for type-II diabetes; 27/04/2005	**2 banned** S.O. 803 Gliclazide 80 mg Metformin 325 mg S.O. 1029 Gliclazide 40mg Metformin 400mg

Figure S1. Excerpt from World Health Organization. Guidelines for registration of fixed-dose combination medicinal products - Annex 5. WHO Technical Report Series, No. 929. Geneva, World Health Organization, 2005.

6.6 Clinical efficacy and safety

6.6.1 General principles

6.6.1.1 The risk–benefit assessment for a new combination may be based on data generated using either the components given as single entity products concurrently or the FDC as a single FPP [finished pharmaceutical product].

6.6.1.2 Any theoretical advantages of a particular combination should be confirmed by means of efficacy studies. The risk– benefit assessment should not be based on theoretical considerations only, or on extrapolation from other data.

6.6.1.3 If the actives in an FDC are intended to relieve different symptoms of a disease state, it is a prerequisite that these symptoms commonly occur simultaneously at a clinically relevant intensity and for a period of time such that simultaneous treatment is appropriate. Occurrence of the individual symptoms in isolation should not be indications for the FDC.

6.6.1.4 Clinical studies should be designed to determine whether the combination has an advantage over the component actives given alone in a substantial patient population. The data should demonstrate that each active contributes to the therapeutic effect of the combination. It may not be essential to show that all of the components have efficacy when administered as single entities; for example clavulanic acid has little or no antimicrobial activity when given alone, but it enhances the efficacy of beta-lactam antibiotics.

6.6.1.5 In situations where comparative clinical trials are not feasible, for example when monotherapy is inappropriate or is unethical, an aggregate of clinical and preclinical data may be substituted. Such data may include:

6.6.1.5.1 Historical clinical data, preferably at an exposure comparable to that for the proposed FDC.

6.6.1.5.2 Bridging pharmacokinetic data.

6.6.1.5.3 Preclinical pharmacology and/or toxicology data.

6.6.1.5.4 In vitro data (e.g. microbiological studies).

6.6.1.6 If the FDC is available in more than one strength or ratio of doses, there should be a risk–benefit assessment for each combination.

6.6.1.7 The choice of comparators for the purposes of safety and efficacy studies should be justified. They should normally represent the recognized treatment for the indication in question. As far as possible, comparators should be licensed products with well-established safety and efficacy profiles and of established quality. Unapproved or novel combinations should be avoided as comparators as they may introduce new efficacy or toxicity characteristics and thus complicate assessment of the combination under test.

6.6.1.8 If the combination is intended for long-term use, data on safety in patients will normally be required for 6 months or longer.

6.6.1.9 If one or more of the component actives has an established use and dosage regimen in indications unrelated to the indications of the FDC, existing experience as to its safety may nevertheless be taken into account, bearing in mind the relative doses for the two sets of indications.

6.6.1.10 End-points in clinical trials should be such as to characterize the advantages and disadvantages of the combination. For example, for a combination designed to reduce the development of drug resistance, end-points might include the frequency of new drug resistance as well as the overall clinical outcome.

6.6.1.11 Parallel group comparisons are one means of demonstrating a therapeutic effect. A parallel placebo group should be included if feasible and if consistent with the indications under treatment. Multifactorial designs are another means by which it may be possible to demonstrate that a combination is superior to the individual actives.

6.6.1.12 In some cases, studies have to be specifically designed to confirm the minimal effective dose and the usual effective dose of the combination. Multiple dose-effect studies may be necessary.

6.6.1.13 The design and analysis of studies of efficacy and safety should consider (among other things) whether the combination is indicated as first- or second-line therapy.

6.6.1.14 In general, all of the actives in a combination should have a similar duration of action. If this is not the case, the applicant should explain and justify the combination.

6.6.1.15 In general, the actives in a combination should have similar pharmacokinetics. If this is not the case, the applicant should explain and justify the combination.

6.6.1.16 If there is an increase in the number or severity of adverse reactions to the FDC as compared with those in response to the individual actives given alone, evidence and argument should be presented showing that the advantages of the combination outweigh the disadvantages. These should be included in the section of the submission entitled "Balancing the advantages and disadvantages of a new FDC".

6.6.1.17 Data generated in clinical safety and efficacy studies should comply with the WHO

Guidelines for good clinical practice (GCP) for trials on pharmaceutical products (1995).

Figure S2. Description and example of electronic search strategy in PubMed conducted 01 April 2016

Simultaneously, five clinical trials databases were searched using the same criteria for relevant unpublished trials: United States' National Institute of Health, Clinical Trials Registry in India, WHO International Clinical Trials Registry Platform, UK Clinical Trials Network, and EU Clinical Trials Register. This search strategy enabled a global search for published and unpublished clinical trials on these metformin FDCs while also allowing us to capture trials conducted specifically in India.

Example:

All fields: metformin AND glibenclamide

Limits: filters set to human, clinical trial

Search details: ("metformin"[MeSH Terms] OR "metformin"[All Fields]) AND ("glyburide"[MeSH Terms] OR "glyburide"[All Fields] OR "glibenclamide"[All Fields]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms])

Figure S3. Flowchart of search strategy and results of literature searches conducted on published trials of five FDCs

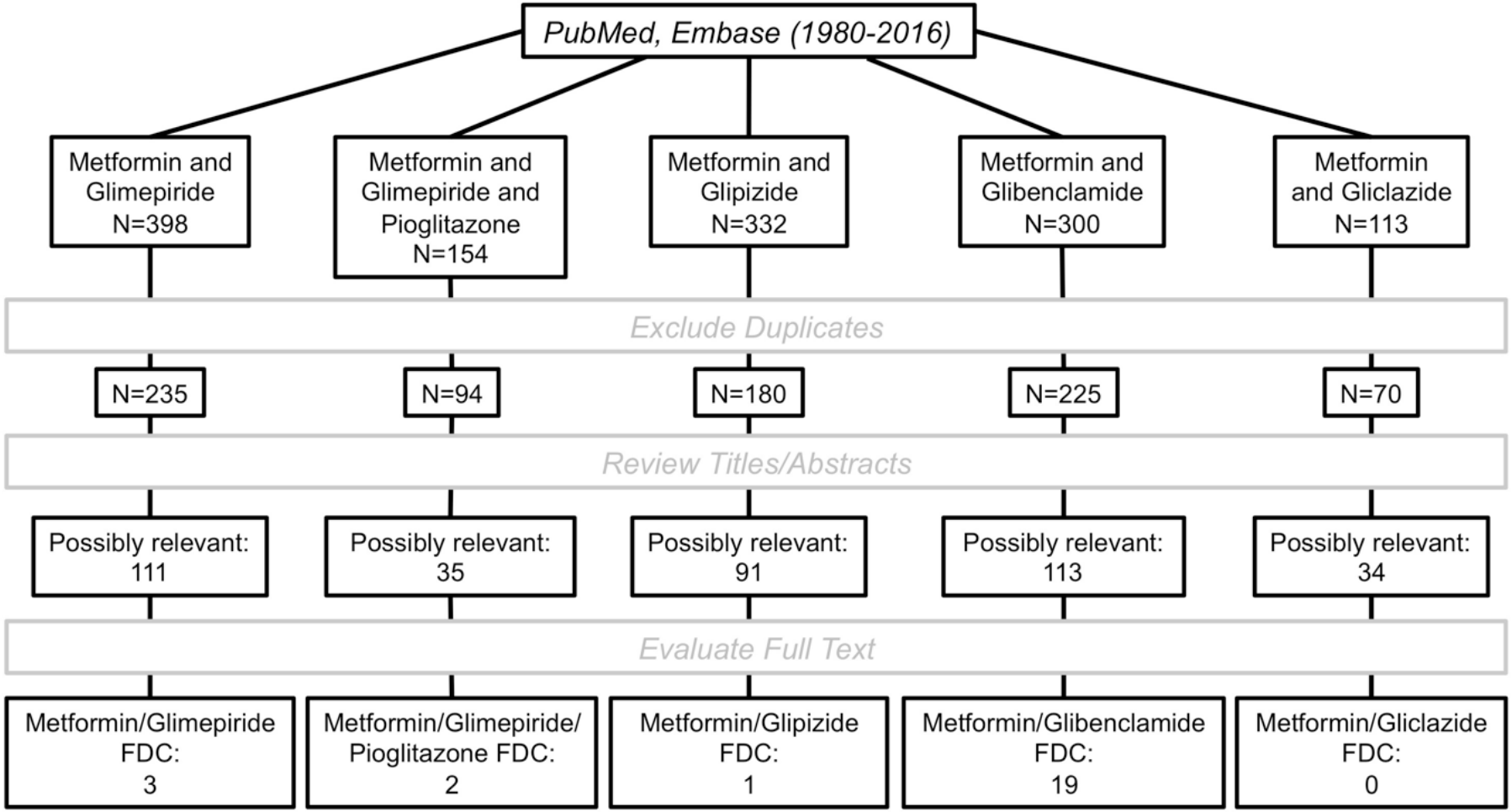

Figure S4. Description of clinical trial inclusion criteria

The trials of primary interest were those evaluating the efficacy and safety in Type 2 diabetes of metformin FDCs compared with the individual FDC components dosed concomitantly as SDFs. We also included trials comparing metformin FDCs with monotherapy, any other anti-diabetic treatment, or with placebo in adults (>18 years) with Type 2 diabetes. Trials on healthy volunteers, *in vitro* or animal studies, all retrospective analyses, cost-effectiveness trials, investigative treatments for gestational diabetes or those conducted in children (<18 years) were excluded. Once the relevant trials were retrieved data were evaluated using a modified critical appraisal tool based on that used by the NHS Centre for Reviews and Dissemination and the Research Council for Complementary Medicine.[3,4] Selected results, such as study duration, number of patients, study arms, primary outcomes, sponsorship, and study country, were then extracted into an Excel file for further analysis.

[3] Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews (2nd Edition). York, UK, Centre for Reviews and Dissemination, University of York, 2001. **4**.

[4] The Research Council for Complementary Medicine. Data Extraction and Appraisal templates. London, UK, The Research Council for Complementary Medicine, London South Bank University, 2011. http://www.rccm.org.uk/sites/default/files/files/DECA%20forms.pdf. Accessed 08 July 2016.

Table S2. Results from the literature search for metformin FDCs in patients with Type 2 diabetes from published clinical trials

Reference	Study Design	N	Sex Age	Blinding	Duration of study	Study description	Intervention	Country	Funding/ Sponsorship
FDC COMPONENTS: GLIMEPIRIDE + METFORMIN									
Charpentier 2001	double-dummy parallel group multicentre	372	M/W 35-70y	randomised double-blind	5 months	To compare the effect of glimepiride in combination with metformin with monotherapy of each drug on glycaemic control in patients with Type 2 diabetes.	(1) metformin + glimepiride placebo (2) glimepiride + metformin placebo (3) glimepiride/metformin FDC	France	Hoechst Marion Roussel
González-Ortiz 2009	multicenter	152	M/W 40-65y	randomised double-blind	12 months	The aim of this study was to compare the efficacy of glimepiride/metformin combination versus glibenclamide/metformin for reaching glycemic control in patients with uncontrolled Type 2 diabetes.	(1) glimepiride/metformin FDC (1mg/500mg) (2) glibenclamide/metformin FDC (5mg/500mg)	Mexico	Laboratorios Silanes
Shimpi 2009	single center parallel group	28	M/W >35y	randomised open-label	3 months	To compare the effect of metformin in combination with glimepiride and glibenclamide in patients with Type 2 diabetes.	(1) glimepiride/metformin FDC (2mg/1000mg) (2) glibenclamide/metformin FDC (10mg/1000mg)	India	Not listed
FDC COMPONENTS: GLIMEPIRIDE + PIOGLITAZONE + METFORMIN									
Bell 2011	multicentric parallel group	101	M/W 18-80y	randomised open-label	3 months	To compare the efficacy of a fixed-dose triple oral diabetes polypill containing 1 or 2 mg glimepiride, 500 mg SR metformin, and 15 mg pioglitazone administered once daily with human insulin 70/30 mix and 500 mg metformin SR administered twice daily in insulin-naïve subjects with Type 2 diabetes inadequately controlled on a combination of glimepiride and metformin.	(1) metformin + insulin 70/30 (2) glimepiride/pioglitazone/metformin SR FDC (1mg or 2mg/15mg/500mg)	India	Not listed

Meshram 2005	multicentric	101	M/W >18y	open-label	2 months	To determine the efficacy and tolerability of the triple drug combination glimepiride 2mg plus pioglitazone hydrochloride 15mg plus metformin SR 500mg for 8 weeks in 101 Indian patients with Type 2 diabetes.	(1) glimepiride/pioglitazone/metformin SR FDC (2mg/15mg/500mg)	India	Unichem Laboratories Ltd.
FDC COMPONENTS: GLIPIZIDE									
Goldstein 2003	multicentric parallel-group active-controlled	178	M/W avg: 56y	randomised double-masked	4.5 months	To determine the efficacy and tolerability of metformin/glipizide in patients uncontrolled with sulfonylurea monotherapy.	(1) glipizide (30mg) (2) metformin (500mg) (3) glipizide/metformin FDC (5mg/500mg) Given for 1 week and titrated for 17 weeks to maintain glucose control.	United States	Bristol-Myers Squibb
FDC COMPONENTS: GLIBENCLAMIDE									
Blonde 2002	parallel group	521	M/W 30-75y	randomised double-blind	4 months	To compare the efficacy, safety and tolerability of a FDC glyburide/ metformin in preparations with those of glyburide and metformin alone in patients with Type 2 diabetes inadequately controlled by sulphonylurea, diet and exercise.	(1) glyburide (10mg) (2) metformin (500mg) (3) glyburide/metformin FDC (2.5mg/500mg) (4) glyburide/metformin FDC (5mg/500mg)	United States	Bristol-Myers Squibb
Blonde 2004	multicenter	304	M/W 30-75y	randomised double-blind	12 months	To evaluate metformin-glibenclamide combination tablets (Glucovance®) in 477 patients with hyperglycaemia despite sulphonylurea therapy.	(1) glibenclamide/metformin FDC (2.5mg/500mg) (2) glibenclamide/metformin FDC (5mg/500mg)	United States	Bristol-Myers Squibb
Bruce 2006	multicenter 3-arm parallel group	45	M/W 20-75y	randomised double-blind	5 months	To investigate the mechanisms of action of the blood glucose-lowering actions of the combination tablets, in comparison with metformin and glibenclamide monotherapies, using	(1) glibenclamide/metformin FDC (Glucovance; 1.25mg/250mg) (2) metformin (500mg) (3) glibenclamide (2.5mg)	United States	Bristol-Myers Squibb

						hyperglycaemic clamp methodology and an oral glucose tolerance test in patients with Type 2 diabetes.			
Brunetti 2004	multicenter prospective crossover	133	M/W 35-70y	randomised double-blind	6 months	To assess the efficacy and safety profile of this new dose-combination compared with the standard glibenclamide 2.5mg/ metformin 400mg dose regimen in patients with Type 2 diabetes and poor glycaemic control.	(1) glibenclamide/metformin FDC (5mg/400mg) (2) glibenclamide/metformin FDC (2.5mg/400mg) Each given for 3 months then switched to the other treatment for 3 months.	Italy	Not listed
Chien 2007	multicenter 4-arm parallel group	76	M/W 30-75y	randomised double-blind	4 months	To evaluate the efficacy and safety of glyburide/ metformin combined tablet compared to glyburide or metformin alone in patients with Type 2 diabetes.	(1) glyburide (5mg) (2) metformin (500mg) (3) glyburide/metformin FDC (2.5mg/500mg) (4) glyburide/metformin FDC (5.0mg/500mg)	Taiwan	Orient Europharma Co. Ltd.
Comaschi 2007 Comaschi 2008	multicenter parallel group	196	M/W ≥35y	randomised open-label	6 months	To compare the effectiveness of co-administration of pioglitazone with metformin or a sulfonlyurea with a fixed-dose combination of metformin and glibenclamide on glycemic control and β-cell function in patients with Type 2 diabetes.	(1) pioglitazone (Actos®; 15-30mg/day) + metformin or sulfonylurea concomitant treatment (2) glibenclamide/metformin FDC (Glibomet®; 2.5mg/500mg)	Italy	Takeda Italy
Dailey III 2004	multicenter	261	M/W 20-78y	randomised double-blind	6 months	To assess the efficacy and safety of adding rosiglitazone to an established regimen of glyburide/metformin in patients with Type 2 diabetes who had not achieved adequate glycemic control.	(1) glyburide/metformin FDC + rosiglitazone (2) glyburide/metformin FDC + placebo Started after a 3 month open-label lead-in phase.	United States	Bristol-Myers Squibb
Donahue 2002	2-way crossover	35	M/W 20-70y	randomised double-blind	0.5 months	To compare the effects of two different formulations of glibenclamide (glyburide) combined with metformin on	(1) glibenclamide/metformin FDC (2.5mg/500mg)	United States	Bristol-Myers Squibb

						postprandial glucose excursions, and to assess their pharmacokinetics.	(2) glibenclamide (2.5mg) + metformin (500mg) concomitant treatment Two-hour postprandial plasma glucose excursion.		
Erle 1999	crossover	33	M/W avg: 60y	randomised double-blind	6 months	To assess and compare the effectiveness and safety of preconstituted, fixed, combinations of low-dose glyburide plus metformin with higher dose glyburide monotherapy in patients with Type 2 diabetes.	(1) glyburide/metformin FDC (Glibomet; 2.5mg/400mg) (2) glyburide (Gliboral; 5mg) + placebo	Italy	Laboratori Guidotti SpA, Pisa
Flores-Murrieta 2003	crossover	19	W avg: 49.6y	randomised	0.5 months	To compare two pharmaceutical formulations manufactured in Mexico, the conventional tablet (Bieuglucon®) and the new partially micronized formulation (Glucovance®), in diabetic patients submitted to treatment with both formulations for 7 days.	(1) glyburide/metformin FDC (Bieuglucon®; 2.5mg/500mg) (2) glyburide/metformin FDC (Glucovance®; 2.5mg/500mg) Each given for 1 week then switched to the other treatment for 1 week.	Mexico	Not listed
Garber 2002	parallel-group placebo-controlled multicentre study	533	M/W avg: 56.6y	randomised	4 months	To prospectively evaluate the efficacy and safety of combination therapy using a glyburide/metfomrin tablet as compared with metformin monotherapy and glyburide monotherapy as an initial treatment in patients with Type 2 diabetes.	(1) placebo (2) glyburide (Micronase®, 2.5mg) (3) metformin (500mg) (4) glyburide/metformin FDC (1.25mg/250mg) (5) glyburide/metformin FDC (2.5mg/500mg) Started after a 2 week single-blind placebo lead-in phase.	United States	Bristol-Myers Squibb
Garber 2003	multicenter 3-arm parallel group study	429	M/W 20-78y	randomised double-blind	4 months	To examine the efficacy of initial therapy with glyburide/metformin tablets compared with traditional glyburide or metformin	(1) glyburide/metformin FDC (1.25mg/250mg) (2) metformin (500mg) (3) glyburide (2.5mg) Started after a 2 week placebo lead-in phase.	United States	Bristol-Myers Squibb

						monotherapy in patients with more severe hyperglycemia.			
Garber 2006	multicentre	280	M/W 20-70y	randomised double-blind	6 months	To evaluate the efficacy and safety of metformin-glibenclamide tablets vs. metformin plus rosiglitazone therapy in patients with Type 2 diabetes inadequately controlled on metformin monotherapy.	(1) glibenclamide/metformin FDC (2.5mg500mg) (2) rosiglitazone (4mg) + metformin (500mg) concomitant treatment Started after a 1 week open-label metformin lead-in phase.	United States	Bristol-Myers Squibb
González-Ortiz 2009	multicenter study	152	M/W 40-65y	randomised double-blind	12 months	The aim of this study was to compare the efficacy of glimepiride/metformin combination versus glibenclamide/metformin for reaching glycemic control in patients with uncontrolled Type 2 diabetes.	(1) glimepiride/metformin (1mg/500 mg) (2) glibenclamide/metformin (5mg/500 mg)	Mexico	Laboratorios Silanes
Marre 2002	multicentre parallel-group study	356	M/W >18y	double-blind double-blind	4 months	To evaluate the efficacy and safety of two dosage strengths of a single tablet metformin–glibenclamide (glyburide) combination compared with the respective monotherapies, in patients with Type 2 diabetes inadequately controlled by metformin monotherapy.	(1) metformin (Glucophage®; 500mg) (2) glibenclamide (Daonil®; 5mg) (3) glibenclamide/metformin FDC (Glucovance®; 2.5mg/500mg) (4) glibenclamide/metformin FDC (Glucovance®; 5mg/500mg) Started after a 2 week run-in period.	France Belgium Netherlands Denmark Portugal	Merck Lipha
Medina Santillán 2002	phase IV study	122	M/W 34-77y	open-label	1 month	To evaluate the effectiveness and safety of preconstituted fixed combinations of glyburide plus metformin in patients with Type 2 diabetes inadequately controlled with monotherapy.	(1) glyburide/metformin (Glucovance®; 1.25mg/250mg) (2) glyburide/metformin (Glucovance®; 2.5mg/500mg) (3) glyburide/metformin (Glucovance®; 5mg/500mg)	Mexico	Not listed

Raptis 1996	crossover prospective study	30	M/W avg: 60.8y	randomised open-label	6 months	To examine the effects of the FDC glibenclamide-metformin 2.5mg and 400mg respectively, compared to the fixed combination glibenclamide-phenformin 2.5mg and 25mg respectively, on the homeostasis of blood glucose in patients with Type 2 diabetes.	(1) glibenclamide/metformin FDC (Daopar® and Sugan M®; 2.5mg/400mg) (2) glibenclamide/phenformin FDC (Daopar® and Sugan M®; 2.5mg/25mg) Each given for 3 months then switched to the other treatment for 3 months.	Greece	Not listed
Shimpi 2009	single center parallel group study	28	M/W >35y	randomised open-label	3 months	To compare the effect of metformin in combination with glimepiride and glibenclamide in patients with Type 2 diabetes.	(1) glimepiride/metformin FDC (1mg/500mg) (2) glibenclamide/metformin FDC (5mg/500mg)	India	Not listed
Tosi 2003	crossover 3-treatment	80	M/W avg: 57.3y	randomised	12 months	To compare efficacy and tolerability of combination treatment with metformin and sulfonylurea with each of these drugs alone in the treatment of type 2 diabetes.	(1) glibenclamide (5mg) (n=22) (2) metformin (500mg) (n=22) (3) glibenclamide/metformin (2.5mg/400mg) (n=44) After 1 week run in period. One tablet twice daily. Crossover after 6 months.	Italy	Guidotti Laboratories Pisa, Italy
FDC COMPONENTS: GLICLAZIDE									
NONE									

N=participants completed; FDC=fixed dose combination; SR=slow release/sustained release; IR=immediate release; ER=extended release; T2DM=Type 2 Diabetes Mellitus

Figure S5. Flowchart of search strategy and results of the clinical trial database searches conducted on unpublished trials of five FDCs

NIH = NIH clinical trials database (clinicaltrials.gov); CTRI = Clinical Trials Registry India; ICTRP = WHO International Clinical Trials Registry Platform; UKCTR = UK Clinical Trials Gateway; EUCTR = EU Clinical Trials Register

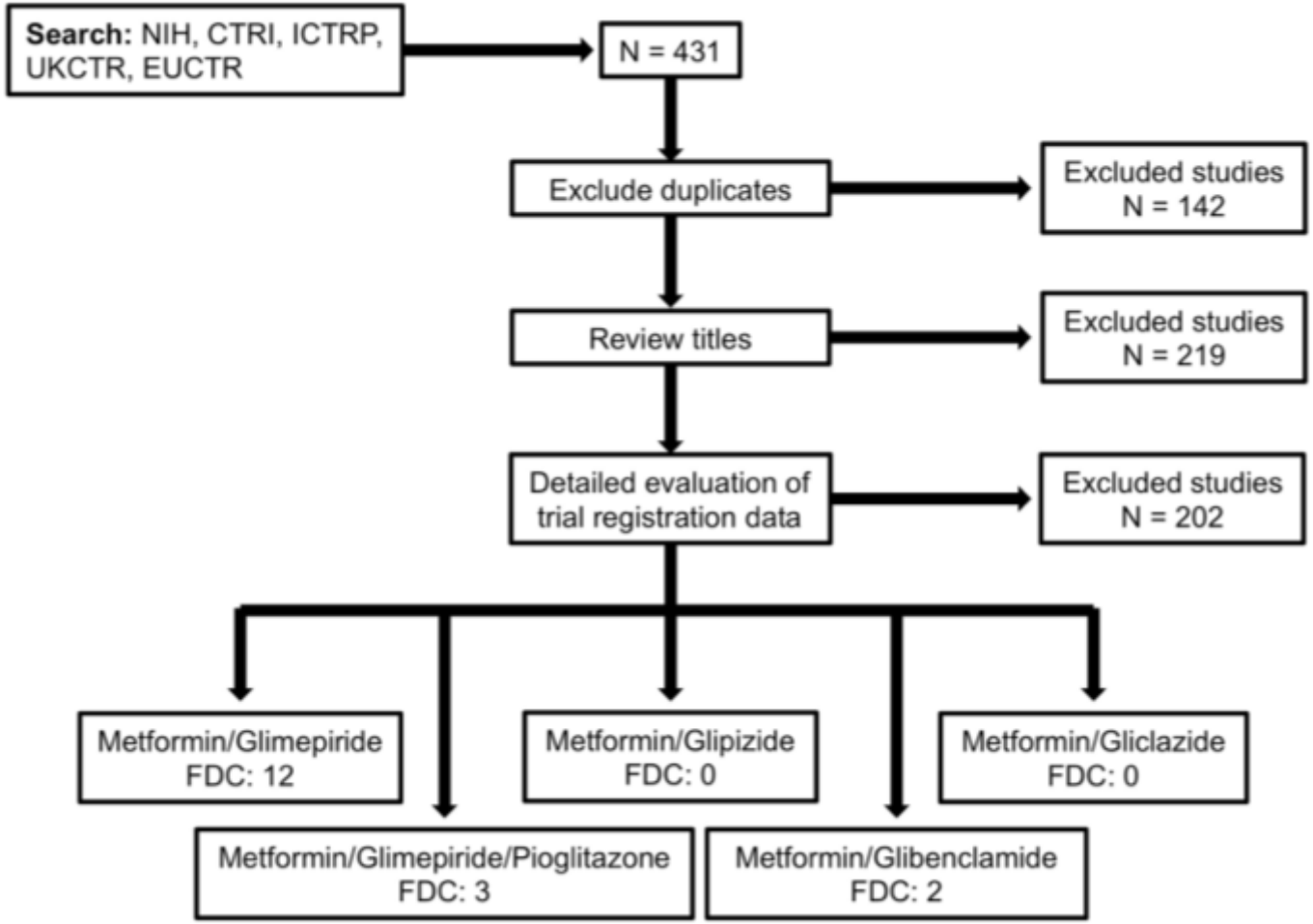

Table S3. Details of unpublished trials on metformin FDCs conducted on Type 2 diabetes patients.

Clinical Trial ID# [reference]	Country of Study	Expected Duration (months)	# Estimated Participants	Gender Age (years)	Status	Intervention	Primary Outcome Measure(s)	Sponsor
FDC COMPONENTS: GLIMEPIRIDE + METFOMRIN								
NCT01457911[1]	China	5	240	M/F (18-80y)	Recruiting	(1) Glimepiride SDF (2) FDC (glimepiride/metformin)	HbA1c level	Sanofi-Aventis
NCT00924573[2]	Japan	6	189	M/F (20-74y)	Completed	(1) Glimepiride SDF (2) FDC (glimepiride/metformin)	HbA1c level	Sanofi-Aventis
NCT01429818[3]	Mexico	2	16	M/F (≥18y)	Completed	(1) Metformin SDF (2) FDC (glimepiride/metformin)	endothelial dysfunction	Laboratorios Silanes S.A. de C.V.
NCT00941161[4]	Mexico	3	28	M/F (40-65y)	Completed	(1) Metformin SDF (2) Glimepiride SDF (3) FDC (glimepiride/metformin)	HbA1c level, fasting plasma glucose	Laboratorios Silanes S.A. de C.V.
NCT00612144[5]	Korea	6	192	M/F (30-75y)	Unknown	(1) Metformin SDF (2) FDC (glimepiride/metformin)	HbA1c level	Handok Pharmaceuticals Co., Ltd.
NCT01204580[6]	Indonesia	3	40	M/F (40-60y)	Completed	(1) FDC (glimepiride/metformin) (2) No comparator	adiponectin (ADMA) plasma level	Sanofi-Aventis
NCT01444248[7]	Korea	6	168	M/F (18-75y)	Completed	(1) FDC (brand 1) (glimepiride/metformin) (2) FDC (brand 2) (glimepiride/metformin)	patient compliance	Handok Pharmaceuticals Co., Ltd.
NCT00437554[8]	Korea	4	188	M/F (30-75y)	Completed	(1) FDC (dose 1) (glimepiride/metformin) (2) FDC (dose 2) (glimepiride/metformin)	HbA1c level, fasting plasma glucose	Handok Pharmaceuticals Co., Ltd.
NCT01144728[9]	Kazakhstan	4	172	M/F (35-75y)	Completed	(1) FDC (glimepiride/metformin) (2) No comparator	HbA1c level, fasting plasma glucose	Sanofi-Aventis

NCT01624116[10]	Pakistan	1	161	M/F	Completed	(1) Metformin SDF (2) FDC (dose 1) (glimepiride/metformin) (3) FDC (dose 2) (glimepiride/metformin)	body weight, fructosamine level	Services Hospital, Lahore
NCT01699932[11]	Lebanon, Russia, Ukraine	6	150	M/F (≥18y)	Recruiting	(1) FDC (glimepiride/metformin) (2) No comparator	HbA1c level	Sanofi
CTRI/2011/091/000266[12]*	India	6.5	104	M/F (>18y)	Completed	(1) FDC (dose 1) (glimepiride/metformin) (2) FDC (dose 2) (glimepiride/metformin) (3) FDC (dose 1) (glimepiride/pioglitazone/metformin) (4) FDC (dose 2) (glimepiride/pioglitazone/metformin)	HbA1c level	Abbott Healthcare Pvt Ltd
FDC COMPONENTS: GLIMEPIRIDE + PIOGLITAZONE + METFORMIN								
CTRI/2011/091/000266[12]*	India	6	104	M/F >18	Completed	(1) FDC (dose 1) (glimepiride/pioglitazone/metformin) (2) FDC (dose 2) (glimepiride/pioglitazone/metformin) (3) FDC (dose 1) (glimepiride/metformin) (4) FDC (dose 2) (glimepiride/metformin)	HbA1c level	Abbott Healthcare
CTRI/2011/09/002024[13]	India	3	44	M/F >18	Completed	(1) FDC (glimepiride/pioglitazone/metformin) (2) FDC (glimepiride/voglibose/metformin)	HbA1c level, postprandial plasma glucose	Abbott Healthcare
CTRI/2011/06/001841[14]	India	3	70	M/F >18	Suspended	(1) Insulin + Metformin	HbA1c level	Abbott Healthcare

						(2) FDC (dose 1) (glimepiride/pioglitazone/metformin) (3) FDC (dose 2) (glimepiride/pioglitazone/metformin)		
FDC COMPONENTS: GLIPIZIDE + METFORMIN								
NONE								
FDC COMPONENTS: GLIBENCLAMIDE + METFORMIN								
NCT00035568[15]	United States	NR	NR	M/F 20-75	Completed	(1) Metformin SDF (2) Glibenclamide SDF (3) FDC (glibenclamide/metformin)	NR	Bristol-Myers Squibb
NCT00541437[16]	Taiwan	NR	12	M/F 20-75	Completed	(1) Metformin + Sulfonylurea (2) FDC (glibenclamide/metformin)	NR	Genovate Biotechnology Co., Ltd.
FDC COMPONENTS: GLICLAZIDE + METFOMRIN								
NONE								

* This trial is listed twice, under both glimepiride/metformin and glimepiride/pioglitazone/metformin as they compare the two treatments.
NR=not reported

Unpublished trials

Searches of the five clinical trial databases identified a total of 17 unpublished trials: glimepiride/metformin, 12; glimepiride/pioglitazone/metformin, 3; and glibenclamide/metformin, 2. No trials investigated glipizide/metformin or gliclazide/metformin. The NIH Clinical Trials database listed 2 studies of glibenclamide/metformin and 11 studies of glimepiride/metformin. The CTRI listed 1 clinical trial for glimepiride/metformin and 3 for glimepiride/pioglitazone/metformin. No additional trials were registered of the other combinations of interest in our review. Subsequent searches of the WHO International Clinical Trials Registry Platform, the UK Clinical Research Network/ISRCTN and the EU Clinical Trials Register found no additional relevant trials.

Description of comparator arms in unpublished trials worldwide and in India

Of the 17 unpublished trials of metformin FDCs in diabetic patients: 13 examined glimepiride/metformin; five, glimepiride/pioglitazone/metformin; two, glibenclamide/metformin; none, glipizide/metformin. In India, there were three unpublished clinical trials of metformin FDCs on Type 2 diabetes patients. All three unpublished trials of this FDC were conducted by Abbott Healthcare in 44, 70, and 104 patients with Type 2 diabetes with a study duration of 3-6 months[12–14].

Evaluation of the 17 unpublished clinical trials against WHO FDC criteria (Table S7)

No trial results were posted on any of the clinical trial databases. Eight trials compared the FDC to SDF monotherapy; none investigated concomitant SDF treatments (Table S7). None of the trials met the WHO criteria of several hundred patients or duration greater than six months. Most trials listed change in HbA1c level as the primary outcome; four trials listed

other primary outcome measures in the trial protocol. The only study not conducted by a pharmaceutical company was a four-week study of 161 patients with Type 2 diabetes during Ramadan in Pakistan. It compared a glimepiride/metformin FDC with a sitagliptin/metformin FDC[10]. Of 12 glimepiride/metformin FDC trials, six were conducted in Asia (China, Japan, Korea (3), Indonesia), two in Mexico, one in India, one in Pakistan, one in Kazakhstan, and one in Lebanon/Russia. The three trials that evaluated triple combination therapy (glimepiride/pioglitazone/metformin) were all conducted in India[12–14]. Two trials compared different doses of glimepiride in the triple combination while the third compared the triple FDC to another triple FDC (glimepiride/voglibose/metformin). The two trials on glibenclamide/metformin were conducted in the United States and Taiwan, respectively[15,16]. The former compared the FDC to monotherapy (metformin or glibenclamide) and the latter FDC after concomitant treatment with a sulfonylurea plus metformin.

Involvement of multinational corporations (MNCs) and country of study

Of the 17 unpublished trials, only the Pakistan study was not conducted by a pharmaceutical company[10]. Sanofi-Aventis conducted five unpublished trials on the glimepiride FDC[1,2,6,9,11]. Abbott Healthcare conducted three of the unpublished trials in India[12–14] investigating the triple combination FDC.

Table S4. Trials listed on USA and India clinical trials registries for metformin FDC clinical trials conducted on patients with Type 2 Diabetes.

Clinical Trials ID No. (other)	Study	Design	Start/End	Status	Interventions	N	Sex Age	Phase	Sponsor	Location
FDC COMPONENTS: GLIMEPIRIDE + METFORMIN										
NCT01457911	Evaluation of fixed dose combination of glimepiride and metformin in Chinese type 2 diabetes patients inadequately controlled with metformin	randomized parallel group open-label efficacy	Oct 2011 - Apr 2013	recruiting	(1) glimepiride/metformin FDC (Amaryl M; 1mg/250mg) (2) glimepiride (Amaryl)	240	M/F 18-80y	3	Sanofi-Aventis	China
NCT00924573	Comparative study of HOE490 O (glimepiride and metformin) compared with placebo on top of glimepiride	randomized parallel group double-blind efficacy	May 2009 - Mar 2010	completed (results on corporate website)	(1) glimepiride/metformin FDC (HOE490 O) (2) glimepiride + placebo	189	M/F 20-74y	3	Sanofi-Aventis	Japan
NCT01429818	Endothelial disfunction treatment with gimepiride/metformin combination (Glimetal) in type 2 diabetes patients	randomized parallel group double-blind efficacy	Jul 2007 - Jan 2008	completed	(1) glimepiride/metformin FDC (Glimetal; 4mg/100mg) (2) metformin (Predial; 100mg)	16	M/F ≥18y	4	Laboratorios Silanes S.A. de C.V.	Mexico
NCT00941161	Effect of oral combination therapy in a single dosage form in patients with type 2 diabetes mellitus	randomized parallel group double-blind safety/ efficacy	Feb 2009 - May 2010	completed	(1) glimepride/metformin long-acting FDC (1g/2mg) (2) metformin long acting (1g) (3) glimepiride (2mg)	28	M/F 40-65y	4	Laboratorios Silanes S.A. de C.V.	Mexico
NCT00612144	Study comparing efficacy and safety of Amaryl M and metformin uptitraion to type 2 dm	randomized parallel group open-label safety/ efficacy	Dec 2007 - Mar 2009	unknown	(1) glimepiride/metformin FDC (Amaryl M) (2) metformin	192	M/F 30-75y	4	Handok Pharmaceuticals Co., Ltd.	Korea

NCT01204580	ADIponectin and asymmetric dimethylarginine (ADMA) level in type-2 diabetes patients after 12 weeks of treatment with glimepiride and metformin fixed dose combination	randomized single group open-label safety/ efficacy	Dec 2010 - Mar 2012	completed	(1) glimepiride/metformin FDC (Amaryl-M)	40	M/F 40-60y	4	Sanofi-Aventis	Indonesia
NCT01444248	Compare the compliance of patients treated with once-daily (od) or twice-daily (bid) glimepiride and metformin fixed combination therapy	randomized parallel group open-label safety/ efficacy	Aug 2010 - Dec 2011	completed	(1) glimepiride/metformin FDC (Amaryl MEX; 4mg/1000mg) (2) glimepiride/metformin FDC (Amaryl M; 4mg/1000mg)	168	M/F 18-75y	4	Handok Pharmaceuticals Co., Ltd.	Korea
NCT00437554	Phase III study for glimepiride + metformin hydrochloride (Amaryl M) slow release (SR)	randomized parallel group double-blind safety/ efficacy	Aug 2006 - Jul 2007	completed	(1) glimepiride + metformin FDC (Amaryl M; 1mg/250 mg) (2) glimepiride + metformin FDC (Amaryl M SR; 2mg/500 mg)	188	M/F 30-75y	3	Handok Pharmaceuticals Co., Ltd.	Korea
NCT01144728	Initiation and titration of Amaryl	single group open-label safety/ efficacy	May 2010 - Dec 2010	completed	(1) glimepiride/metformin FDC	172	M/F 35-75y	4	Sanofi-Aventis	Kazakhstan
NCT01624116	Comparison of hypoglycaemic regimens during Ramadan fasting in type 2 diabetes	randomized parallel group open-label safety/ efficacy	Aug 2011 - Sep 2011	completed	(1) diet and lifestyle measures (2) metformin (3) glimepiride/metformin FDC (1mg/500mg) (4) sitagliptin/metformin FDC (50mg/500mg)	161	M/F	not listed	Services Hospital, Lahore	Pakistan
NCT01699932 (GLMET_R_05823, U1111-1120-0058)	Efficacy and dafety of the fixed dose combination of glimepiride+metformin in type 2 diabetic patients inadequately controlled	non-randomized single group open-label efficacy	Sep 2012 - Mar 2014	recruiting	(1) glimepiride/metformin FDC (Amaryl M®, HOE4900)	150	M/F ≥18y	3	Sanofi	Lebanon, Russian Federation

CTRI/2011/091/000266 (TRIED 3-AHPL/06/10)	A clinical trial to study the effects of fixed dose combination of glimepiride + metformin SR + poglitazone vs fixed dose combination of glimepiride + metformin SR in treatment of patients with type 2 diabetes inadequately controlled with monotherapy of either glimepiride or metformin plain/SR formulation	randomized open-label multicentric comparative safety/ efficacy	Dec 2010 - unknown	completed	(1) glimepiride/metformin SR FDC (1mg/500mg) (2) glimepiride/metformin SR FDC (2mg/500mg) (3) glimepiride/pioglitazone /metformin SR FDC (1mg/15mg/500mg) (4) glimepiride/pioglitazone /metformin SR FDC (2mg/15mg/1500mg)	104	M/F >18y	4	Abbott Healthcare Pvt Ltd	India
FDC COMPONENTS: GLIMEPIRIDE + PIOGLITAZONE + METFORMIN										
CTRI/2011/091/000266 (TRIED 3-AHPL/06/10)	A clinical trial to study the effects of fixed dose combination of glimepiride + metformin SR + poglitazone vs fixed dose combination of glimepiride + metformin SR in treatment of patients with type 2 diabetes inadequately controlled with monotherapy of either glimepiride or metformin plain/SR formulation	randomized open-label multicentric comparative safety/ efficacy	Dec 2010 - unknown	completed	(1) glimepiride/metformin SR FDC (1mg/500mg) (2) glimepiride/metformin SR FDC (2mg/500mg) (3) glimepiride/pioglitazone /metformin SR FDC (1mg/15mg/500mg) (4) glimepiride/pioglitazone /metformin SR FDC (2mg/15mg/1500mg)	104	M/F >18y	4	Abbott Healthcare Pvt Ltd	India
CTRI/2011/09/002024 (VOGLIMET/APHL/01/11)	To compare the safety and efficacy of two antidiabetic drugs in treatment of patients with type II diabetes	randomized parallel group open-label safety/efficacy	Sep 2011 - unknown	completed	(1) glimepiride/pioglitazone /metformin SR (1mg/15mg/500mg) (2) glimepiride/voglibose/metformin SR (1mg/0.3mg/500mg)	44	M/F >18y	4	Abbott Healthcare Pvt Ltd	India

CTRI/2011/06/001841 (SCARC/2011/02)	This study is done to assess effectiveness and safety study of a three drug combination with a two drug combination for the treatment of type 2 diabetes mellitus in patients who have never reveived insulin	randomized parallel group open-label single centre safety/efficacy	Jul 2011 - unknown	suspended	(1) insulin 70/30 + metformin (2) glimepiride/pioglitazone /metformin SR (1mg/15mg/500mg) (3) glimepiride/pioglitazone /metformin SR (2mg/15mg/500mg)	70	M/F >18y	not listed	Abbott India Limited	India
FDC COMPONENTS: GLIPIZIDE + METFORMIN										
NONE										
FDC COMPONENTS: GLIBENCLAMIDE + METFORMIN										
NCT00035568 (CV138-062)	A research study to assess the mechanism by which glucovance, metformin, and glyburide work to control glucose levels in patients with type 2 diabetes	interventional	Feb 2002 - Jun 2003	completed	(1) glyburide/metformin FDC (Glucovance) (2) metformin (3) glyburide		M&F 20-75y	4	Bristol-Myers Squibb	United States
NCT00541437 (GBL L-13)	Type 2 diabetes patients switched from sulfonylurea with metformin to glyburide/metformin combination tablet	prospective	May 2006	completed	(1) switched from sulfonylurea + metformin to glyburide/metformin FDC (GlucoMet®)	12	M&F 20-75y	not listed	Genovate Biotechnology Co., Ltd.	Taiwan
FDC COMPONENTS: GLICLAZIDE + METFORMIN										
NONE										

N=participants recruited; NCT=Clinical Trials Registry USA; CTRI=Clinical Trials Registry of India; LA=long-acting; SR=slow release; ER=extended release; PR=prolonged release

Additional References (unpublished trials)

1 Abbott Healthcare Pvt., Ltd. A clinical trial to study the effects of fixed dose combinations of glimepiride + metformin SR + pioglitazone vs fixed dose combination of glimepiride + metformin SR in treatment of patients with Type 2 diabetes inadequately controlled with monotherapy of either glimepiride or metformin plain/SR formulation (CTRI/2011/091/000266) In: Clinical Trials Registry - India [Internet]. New Delhi: National Institute of Medical Statistics (India). 1980-2013. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=2774 (accessed April 2013).

2 Abbott Healthcare Pvt., Ltd. To compare the safety and efficacy of two antidiabetic drugs in treatment of patients with Type II diabetes (CTRI/2011/09/002024). In: Clinical Trials Registry - India [Internet]. New Delhi: National Institute of Medical Statistics (India). 1980-2013. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3494 (accessed April 2013).

3 Abbott India Limited. This study is done to access effectiveness and safety study of a three drug combination with a two drug combination for the treatment of Type 2 diabetes mellitus in patients who have never received insulin (CTRI/2011/06/001841). In: Clinical Trials Registry - India [Internet]. New Delhi: National Institute of Medical Statistics (India). 1980-2013. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=2755 (accessed April 2013).

4 Services Hospital, Lahore. Comparison of hypoglycaemic regimens during Ramadan fasting in Type 2 diabetes (NCT01624116). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT01624116 (accessed April 2013).

5 Bristol-Myers Squibb. A research study to access the mechanism by which glucovance, metformin, and glyburide work to control glucose levels in patients with Type 2 diabetes (NCT00035568). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT00035568 (accessed April 2013).

6 Genovate Biotechnology Co., Ltd. Type 2 diabetes patients switched from sulfonylurea with metformin to glyburide/metformin combination tablet (NCT00541437). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT00541437 (accessed April 2013).

7 Sanofi. Evaluation of fixed dose combination of glimepiride and metformin in Chinese Type 2 diabetes patients inadequately controlled with metformin (NCT01457911). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT01457911 (accessed April 2013).

8 Sanofi. Comparative study of HOE490 O (glimepiride and metformin) compared with placebo on top of glimepiride (NCT00924573). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT00924573 (accessed April 2013).

9 Sanofi. ADIponectin and asymmetric dimethylarginine (ADMA) level in Type-2 diabetes patients after 12 weeks of treatment with glimepiride and metformin fixed dose combination (DIAGRAM) (NCT01204580). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT01204580 (accessed April 2013).

10 Sanofi. Initiation and titration of Amaryl (AMIT KZ) (NCT01144728). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT01144728 (accessed April 2013).
11 Sanofi. Efficacy and safety of the fixed dose combination of glimepiride+metformin in Type 2 diabetic patients inadequately controlled (LEGEND) (NCT01699932). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT01699932 (accessed April 2013).
12 Laboratorios Silanes S.A. de C.V. Endothelial dysfunction treatment with glimepiride/metfomrin combination (Glimetal) in Type 2 diabetes patients (NCT01429818). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT01429818 (accessed April 2013).
13 Laboratorios Silanes S.A. de C.V. Effect of oral combination therapy in a single dosage form in patients with Type 2 diabetes mellitus (NCT00941161). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT00941161 (accessed April 2013).
14 Handok Pharmaceuticals Co., Ltd. Compare the compliance of patients treated with once-daily (od) or twice-daily (bid) glimepiride and metformin fixed dose combination therapy (NCT01444248). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT01444248 (accessed April 2013).
15 Handok Pharmaceuticals Co., Ltd. Study comparing efficacy and safety of Amaryl M and metformin uptitration to Type 2 DM (NCT00612144). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT00612144 (accessed April 2013).
16 Handok Pharmaceuticals Co., Ltd. Phase III study for glimepiride + metformin hydrochloride (Amaryl M) slow relsease (SR) (NCT00437554). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 1980-2013. http://clinicaltrials.gov/show/NCT00437554 (accessed April 2013).