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Research Article

Bioequivalence study of a fixed-dose combination of Dapagliflozin/ Vildagliptin Sustained Release tablets in healthy adult male subjects: A Randomized, Open-Label, Crossover Study

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Abstract

A fixed-dose combination (FDC) of Dapagliflozin and Vildagliptin sustained release (SR) was developed, and its bioequivalence with coadministration of the individual tablets was evaluated in an open-label, randomized, two-treatment, two sequences, two-period, cross-over single-dose study. The study's primary objective was to compare and assess the rate and extent of absorption of Dapagliflozin 10 mg /Vildagliptin SR 100 mg FDC with individual drugs. Twenty-four healthy subjects were randomized, and 23 completed the study. For both Dapagliflozin and Vildagliptin SR, the 90% confidence intervals (CIs) for the ratio (Test product: Reference product) of geometric means of peak plasma concentration (C_{max}), the area under the curve from 0 hours to the last measurable concentration (AUC_{0-t}), and AUC-time curve up to infinity ($AUC_{0-\infty}$), were within acceptance criteria for bioequivalence, i.e., 80% to 125%. Overall, both reference and test products were safe and well tolerated.

Keywords: Bioequivalence, Dapagliflozin, Fixed-dose combination, Pharmacokinetic, Sustained release, Vildagliptin, Type 2 diabetes

INTRODUCTION

Type 2 diabetes (T2D) is a complex disease with multiple defects, which generally requires a combination of several pharmacological approaches to control hyperglycemia. [1] A rational and synergistic fixed-dose combination (FDC) of antidiabetic drugs may be a good option. Besides reducing pill burden and improving compliance, combination therapy with two drugs can help patients reach their target glycated hemoglobin (HbA1c) in a quick man faster. The studies have also proven that early intensive therapeutic control significantly reduces any diabetes-related endpoint.[2] The effectiveness of combination therapies is that they address different pathophysiologic aspects of the disease, which results in additive, synergistic, or complementary glucose-lowering effects.[3]

The FDC of dipeptidyl peptidase-4 inhibitor (DPP-4i) and sodium-glucose cotransporter type 2 inhibitor (SGT2i) offer an attractive approach. [1] Vildagliptin is an orally active DPP-4i that prevents the inactivation of glucagon-like peptide-1 and improves islet function. The binding of Vildagliptin to the catalytic site of DPP-4 is long-lasting, enabling inhibition of DPP-4 over a more extended period than expected from its circulating half-life. Vildagliptin efficiently lowers HbA1c in subjects when used as monotherapy and add-on to ongoing therapy. [4] In a fasting state, Vildagliptin is rapidly absorbed following oral administration. Peak plasma concentrations (C_{max}) are observed at 1.7 hours following administration. About 69% of orally administered Vildagliptin is eliminated via metabolism not mediated by cytochrome P450 enzymes. The plasma concentrations of Vildagliptin increase in an approximately dose-proportional manner. [5]

Dapagliflozin is the highly potent and reversible SGLT2i, and it is > 1400 times more selective for SGLT2 than SGLT1, the primary transporter responsible for glucose absorption in the gut. In multiple well-designed clinical studies, Dapagliflozin effectively controlled blood sugar levels, decreased body weight, and decreased blood pressure (BP). Additionally, the cardioprotective and possibly renoprotective properties and generally favorable tolerability profile make Dapagliflozin an essential option for managing a broad spectrum of patients.[6] Following oral administration of Dapagliflozin, the time to reach C_{max} is usually attained within 2 hours under a fasting state. The C_{max} and area under the curve (AUC) values increase dose proportionally with the Dapagliflozin dose in the therapeutic dose range. UGT1A9 primarily mediates the metabolism of Dapagliflozin.[7]

Due to their distinct but complementary modes of action and distinct degradation pathways (i.e., metabolism), the

combination of Dapagliflozin and Vildagliptin for treating T2D may be rational and appealing. Thus, a single pill combination of Dapagliflozin/Vildagliptin sustained release (SR) has been developed to capitalize on these advantages. However, it is necessary to demonstrate the bioequivalence of the FDC tablets and individual tablets, mainly if crucial safety and efficacy studies were carried out using single tablets.[3]

This study assessed the bioequivalence of an oral FDC of Dapagliflozin 10 mg/Vildagliptin SR 100 mg with individual tablets of Dapagliflozin 10 mg and Vildagliptin SR 100 mg.

METHODS

- **Subjects**

The study was conducted on healthy, adult male subjects aged 18 - 45 (inclusive). Written informed consent was obtained from eligible/fit volunteers who expressed willingness to participate in the study and the enrolled subjects who fulfilled the inclusion and exclusion criteria. All subjects underwent a screening procedure before the start of the study, and medical history and detailed demographic data were recorded. A complete general physical examination, vital signs assessment, 12-lead ECG, chest X-ray, and clinical laboratory assessments were conducted on each subject. Subjects were selected based on abstinence from any prescription medications within 14 days before study check-in, and they were instructed not to take prescription medications throughout the study.

- **Study design**

An open-label, randomized, balanced, two treatment, two sequence, two-period, cross-over, single-dose oral bioequivalence study of Dapagliflozin 10 mg + Vildagliptin SR 100 mg FDC tablets(manufactured by Exemed Pharmaceuticals, India) (T) and Dapagliflozin Tablet 10 mg (FORXIGA® marketed by AstraZeneca Pharmaceuticals LP, USA) (R1) and one tablet of Vildagliptin SR Tablet 100 100 mg (Vinglyn SR marketed by Zydus Healthcare Limited, India) (R2) in normal healthy, adult human subjects under fasting condition. The bio-analytical analysts were blinded to randomization during the entire course of the analysis. The clinical study was conducted over 15 days, and a washout of 10 days was maintained between each consecutive dosing period. In each period, at least 10 hours of overnight fasting was ensured before administering investigational products. Subjects were housed in the clinical facility from 11 hours before dosing until 24 hours post dose in each period. They returned to the clinical facility for ambulatory sampling at 48 and 72 -hours post-dose in each period.

- **Objective**

- ***Primary objective***

To compare and assess the rate and extent of absorption of Dapagliflozin 10 mg + Vildagliptin SR 100 mg FDC tablets and Dapagliflozin Tablet 10 mg and Vildagliptin SR Tablet 100 mg.

- ***Secondary objective***

To monitor the adverse events and ensure the subjects' safety following the administration of a single dose of Dapagliflozin 10 mg + Vildagliptin SR 100 mg FDC tablets.

- **Assessment**

- ***Bioanalysis***

In each period, pre-dose blood (00.00hr) sample (5 mL each) was collected within 2 hours before dosing. The post-dose blood samples (5 mL each) were collected at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, and 24.00 hours after dosing in pre-labeled K2EDTA – vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Samples at 48.00 and 72.00 hours were collected by direct vein puncture in pre-labeled K2EDTA – vacutainers. Blood samples were placed in a refrigerated centrifuge and spun at 3500 rpm at 2-5°C for 10 minutes. Dapagliflozin in human plasma was determined using the liquid chromatography-mass spectrometry (LC-MS) method over a concentration range of 2.060 to 253.824 ng/mL. Vildagliptin in human plasma was determined using the LC-MS method over a concentration range of 2.570 to 250.748 ng/ml.

- ***Pharmacokinetics***

The pharmacokinetic analysis was performed on subjects who completed both study periods. The pharmacokinetic variables included C_{max}, the AUC from 0 hours to the last measurable concentration (AUC_{0-t}), and AUC-time curve up to infinity ($AUC_{0-\infty}$), time to C_{max} (Tmax), and half-life (t1/2).

- ***Safety***

The safety and tolerability were assessed via adverse event (AE) monitoring, physical examination, BP, pulse rate, body temperature, vital signs, and blood glucose measurement. For the safety of the subjects who have completed the study, hematology and biochemistry investigations performed at screening were repeated at the end of the study.

- **Statistical analysis**

Statistical analysis was conducted using the SAS® statistical software, version 9.4 of SAS Institute Inc, USA. The log (Ln)-transformed pharmacokinetic parameters (AUC_{0-t} and $AUC_{0-\infty}$) were analyzed using the analysis of variance (ANOVA) model. To test the two one-sided tests for bioequivalence, and ratio analysis, 90% confidence intervals (CIs) for the difference between the treatment's least-square mean (LSM) were calculated for Ln transformed AUC_{0-t} and $AUC_{0-\infty}$. Bioequivalence of FDC tablets versus individual components was concluded if the 90% CIs for FDC to individual component geometric mean ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of both analytes were between 80% and 125% for Ln- transformed data.

- **Ethical standards**

The study was conducted in accordance with the independent ethics committee-approved protocol and all other applicable regulatory requirements.

RESULTS

- **Subject disposition and demographics**

A total of 24 subjects were enrolled in the study; of these, 23 completed both periods. The eligible subjects, who fulfilled the inclusion and exclusion criteria for the study, were randomly assigned to test products and reference products using SAS® for windows (SAS Institute Inc., USA) version 9.4. All subjects included in the study were from the Asian region. The baseline demographics of subjects who completed the study are summarized in Table 1.

Table 1: Demographic details of subjects who completed the study (N=23)

Parameter	Mean	SD	Min	Max	CV%
Age (years)	32.17	6.12	21.00	41.00	19.01
Height (M)	1.70	0.06	1.56	1.83	3.42
Weight (Kg)	70.03	13.06	23.80	90.00	18.66
BMI (Kg/m²)	25.23	2.48	20.48	28.66	9.81

BMI: Body mass index; CV: Coefficient of variation; Max: Maximum; Min: Minimum; SD: Standard deviation

- **Pharmacokinetic results**

The Dapagliflozin profiles in the fasting state were the same whether each component was administered separately or as an FDC. The overall drug exposure (C_{max} and AUC) was similar (Figure 1) for both the test and reference product. For each treatment (FDC and coadministered tablets), the mean time to peak plasma concentration was ~1.6 hours and ~1.5 hours, indicating rapid oral absorption. The mean t1/2 was ~7.9 hours for the reference product and 10 hours for Dapagliflozin FDC.

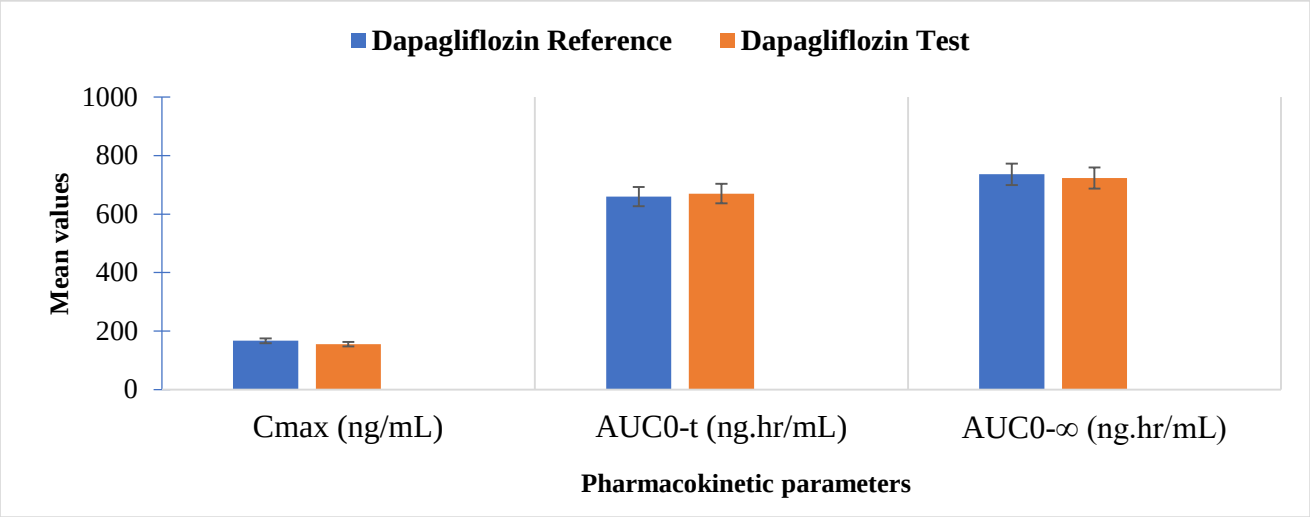

Figure 1: Pharmacokinetic profile of Dapagliflozin reference and test product

The 90% CIs for Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ are within the bioequivalence limits of 80 to 125% (Table 2).

Table 2: Statistical results of Ln-transformed test product (T) VS reference product (R) Dapagliflozin

Pharmacokinetic parameter	Geometric LSM		ISCV (%)	T/R Ratio (%)	Power (%)	90% CI
	Test Product (T)	Reference Product (R)				
C_{max} (ng/mL)	152.9264	160.3442	17.12	95.37	98.29	87.49 - 103.97
AUC_{0-t} (ng.hr/mL)	651.9003	639.0446	9.16	102.01	100.0	97.38 - 106.86
$AUC_{0-\infty}$ (ng.hr/mL)	699.6789	702.1710	14.14	99.65	99.73	92.77 - 107.03

AUC: Area Under the Curve; CI; Confidence interval; C_{max}: Peak plasma concentration; ISCV: Intrasubject coefficient of variation; LSM: Least mean square.

For Vildagliptin, C_{max} and AUC values were similar for FDC formulations and the coadministration of their respective components (Figure 2). The plasma concentrations of Vildagliptin FDC and coadministered tablets peaked at ~4.7 and ~ 4.47 hours (mean Tmax). The mean t ½ of Vildagliptin FDC was ~ 4.83 hours, and the reference product was ~6.23 hours.

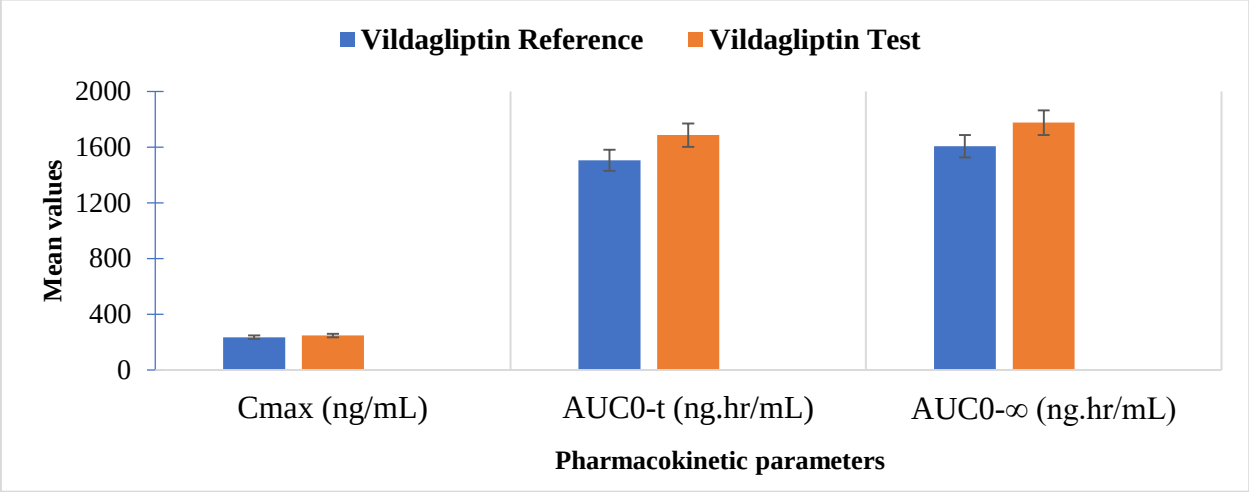

Figure 2: Pharmacokinetic profile of Vildagliptin reference and test product

Bioequivalence was confirmed as 90% CIs for FDC to individual component geometric mean ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within 80 to 125 % (Table 3).

Table 3: Statistical results of Ln-transformed test product (T) VS reference product (R) Vildagliptin

Pharmacokinetic Parameter	Geometric LSM		ISCV (%)	T/R Ratio (%)	Power (%)	90%CI
	Test Product (T)	Reference Product (R)				
C_{max} (ng/mL)	226.3107	228.2453	27.77	99.15	77.38	86.34 - 113.87
AUC_{0-t} (ng.hr/mL)	1574.1128	1460.1716	28.23	107.80	76.21	93.66 - 124.08
$AUC_{0-\infty}$ (ng.hr/mL)	1667.4759	1557.4085	27.93	107.07	76.98	93.16 - 123.06

AUC: Area Under the Curve; CI; Confidence interval; C_{max}: Peak plasma concentration; ISCV: Intrasubject coefficient of variation; LSM: Least mean square.

- **Safety results**

There were no deaths, severe AEs, or temporary or permanent therapy discontinuations due to AEs following a single oral dose of Dapagliflozin and Vildagliptin when administered either as an FDC or individual therapy. There were no clinically abnormal changes in vital signs in the study. The clinical event of elevated BP was reported in one subject before period one dosing and was resolved without any sequelae. There were no abnormal laboratory findings. Upon completion of the clinical phase of the study, all the participants' overall state of health was concluded to be clinically fit.

DISCUSSION

Bioequivalence studies are carried out to ascertain how closely a generic drug resembles its comparable innovator drug in terms of pharmacokinetic parameters, safety, quality, efficacy, dosage form, strength, and route of administration. In general, bioequivalence guidelines for FDCs include evaluating pharmacokinetic parameters such as AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. For these pharmacokinetic parameters, the 90% CI for the ratio of an FDC and individual components should fall within the acceptable range of 80% to 125%. The bioequivalence of FDC tablets and individual tablets must be proven to support regulatory approval especially if critical safety and effectiveness studies were carried out using the individual tablets. [3,11]

The present study evaluated the bioequivalence of Dapagliflozin 10 mg/Vildagliptin SR 100 mg as an FDC with individual tablets of Dapagliflozin 10 mg and Vildagliptin SR 100 mg. Coadministration of Dapagliflozin and Vildagliptin SR, either as individual components separately or as an FDC tablet, yielded a similar pharmacokinetic profile (C_{max} and AUC). At the usual doses of Dapagliflozin 10 mg and Vildagliptin, SR 100 mg, the Tmax for both Dapagliflozin and Vildagliptin SR were the same when used as FDC or monotherapy. The 90% CIs for FDC to individual component geometric mean ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the acceptable range for bioequivalence, i.e., 80% to 125%. The Dapagliflozin 10 mg /Vildagliptin SR 100 mg FDC and individual treatments were found safe and well tolerated in participants. The study results show the bioequivalence of Dapagliflozin 10 mg /Vildagliptin SR 100mg FDC tablets with coadministration of the respective individual components in healthy subjects under fasted conditions.

Previously, combination treatments were often added sequentially and taken as separate tablets. FDC medications, however, are becoming more frequently used in clinical settings for the treatment of T2D. Improved adherence, which has been linked to better glycemic control and less drug waste, is one benefit of an FDC treatment over the administration of separate pills.[3] Published clinical trials have demonstrated the efficacy and safety of Dapagliflozin and Vildagliptin in T2D patients when used alone or in combination with other antidiabetic medications.[8,9] The systematic review and meta-analysis results showed that the SGLT2i/DPP4i combination

improved glycemic control, with more significant reductions in HbA1c, fasting plasma glucose, and 2-hour postprandial plasma glucose, as well as a higher rate of HbA1c goal achievement. These benefits of the combination may be explained by the complimentary modes of action of SGLT2i and DPP4i. The combination also showed a significant reduction in body weight.[10] So, combining them in an FDC product can offer advantages like reduction of pill burden along with better glycemic control.

CONCLUSION

The FDC of Dapagliflozin 10 mg and Vildagliptin SR 100 mg tablets are bioequivalent to that of the individual tablet of Dapagliflozin 10 mg and Vildagliptin SR 100 mg in normal healthy adult human subjects under fasting conditions. Additionally, test and reference products were well tolerated, as evident by no therapy discontinuation due to AEs and no change in vital parameters. These results support Dapagliflozin/ Vildagliptin SR FDC as a suitable treatment for T2D, which is likely to benefit T2D patients by increasing treatment adherence, thereby effective glycemic control.

DECLARATIONS

Ethics approval and consent to participate: An independent ethics committee reviewed the ethical, scientific, and medical appropriateness of the study protocol. The study was conducted according to the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human subjects, Brazil 2013), current ICH GCP guidelines, and relevant National Laws and Regulations, ICMR guidelines, and CDSCO guidelines.

Ethics Committee (EC)

The Study Protocol No.: S-21-602 (version 01) Dated: 09 Apr 2021 and Informed Consent Documents Version: 01, Dated: 09 Apr 2021 was reviewed and approved by Ethics Committee on 18 may 2021. Study activities commenced only after the receipt of protocol approval from the IEC.

Ethical Conduct of the Study

The study was conducted in accordance with the IEC approved protocol and all other applicable regulatory requirements.

Consent for publication: All the subjects voluntarily gave written consent for participation in the study. The eligible subjects were allotted a subject number to maintain the confidentiality of their identity.

Availability of data and material: NA

Competing interests: There are no conflicts of interest. Dr Ashish Birla, Dr Ashish Prasad and Dr Sona Warrier are the employees of USV Pvt Ltd.

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REFERENCES

1. Scheen AJ. DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. Expert Opin Drug Metab Toxicol. 2016 Dec; 12(12):1407-1417. https://doi.org/10.1080/17425255.2016.1215427

2. Chadha M, Das AK, Deb P, Gangopadhyay KK, Joshi S, Kesavadev J, Kovil R, Kumar S, Misra A, Mohan V. Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i + DPP4i in the Indian Diabetes Setting. Diabetes Ther. 2022 May; 13(5):1097-1114. https://doi.org/10.1007/s13300-022-01219-x

3. Vakkalagadda B, Vetter ML, Rana J, Smith CH, Huang J, Karkas J, Boulton DW, LaCreta F. Bioequivalence of saxagliptin/Dapagliflozin fixed-dose combination tablets compared with coadministration of the individual tablets to healthy subjects. Pharmacol Res Perspect. 2016 Jan 12; 3(6):e00201. https://doi.org/10.1002/prp2.201

4. Ahrén B. Vildagliptin: a DPP-4 inhibitor for the treatment of Type 2 diabetes. Diabetes Management. 2012 Sep 1; 2(5):453. https://doi.org/10.2217/dmt.12.40

5. https://pubchem.ncbi.nlm.nih.gov/compound/Galvus#section=Absorption-Distribution-and-Excretion

6. Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes. Drugs. 2019 Jul; 79(10):1135-1146. https://doi.org/10.1007/s40265-019-01148-3

7. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s020lbl.pdf

8. Fioretto P, Giaccari A, Sesti G. Efficacy and safety of Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, in diabetes mellitus. Cardiovasc Diabetol. 2015 Oct 17; 14:142. https://doi.org/10.1186/s12933-015-0297-x

9. Profit L, Chrisp P, Nadin C. Vildagliptin: the evidence for its place in the treatment of type 2 diabetes mellitus. Core Evid. 2008 Jun; 3(1):13-30.

10. Min SH, Yoon JH, Moon SJ, Hahn S, Cho YM. Combination of sodium-glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor in type 2 diabetes: a systematic review with meta-analysis. Sci Rep. 2018 Mar 13; 8(1):4466. https://doi.org/10.1038/s41598-018-22658-2

11. Kalra S, Bhattacharya S. Bioequivalence study of two different dapagliflozin tablet formulations in healthy adult Indian volunteers. Journal of Diabetology. 2022 Jul 1; 13(3):235.