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Meta-analysis for Favipiravir Bioequivalence Studies

Favipiravir Biyoeşdeğerlik Çalışmaları İçin Meta-analiz

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ABSTRACT Objective: A global pandemic called coronavirus disease-2019 (COVID-19) has devastatingly hit the world since December 2019. Favipiravir has widely been used in treatment of COVID-19 and generic pharmaceutical companies took an action to manufacture generic drugs of favipiravir. In favipiravir treatment, when the patient needs to switch from one generic drug to another generic drug, the interchangeability of the generic drugs becomes important. For this purpose, meta-analysis is used between generic drugs based on data obtained from independent favipiravir bioequivalence studies. **Material and Methods:** Pharmacokinetics data of 6 favipiravir bioequivalence studies performed by Novagenix Bioanalytical R&D Centre in Turkey in 2020 were used. The 90% confidence intervals for the differences between the means of pharmacokinetic parameters, area under the curve ($AUC_{0\text{-}tlast}$) and maximum plasma concentration (C_{max}), were determined for each binary combinations of six generic drugs by meta-analysis used in average bioequivalence. These confidence intervals are compared with the bioequivalence acceptance limit of 80.00-125.00%. **Results:** Considering the 90% confidence intervals, 33.33% of the binary combinations of six generic drugs for only C_{max} and 53.33% of the binary combinations of six generic drugs for only $AUC_{0\text{-}tlast}$ have been concluded as bioequivalent. Three of the binary combinations fulfilled the bioequivalence criteria for both C_{max} and $AUC_{0\text{-}tlast}$. **Conclusion:** When assessing the interchangeability between generic drugs, some of the combinations did not meet the acceptance criteria. Therefore, when a patient switches between favipiravir generic drugs, the pharmacokinetic behaviour of the drug product and thus its efficacy may change.

Keywords: Meta-analysis; bioequivalence; favipiravir; generic drug

ÖZET Amaç: Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] adlı küresel bir salgın, Aralık 2019'dan beri dünyayı yıkıcı bir şekilde etkiledi. Favipiravir, COVID-19'un tedavisinde yaygın olarak kullanılmakta olup; jenerik ilaç şirketleri, jenerik favipiravir üretmek için harekete geçti. Favipiravir tedavisinde hasta, bir jenerik ilaçtan başka bir jenerik ilaca geçiş yapması gerektiğinde jenerik ilaçların değiştirilebilirliği önem kazanır. Bu amaçla bağımsız favipiravir biyoeşdeğerlik çalışmalarından elde edilen verilere dayalı olarak jenerik ilaçlar arasında metaanalizi kullanılmaktadır. **Gereç ve Yöntemler:** Novagenix Biyoanalitik Ar-Ge Merkezi tarafından 2020 yılında yapılan 6 favipiravir biyoeşdeğerlik çalışmalarının farmakokinetik verileri kullanılmıştır. Ortalama biyoeşdeğerlikte kullanılan metaanaliz ile 6 jenerik ilacın 2'li kombinasyonlarının farmakokinetik parametreleri için eğri altındaki alan (EAA) ve maksimum plazma konsantrasyon (C_{maks}), ortalamalar arasındaki fark için %90 güven aralıkları elde edilmiştir. Bu güven aralıkları, %80,00-125,00 biyoeşdeğerlik kabul limitleri ile karşılaştırılmıştır. **Bulgular:** Yüzde 90 güven aralıkları dikkate alındığında, yalnızca C_{maks} için 6 jenerik ilacın 2'li kombinasyonlarının %33,33'ü ve sadece $EAA_{0\text{-}tlast}$ için 6 jenerik ilacın 2'li kombinasyonlarının %53,33'ü biyoeşdeğer olarak sonuçlanmıştır. İkili kombinasyonların 3'ü, hem C_{maks} hem de $EAA_{0\text{-}tlast}$ için biyoeşdeğerlik kriterlerini karşıladı. **Sonuç:** Jenerik ilaçlar arasındaki değiştirilebilirliği değerlendirirken, bazı kombinasyonların kabul kriterini sağlamadığı görülmüştür. Bu nedenle, bir hasta favipiravir jenerik ilaçlar arasında geçiş yaptığında, ilaç ürününün farmakokinetik davranışı ve dolayısıyla etkinliği değişebilir.

Anahtar kelimeler: Metaanalizi; biyoeşdeğerlik; favipiravir; jenerik ilaç

A global pandemic called coronavirus disease-2019 (COVID-19) has devastatingly hit the world since December 2019. Although there is no significantly effective treatment or vaccination that has been found against COVID-19, infected patients are treated with a number of agents which might be considered as valuable in cure. One of these agents, favipiravir, used for influenza treatment in Japan has repurposed against severe acute respiratory syndrome-CoV-2 infection.[1,2] Favipiravir has widely been used in treatment of

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COVID-19 already and seems it is going to be the major agent until a treatment directly targeting the virus is discovered. The pandemic is still raging and the need for favipiravir is desperately rising. In order to supply the demand and make it accessible, the generic pharmaceutical companies took an action to manufacture generic products of favipiravir.

Bioequivalence assessment for generic drug products is based on the Fundamental Bioequivalence Assumption and is considered as a substitute for clinical evaluation of the therapeutic equivalence of drug products.[3] Two drug products containing the same active ingredient are considered bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptance limits.[4]

To investigate bioequivalence, the pharmacokinetic parameters are area under the curve ($AUC_{0\text{-}tlast}$), area under the time-concentration curve from dosing (time zero) to the time of last measurable concentration, which reflects the extent of exposure, and maximum plasma concentration (C_{max}), maximum plasma concentration, which reflects the rate of exposure. Before analysis, the data should be transformed using a logarithmic transformation. The 90% confidence intervals (CI) for the geometric mean ratio of the test and reference products for $AUC_{0\text{-}tlast}$ and C_{max} should be contained within the acceptance limits of 80.00-125.00%.[4]

For average bioequivalence, study design is often used as 2x2 crossover (two-period, two-sequence). The following statistical mixed effect model was assumed:

$$y_{ijk} = \mu + F_l + P_j + Q_k + S_{ikl} + e_{ijk} \quad (1)$$

where y_{ijk} is the pharmacokinetic characteristic of interest [$AUC_{0\text{-}tlast}$ or C_{max}] with i=1,..,nk the number of subjects per sequence, j=1, 2 the number of periods and k=1, 2 the number of sequences, μ is the overall mean; P_j is the fixed effect of the j^{th} period (j=1, 2, and $P_1+P_2=0$); Q_k is the fixed effect of the k^{th} sequence (k=1, 2, and $Q_1+Q_2=0$); F_l is the fixed effect of the l^{th} drug formulation when j=k, l=T, test formulation; when j≠k, l=R, the reference (brand-name) formulation ($F_T+F_R=0$); S_{ikl} is the random effect of the i^{th} subject in the k^{th} sequence under drug formulation l; and $S_{ik}=(S_{ikT}, S_{ikR})$, i=1, . . . , nk, k=1, 2, are independent and identically distributed (i.i.d.) bivariate normal random vectors with mean 0 and variance σ_S^2; e_{ijk}'s are independently distributed with mean 0 and variance σ_e^2. S_{ik}'s and e_{ijk}'s are mutually independent.[5,6]

Although each generic copy can be used as a surrogate for brand-name (reference) drug, it is indicated that generic copies of the same reference drug cannot be used interchangeably. For this purpose, Chow and Liu proposed meta-analysis to investigate average bioequivalence and interchangeability between generic drugs.[7]

According to Chow and Liu's approach, all studies should have the same intra-individual and inter-individual variability, which in turn limits meta-analysis's practical use. Chow and Shao suggested another method to relax this assumption for meta-analysis.[5,8]

In our previous article, we applied the meta-analysis method used in average bioequivalence for the active ingredient of naproxen.[9] This sort of analysis is found particularly important in this pandemic period during which the need for generic drugs is elevated for a global epidemic such as COVID-19.

Thus, a meta-analysis was conducted that brought together the results of several favipiravir bioequivalence studies conducted at Novagenix Bioanalytical R&D Center.

MATERIAL AND METHODS

INFORMATION SOURCES AND SEARCH STRATEGY

In 2020, six favipiravir bioequivalence studies have been conducted at Novagenix Bioanalytical R&D Center with design of cross-over, two-sequence and two-period. These studies were reviewed and approved by the

Ethical Committee and Turkish Medicines and Medical Devices Agency, and were held in Turkey according to the regulations run by Ministry of Health of the Republic of Turkey which are in compliance with Declaration of Helsinki and Good Clinical Principles.[10,11]

Identities of the test drugs' (generic copy) sponsors and manufacturer of reference drug (brand-name drug) are protected.

ELIGIBILITY CRITERIA

To perform meta-analysis methodology, favipiravir bioequivalence studies that meet the following conditions conducted at Novagenix Bioanalytical R&D Center were selected:

1. Having the same experimental design as 2x2 crossover,
2. Meeting the acceptance criteria of bioequivalence,
3. Having the same reference drug with different batch numbers.

STUDY SELECTION

A flow chart for the meta-analysis of favipiravir bioequivalence studies was illustrated in Figure 1. Six favipiravir bioequivalence studies using the same reference drug in different batch numbers were included in the meta-analysis.

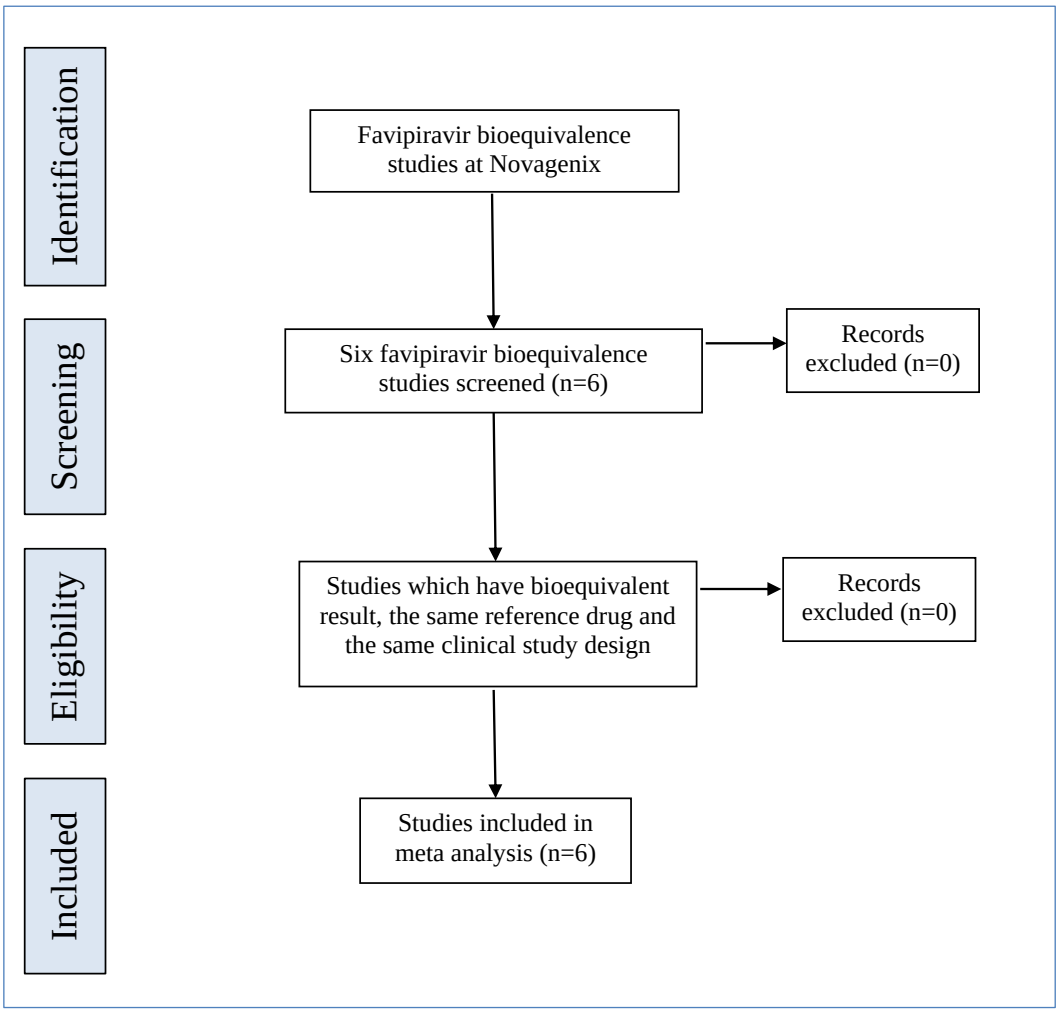

FIGURE 1: Flow diagram of the selection of favipiravir bioequivalence studies.

STATISTICAL ANALYSIS

For meta-analysis between test drugs, the method and the fixed effect model proposed by Chow and Shao was applied. Since the pharmacokinetic outcome measure is continuous data in bioequivalence studies, the ratio of log-transformed geometric means of the treatments and the 90% CI of the mean ratio of each parameter (C_{max} and $AUC_{0\text{-}tlast}$) were calculated for each pairwise combination of test drugs to investigate the interchangeability between them.

It was assumed that there was H independent bioequivalence studies. An additional subscript, h, was added to the responses y_{ijk} to indicate that y_{ijkh} came from h^{th} study.

Bioequivalence of two test drugs (h and h´) are assessed as below:

$\tilde{\delta}_h - \tilde{\delta}_{h'} = \bar{y}_{Th} - \bar{y}_{Th'}$,

where $\bar{y}_{Th} = (\bar{y}_{11h} + \bar{y}_{22h})/2$.

The method differs according to the sample size of sequences (n_{kh}). For small and equal sample sizes of sequences, the exact method shown below was implemented:

For $n_{kh} = n_{kh'}$, k= 1, 2, $c_h = c_{h'}$ where $c_h = \frac{1}{4}\left(\frac{1}{n_{1h}} + \frac{1}{n_{2h}}\right)$.

Define

$d_{i1hh'} = y_{i11h} - y_{i11h'}$, i=1,...,$n_{1h}$, (2)

$d_{i2hh'} = y_{i22h} - y_{i22h'}$, i=1,...,$n_{2h}$. (3)

$s^2_{khh'}$ is the sample variance of $d_{ikhh'}$, i=1,..., n_{kh}, k=1, 2 and

$$s^2_{hh'} = \frac{(n_{1h} - 1)s^2_{1hh'} + (n_{2h} - 1)s^2_{2hh'}}{n_{1h} + n_{2h} - 2}$$

Then an exact 90% CI for $\delta_{hh'}$ is

$$\tilde{\delta}_h - \tilde{\delta}_{h'} \pm t_{.05}(n_{1h} + n_{2h} - 2)\sqrt{2c_h s^2_{hh'}} \quad (4)$$

Since sample sizes in favipiravir bioequivalence studies were not equal and between 30 and 36 (unbalanced design), above formulas can still be used by changing n_{1h} and n_{2h} with $\min(n_{1h}, n_{1h'})$ and $\min(n_{2h}, n_{2h'})$, respectively.

Before meta-analysis, a test of homogeneity of the distribution of reference drug data in all studies was required. An H-1 degrees of freedom chi-squared test was applied.

The calculations for meta-analysis were performed using the Microsoft Excel 2010®.

RESULTS

The test statistics for homogeneity of the reference drugs among six studies calculated as $\chi^2_R = 1.966$ for C_{max} and $\chi^2_R = 2.538$ for $AUC_{0\text{-}tlast}$. Since χ^2_Rs are less than $\chi^2(0.05,5) = 11.070$, the reference drugs were found homogeneous at the 5% significance level and we combined the data for meta-analysis.

The 90% CI of the mean ratio for C_{max} and $AUC_{0\text{-}tlast}$ between pairwise combinations of six test drugs were calculated and listed in Table 1 and Table 2, and illustrated in Figure 2 and Figure 3, respectively.

TABLE 1: Confidence intervals and conclusion of the binary combinations of test drugs in the meta-analysis for C_{max}.

Combinations	Mean* of test h	Mean* of test h´	D*	Var (D)*	Ratio**	Lower limit of 90% CI**	Upper limit of 90% CI**	Bioequivalent Yes/No
Test 1xTest 2	8.535	8.652	-0.116	0.150	89.019	74.617	106.201	No
Test 1xTest 3	8.572	8.510	0.062	0.243	106.400	83.622	135.384	No
Test 1xTest 4	8.540	8.473	0.067	0.205	106.953	87.350	130.955	No
Test 1xTest 5	8.535	8.457	0.079	0.136	108.202	91.460	128.008	No
Test 1xTest 6	8.540	8.616	-0.076	0.077	92.708	81.865	104.987	**Yes**
Test 2xTest 3	8.653	8.510	0.143	0.214	115.394	92.044	144.667	No
Test 2xTest 4	8.652	8.481	0.171	0.157	118.611	98.212	143.247	No
Test 2xTest 5	8.652	8.457	0.195	0.149	121.549	101.934	144.937	No
Test 2xTest 6	8.637	8.621	0.016	0.105	101.638	87.893	117.533	**Yes**
Test 3xTest 4	8.510	8.471	0.038	0.098	103.892	89.191	121.016	**Yes**
Test 3xTest 5	8.510	8.475	0.034	0.065	103.490	91.350	117.242	**Yes**
Test 3xTest 6	8.510	8.611	-0.102	0.165	90.341	74.080	110.171	No
Test 4xTest 5	8.481	8.457	0.024	0.150	102.476	85.889	122.267	**Yes**
Test 4xTest 6	8.473	8.616	-0.143	0.171	86.682	72.046	104.290	No
Test 5xTest 6	8.457	8.612	-0.155	0.111	85.647	73.603	99.663	No

CI: Confidence interval; D: Difference; *Logarithmic scale; **Original scale.

TABLE 2: Confidence intervals and conclusion of the binary combinations of test drugs in the meta-analysis for $AUC_{0\text{-tlast}}$.

Combinations	Mean* of test h	Mean* of test h´	D*	Var (D)*	Ratio**	Lower limit of 90% CI**	Upper limit of 90% CI**	Bioequivalent Yes/No
Test 1xTest 2	9.143	9.307	-0.164	0.147	84.863	71.235	101.098	No
Test 1xTest 3	9.157	9.189	-0.032	0.111	96.821	82.291	113.917	**Yes**
Test 1xTest 4	9.144	9.280	-0.137	0.205	87.209	71.219	106.788	No
Test 1xTest 5	9.143	9.297	-0.154	0.172	85.701	70.933	103.543	No
Test 1xTest 6	9.144	9.241	-0.097	0.077	90.735	80.146	102.723	**Yes**
Test 2xTest 3	9.328	9.189	0.138	0.276	114.847	88.845	148.459	No
Test 2xTest 4	9.307	9.281	0.026	0.159	102.596	84.844	124.062	**Yes**
Test 2xTest 5	9.307	9.297	0.010	0.165	100.987	83.923	121.520	**Yes**
Test 2xTest 6	9.299	9.259	0.040	0.142	104.031	87.905	123.116	**Yes**
Test 3xTest 4	9.189	9.265	-0.075	0.182	92.733	75.315	114.181	No
Test 3xTest 5	9.189	9.310	-0.120	0.124	88.652	74.649	105.284	No
Test 3xTest 6	9.189	9.251	-0.062	0.142	94.005	78.209	112.991	No
Test 4xTest 5	9.281	9.297	-0.016	0.182	98.432	81.024	119.579	**Yes**
Test 4xTest 6	9.280	9.241	0.040	0.150	104.043	87.508	123.702	**Yes**
Test 5xTest 6	9.297	9.243	0.054	0.096	105.578	91.660	121.610	**Yes**

CI: Confidence interval; D: Difference; *Logarithmic scale; **Original scale.

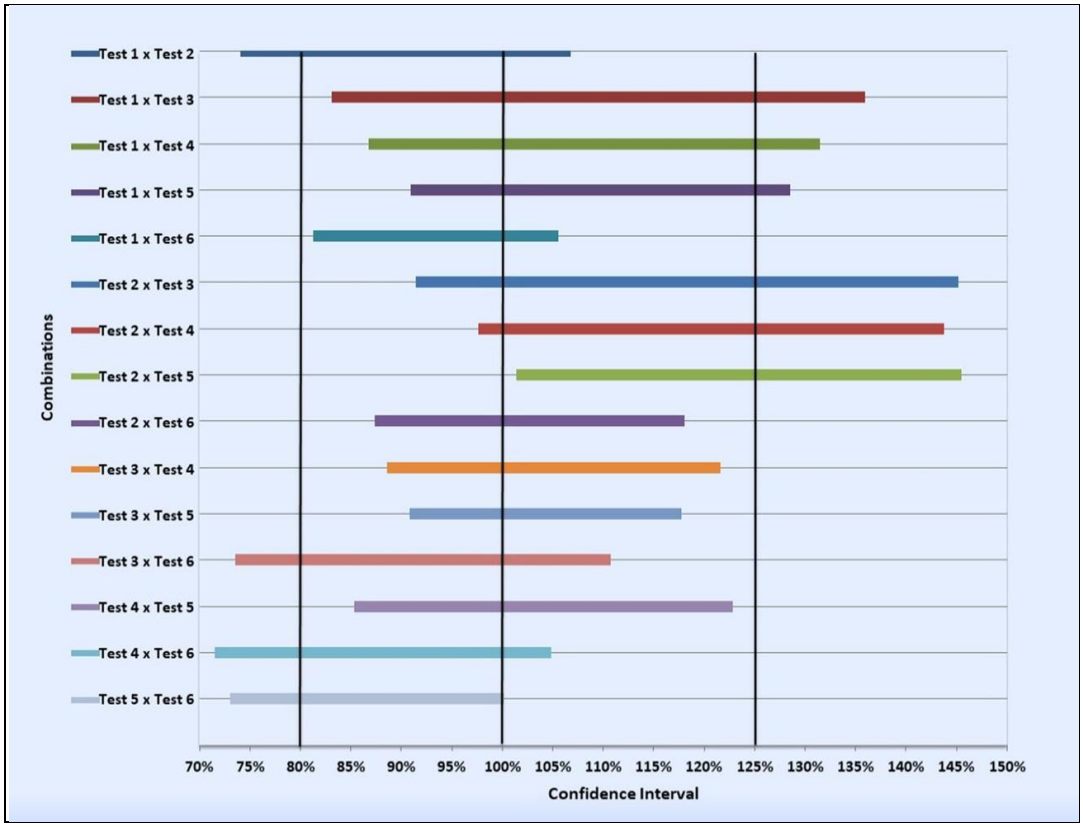

FIGURE 2: Confidence intervals of the binary combinations of test drugs in the meta-analysis for $C_{max.}$

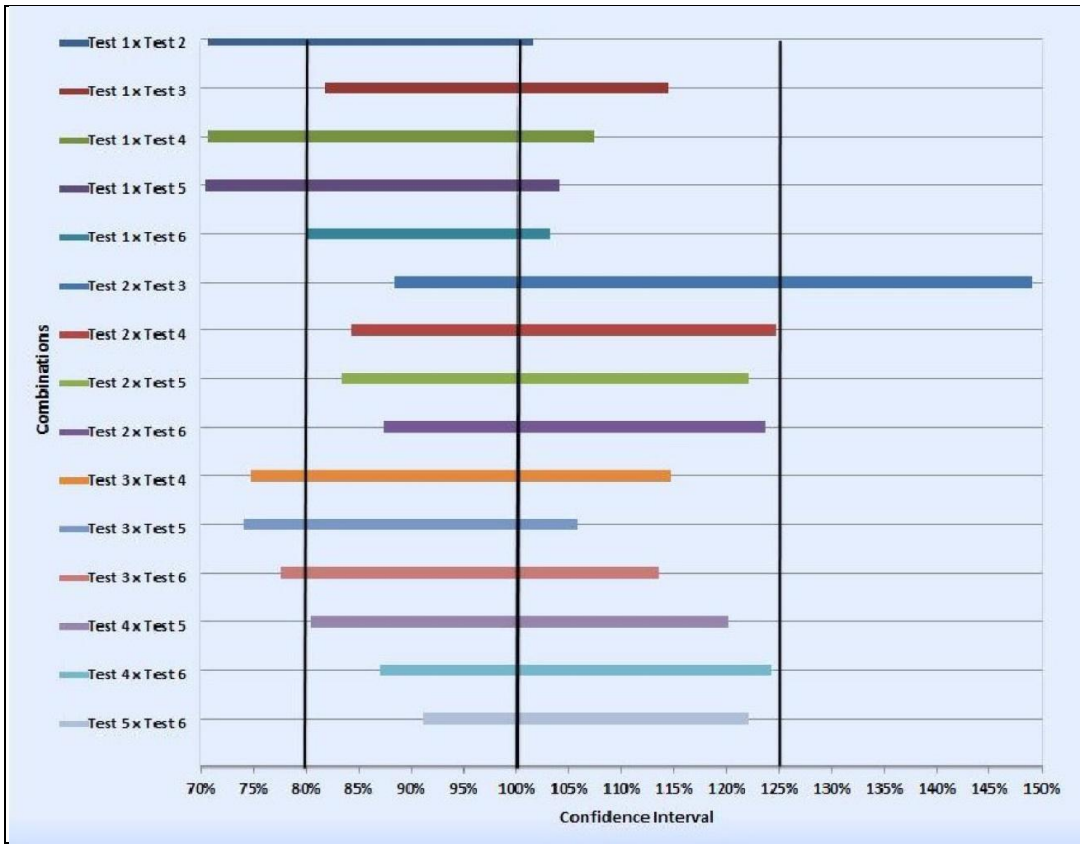

FIGURE 3: Confidence intervals of the binary combinations of test drugs in the meta-analysis for $AUC_{0\text{-tlast.}}$

Meta-analysis result of C_{max} showed that some of the combinations listed below were not within the 80.00% to 125.00% bioequivalence limits (Table 1 and Figure 2): T1xT2 (74.617% to 106.201%), T1xT3 (83.622% to 135.384%), T1xT4 (87.350% to 130.955%), T1xT5 (91.460% to 128.008%) and T2xT3 (92.044% to 144.667%), T2xT4 (98.212% to 143.247%), T2xT5 (101.934% to 144.937%), T3xT6 (74.080% to 110.171%), T4xT6 (72.046% to 104.290%) and T5xT6 (73.603% to 99.663%).

Meta-analysis result of $AUC_{0\text{-}tlast}$ showed that some of the combinations listed below were not within the 80.00% to 125.00% bioequivalence limits (Table 2 and Figure 3): T1xT2 (71.235% to 101.098%), T1xT4 (71.219% to 106.788%), T1xT5 (70.933% to 103.543%), T2xT3 (88.845% to 148.459%), T3xT4 (75.315% to 114.181%) , T3xT5 (74.649% to 105.284%) and T3xT6 (78.209% to 112.991%).

DISCUSSION

For C_{max}, 5 of the 15 binary combinations (33.33%) were found bioequivalent. T1 was only interchangeable with T6. T2 had the highest mean C_{max} value and the closest and only interchangeable drug to the T2 drug was found as T6 drug. T3, T4 and T5 drugs were found interchangeable between themselves.

For $AUC_{0\text{-}tlast}$, 8 of the 15 binary combinations (53.33%) were found bioequivalent. The mostly not interchangeable generic drug was T3 and only interchangeable with T1. T1 and T3 have the lowest mean value for $AUC_{0\text{-}tlast}$. T5 is interchangeable with T2, T4 and T6. T2 has the highest mean value and T1 has the lowest mean value for $AUC_{0\text{-}tlast}$.

Since intrasubject variability of favipiravir active ingredient for C_{max} is higher than $AUC_{0\text{-}tlast}$, it is more difficult to achieve interchangeability in generic drugs for C_{max}. Therefore, there is a different bioequivalence rate of 33% and 53% for C_{max} and $AUC_{0\text{-}tlast}$, respectively.[12]

The 90% CI for both C_{max} and $AUC_{0\text{-}tlast}$ should be within the acceptance limits of 80.00%-125.00%. 3 of the 15 binary combinations which provided this condition were T1xT6, T2xT6 and T4xT5.

Non-interchangeability is particularly important for a narrow therapeutic index drug for which small differences in dose or blood concentration may lead to significant changes in efficacy and safety (serious therapeutic failures/adverse reactions).[13] Despite favipiravir being an active ingredient with wide therapeutic window, the results showed that replacing one favipiravir generic drug with another may produce dissimilar therapeutic responses.

CONCLUSION

Generic drugs are the cornerstones of pharmaceutical market. Several novel generic formulations of favipiravir, an antiviral compound with a wide range of antiviral activity against various influenza virus strains including the new variant COVID-19 were developed.

We combined the independent favipiravir bioequivalence studies conducted at the Novagenix Bioanalytical R&D Center based on the criteria of having the same reference drug with different serial numbers, the same experimental design and meeting the acceptance criteria of bioequivalence. When assessing the interchangeability between generic drugs, some of the combinations may not match the acceptance criteria. Therefore, when a patient switches between favipiravir generic drugs, the pharmacokinetic behaviour of the drug product and thus its efficacy may change.

Further research is required to investigate the clinical significance of these findings for favipiravir generics in terms of efficacy and safety.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Emel Doğan Kurtoğlu, Onursal Sağlam;* ***Design:*** *Emel Doğan Kurtoğlu, Onursal Sağlam;* ***Control/Supervision:*** *Onursal Sağlam;* ***Data Collection and/or Processing:*** *Emel Doğan Kurtoğlu;* ***Analysis and/or Interpretation:*** *Emel Doğan Kurtoğlu, Onursal Sağlam;* ***Literature Review:*** *Emel Doğan Kurtoğlu;* ***Writing the Article:*** *Emel Doğan Kurtoğlu;* ***Critical Review:*** *Onursal Sağlam.*

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