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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Prezista

darunavir

Procedure no: EMEA/H/C/000707/P46/072.1

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 15 May 2018, the MAH submitted a completed paediatric study for Prezista, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study TMC114-TiDP29-C232: 'Continued access to darunavir/ritonavir (DRV/rtv) in HIV-1 infected children and adolescents aged 3 years and above' (EUDRACT: 2009-017013-29) is a standalone study.

This study is not part of a Paediatric Investigation Plan.

2.2. Information on the pharmaceutical formulation used in the study

Darunavir:

- Formulations F029, F050, F030, and F032: oral tablet containing DRV ethanolate eq. 75 mg, 150 mg, 400 mg, and 600 mg, respectively.
- Formulation F052: oral suspension composed of DRV ethanolate eq. 100 mg per mL.

Commercial ritonavir (Norvir®) was formulated as a capsule or tablet, depending on availability, containing 100 mg rtv, as a sachet of 100 mg rtv powder for oral suspension (at a rtv concentration of 10 mg/mL), or as a liquid solution containing 80 mg/mL rtv.

The optimized background regimen (OBR) was composed according to the local standard of care and based on experience with previous therapies.

2.3. Clinical aspects

2.3.1. Introduction

Darunavir (formerly known as TMC114) is an HIV PI with potent in vitro activity against wild-type HIV-1, and is also active against a large panel of HIV-1 strains resistant to currently licensed HIV PIs. Darunavir in combination with the pharmacokinetic enhancer rtv (DRV/rtv), and with other ARVs, is indicated for the treatment of HIV infection in adults and in paediatric subjects of 3 years and above.

The MAH submitted a final report for study TMC114-TiDP29-C232: 'Continued access to darunavir/ritonavir (DRV/rtv) in HIV-1 infected children and adolescents aged 3 years and above'.

The aim of this study was to provide continued access to darunavir (DRV) for paediatric subjects who had completed treatment with DRV in one of the following clinical Studies TMC114-C212, TMC114-TiDP29-C228, or TMC114-TiDP29-C230 sponsored by Tibotec Pharmaceuticals (now Janssen Sciences Ireland UC) and who continued to benefit from treatment with DRV:

- TMC114-C212, in treatment-experienced HIV-1 infected children/adolescents aged from 6 to <18 years and weighing ≥20 kg;

- TMC114-TiDP29-C228 in treatment-experienced HIV-1 infected children aged from 3 to <6 years and weighing between 10 kg and <20 kg;
- TMC114-TiDP29-C230 in treatment-naïve HIV-1 infected adolescents aged from 12 to <18 years and weighing ≥40 kg.

At the start of the study, DRV was available as the marketed tablet formulation in different strengths. A suspension of DRV (100 mg/mL) was developed to be used in children and was used in the current study as well, with the possibility of choice between the tablet formulation and the suspension by the subjects. The relative bioavailability for DRV after administration of the 300 mg tablet and the oral suspension in the presence of rtv was shown to be similar under fasted and fed conditions.

2.3.2. Clinical study

Study TMC114-TiDP29-C232: Continued access to darunavir/ritonavir (DRV/rtv) in HIV-1 infected children and adolescents aged 3 years and above.

Description

This was a continued-access study for paediatric subjects who had completed treatment with DRV in the clinical studies TMC114-C212, TMC114-TiDP29-C228, or TMC114-TiDP29-C230 sponsored by Tibotec Pharmaceuticals (now Janssen Sciences Ireland UC), and who continued to benefit from the use of DRV.

Methods

Objective(s)

The primary objective of this study was to continue the provision of DRV for paediatric subjects who had completed treatment with DRV in the clinical Studies TMC114-C212, TMC114-TiDP29-C228, or TMC114-TiDP29-C230 sponsored by Tibotec Pharmaceuticals (now Janssen Sciences Ireland UC), and who continued to benefit from using it, in countries where DRV was not commercially available for the paediatric subject, was not reimbursed, or could not be accessed through another source (eg, access program, governmental program).

In addition, information on the safety of DRV/rtv in combination with other ARVs was assessed.

Study design

This was a continued-access, open-label, single-arm study.

Assessment visits were desirable every 3 months or according to local generally accepted standard of care. The interval between 2 consecutive safety assessments was not to exceed 6 months.

Treatment continued until 1 of the following criteria was met (whichever occurred first): Virologic failure; Treatment-limiting toxicity; Loss to follow-up; Withdrawal of consent/assent by the subject or withdrawal of consent by the parent(s)/legal representative(s); Pregnancy; Termination of the study by the sponsor; or DRV became commercially available for the paediatric subject, was reimbursed, or could be accessed through another source (eg, access program, government program) in the region the subject was living in.

Study population /Sample size

Subjects enrolled in this study were male or female subjects, aged 3 years and above, who had completed the TMC114-C212, TMC114-TiDP29-C228, or TMC114-TiDP29-C230 study, and in the opinion of the investigator continued to receive benefit from using DRV.

Treatments

Subjects had to either continue on the DRV/rtv dose they received in the original study or on an adjusted dose if necessary due to a change in body weight.

- HIV-1 infected subjects who were participating in the TMC114-TiDP29-C230 study continued on DRV/rtv 800/100 mg qd (ie, 2 tablets of 400 mg DRV and 100 mg rtv qd).
- HIV-1 infected subjects who were participating in the TMC114-C212 or TMC114-TiDP29-C228 study continued on the bid dosing regimen.

Outcomes/endpoints

During the visits, weight, adverse events considered at least possibly related to DRV, adverse events leading to discontinuation or treatment interruption, serious adverse events and pregnancies were recorded. In addition it was considered desirable to perform the following efficacy assessments locally every 3 months or according to the local generally accepted standard of care:

- Immunology; and

- Plasma viral load

Rapporteur's comment:

No information regarding the above mentioned preferred efficacy assessments could be located in the CSR. The MAH is requested to provide data on immunologic assessments and plasma viral load levels. See also the comment in Efficacy results.

Statistical Methods

The study was not set up to show a specific statistical hypothesis.

Demographic characteristics of the subjects included in this study were tabulated, all safety and tolerability data of DRV/rtv in combination with other ARVs, in terms of AEs and pregnancy tests, for the treatment and follow-up phase, were included in listings.

Results

Recruitment/ Number analysed

On 13 October 2010, the first subject in the study signed the informed consent. The last visit of the last subject in this study was on 23 November 2017.

In total, 46 subjects rolled over to this study and received at least one dose of DRV:

- 16 treatment-experienced subjects rolled over from Study TMC114-C212 and received DRV/rtv bid, further referred to as the TE DRV/rtv bid (C212) subgroup;
- 20 treatment-experienced subjects rolled over from Study TMC114-TiDP29-C228 and received DRV/rtv bid, further referred to as the TE DRV/rtv bid (C228) subgroup; and

- 10 treatment-naïve subjects rolled over from Study TMC114-TiDP29-C230 and received DRV/rtv qd, further referred to as the TN DRV/rtv qd (C230) subgroup.

These 46 subjects were included in the ITT population, defined as the set of all subjects who had taken at least one dose of DRV, regardless of their compliance with the CTP and adherence to the dosing regimen.

The most common reason for study termination was a switch to commercially available medication (in 12 [26.1%] subjects). Nine (19.6%) subjects rolled over to another study. The other 25 (54.3%) subjects discontinued the study for a variety of reasons (Table 2).

Table 2: Study Termination; Intent-to-treat

	Darunavir			
	DRV/rtv b.i.d. (C212) (N=16)	DRV/rtv b.i.d. (C228) (N=20)	DRV/rtv q.d. (C230) (N=10)	All Subjects (N=46)
Analysis set: Intent-to-treat, N	16	20	10	46
Adverse event/HIV related[a]	1 (6.3%)	0	1 (10.0%)	2 (4.3%)
Subject lost to follow-up	1 (6.3%)	1 (5.0%)	0	2 (4.3%)
Subject/legal representative withdrew consent/assent	0	3 (15.0%)	0	3 (6.5%)
Subject non-compliant	1 (6.3%)	2 (10.0%)	2 (20.0%)	5 (10.9%)
Subject ineligible to continue the trial	1 (6.3%)	1 (5.0%)	2 (20.0%)	4 (8.7%)
Investigator no longer thinks the subject benefits from DRV treatment	1 (6.3%)	0	0	1 (2.2%)
Switch to commercially available medication	7 (43.8%)	3 (15.0%)	2 (20.0%)	12 (26.1%)
Other[b]	4 (25.0%)	10 (50.0%)	3 (30.0%)	17 (37.0%)

N: number of subjects with data
[a] Both AEs leading to discontinuation were pregnancies
[b] Reasons for trial termination under the category 'Other' were:
End of TMC114-C232 trial (3)
Participant relocating to limpopo (1)
Site closure (1)
Subject rolled over to another study (9)
The patient reached the age of majority (2)
The subject was moved from the study to standard of care following the options provided by the sponsor (1)

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Baseline data

At baseline, the majority of subjects in the TE DRV/rtv bid (C212) subgroup (15 [93.8%] subjects) and in the TN DRV/rtv qd (C230) subgroup (10 [100%] subjects) were in the age category of 12 to <18 years. The median (min; max) age at baseline of the subjects in these subgroups was 15.0 (11; 17) years and 14.5 (13; 17) years, respectively. In the TE DRV/rtv bid (C228) subgroup, the majority of subjects (15 [75.0%] subjects) was in the age category of 3 to <6 years at baseline. The median (min; max) age was 5.0 (4; 6) years.

The median (min; max) weight at baseline of the subjects in the TE DRV/rtv bid (C212) and the TN DRV/rtv qd (C230) subgroup was 46.85 (28.6; 95.3) kg and 52.50 (43.5; 72.0) kg, respectively. The median weight (min; max) at baseline of the subjects in the TE DRV/rtv bid (C228) subgroup was 17.00 (13.2; 21.4) kg.

Most subjects were enrolled in South Africa (14 [30.4%] subjects) and South America, ie, in Argentina (13 [28.3%] subjects) and Brazil (8 [17.4%] subjects). Subjects in the TN DRV/rtv qd (C230) subgroup, were enrolled in European countries (Table 3).

Table 3: Demographic Data; Intent-to-treat

	Darunavir			
	DRV/rtv b.i.d. (C212) (N=16)	DRV/rtv b.i.d. (C228) (N=20)	DRV/rtv q.d. (C230) (N=10)	All Subjects (N=46)
Sex, n (%)				
N	16	20	10	46
Female	6 (37.5%)	10 (50.0%)	6 (60.0%)	22 (47.8%)
Male	10 (62.5%)	10 (50.0%)	4 (40.0%)	24 (52.2%)
Age at baseline (years)				
N	16	20	10	46
Mean (SD)	14.6 (1.71)	4.9 (0.79)	14.6 (1.51)	10.4 (5.04)
Median (Min; Max)	15.0 (11; 17)	5.0 (4; 6)	14.5 (13; 17)	13.0 (4; 17)
Age category at baseline (years), n (%)				
N	16	20	10	46
3 to <6 years	0	15 (75.0%)	0	15 (32.6%)
6 to <12 years	1 (6.3%)	5 (25.0%)	0	6 (13.0%)
12 to <18 years	15 (93.8%)	0	10 (100.0%)	25 (54.3%)
Country/ Study site identifier, n (%)				
Argentina	9 (56.3%)	4 (20.0%)	0	13 (28.3%)
AR00002	4 (25.0%)	0	0	4 (8.7%)
AR00004	0	2 (10.0%)	0	2 (4.3%)
AR00038	4 (25.0%)	1 (5.0%)	0	5 (10.9%)
AR00052	0	1 (5.0%)	0	1 (2.2%)
AR00066	1 (6.3%)	0	0	1 (2.2%)
Brazil	3 (18.8%)	5 (25.0%)	0	8 (17.4%)
BR00026	2 (12.5%)	1 (5.0%)	0	3 (6.5%)
BR00049	1 (6.3%)	0	0	1 (2.2%)
BR00095	0	2 (10.0%)	0	2 (4.3%)
BR00096	0	2 (10.0%)	0	2 (4.3%)
France	0	0	1 (10.0%)	1 (2.2%)
FR00052	0	0	1 (10.0%)	1 (2.2%)
India	0	1 (5.0%)	0	1 (2.2%)
IN00014	0	1 (5.0%)	0	1 (2.2%)
Italy	0	0	1 (10.0%)	1 (2.2%)
IT00041	0	0	1 (10.0%)	1 (2.2%)
South Africa	4 (25.0%)	10 (50.0%)	0	14 (30.4%)
ZA00078	3 (18.8%)	4 (20.0%)	0	7 (15.2%)
ZA00164	0	5 (25.0%)	0	5 (10.9%)
ZA00167	1 (6.3%)	1 (5.0%)	0	2 (4.3%)
Spain	0	0	1 (10.0%)	1 (2.2%)
ES00049	0	0	1 (10.0%)	1 (2.2%)
Ukraine	0	0	6 (60.0%)	6 (13.0%)
UA00019	0	0	6 (60.0%)	6 (13.0%)
United Kingdom	0	0	1 (10.0%)	1 (2.2%)
GB00092	0	0	1 (10.0%)	1 (2.2%)
Weight at baseline (kg)				
N	16	20	10	46
Mean (SD)	49.94 (14.771)	16.92 (2.060)	54.32 (9.427)	36.54 (19.937)
Median (Min; Max)	46.85 (28.6; 95.3)	17.00 (13.2; 21.4)	52.50 (43.5; 72.0)	40.25 (13.2; 95.3)

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Efficacy results

N/A

Rapporteur's comment:

It is common practice to measure HIV viral load in HIV-1 infected patients at regular basis, and hence efficacy data should be available. The MAH is requested to provide the available data for each of the 46 subjects included in the study.

Safety results

The overall median (min; max) duration of DRV/rtv intake in this roll-over study was 4.20 (0.1; 7.1) years. The median (min; max) duration of study drug intake in the TE DRV/rtv bid (C212) and the TN DRV/rtv qd (C230) subgroup was 2.41 (0.2; 7.0) years and 3.62 (1.7; 7.0) years, respectively.

The incidence of AEs, overall or by attributes (seriousness, severity grading, discontinuation, and relatedness) in the treatment phase, is summarized in Table 7. Overall, 15/46 (32.6%) subjects experienced at least 1 AE. No deaths occurred during the treatment phase.

Table 7: Adverse Events Incidence in the Treatment Phase – Summary Table; Intent-to-treat[a]

	Darunavir			
	DRV/rtv b.i.d. (C212) (N=16)	DRV/rtv b.i.d. (C228) (N=20)	DRV/rtv q.d. (C230) (N=10)	All Subjects (N=46)
Analysis set: Intent-to-treat, N	16	20	10	46
with at least one AE	6 (37.5%)	5 (25.0%)	4 (40.0%)	15 (32.6%)
with at least one SAE	5 (31.3%)	4 (20.0%)	3 (30.0%)	12 (26.1%)
with at least one fatal AE	0	0	0	0
with at least one worst grade 1 or 2 AE[b]	1 (6.3%)	2 (10.0%)	1 (10.0%)	4 (8.7%)
with at least one worst grade 3 or 4 AE	4 (25.0%)	3 (15.0%)	3 (30.0%)	10 (21.7%)
with at least one AE for which study drug was permanently stopped	1 (6.3%)	0	1 (10.0%)	2 (4.3%)
with at least one AE which is at least possibly related to DRV	0	0	1 (10.0%)	1 (2.2%)
with at least one SAE which is at least possibly related to DRV	0	0	0	0
with at least one worst grade 3 or 4 AE at least possibly related to DRV	0	0	0	0
with at least one HIV-related AE	1 (6.3%)	2 (10.0%)	0	3 (6.5%)

[a] Note that in this roll-over study, only AEs leading to discontinuation or treatment interruption, AEs considered at least possibly related to treatment with DRV, SAEs, and pregnancies were to be reported. All other AEs only had to be collected if required by local regulations.

[b] For pregnancies, no toxicity grading was reported.

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Adverse events were most frequently reported in the SOC Infections and infestations, overall (in 7/46 [15.2%] subjects) and in the TE DRV/rtv bid (C212) (in 3 [18.8%] subjects) and TE DRV/rtv bid (C228) (in 3 [15.0%] subjects) subgroup. In the TN DRV/rtv qd (C230) subgroup, AEs in the SOC Infections and infestations were reported for only 1 (10.0%) subject. Adverse events in all other SOCs were reported in at most 1 subject in either subgroup.

Per PT, pneumonia was the most frequently reported AE, overall (in 3/46 [6.5%] subjects) and in the TE DRV/rtv bid (C212) subgroup (in 2 [12.5%] subjects). Pneumonia was reported in 1 (5.0%) and 0 subjects in the TE DRV/rtv bid (C228) and TN DRV/rtv qd (C230) subgroup, respectively. All other AEs by PT were reported in at most 1 subject in either subgroup.

Overall, in 10/46 (21.7%) subjects, grade 3 or 4 AEs were reported. The most common grade 3 or 4 AE was pneumonia; 2 (12.5%) subjects in the TE DRV/rtv bid (C212) subgroup had a grade 3

pneumonia and 1 (5.0%) subject in the TE DRV/rtv bid (C228) subgroup had a grade 4 pneumonia. Pneumonia was the only grade 3 or 4 AE reported in more than 1 subject in either subgroup.

There was 1 event considered probably related to DRV/rtv by the investigator; ie, grade 1 lipoatrophy reported in 1 (10.0%) subject in the TN DRV/rtv qd (C230) subgroup. All other AEs were considered not or doubtfully related to DRV/rtv.

Serious Adverse Events

Overall, 12/46 (26.1%) subjects experienced at least one SAE during the treatment phase (Table 7). The SAE pneumonia was reported in 3/46 (6.5%) subjects and asthma in 2/46 (4.3%) subjects overall. All other SAEs were reported in at most 1 subject overall. The SAE pneumonia was reported in 2 (12.5%) and 1 (5.0%) subjects in the TE DRV/rtv bid (C212) and TE DRV/rtv bid (C228) subgroup, respectively. All other SAEs were reported in at most 1 subject in either subgroup. For 1 (6.3%) subject in the TE DRV/rtv bid (C212) subgroup, grade 3 SAEs of intentional overdose and suicide attempt were reported. Study treatment and background therapy were interrupted temporarily. Both SAEs resolved.

None of the SAEs were considered to be related to DRV/rtv by the investigator. None of the subjects had to discontinue the study due to an SAE

HIV-related Adverse Events

Overall, 3/46 (6.5%) subjects experienced an HIV-related AE (Attachment 1). In 1 (6.3%) subject in the TE DRV/rtv bid (C212) subgroup, a grade 3 SAE pneumonia was considered to be HIV-related. In the TE DRV/rtv bid (C228) subgroup, a grade 2 SAE tuberculosis and a grade 2 AE lipoatrophy (in 1 [5.0%] subject each) were considered HIV-related.

None of these events were considered to be related to DRV/rtv by the investigator. None of the subjects had to discontinue the study due to an HIV-related AE.

Pregnancies

Three of the 46 (6.5%) subjects overall had a pregnancy test positive for human chorionic gonadotropin. As per CTP, all 3 subjects discontinued treatment with study medications as a result of pregnancy and terminated the study.

For 1 (6.3%) subject in the TE DRV/rtv bid (C212) subgroup and 1 (10.0%) subject in the TN DRV/rtv qd (C230) subgroup, pregnancy was reported during the treatment period and led to a permanent stop of the study. For the subject in the TE DRV/rtv bid (C212) subgroup, the investigator reported having no access to the information related to the delivery. The subject in the TN DRV/rtv qd (C230) subgroup delivered a male baby at 35 weeks gestation. No abnormalities were noted at birth. One (10.0%) subject in the TN DRV/rtv qd (C230) subgroup was reported to be ineligible to continue in the study due to pregnancy, and the grade 3 pregnancy-related SAEs blighted ovum and abortion spontaneous were reported during the follow-up period.

Rapporteur's comment:

The data from this study do not reveal any new safety findings.

2.3.3. Discussion on clinical aspects

The aim of this study was to provide continued access to DRV for paediatric subjects who had completed treatment with DRV in the clinical Studies TMC114-C212, TMC114-TiDP29-C228, or TMC114-TiDP29-C230, and who continued to benefit from treatment with DRV.

The safety analyses of this study demonstrated that DRV/rtv was generally safe and well tolerated overall and in all subgroups. No new safety findings compared to the known safety profile of DRV in paediatric and adult subjects were identified.

It is however remarkable that the MAH did not provide any efficacy results, although it was described in the clinical study protocol that viral load and immunology assessments should preferably be performed at each visit (usually every three months). It is considered common practice to measure HIV viral load at regular basis in HIV-1 infected patients, and hence some data should be available. The MAH is requested to provide the available data for each of the 46 subjects included in the study.

The MAH considers no update of the SmPC is warranted in relation to the outcomes of this study. There was an outstanding request to provide efficacy data, but the MAH explained that no data was collected (see section 4 and 5 below). Based on the available data, it is agreed that no update of the SmPC is warranted.

3. Rapporteur's overall conclusion and recommendation

The data submitted do not influence the benefit-risk balance for Prezista (darunavir) which remains unchanged. The MAH was asked to provide additional efficacy information, but explained that no such data was collected. As such, the issue is not further pursued. No further action is required based on the submitted information.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

The MAH is requested to provide efficacy data (i.e. viral load data and immunological data, if available), for each of the 46 subjects included in the study.

5. MAH responses to Request for supplementary information

1. The MAH is requested to provide efficacy data (i.e. viral load data and immunological data, if available), for each of the 46 subjects included in the study.

Response MAH

Study TMC114-TiDP29-C232 was a rollover study for pediatric subjects who have completed treatment with darunavir (DRV) in the clinical studies TMC114-C212, TMC114-TiDP29-C228, or TMC114-TiDP29-C230.

The aim of study TMC114-TiDP29-C232 was to offer human immunodeficiency virus type 1- infected children and adolescents aged 3 years and above, who continued to benefit from the use of DRV treatment, the opportunity to get access to DRV while the product was not yet available through the usual channels in the regions the subjects are living in. In addition, information on the safety of DRV/ritonavir in combination with other antiretrovirals was assessed. As indicated in the short critical expert overview that was included in the submission, no efficacy data are available for the subjects included in the study. The study protocol also did not foresee efficacy data to be collected nor a formal efficacy analysis to be performed.

The TMC114-TiDP29-C232 study started on 13 October 2010 and enrolled 46 subjects in 9 countries (Argentina, Brazil, France, India, Italy, South Africa, Spain, United Kingdom, and Ukraine). The study was set-up in analogy with the set-up of Pre-Approval Access and Post-Trial Access programs in terms of principles for drug supply and safety follow-up. In these programs, follow-up on efficacy outcome was done exclusively by the investigator as per local regulations and no data on efficacy outcomes were collected by the sponsor.

In summary, the protocol of study TMC114-TiDP29-C232 foresaw for the efficacy outcomes (viral load and/or CD4 assessments) that:

- assessments were to be done locally and according to local practices. Hence, no central laboratory was assigned and data of these assessments were not collected centrally.
- the purpose was to allow sites to follow their local practices and the investigator had to judge whether the subject continued to benefit from the drug or not.
- given the need to stick as closely as possible to the local practices, there was no standardization of the measurements (with regards to methods, timing, repeated testing rules, adherence, etc...) which means that no firm conclusions on the efficacy profile of the drug could be drawn. Therefore, it was considered not relevant to collect these data in the Case Report Form.

This study set-up was considered an appropriate way to guarantee continuity of treatment for subjects having participated to the Applicant's studies and to collect any relevant safety data that emerge from such use and may contribute to the understanding of the safety profile of PREZISTA in children.

Assessment Response

The MAH explained that no efficacy data have been collected by the sponsor. As the main aim of the study was to provide HIV-1 infected children with DRV while the product was not yet available commercially, this is accepted. The MAH is however requested to collect efficacy data in future continued access studies (for any product), as this could provide valuable longer-term information.

Conclusion
Issue not further pursued.