2. SYNOPSIS

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

Title of Study: A randomized, double-blind, multi-centre, Placebo controlled phase II clinical study to evaluate the efficacy, tolerance and safety of an aqueous gel containing 2% (w/w) of Cidofovir, directly applied on the cervix exhibiting high grade intraepithelial lesion(s) (CIN 2 and 3)

Investigator: The Principal Investigator was [redacted] from the [redacted] in Brussels (Belgium).

Study Center(s): 9 centers in Belgium were involved in this study.

Publications (reference): Not published at the date of the report.

Studied Period: March 2011 – February 2013 **Date of First Patient Enrolled:** 14 March 2011 **Date of Last Patient Completed:** 26 February 2013	**Phase of Development:** Phase II

Objectives:

Primary Objectives:

- To evaluate the efficacy of 2% (w/w) Cidofovir aqueous gel, directly applied on cervix exhibiting high grade squamous intraepithelial neoplasia (CIN 2 and 3), in the aim to avoid conization (standard treatment for CIN 2+ lesions).
- To evaluate the safety and the local tolerance of this treatment.

Secondary Objectives:

- To evaluate the HPV viral load and genotype evolution.
- To evaluate colposcopical changes during and after treatment.

Exploratory Objectives:

There were no exploratory objectives.

Methodology: This was a phase-II, randomized, prospective, Placebo controlled, efficacy and safety study of an aqueous gel containing 2% (w/w) Cidofovir, administered directly on the cervix exhibiting high grade squamous or glandular intraepithelial lesions (CIN 2 and 3). One hundred and forty five eligible patients were to receive 3 applications of either Placebo or Cidofovir gel on the endo- and exocervix for 10 hours on Days 0, 7 and 14. The study was carried out in a double blinded manner in a 1:2 ratio at each site (1 Placebo for 2 Cidofovir). Blood samples for clinical biology (creatinine, differential leukocyte count and C reactive protein [CRP]) were collected prior to treatment and 1 week after the last treatment. Biopsies and cervical smears were collected at screening and follow-up visits. Gynecological examination and colposcopy were done at screening visit and each visit before and after treatment application. Follow-up visits occurred at Visit 4 (Week 3) for assessment of tolerance and safety; at Visit 5 (Week 12) for assessment of efficacy and safety; at Visit 6 (Week 14) for assessment of efficacy with results obtained at Week 12; at Visit 7 (Week 28) for assessment of recurrence and safety in case of success at Week 12; and at Visit 8 (Week 30) for efficacy assessment with results obtained at

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

Week 28.

Number of Patients (Planned and Analyzed):
194 screened and 145 randomized patients (52 in the Placebo group and 93 in the Cidofovir group)

Diagnosis and Main Criteria for Inclusion/Exclusion:
Patients who met all of the following criteria were eligible for the study:

- Women aged between 18 and 50 years old;
- Informed consent signed;
- Cervical lesion classified CIN 2 or 3, on a biopsy made during the 60 preceding days;
- No sexual activity, or proved sterility, or use of effective mechanical, hormonal or intrauterine contraception (except vaginal ring Nuvaring®, diaphragm and spermicide).

Patients were excluded from the study for any of the following reasons:

- Invasive or microinvasive cervical neoplasia;
- Pregnancy or breast feeding;
- Subtotal hysterectomy;
- Current renal impairment;
- Current immune disorder including serology HIV+;
- Current systemic use of drugs interfering with renal function (intravenous contrast media, aminoglycosides, glycopeptides);
- Current systemic treatment for any cancer;
- Current systemic use of treatment interfering with immunity, except vaccines;
- Current systemic use of anti-viral treatment;
- Current vaginal application of drugs or cosmetics;
- Previous topical treatment by Cidofovir on cervix;
- Local or general condition incompatible with the experimental treatment in the opinion of the Principal Investigator;
- Current or recent participation to another experimental study during the last 3 months before the screening visit.

Test Product, Dose, Mode of Administration:
The 2% non-sterile Cidofovir gel was packaged in individual labeled aluminum tubes. The Investigator transferred 3 g of gel in a cervical cap. The cap containing the gel was placed by the Investigator on the exocervix, pushed in the endocervix if judged necessary by the Investigator and kept in place for 10 hours. After this application time, the patients removed the cap themselves by pulling the nylon thread.
Batch numbers:

- CT-11B05: Treatment 001 to Treatment 072
- 1190 0014: Treatment 073 to Treatment 090

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

- CT-11F06: Treatment 091 to Treatment 180
- CT-12B10: Treatment 181 to Treatment 252

Duration of Treatment: 3 weeks

Reference Therapy, Dose, Mode of Administration, and Batch Number(s):
The comparator was a non-sterile Placebo gel. The dose administered at each application was 3 g and followed the same process of application as for Cidofovir gel.
Batch numbers:

- CT-11B05: Treatment 001 to Treatment 072
- 1190 0014: Treatment 073 to Treatment 090
- CT-11F06: Treatment 091 to Treatment 180
- CT-12B10: Treatment 181 to Treatment 252

Criteria for Evaluation:
The oncogenic HPV such as types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 are identified as high-risk HPVs (HPVhr).
CIN lesions are classified in three grades: (1) mild dysplasia, (2) moderate dysplasia and (3) severe dysplasia and carcinoma *in situ*.
Cellular changes associated with HPVhr infection are commonly seen in CIN and abnormal cytological results include:

- Atypical squamous cells (ASC)
  - ASC of undetermined significance (ASC-US)
  - ASC – cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Atypical glandular cells (AGC)
  - AGC not otherwise specified (AGC-NOS)
  - Atypical endocervical cells (AGC-ecc)
  - AGC – favor neoplastic process (AGC – favor neoplastic)
- Adenocarcinoma *in situ* (AIS).

LSIL generally corresponds to CIN 1, while HSIL generally corresponds to CIN 2 and 3, also referred as CIN of grade minimum 2 (CIN 2+).
Efficacy:
Primary endpoints:
The primary endpoint of efficacy was

- The mean change of histological and cytological parameters in each treatment group (Cidofovir vs Placebo) and the comparison between them.

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

At Visit 5 (Week 12), the success, partial success, and failure rates in term of histological and cytological signs of disappearance of the CIN 2+ lesion were evaluated in each group. The decision criteria to determine success, partial success, and failure were defined as follows:

- Failure was defined as the persistence at Week 12 (or at any time between Visit 4 and 5 (Week 3 and 12)) of histological or cytological signs of HSIL or AIS, or ASC-H with HPVhr, or of AGC-favor neoplastic with HPVhr, or invasive lesion.
- Partial success was defined as the persistence at Week 12 of histological signs of LSIL–CIN 1, or of ASC-US with HPVhr, or AGC-eec with HPVhr, or AGC-NOS with HPVhr.
- Complete success was defined as the histological and cytological disappearance of CIN at Week 12; were considered as normal: ASC-US, LSIL, or ASC-H without HPVhr, AGC-eec, AGC-favor neoplastic and AGC-NOS without HPVhr.

At Visit 7 (Week 28), the recurrence rate of CIN 1 and CIN 2+ was measured in the population of success at Visit 5 (Week 12) (population who continued in the study). The recurrence of new CIN 2+ lesions, the regression from CIN 1 to normal, and the progression from normal to CIN 1 was calculated and compared with this population (partial and complete success at Week 12). The efficacy assessment at Visit 7 (Week 28) was done according to the same criteria used at Visit 5 (Week 12).

In case of inconclusive or missing results at Visits 5 or 7 (Weeks 12 or 28), results of any supplementary visit performed were to be considered in a sensitivity analysis. Patients with inconclusive (missing or non-contributive) results at study end (Visit 8, Week 30 ± 2 weeks) were to be advised to undergo diagnostic conization. If conization was performed within the 60 days after follow-up Visit 7, histological results from this biopsy (presence or absence of CIN 2+).were considered as the final study outcome.

For each treatment group at Visit 5 (Week 12), association between success and age (estimated by [year at screening] – [year of birth]), tobacco use, viral type, number of HPVhr, viral load in the first samples, and type of contraception were evaluated. At Visit 7 (Week 28), the association with the different covariates considered as risk factors was evaluated on the recurrence rate rather than on the success rate.

Secondary endpoints:

The secondary endpoints of efficacy were:

- The viral load and genotype of HPVhr.
- The colposcopic description of the lesion.

The viral load and genotype of HPV were determined before treatment, at Visit 4 (Week 3), Visit 5 (Week 12), and Visit 7 (Week 28) (end of the study) by using a TaqMan-based real-time quantitative Polymerase Chain Reaction (qPCR) analysis.

In each treatment group, the lesion was evaluated by colposcopy qualitatively (probably HSIL, probably LSIL, doubt or minimal lesion, or normal) and quantitatively (lesion size) at each study visit (except, if unnecessary, at Weeks 0, 14 and 30). The colposcopic changes at study end were classified by the

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

Investigator as: "progression, unchanged, partial regression, or total regression". The same evaluation was made with a centralized blinded reading of an expert in colposcopy who reviewed the standardized colpophotography made by the Investigator at each colposcopy examination.

Safety:

The primary endpoints of safety and local tolerance were:

- The adverse events (AEs) reporting.
- The absence of renal impairment (blood creatinine level).
- The absence of inflammation markers in plasma (CRP, differential leukocyte count).
- The local tolerance (local symptoms and gynecological examination).
- The difficulty of cap removal.

The local tolerance was measured by patient questionnaires and by a gynecological examination of the vagina and cervix, and by systematic record of vaginal symptoms. It was expected that the parameters to be observed by the Investigator were notably erythema, leukorrhea and erosion.

The patients had to indicate on the diary card any medical problems that they experienced, the time of removal of cervical cap and any difficulties associated with removal (pain, bleeding, help by another person…). The Investigator reviewed all diary entries and asked patients about their medical problems. If any of the medical problems met the definition of an AE, they were entered into the eCRF.

The Investigator evaluated the severity of AEs (intensity) according to a 3 point scale (mild, moderate, or severe) and rated the causal relationship between the AEs and the investigational product (unrelated, unlikely, possible, probable, or certainly related).

Treatment-emergent changes in clinical laboratory values (*i.e.*, hematology, clinical chemistry) classified as clinically significant according to the judgment of the Investigator were recorded as AEs.

Statistical Methods:

The populations used for the statistical analyses were defined as follows:

- Intention To Treat (ITT) population: participants who received at least one administration of the tested product.
- Per-Protocol (PP) population: participants who fulfilled the protocol in terms of eligibility, interventions, and outcome assessment.
- Safety population (whole population): participants for whom information and informed consent were collected (including screening failure).

Additional "V7" subpopulations (ITT V7, PP V7 and Safety V7) were defined as consisting of patients from the main population who were allowed to participate to Visit 7 (Week 28).

Efficacy analyses were performed on PP and ITT populations (and V7 subpopulations, where applicable). Safety analyses were performed on the Safety population (and on Safety V7 subpopulation where applicable) for treatment-emergent AEs, concomitant treatments, physical examinations, and

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

clinical laboratory results.

Efficacy:

Statistical Analyses for the Primary Endpoints:

If not otherwise specified, the following descriptive statistics were computed:

- For continuous variables: N (number of non-missing observations), Nmiss (number of missing observations), Mean, SD (standard deviation), CV% (coefficient of variation, %), median, minimum and maximum.
- For categorical variables: absolute (N) and relative (%) frequencies. The percentages were calculated from the total number of patients included in the applicable study population.

Treatment success outcomes at Visit 5 (Week 12)

The proportion of patients out of the PP or of the ITT population with different success outcomes at Visit 5 (Week 12) (*i.e.*, overall success, complete success, partial success or failure, based on conclusions recorded at Visit 6) were statistically compared between treatments using the Cochran-Mantel-Haenszel test stratified by study sites.

The primary analysis was the comparison of the overall success rates.

In addition, the following secondary analyses were performed as sensitivity analyses:

- Comparison of complete success, partial success and failure proportions between treatments out of the PP or of the ITT population using the Cochran-Mantel-Haenszel test with stratification by study center.
- Comparison of all types of success outcomes (overall success, complete success, partial success or failure) out of the PP or of the ITT population, but including results of any supplementary visit performed after Visit 5 in case of inconclusive results at Visit 5 (Week 12).

Disease evolution from Visit 5 (Week 12) to Visit 8 (Week 28)

The following outcomes were compared between both treatment groups out of the PP V7 or of the ITT V7 population for the evolution between Visit 5 (Week 12) and Visit 7 (Week 28) using the CMH test with stratification by study center:

- Recurrence: treatment failure at Week 28 for patients with partial or complete success at Week 12.
- Progression: partial success at Week 28 for patients with complete success at Week 12.
- Stabilization: complete success at Week 28 for patients with complete success at Week 12 and partial success at Week 28 for patients with partial success at Week 12.
- Regression: complete success at Week 28 for patients with partial success at Week 12.

The proportion of patients with each outcome at Visit 7 (Week 28) (*i.e.*, based on conclusions recorded at Visit 8) was statistically compared by a Cochran-Mantel-Haenszel test with stratification by study center.

In addition, a secondary analysis was performed as a sensitivity analysis on inconclusive results at Week

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

12 or Week 28 updated with the results of any supplementary visit performed within 2 weeks after the visit of interest.

Association between colposcopic and histological/cytological evolutions

The association between the histological/cytological and the colposcopic results of Investigators at study end was estimated. The statistical association between both types of results was evaluated by a Cochran-Mantel-Haenszel test with stratification on study center.

Statistical Analyses for the Secondary Endpoints:

The total viral load was computed by summing the viral load of each HPV type, excluding L1 epitope load (common to HPV 33,52,58,67). In each treatment group, the change of viral load was computed for each group.

The number and percentage of each HPVhr type was computed as the number of each HPV type with a viral load >0, excluding HPV 6, HPV 11 and HPV 33,52,58,67 L1 epitope load; HPV 6 and HPV 11 being non-oncogenic HPV and L1 epitope being duplicate of available HPV. The analyses on the evolution of viral genotypes were descriptive.

In each treatment group the mean lesion size was measured for each visit and the rate of probably HSIL/(normal + probably LSIL) was calculated.

Associations between colposopic evolution and histological regression or progression were evaluated by a Cochran-Mantel-Haenszel test stratified by study center.

Safety:

Safety parameters were examined and abnormalities were presented. All safety analyses included descriptive summaries for AEs and discontinuations due to AEs. Descriptive summaries by treatment group were generated for:

- Incidence of AEs and SAEs.
- Discontinuations due to AEs and SAEs.
- Changes in physical examinations.
- Local tolerance.
- Cap removal difficulties.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA 15.1) and grouped by preferred terms (PTs) and system organ classes (SOCs). Incidence rates (frequencies and percentages), intensity, duration, and relationship to study drug of AEs and SAEs were summarized within each PT per recording period. If a patient experienced more than one AE within a PT for the same recording period, only the AE with the strongest relationship and/or the highest known intensity was included in the summary of relationship and intensity.

Changes in physical examinations observed during the course of the study were summarized in a listing. Descriptive statistics were calculated and presented for vital signs and for treatment-emergent clinically relevant abnormalities in vital signs.

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

The numbers of patients with normal, abnormal but not clinically significant, and abnormal and clinically significant results were summarized.

RESULTS:

Disposition of Patients and Population of Analyses

A total of 194 patients were enrolled and screened for inclusion in the study. Of these, 145 patients were included and treated and 49 patients were not treated. The most frequent reason for not treating a patient was screening failure (40 patients; 81.6%), due to the absence of a CIN 2+ lesion.

The completion rate was high overall with similar proportions of treated patients who completed the study in the Placebo group (96.2%) and the Cidofovir group (91.4%).

All 194 enrolled patients were included in the Safety population and all the 145 treated patients were included in the ITT population (80 patients were eligible for participation to Visit 7 and were included in the ITT V7 population). The overall proportion of patients from the Safety and the ITT populations included in the PP population was 45.9% and 61.4%, respectively; overall, 29.4% and 39.3% of these patients were randomized to the Cidofovir group and 16.5% and 22.1% of these patients were randomized to the Placebo group.

Baseline Characteristics

All treated patients were aged between 20 and 50 years. The most frequently reported medical histories in the ITT population were surgical (65.5%), general (53.8%), gynecologic (44.1%), allergic (35.9%), and dermatologic (24.1%) history.

Treatment compliance

Most treated patients (76.6%) used the small cap for each administration. All patients in both groups received the first administration. Three patients in the Cidofovir group did not receive the second application: [redacted] and [redacted]. One patient did not receive the third administration of Placebo: [redacted] Two patients did not receive the third administration of Cidofovir: [redacted]

Treatment application time was the most reported protocol deviation (rated as major for 19 patients and as minor for 27 patients). Of these patients, 14 patients (major) and 15 patients (minor) reported having difficulties in removing the cervical cap and often reported that the thread broke during removal (6 patients for major and 8 patients for minor). The cap was removed at the hospital emergency for 7 patients (major) and 7 patients (minor).

Overall, the mean amount of gel applied in the cap was 3.0 g for each administration (the mean amount

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

of gel applied was similar between treatment groups). In few cases, the amount of gel not respected was reported as a deviation.

EFFICACY

Primary Objectives*:*

Treatment Success Outcome at Visit 5 (Week 12)

The rate of success (failure, partial success, or complete success) at Visit 5 (Week 12) was compared between Cidofovir group and Placebo group, and the results from the comparisons performed on the PP population are presented in Table 1.

Table 1: Statistical comparison of the different success outcomes at Visit 5 (Week 12) (PP population)

	Placebo (N= 32)		**Cidofovir (N= 57)**		
Success outcome	**n**	**%**	**n**	**%**	**p-value***
Overall success	12	37.5	37	64.9	**0.022**
Complete success	5	15.6	22	38.6	**0.044**
Partial success	7	21.9	15	26.3	0.674
Failure	19	59.4	19	33.3	**0.023**
Inconclusive	1	3.1	1	1.8	

Bold number: reached the level of statistical significance <0.05

Overall success type included complete and partial success

* Probability (Cochran-Mantel-Haenszel with stratification by site) associated with the hypothesis of equal outcome rate between treatment groups

The proportion of patients showing overall success was significantly higher with Cidofovir (64.9%) than with Placebo (37.5%) (p=0.022), mainly because of complete success achieved by a significantly higher proportion of patients (p=0.044) in the Cidofovir group (38.6% of patients) than in the Placebo group (15.6% of patients). In contrast, failure was significantly more frequently reported (p=0.023) in the Placebo group (59.4%) than in the Cidofovir group (33.3%). The results for the ITT population were similar to those for the PP population.

Disease Evolution from Visit 5 (Week 12) to Visit 7 (Week 28)

From the PP population, 12 patients in the Placebo group and 35 patients in the Cidofovir group who showed success at Visit 5 (Week 12) attended Visit 7 at Week 28 for further evaluations of recurrence, progression, stabilization, and regression (PP V7 population) (Table 2).

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

Table 2: Statistical comparison of the different evolution outcomes at Visit 7 (Week 28) (PP V7 population)

	Placebo (N= 12)		Cidofovir (N= 35)		
Evolution outcome	**n**	**%**	**n**	**%**	**p-value***
Recurrence	1	8.3	4	11.4	0.526
Progression	1	8.3	3	8.6	0.696
Stabilization	6	50.0	22	62.9	0.323
Regression	4	33.3	5	14.3	0.076
Inconclusive or missing			1	2.9	

* Probability (Cochran-Mantel-Haenszel with stratification by site) associated with the hypothesis of equal outcome rate between treatment groups

Few patients experienced recurrence or progression in both treatment groups. Most patients showed stabilization, with a higher proportion in the Cidofovir group (62.9%) than in the Placebo group (50.0%). However, the differences between groups were not significant due to low number of patients, especially in the Placebo group. In the ITT population, the difference in stabilization rates was significantly higher in the Cidofovir than in the Placebo group (p=0.018) due to the larger number of patients, especially regarding the Placebo group.

Association Between Success and Risk Factor

At Visit 5 (Week 12), the associations between each risk factor and success rate were as follows (descriptive analysis, no significativity value available):

- In the Cidofovir group, no clear influence of age on the success rate was observed, except for a lower success rate in oldest patients (>36 years). No associations were observed between success and age in the Placebo group.
- Complete success with Cidofovir was more often observed in no-smoker or past-smoker patients. No associations were observed between overall success and tobacco use in the Placebo group.
- There were no associations between overall success and the number of HPVhr types at screening. However, complete success of Cidofovir was observed only in patients infected with a maximum of 2 HPVhr types, while the partial success rate was higher in patients infected with more than 3 HPVhr types.
- In the Cidofovir group, a higher rate of *overall success* was observed for patients with lower viral loads at Screening, while in the Placebo group, a higher *partial success* was observed in patients with lower viral loads at Screening
- No associations were observed between success (overall, partial, or complete) and the type of contraception.

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

A *post hoc* analysis of success as a function of histological grade at Screening showed that the success rate tended to be lower in patients with more severe lesions and this tendency was less marked in the Cidofovir group than in the Placebo group.

Secondary Objectives:

Viral Parameters

At Visit 4, the proportion of patients from the PP population who cleared HPV (indicated as negative for viral DNA) was higher in the Cidofovir group (54.4%) than in the Placebo group (15.6%). At Visit 5, this proportion was still higher in the Cidofovir group (35.1%) than in the Placebo group (15.6%). Similar results were observed in the ITT population. In the PP V7 population, the proportion of patients who cleared HPV increased in both groups and was 50.0% in the Placebo group and 45.7% in the Cidofovir group at Visit 7. Similar results were observed in the ITT V7 population.

Of the HPV types detected at Screening in the PP population, HPV 16 was far the most prevalent HPVhr type, with 62% of all patients infected by HPV 16.

Colposcopy Parameters - association between colposcopic evolution and histological regression or progression

There was a clear association between colposcopic (as assessed by the Investigator) and histological/cytological results ($p < 0.001$ Cochran-Mantel-Haenszel with stratification by site), with complete success being more often observed in patients with complete regression of the lesion, partial success being more often observed in patients with partial regression or complete regression of the lesion, and failure being more often observed in patients with unchanged colposcopic results or partial regression of the lesion in the PP population.

SAFETY

Cap application/removal difficulties

Difficulties in placing the cap were assessed at treatment application by size of cervical cap. As the cap exerted a suction effect on the cervix, difficulties in removing the cap were also assessed.

For > 84% of patients for each administration, the cap was not difficult to put in place for both cap sizes (this proportion was similar between treatment groups). In contrast, a large proportion of patients reported difficulties in removing the cap. The large cap was more often reported as being difficult to remove than the small cap.

- After the first application, 51.3% of patients in the Placebo group and 40.3% in the Cidofovir group reported difficulties in removing the small cap, and these proportions were 75.0% and 76.2%,

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

respectively, for the large cap.

- After the second administration, the proportions of patients reporting difficulties decreased in both groups as compared to the first application: 37.5% of patients in the Placebo group and 32.4% in the Cidofovir group reported difficulties in removing the small cap, and these proportions were 54.5% and 52.6%, respectively, for the large cap.
- After the third application, the proportions of patients reporting difficulties further decreased in the Placebo group and were similar than after the second application in the Cidofovir group: 17.5% of patients in the Placebo group and 35.2% in the Cidofovir group reported difficulties in removing the small cap and these proportions were 45.5% and 47.1%, respectively, for the large cap.

Reporting of AEs

Only treatment emergent AEs, defined as events which started or worsened during or after the administration of the treatment were considered for the analyses of AEs. The overall incidence of treatment emergent AEs reported during the study is presented in Table 3.

Table 3: Overall incidence of AEs (Safety population)

	Placebo (N=52)		Cidofovir (N=93)		Overall (N=145)	
Total number of patients	**n**	**%**	**n**	**%**	**n**	**%**
with at least one AE	46	88.5	90	96.8	136	93.8
with at least one drug-related AE *	32	61.5	82	88.2	114	78.6
with at least one severe AE *	5	9.6	22	23.7	27	18.6
with at least one SAE *	2	3.8	2	2.2	3	2.1
Died	0	0.0	0	0.0	0	0.0

Only patients having received one of the study treatments were included in the analysis
% : (n/N)*100 (N: number of patients)
* Derived AEs (AEs collected from the technical field of the eCRF related to the biopsy and cap application procedures) are not included as the information on severity and relationship was not available

Most patients in both treatment groups reported at least one AE, with slightly less patients in the Placebo group than in the Cidofovir group (88.5% of patients in the Placebo group and 96.8% in the Cidofovir group). Most patients reported AEs considered by the Investigator as related to treatment in both treatment groups, but the proportion was higher in the Cidofovir group (88.2%) than in the Placebo group (61.5%). Less than 10% of the patients in the Placebo group reported a severe AE, while this percentage was 23.7% in the Cidofovir group. Only 2 patients (2.2%) in the Cidofovir group and 2 patients (3.8%) in the Placebo group reported an SAE (all not related to treatment). No death was reported.
The incidence and occurrence of the most frequent AEs (based on the total number of AEs) that occurred in select organ classes counted once per subject are presented in Table 4.

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Colvir	Volume:	
Name of Active Ingredient: Cidofovir	Page:	

Table 4: Incidence and occurrence of the most frequent AEs – Selected SOCs (Safety population)

		Placebo (N=52)			Cidofovir (N=93)			Overall (N=145)		
System Organ Class	**Preferred Term**	**n**	**%**	**Occ.**	**n**	**%**	**Occ.**	**n**	**%**	**Occ.**
All	**All**	46	88.5	306	90	96.8	822	136	93.8	1128
Reproductive system and breast disorders	**All**	36	69.2	99	83	89.2	337	119	82.1	436
	Genital discharge	19	36.5	42	68	73.1	120	87	60.0	162
	Uterine cervical erosion	4	7.7	6	26	28.0	38	30	20.7	44
	Vaginal hemorrhage	7	13.5	9	20	21.5	33	27	18.6	42
	Vulvovaginal pruritus	4	7.7	7	22	23.7	29	26	17.9	36
	Pelvic pain	4	7.7	8	19	20.4	25	23	15.9	33
	Vulvovaginal pain	5	9.6	6	13	14.0	15	18	12.4	21
General disorders and administration site condition	**All**	19	36.5	46	51	54.8	92	70	48.3	138
	Fatigue	16	30.8	35	44	47.3	70	60	41.4	105

Only patients having received one of the study treatments are included in the analysis
n: number of subjects with at least one AE by primary system organ class and preferred term
%: (n/N)*100 (N: number of subjects)
Occ.: occurrences of the AE

Most patients in both treatment groups reported an AE. The most frequent disorders were reproductive system and breast disorders (reported by 82.1% of all patients), with an incidence of any reproductive system and breast disorders higher in the Cidofovir group (89.2%) than in the Placebo group (69.2%). Among these types of disorders, the most frequently reported ones were genital discharge (73.1% in the Cidofovir group and 36.5% in the Placebo group), followed by uterine cervical erosion, vaginal hemorrhage, vulvovaginal pruritus, pelvic pain and vulvovaginal pain (reported by 14.0% to 28.0% of patients in the Cidofovir group and by 7.7% to 13.5% in the Placebo group).
Severe and moderate AEs coding to the SOC reproductive system and breast disorders were more frequently reported by patients in the Cidofovir group (5.4% and 49.5% of all patients, respectively, reporting at least one event in these categories) than in the Placebo group (1.9% and 11.5% of all patients, respectively).
Treatment-related AEs coding to the SOC reproductive system and breast disorders were more frequently reported in the Cidofovir group (80.6% of all patients reporting at least one treatment-related AE in this SOC) than in the Placebo group (40.4% of all patients reporting at least one treatment-related AE in this SOC), mostly because of treatment-related genital discharge (reported as treatment-related by 61.3% of patients in the Cidofovir group and 30.8% patients in the Placebo group), vulvovaginal pruritus, vaginal hemorrhage, vulvovaginal pain, and uterine cervical erosion (12.9% to 20.4% of all patients in the Cidofovir group and 0.0% to 9.6% of all patients in the Placebo group).
Only 1 patient ([redacted] in the Cidofovir group) reported AEs [redacted]

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

[redacted] which lead to treatment discontinuation.

Biological parameters

No worsening of the biological parameters could be observed with Cidofovir.

Serious Adverse events

Three SAEs were reported. [redacted]

All 4 patients recovered and the SAEs were considered as not related to treatment.

Pregnancies

At Visit 1, the pregnancy test was negative for all patients. [redacted]

OVERALL CONCLUSIONS:

- The proportion of patients showing overall success was significantly higher with Cidofovir (p=0.022) mainly because of a higher rate of complete success (p=0.044). In contrast, the failure rate was higher with Placebo (p=0.023).
- In the patients who showed overall success after treatment, the stabilization rate at Week 28 was higher in the Cidofovir group (62.9%) than in the Placebo group (50.0%), whereas the rate of regression was higher in the Placebo group (33.0%) than in the Cidofovir group (14.3%). The rate of recurrence was 8.3% in the Placebo group and 11.4% in the Cidofovir group. The differences between groups were not statistically significant due to the small number of subjects.
- The proportion of patients who cleared HPVhr (indicated as negative for viral DNA of HPVhr) was higher in the Cidofovir group (54.4% at Visit 4 and 35.1% at Visit 5) than in the Placebo group (15.6% at Visit 4 and 15.6% at Visit 5).
- At screening, HPV 16 was far the most prevalent HPVhr type in the PP population (62% of all patients).
- The colposcopic results reported by the Investigator were clearly associated with the

Name of Sponsor/Company: Mithra Pharmaceuticals	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Colvir		
Name of Active Ingredient: Cidofovir		

histological/cytological results ($p < 0.001$).

- The inconveniences and difficulties which were observed during the cap removal procedure were anticipated due to expected suction effect of the cap on the cervix; no differences in reporting frequencies were observed between the Placebo and the Cidofovir groups
- Overall, AEs were more frequent, more often severe and more often considered as related to treatment in the Cidofovir group as compared to the Placebo group. The most frequently reported events coded to the SOC reproductive system and breast disorders and were reported by 89.2% of the patients in the Cidofovir group and 69.2% of the patients in the Placebo group. These observations can be explained by the known erosive effect of Cidofovir, an effect that was particularly evident in regards to the number and nature of the adverse events (*e.g.* genital discharge, uterine cervical erosion and vulvovaginal pruritus) reported by Cidofovir-treated patients. Notwithstanding these events, treatment compliance was high, with only one patient in the Cidofovir group discontinuing treatment due to AEs.
- All 4 treatment-emergent SAEs were considered as not related to treatment.
- No other safety concerns were readily apparent; no worsening of biological parameters was observed.
- In conclusion, in this proof of concept study, three applications of Cidofovir gel for 10 hours at 1-week interval showed clear benefits on histological and cytological disappearance of high grade CIN after treatment. Treatment led to a reduction in HPVhr viral load, especially for HPV16. The treatment regimen was well-tolerated.

Date of the Report: 31 July 2013
Amended on 22 August 2013