ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2019; 24: 268-272
DOI: 10.12659/AOT.909693

Received: 2018.02.28
Accepted: 2018.09.06
Published: 2019.05.14

Pharmacokinetic Profile of Prolonged-Release Tacrolimus When Administered via Nasogastric Tube in *De Novo* Liver Transplantation: A Sub-Study of the DIAMOND Trial

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ADE 1 Nasrullah Undre
ABDE 2 Umberto Baccarani
ABDE 3 Russel Britz
ABDE 4 Irinel Popescu*

1 Medical Affairs, Astellas Pharma Global Development, Inc., Chertsey, U.K.
2 Liver Transplant Unit, Department of Medicine, University of Udine, Udine, Italy
3 Department of Transplant Surgery, Wits University Donald Gordon Medical Center, Johannesburg, South Africa
4 Center of General Surgery and Liver Transplantation, Fundeni Clinical Institute, Bucharest, Romania

* On behalf of the DIAMOND** pharmacokinetic study group
** DIAMOND – A**D**VAGRAF™ stud**I**ed in combin**A**tion with **M**yc**O**phenolate mofetil a**ND** basiliximab in liver transplantation

Corresponding Author: Nasrullah Undre, e-mail: nas.undre@astellas.com
Source of support: This study was funded by Astellas Pharma Global Development, Inc., Chertsey, UK. Editorial support was funded by Astellas Pharma, Inc.

Background: For patients unable to swallow during the immediate post-transplant period, immunosuppressant therapy may be initiated by administering prolonged-release tacrolimus as a suspension via a nasogastric tube.

Material/Methods: In this sub-study of the DIAMOND randomized controlled trial of prolonged-release tacrolimus in *de novo* liver transplant recipients, we investigated the pharmacokinetic (PK) profile of prolonged-release tacrolimus when administered via nasogastric tube immediately post-transplant. PK analyses were performed on whole-blood samples collected on Day 1 of tacrolimus administration and on Day 3 post-transplantation. Endpoints included $AUC_{0–24,}$ C_{max}, T_{max}, and C_{min}.

Results: In total, 10 patients were included in the PK sub-study. The overall mean daily dose of prolonged-release tacrolimus administered via nasogastric tube was higher on Day 1 (0.179 mg/kg) *vs.* Day 3 (0.140 mg/kg). Mean $AUC_{0–24}$ was higher and less variable on Day 3 *vs.* Day 1 ($AUC_{0–24}$ (coefficient of variation; CV): 301 (50.8) *vs.* 193 (94.5) ng·h/mL). Mean C_{max} was lower and median T_{max} was shorter on Day 1 *vs.* Day 3 (C_{max} (CV): 15.1 (73.9) *vs.* 19.1 (47.9) ng/mL; T_{max} (range): 2.0 (2.0–24.0) *vs.* 4.5 (0.5–24.0) h). A similar pattern was also observed when data were normalized for dose and body weight.

Conclusions: In contrast to previously reported findings in healthy volunteers, nasogastric administration of prolonged-release tacrolimus suspension in liver transplant patients did not substantially affect the PK profile of tacrolimus *vs.* intact capsules. Nasogastric administration is thus a feasible option to ensure appropriate early tacrolimus exposure in *de novo* liver transplant recipients.

MeSH Keywords: **Delayed-Action Preparations • Immunosuppression • Liver Transplantation • Pharmacokinetics • Tacrolimus**

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/909693

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

The management of liver transplant recipients has been transformed over the past 2 decades by advances in immunosuppressive regimens [1]. During this time, the extensive therapeutic experience gained with tacrolimus in the clinical and trial settings [2–6] has demonstrated that absorption of tacrolimus early post-transplant is of particular importance. This is because tacrolimus has a narrow therapeutic index, such that small changes in systemic exposure can markedly affect pharmacodynamic response [7–9]. Tacrolimus is absorbed throughout the gastrointestinal tract, and is primarily metabolized by cytochrome P450-3A4 in the liver, as well as in the intestinal wall [10]. As pharmacokinetic (PK) studies demonstrated that oral bioavailability of tacrolimus is unaffected by the presence/absence of bile in the intestine [11–13], tacrolimus therapy is initiated by the oral route whenever possible. During the immediate post-liver transplant period, the established practice is to manage oral therapy by administering the contents of immediate-release tacrolimus capsules as a suspension via a nasogastric tube. In current clinical practice, this is also the case with the prolonged-release tacrolimus capsule formulation. It is, therefore, important to assess the PK profile of tacrolimus when the contents of prolonged-release capsules are administered via a nasogastric tube [14].

A previous Phase I study designed to assess the PK profile of tacrolimus administered to 20 healthy male volunteers found that when prolonged-release tacrolimus capsules were opened, and a suspension was prepared and administered via a nasogastric tube, there was a 28% increase in C_{max}, a 75% faster T_{max}, and a 17% lower $AUC_{0-\infty}$ of tacrolimus relative to intact capsules [14]. The study suggested that creating a suspension of prolonged-release tacrolimus may dissolve the more immediate-release component of the formulation before administration, potentially resulting in a more rapid absorption rate compared with intact capsules [14]. However, the PK profile of prolonged-release tacrolimus administered by nasogastric tube immediately post-liver transplant has not previously been reported.

Pharmacokinetics of tacrolimus following oral administration of intact prolonged-release capsules in the immediate post-liver transplant period have been assessed previously. In a Phase II study, prolonged-release tacrolimus capsules (0.1 mg/kg/day) resulted in an AUC_{0-24} of 146 ng·h/mL on Day 1 and 324 ng·h/mL on Day 14 [8]. In a Phase III study, prolonged-release tacrolimus capsules (0.2 mg/kg/day) resulted in an AUC_{0-24} of 320 ng·h/mL on Day 1 and 452 ng·h/mL on Day 3 [15].

Here, we present data from a PK sub-study of the DIAMOND trial, a Phase IIIb, randomized controlled trial of prolonged-release tacrolimus plus mycophenolate mofetil (MMF) (with and without basiliximab) and a single bolus of corticosteroid in *de novo* liver transplant recipients over 24 weeks of treatment [5]. This sub-study was designed to assess the absorption and PK profile of prolonged-release tacrolimus when administered by nasogastric tube immediately post-transplant.

Material and Methods

The materials and methods of the DIAMOND study (*ClinicalTrials.gov* number: NCT01011205) have been presented previously [5]. Patients undergoing liver transplantation were randomized to 1 of 3 study arms (1: 1: 1) to receive prolonged-release tacrolimus. In Arms 1 and 2, patients received prolonged-release tacrolimus at an initial dose of 0.2 mg/kg/day and 0.15–0.175 mg/kg/day on Day 1 post-transplant, respectively, while in Arm 3 tacrolimus initiation at a dose of 0.2 mg/kg/day was delayed until Day 5 post-transplant. All patients received MMF and 1 bolus of corticosteroid, and patients in Arms 2 and 3 also received basiliximab. In this sub-study, the PK profile of prolonged-release tacrolimus was evaluated only in patients randomized to Arms 1 and 2 who received prolonged-release tacrolimus via nasogastric tube immediately post-transplant.

To produce the tacrolimus suspension, prolonged-release tacrolimus capsules were opened and the contents emptied into a container and mixed with 50 mL of water. This suspension was drawn into a syringe and administered via the nasogastric tube. The container was then refilled with 50 mL of water and drawn into the same syringe to flush the nasogastric tube and the container. After administration, the nasogastric tube was clamped for 45–60 min. Polyvinyl chloride-containing material was avoided when administering tacrolimus capsule contents via a nasogastric tube.

In Arm 1, patients received prolonged-release tacrolimus (Advagraf™, Astellas Pharma Europe BV, Netherlands) at an initial dose of 0.2 mg/kg/day. In Arm 2, patients received prolonged-release tacrolimus at an initial dose of 0.15–0.175 mg/kg/day plus basiliximab (20 mg) on Days 0 and 4. In both groups, tacrolimus doses were adjusted to maintain target whole blood trough levels in the range of 5–15 ng/mL from Days 0 to 42. All patients enrolled in the DIAMOND study also received intravenous MMF (1 g) within 12 h of skin closure, and 1 g twice-daily until Day 14 (intravenous for Days 1–5, orally for Days 6–14). A bolus of intra-operative corticosteroid (≤1000 mg) was permitted according to center policy, but post-transplant maintenance steroids were not administered routinely.

PK analyses were performed on whole-blood samples collected on the morning of the first day of tacrolimus administration and on Day 3 post-transplantation, to provide 2 blood

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

concentration – time profiles. On the first day of tacrolimus administration, PK profiles were assessed immediately after tacrolimus administration. On Day 3, the first blood sample was drawn in the morning no earlier than 5 min before administration of prolonged-release tacrolimus (Time 0 (pre-dose)). For each profile, blood samples were collected at Time 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 h post-dose. This resulted in samples from 11 time points for each assessment period.

Tacrolimus concentrations were determined using a validated high-performance liquid chromatography (HPLC) tandem mass-spectrometric (MS) (HPLC/MS/MS) assay (lower limit of quantification, 0.059 ng/mL). The assay was based on the method developed by Alak et al. [16]. Whole-blood calibrators, quality control samples, and study samples were thawed, and 1-mL aliquots taken. An analog internal standard of tacrolimus (FR900520; 20 mL, 50 ng/mL) was added and mixed briefly. Aliquots were extracted using protein precipitation and solid-phase extraction, using C18 200 mg/3 mL cartridges. Elutes were evaporated to dryness under a stream of nitrogen at 40°C, and residues were redissolved in a 50: 50 (volume: volume) mix of acetonitrile and water (mixed and centrifuged) before being submitted for HPLC/MS/MS. All procedures were performed in compliance with the principles of Good Laboratory Practice.

Analyses for the sub-study included area under the concentration–time curve from 0 to 24 h post-tacrolimus dose (AUC_{0-24}), maximum observed concentration of tacrolimus (C_{max}), time to C_{max} (T_{max}), minimum observed concentration of tacrolimus at 24-h post-dose (C_{min}), and dose and body weight normalized AUC_{0-24}, $C_{max,}$ and C_{min}. Adjustments for dose and body weight were calculated by dividing the parameter by the dose per kg of body weight and are described in this publication as AUC_{24} (norm), C_{max} (norm), and C_{min} (norm). The arithmetic mean and standard deviation (SD) were calculated for dose and C_{min}. Geometric mean and geometric coefficient of variation (CV) were calculated for all PK analyses except T_{max}, for which the median (range) was reported. Analyses were undertaken on the PK population, defined as all randomized patients who received ≥1 dose of the study drug and who had evaluable PK data with complete profiles for both Days 1 and 3.

A total sample size ≥16 patients (8 evaluable patients in each of the 2 treatment arms in the DIAMOND sub-study) was considered necessary to evaluate the PK profile of prolonged-release tacrolimus administered via nasogastric tube. No separate analysis of safety or efficacy was performed for the PK sub-set.

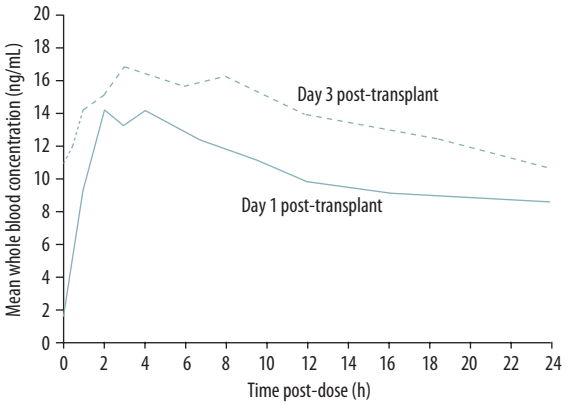

Figure 1. Arithmetic mean of 24-hour whole blood concentrations of prolonged-release tacrolimus administered by nasogastric tube on Day 1 and Day 3 in the pharmacokinetic population. Only patients who were randomized to Arms 1 and 2 of the DIAMOND study and who received tacrolimus via nasogastric tube immediately post-transplant were eligible for inclusion in the sub-study; patients in Arm 3 were not included as their initiation of tacrolimus was delayed until Day 5 post-transplant. For each profile, blood samples were collected at Time 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 h post-dose. This resulted in samples from 11 time points for each assessment period.

Results

Patient and donor demographics

Due to early completion of the main DIAMOND clinical study, it was not possible to recruit 16 patients into the PK sub-study. While 11 patients from 3 centers were eligible for inclusion, 1 patient had an incomplete PK profile and was excluded from the analysis. The remaining 10 patients (5 per treatment arm) were included in the analyses. The mean (range) body weight for these patients was 76.6 kg (range 60–89 kg).

Treatment dose and exposure

Overall mean daily dose of prolonged-release tacrolimus was higher on Day 1 (0.179 mg/kg) compared with Day 3 (0.140 mg/kg). The arithmetic mean (SD) tacrolimus trough levels, measured by C_{min}, were lower on Day 1 (8.16 (7.75) ng/mL) *vs.* Day 3 (10.7 (6.66) ng/mL). The PK profiles for Days 1 and 3 are presented in Figure 1.

Pharmacokinetic profile

For both treatment arms combined, the geometric mean of AUC_{0-24} for tacrolimus was lower on Day 1 compared with Day 3,

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 1. Summary of pharmacokinetic parameters of prolonged-release tacrolimus administered by nasogastric tube.

	Day 1 (n=10)		Day 3 (n=10)	
Mean dose, mg/kg	0.179		0.140	
AUC_{0-24}, ng·h/mL	193	(94.5)	301	(50.8)
T_{max}, hour	2.0 (2.0–24.0)		4.5 (0.5–24.0)	
C_{max}, ng/mL	15.1	(73.9)	19.1	(47.9)
C_{min}, ng/mL	5.3	(141.0)	8.8	(80.3)
Normalized for dose and body weight				
AUC_{0-24} (norm), mg/kg	1090	(97.5)	2230	(54.2)
C_{max} (norm), mg/kg	85.2	(78.5)	141	(55.6)
C_{min} (norm), mg/kg	29.7	(145.0)	64.9	(77.0)

Geometric mean and geometric coefficient of variation (CV) are presented, with the exception of dose which is presented as arithmetic mean, and T_{max}, which is presented as median (range). AUC_{0-24}, area under the concentration–time curve from 0 to 24 hours post-dose; C_{max}, maximum observed concentration of tacrolimus; C_{min}, minimum observed concentration of tacrolimus at 24-hours post-dose; T_{max}, time to C_{max}; (norm), indicates normalized values calculated by dividing the pharmacokinetic parameter by the dose per kg of body weight.

while the interpatient variability in systemic exposure to tacrolimus, measured by CV, was higher on Day 1 *vs.* Day 3 (mean (CV) AUC_{0-24} Day 1: 193 (94.5) *vs.* Day 3: 301 (50.8) ng·h/mL) (Table 1). C_{max} was lower on Day 1, and T_{max} was shorter on Day 1 compared with Day 3 (mean (CV) C_{max}: 15.1 (73.9) *vs.* 19.1 (47.9) ng/mL; median (range) T_{max}: 2.0 (2.0–24.0) *vs.* 4.5 (0.5–24.0) h). The geometric mean (CV) of C_{min} was lower on Day 1 compared with Day 3 (5.27 (141.0) *vs.* 8.77 (80.3) ng/mL, respectively).

When the data were normalized for dose and body weight, a similar pattern in the PK profile was observed (Table 1). AUC_{0-24} (norm) (CV) remained lower and more variable on Day 1 compared with Day 3 (1090 (97.5) *vs.* 2230 (54.2) mg/kg), and C_{max} (norm) and C_{min} (norm) were also lower on Day 1 compared with Day 3 (mean (CV) C_{max} (norm): 85.2 (78.5) *vs.* 141 (55.6) mg/kg; mean (CV) C_{min} (norm): 29.7 (145) *vs.* 64.9 (77.0)) (Table 1).

Discussion

Results from the DIAMOND PK sub-study indicate that, for patients who cannot swallow capsules in the immediate post-transplant period, prolonged-release tacrolimus capsules can be opened and administered as a suspension via nasogastric tube.

Overall systemic exposure to tacrolimus, as measured by AUC_{0-24} and C_{min}, was higher on Day 3 *vs.* Day 1. This is consistent with data from earlier Phase II [8] and Phase III PK studies [15], in which intact prolonged-release tacrolimus capsules were administered. Considering the reasons for requiring nasogastric administration of tacrolimus and the gut motility of patients post-surgery, these findings are consistent with our understanding of liver transplant recipients in the immediate post-transplant period.

A previous Phase I study [14] compared systemic exposure of tacrolimus after administration of the contents of prolonged-release tacrolimus capsules via intact capsules, oral suspension, or nasogastric suspension in healthy volunteers. The data indicated that administration of prolonged-release tacrolimus suspension, orally or via nasogastric tube, resulted in a faster absorption profile (shorter T_{max} and higher C_{max}) compared with intact capsules. Mean exposure (estimated using AUC) was approximately 17% lower for nasogastric tube administration compared with intact capsules [14]. The authors speculated that incomplete tacrolimus absorption profiles were recorded for the participants who reached C_{max} at the first blood-sampling time point, leading to an underestimation of the overall systemic exposure to tacrolimus.

When comparing the DIAMOND PK sub-study data for Day 1 with data from healthy volunteers [14], the median T_{max} following nasogastric administration of prolonged-release tacrolimus on Day 1 in patients undergoing *de novo* liver transplantation was longer (2.5 h) *vs.* that in healthy volunteers (0.5 h). This suggests a more 'normal' absorption profile of prolonged-release tacrolimus when administered via nasogastric tube in liver transplant patients compared with healthy subjects. These differences could be due to the reduced gastrointestinal motility found in liver transplant patients immediately post-transplant, thereby limiting tacrolimus bioavailability.

The PK profile of tacrolimus, administered as a prolonged-release intact capsule and as an immediate-release intact capsule, have been studied previously in a Phase III trial [15]. The PK parameters of tacrolimus (AUC_{0-24}, C_{max}, T_{max}, and C_{min}) in the DIAMOND PK sub-study following once-daily nasogastric administration were broadly consistent with results from this study [15]. In addition, when comparing the DIAMOND PK sub-study data with those from a previously published Phase II study of *de novo* liver transplant recipients receiving intact capsules, the overall absorption and PK profile (C_{max}, T_{max} and C_{min}) of tacrolimus were generally comparable when administered by nasogastric tube or intact capsules [8]. Taken together, these data indicate that once-daily nasogastric administration of prolonged-release tacrolimus early post-transplant does not substantially affect the absorption and disposition of tacrolimus when compared with *de novo* liver transplant patients receiving intact prolonged-release tacrolimus capsules.

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

The main limitations of the PK sub-study were that only 11 patients were eligible for inclusion in the study instead of the planned 16, and a full PK data set was only available for 10 of these patients. The lack of a PK comparator arm of patients who received intact prolonged-release tacrolimus capsules is also a limitation, and comparing data between trials should be undertaken with caution. Despite these limitations, the findings were broadly consistent with other PK studies of patients undergoing liver transplantation who received prolonged-release tacrolimus via intact capsules [8,15].

Conclusions

In contrast to the findings in healthy volunteers [14], data from this study suggest that once-daily nasogastric administration of prolonged-release tacrolimus does not have a substantial effect on the PK profile of tacrolimus compared with oral administration of prolonged-release tacrolimus capsules in *de novo* liver transplant recipients. Administration of prolonged-release tacrolimus via nasogastric tube is, therefore, a feasible option to ensure appropriate tacrolimus exposure in patients who are unable to swallow intact capsules in the first few days post-transplant.

Acknowledgments

This study was funded by Astellas Pharma Europe, Ltd., Chertsey, UK. Editorial support was funded by Astellas Pharma, Inc. The authors would like to thank Graham Wetherill and Gbenga Kazeem (of Astellas Pharma Europe Ltd., Chertsey, United Kingdom) for their support with statistical analyses and data interpretation in the development of this publication. The authors would also like to thank Nina C Kennard, BSc and Amy MacLucas, PhD from Cello Health MedErgy (Europe) who assisted in drafting the initial version of the manuscript under the direction of the authors, and provided editorial support throughout its development.

Conflicts of interest

Nasrullah Undre reports non-financial support from Astellas during the conduct of the study, and is an employee of Astellas. Umberto Baccarani reports non-financial support from Astellas during the conduct of the study, and reports non-financial support and personal fees from Astellas, outside the submitted work. Russel Britz and Irinel Popescu report non-financial support from Astellas during the conduct of the study.

References:

1 Germani G, Theocharidou E, Adam R et al: Liver transplantation for acute liver failure in Europe: Outcomes over 20 years from the ELTR database. J Hepatol, 2012; 57: 288–96.

2. Trunečka P, Boillot O, Seehofer D et al: Once-daily prolonged-release tacrolimus (ADVAGRAF) versus twice-daily tacrolimus (PROGRAF) in liver transplantation. Am J Transpl, 2010; 10: 2313–23

3. Beckebaum S, Iacob S, Sweid D et al: Efficacy, safety, and immunosuppressant adherence in stable liver transplant patients converted from a twice-daily tacrolimus-based regimen to once-daily tacrolimus extended-release formulation. Transpl Int, 2011; 24: 666–75

4. van Hooff JP, Alloway RR, Trunečka P et al: Four-year experience with tacrolimus once-daily prolonged release in patients from phase II conversion and *de novo* kidney, liver, and heart studies. Clin Transplant, 2011; 25: 1–12

5. Trunečka P, Klempnauer J, Bechstein WO et al: Renal function in *de novo* liver transplant recipients receiving different prolonged-release tacrolimus regimens-the DIAMOND study. Am J Transplant, 2015; 15: 1843–54

6. Adam R, Karam V, Delvart V et al: Improved survival in liver transplant recipients receiving prolonged-release tacrolimus in the European Liver Transplant Registry. Am J Transplant, 2015; 15: 1267–82

7. Undre N, Van Hooff J, Christiaans M et al: Low systemic exposure to tacrolimus correlates with acute rejection. Transplant Proc, 1999; 31: 296–98

8. Fischer L, Trunečka P, Gridelli B et al: Pharmacokinetics for once-daily versus twice-daily tacrolimus formulations in *de novo* liver transplantation: A randomized, open-label trial. Liver Transplant, 2011; 17: 167–77

9. de Mare-Bredemeijer ELD, Metselaar HJ: Optimization of the use of calcineurin inhibitors in liver transplantation. Best Pract Res Clin Gastroenterol, 2012; 26: 85–95

10. Astellas Pharma Europe Ltd. Advagraf 0.5 mg, 1 mg, 3 mg and 5 mg prolonged-release hard capsules summary of product characteristics. 2015

11. Venkataramanan R, Jain A, Warty VW et al: Pharmacokinetics of FK 506 following oral administration: A comparison of FK 506 and cyclosporine. Transplant Proc, 1991; 23: 931–33

12. Jain AB, Venkataramanan R, Cadoff E et al: Effect of hepatic dysfunction and T tube clamping on FK 506 pharmacokinetics and trough concentrations. Transplant Proc, 1990; 22: 57–59

13. Böttiger Y, Undre NA, Säwe J et al: Effect of bile flow on the absorption of tacrolimus in liver allograft transplantation. Transplant Proc, 2002; 34: 1544–45

14. Undre N, Dickinson J: Relative bioavailability of single doses of prolonged-release tacrolimus administered as a suspension, orally or via a nasogastric tube, compared with intact capsules: A phase 1 study in healthy participants. BMJ Open, 2017; 7: e012252

15. Ericzon BG, Varo E, Trunečka P et al: Pharmacokinetics of prolonged-release tacrolimus versus immediate-release tacrolimus in *de novo* liver transplantation: A randomized phase III substudy. Clin Transplant, 2017; 31: 1–7

16. Alak AM, Moy S, Cook M et al: An HPLC/MS/MS assay for tacrolimus in patient blood samples. Correlation with results of an ELISA assay. J Pharm Biomed Anal, 1997; 16: 7–13

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]