Daptomycin in the Clinical Setting: 8-Year Experience with Gram-positive Bacterial Infections from the EU-CORESM Registry

Armando Gonzalez-Ruíz · Panayiotis Gargalianos-Kakolyris · Artur Timerman · Jayanta Sarma · Víctor José González Ramallo · Kamel Bouylout · Uwe Trostmann · Rashidkhan Pathan · Kamal Hamed

ABSTRACT

Introduction: The aim of this study was to evaluate the clinical outcomes and safety of daptomycin therapy in patients with serious Gram-positive infections.

Methods: Patients were enrolled in the European Cubicin® Outcomes Registry and Experience (EU-CORESM), a non-interventional, multicenter, observational registry. The real-world data were collected across 18 countries (Europe, Latin America, and Asia) for patients who had received at least one dose of daptomycin between January 2006 and April 2012. Two-year follow-up data were collected until 2014 for patients with endocarditis, intracardiac/intravascular device infection, osteomyelitis, or orthopedic device infection.

Results: A total of 6075 patients were enrolled. The most common primary infections were complicated skin and soft tissue infection (31.7%) and bacteremia (20.7%). Staphylococcus aureus was the most frequently reported pathogen (42.9%; methicillin-resistant S. aureus [MRSA], 23.2%), followed by Staphylococcus epidermidis and other coagulase-negative staphylococci (CoNS, 28.5%). The most commonly prescribed dose of daptomycin was 6 mg/kg/day (43.6%), and the median duration of therapy was 11 (range 1–300) days. Overall clinical success rate was 80.5%, and was similar whether daptomycin...
was used as first-line (82.9%) or second-line (79.2%) therapy. Clinical success rates were high in patients with *S. aureus* (83.9%; MRSA 83.0%) and CoNS (including *S. epidermidis*, 82.5%) infections. The majority of patients with endocarditis or intracardiac/intravascular device infection (86.7%) or osteomyelitis/orthopedic device infection (85.9%) had a sustained response during the 2-year follow-up period. There were no new or unexpected safety findings.

**Conclusion:** Results from real-world clinical experience showed that daptomycin is a valuable therapeutic option in the management of various difficult-to-treat Gram-positive infections.

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**Keywords:** Clinical response; Daptomycin; Gram-positive infections; Registry; Safety; *Staphylococcus aureus*

**INTRODUCTION**

Infections caused by Gram-positive pathogens are frequently encountered in the healthcare setting and are associated with high morbidity and mortality [1]. Complicated skin and soft tissue infections (cSSTIs) caused by *Staphylococcus aureus* are among the most common bacterial infections, accounting for approximately 25% of all infections in clinical practice [1, 2]. Other Gram-positive bacterial infections include endocarditis, bacteremia, osteomyelitis, and foreign body or prosthetic device-related infections which are known to be difficult to treat.

*Staphylococcus aureus* is considered to be the most important cause of healthcare and community-associated infections worldwide [3, 4]. The European Union/European Economic Area population-weighted mean percentage of methicillin-resistant *S. aureus* (MRSA) infection was 18%, whereas 7 out of the 30 reporting countries had a prevalence of MRSA infections above 25% [5]. Among the available conventional therapies, vancomycin has been considered to be the main treatment option for MRSA infections [6]. Nonetheless, development of resistance and changes in MRSA susceptibility to vancomycin with increasing minimum inhibitory concentrations (MICs) have been observed [7]. Evidence supports the association between increased vancomycin MIC and worse patient outcome, with higher mortality in patients with bacteremia [8, 9]. In addition, slower clinical response and increased relapse rate have been associated with infections caused by MRSA with a high vancomycin MIC [10].

Although vancomycin has been used as an alternative treatment for enterococci, the emergence of vancomycin-resistant enterococci (VRE) as leading cause of several nosocomial infections is a serious concern. Several other limitations of vancomycin use have been recognized such as poor tissue penetration, dosing in patients with renal failure and synergistic toxicity with concomitant aminoglycoside administration [6, 11].

Resistance to currently available antibiotics is an alarming challenge in clinical settings [12–14]. As empirical treatment is often initiated where appropriate before identification of the infecting pathogen, first-line use of an antibiotic effective against resistant pathogens including MRSA is therefore preferable. The increased frequency of Gram-positive infections and the rise in resistance to commonly used antibiotics have led to the need for novel antibiotics [6, 14].

Daptomycin is a cyclic lipopeptide with rapid bactericidal activity against a wide range of
Gram-positive bacteria including MRSA and S. aureus with increased vancomycin MIC values. It is approved for the treatment of cSSTIs (4 mg/kg/day), right-sided infective endocarditis (RIE) due to S. aureus and bacteremia associated with cSSTIs or RIE (6 mg/kg/day) [15]. It offers rapid recovery from infections, which reduces the risk of resistance development, and may shorten hospitalization and overall treatment costs [16, 17]. Further, as compared to vancomycin, daptomycin has a favorable renal safety profile with prolonged use [18, 19].

The clinical experience with daptomycin since its approval in Europe, Latin America, and Asia has been captured by the European Cubicin® Outcomes Registry and Experience (EU-CORESM). EU-CORE, a retrospective, multicenter, and non-interventional study, was designed to collect real-world data of daptomycin treatment for Gram-positive infections. Interim results of EU-CORE were also published by Gonzalez-Ruiz and colleagues [20]. The objectives of this observational registry were to assess the clinical outcomes and safety of daptomycin in a large multicenter cohort of patients in clinical practice to reflect the real-world experience with daptomycin use.

METHODS

Patients and Data Collection

This analysis included data from patients across 18 countries in Europe (12), Latin America (5), and Asia (1) who had received at least one dose of daptomycin between January 2006 and April 2012 for the treatment of serious Gram-positive bacterial infections. All patients were followed up for a period of 30 days post-treatment, and patients with endocarditis, intracardiac/ intravascular device infection, osteomyelitis, or orthopedic device infection were followed up for 2 years until 2014. The protocol was approved by the health authority and the Institutional Review Board (IRB) or Ethics Committee (EC) in each country and written informed consent was obtained according to the requirements of the IRB or EC and/or the local data privacy regulations. Patients were included in the study if they were treated with at least one dose of daptomycin and if all mandatory information was available in the hospital files. Patients who received daptomycin as part of a controlled clinical trial were not eligible for inclusion in the study.

Investigators collected demographic, antibiotic, clinical, and microbiologic data from medical records at each site, as previously reported [20].

Clinical Outcomes

Clinical outcomes were assessed by the investigators at the end of daptomycin therapy according to protocol-defined criteria: cured, clinical signs and symptoms resolved, no additional antibiotic therapy was necessary, or infection cleared with a negative culture reported; improved, partial resolution of clinical signs and symptoms and/or additional antibiotic therapy was warranted; failed, inadequate response to daptomycin therapy, worsening or new/recurrent signs and symptoms, need for a change in antibiotic therapy, or a positive culture reported at the end of the therapy; and non-evaluable, unable to determine response due to insufficient information. Clinical success was defined as outcome of cured or improved. Time to improvement was recorded. The reasons for stopping daptomycin therapy and other antibiotics prescribed following daptomycin were also collected.
The duration of treatment was evaluated as the number of inpatient and outpatient days during which the patient received daptomycin therapy, even if they were non-consecutive. There were no restrictions on concomitant treatment. Data on prior and concomitant antibiotic therapy were collected.

**Safety**

Adverse events (AEs) and serious AEs (SAEs) reported during daptomycin treatment and after 30 days from the end of daptomycin therapy were recorded, regardless of the study drug relationship. Microbiologic data included the culture results obtained before or shortly after the initiation of daptomycin therapy.

**Statistical Analysis**

Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Due to the nature of the trial, inferential analyses were not conducted and no formal statistical methodology other than simple descriptive statistics was used. All analyses were considered to be explanatory.

Numerical variables were summarized as arithmetic mean, standard deviation, median, minimum, first quartile, third quartile, and maximum for continuous variables. Categorical variables were summarized by absolute and relative frequencies.

**RESULTS**

**Patient Demographics and Clinical Characteristics**

Overall, 6075 patients were included in the safety population; of these, 81 were pediatric patients. The patient demographic and clinical characteristics are described in Table 1. The median age was 62.0 years. A total of 2777 (45.7%) patients were aged ≥65 years, including 1284 (21.1%) aged ≥75 years. Comorbidity was frequent as would be expected in seriously

| Characteristics | N = 6075 | n (%) |
|-----------------|----------|-------|
| **Gender**      |          |       |
| Male            | 3788     | (62.4)|
| Female          | 2287     | (37.6)|
| **Age (years), median (range)** | 62 (1–103) | (1.3) |
| <18             | 81       | (1.3) |
| ≥18 to <65      | 3212     | (52.9)|
| ≥65 (including ≥75) | 2777     | (45.7)|
| ≥75             | 1284     | (21.1)|
| **Race, Caucasian** | 5224     | (86.0)|
| **Body weight (kg), median (range)** | 75.0 (6–200) | (13.0) |
| **Renal impairment at the initiation of daptomycin therapy (CrCl <30 mL/min)** | 787     | (13.0)|
| **Patients on renal replacement therapy at the initiation of daptomycin therapy** | 552     | (9.1) |
| **Significant underlying disease (>10%)** |            |       |
| Cardiovascular  | 3322     | (54.7)|
| Diabetes mellitus | 1598     | (26.3)|
| Renal           | 974      | (16.0)|
| Malignancy      | 925      | (15.2)|
| Pulmonary       | 804      | (13.2)|
| Gastrointestinal | 719     | (11.8)|

Data are presented as n (%) unless otherwise indicated.
unwell and older patients, and 87.9% of patients had significant underlying disease. The most common underlying conditions were cardiovascular disease (54.7%) and diabetes mellitus (26.3%). The most frequently reported primary infections were cSSTIs (31.7%) and bacteremia (20.7%), followed by uncomplicated skin and soft tissue infections (uSSTIs, 10.6%) and endocarditis (10.0%; Table 2).

**Microbiology**

Samples for cultures were obtained from 5038 (82.9%) patients, of whom 3910 (77.6%) had positive cultures. *S. aureus* was the most commonly isolated primary pathogen (42.9%) in patients with positive cultures and MRSA was identified in 23.2% of patients (Table 3). *Staphylococcus epidermidis* was the most common coagulase-negative staphylococcal (CoNS) pathogen (16.5%; Table 3).

### Table 2 Type of primary infection (safety population)

| Infection type                                      | N = 6075 | n (%)   |
|-----------------------------------------------------|----------|---------|
| Complicated skin and soft tissue infections         | 1927     | (31.7)  |
| Bacteremia                                          | 1255     | (20.7)  |
| Uncomplicated skin and soft tissue infections       | 646      | (10.6)  |
| Endocarditis                                        | 610      | (10.0)  |
| Foreign body/prosthetic infection                   | 595      | (9.8)   |
| Osteomyelitis (non-prosthetic and prosthetic device related) | 432 | (7.1) |
| Other<sup>a</sup>                                    | 610      | (10.0)  |

<sup>a</sup> Includes septic arthritis, urinary tract infection/pyelonephritis, necrotizing infections, necrotizing fasciitis, surgical/non-surgical antibiotic prophylaxis, neutropenic fever, CNS infection, metastatic abscess, and unknown or not otherwise specified infections

### Table 3 Primary pathogens in patients with positive cultures

| Primary pathogen isolated                      | N = 3910 | n (%)   |
|------------------------------------------------|----------|---------|
| *Staphylococcus aureus*                        | 1676     | (42.9)  |
| Methicillin-resistant                          | 906      | (23.2)  |
| Methicillin-susceptible                        | 643      | (16.4)  |
| Methicillin susceptibility unknown             | 127      | (3.2)   |
| Coagulase-negative staphylococci               | 1116     | (28.5)  |
| *Staphylococcus epidermidis*                   | 644      | (16.5)  |
| Other                                           | 472      | (12.1)  |
| *Staphylococcus* species coagulate not specified| 41       | (1.0)   |
| *Streptococcus agalactiae* or group B streptococci | 30 | (0.8) |
| *Streptococcus pyogenes* or group A streptococci | 27      | (0.7)   |
| Viridans streptococci group                    | 57       | (1.5)   |
| Other *Streptococcus* species                  | 64       | (1.6)   |
| *Enterococcus faecalis*                        | 236      | (6.0)   |
| *Enterococcus faecium*                         | 184      | (4.7)   |
| Vancomycin-resistant                           | 64       | (1.6)   |
| (*E. faecalis* or *E. faecium*)                |          |         |
| Other *Enterococcus* species                   | 52       | (1.3)   |
| Gram-negative bacilli                          | 231      | (5.9)   |
| Other<sup>a</sup>                              | 196      | (5.0)   |

<sup>a</sup> Includes *Clostridium perfringens*, *Clostridium* species, *Corynebacterium* species, *Peptostreptococcus* species, Gram-negative cocci, Gram-positive bacilli, Gram-positive cocci, viruses, fungi/yeast, and invalid/ambiguous pathogen code.

**Previous and Concomitant Antibiotic Therapies**

Daptomycin was administered empirically in 3438 (56.6%) patients. A total of 3966 (65.3%) patients received antibiotics prior to daptomycin therapy. The most commonly...
used prior antibiotics were penicillins (25.4%) and glycopeptides (24.4%). Vancomycin was administered as prior therapy in 1052 (17.3%) patients. The main reasons for the switch to daptomycin were failure of the previous antibiotic and narrowing of antibiotic therapy. A majority of patients ($n=3934$, 64.8%) received concomitant antibiotics with daptomycin as inpatient therapy, most commonly carbapenems (23.2%) and penicillins (13.9%).

**Daptomycin Prescribing Patterns**

The most frequently prescribed dose of daptomycin was 6 mg/kg/day in 2649 (43.6%) patients; 1554 (25.6%) patients received 4 mg/kg/day. A dose of 4 mg/kg/day was most frequently used in skin infections and 6 mg/kg/day dose was used for other infections such as bacteremia, endocarditis, and osteomyelitis. A total of 1097 (18.1%) patients received doses $> 6$ mg/kg/day and 645 (10.6%) patients received doses $\geq 8$ mg/kg/day. Daptomycin treatment was received by 5879 (96.8%) patients as inpatient therapy and 709 (11.7%) patients as outpatient therapy. The median duration of daptomycin therapy was 11 (range 1–300) days; 10 (range 1–246) days for inpatients ($n=5879$) and 14 (range 1–290) days for outpatients ($n=709$). A total of 1892 (31.1%) patients received daptomycin as first-line therapy and 3965 (65.3%) patients as second-line therapy.

**Clinical Outcomes**

The overall clinical success rate achieved with daptomycin treatment was 80.5%, and the rates were similar when daptomycin was used as first-line (82.9%) or second-line therapy (79.2%). The clinical success rates across different infections were similar (Fig. 1). Success rate by infection type independent of the treatment

![Proportion of patients (%)](image)

**Fig. 1** Clinical outcome by primary infection. cSSTI complicated skin and soft tissue infection, uSSTI uncomplicated skin and soft tissue infection
dose ranged between 73.9% for bacteremia and 89.3% for uSSTIs. Low failure rates were reported for various primary infections (Fig. 1). As shown in Fig. 2, the clinical success rates by infecting pathogen were high for \textit{S. aureus}. The clinical success rates showed an increasing trend with increasing daptomycin dose for endocarditis and foreign body/prosthetic infections (Fig. 3). Higher clinical success rates were also observed with increased duration of daptomycin therapy (Fig. 4). The overall median time to improvement from initiation of daptomycin treatment was 4 (range 0–400) days.

The majority of patients (59.4%) completed daptomycin therapy without further antibiotic treatment and 22.0% switched to another antibiotic after the end of the daptomycin therapy following improvement (e.g., step-down to oral antibiotic therapy) or treatment failure. Within the subset of patients who received concomitant antibiotic therapy, the

![Fig. 2 Clinical outcome by infecting pathogen. Enterococci include Enterococcus faecalis, Enterococcus faecium and Enterococcus species. CoNS coagulase-negative staphylococci, MRSA methicillin-resistant \textit{Staphylococcus aureus}, MSSA methicillin-susceptible \textit{Staphylococcus aureus}](image)

![Fig. 3 Clinical success rates for endocarditis and foreign body/prosthetic infections by daptomycin dose. Patients with unknown dose information (86 overall, 13 endocarditis and 6 foreign body/prosthetic infection) were not included](image)
The clinical success rate was 77.7% as compared to 86.7% in patients who received no concomitant antibiotic therapy. The majority of patients with endocarditis or intracardiac/intravascular device infection (86.7%) or osteomyelitis/orthopedic device infection (85.9%) had a sustained response during the 2-year follow-up period.

Safety

Safety data from 6075 patients were included in this analysis. A total of 866 (14.3%) patients reported at least one AE and 581 (9.6%) patients reported SAEs (Table 4). AEs and SAEs possibly related to daptomycin therapy were reported in 193 (3.2%) and 49 (0.8%) patients, respectively. The most common AEs, possibly related to daptomycin, by system organ class were investigations (n = 62, 1.0%), skin and subcutaneous tissue disorders (n = 33, 0.5%), and general disorders and administration site conditions (n = 21, 0.3%). The most frequently reported SAEs, possibly related to daptomycin, by system organ class were investigations (n = 12, 0.2%), renal and urinary disorders (n = 11, 0.2%), and general disorders and administration site conditions (n = 6, 0.1%). Infections and infestations (n = 78, 1.3%),

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**Table 4** Safety of daptomycin treatment in overall EU-CORE population

| Safety parameters | N = 6075 | n (%) |
|-------------------|----------|-------|
| Any AE           | 866      | (14.3)|
| AE possibly related to daptomycin | 193      | (3.2)|
| AE leading to study drug discontinuation | 252      | (4.1)|
| Any SAE          | 581      | (9.6)|
| SAE possibly related to daptomycin | 49       | (0.8)|
| SAE leading to study drug discontinuation | 175      | (2.9)|
| AEs occurring in >1% patients, n (%) |          |       |
| Multi-organ failure | 86       | (1.4)|
| Blood CPK increased | 76       | (1.3)|
| Septic shock     | 75       | (1.2)|
| Sepsis           | 73       | (1.2)|

AE adverse event, CPK creatine phosphokinase, SAE serious AE
general disorders and administration site conditions ($n = 41, 0.7\%$), and investigations ($n = 38, 0.6\%$) were the most frequently reported AEs by system organ class, regardless of relationship to daptomycin, which led to discontinuation of study medication.

An increased blood creatine phosphokinase (CPK) level was reported as an AE in 76 (1.3\%) patients, including 11 reported as SAEs. Musculoskeletal and connective tissue disorders were reported as AEs in 25 (0.4\%) patients. Out of these 25 patients, 12 had CPK levels increased to $>10 \times$ upper limit of normal (ULN) from baseline and 13 reported musculoskeletal and connective tissue disorders as SAEs of which 5 were reported as possibly related to daptomycin. Severe skeletal muscle toxicity was reported in 9 (0.1\%) patients. Rhabdomyolysis was reported as a SAE in 6 (0.1\%) patients, with 5 of the 6 SAEs considered as possibly related to daptomycin treatment by the investigator.

Serum CPK levels were measured at baseline in 3511 patients and the majority ($n = 2843, 81.0\%$) had normal CPK values. At baseline, 92 (2.6\%) patients had CPK levels $>10 \times$ ULN. Fifty-two patients (40, 6, and 6 patients treated with $\leq 6$, $>6$ to $<8$, and $\geq 8$ mg/kg/day, respectively) experienced a shift of CPK elevation from $\leq 10 \times$ ULN at baseline to $>10 \times$ ULN and 49 patients had a missing assessment. Peak serum CPK concentrations were in the range of the ULN throughout the analysis period in most patients (Fig. 5).

The total number of reported deaths during the study was 408 (6.7\%). Five (0.1\%) deaths were reported to be related to the study medication. The main causes of death were infections and infestations (3.4\%), general disorders and administration site conditions (1.8\%), multi-organ failure (1.4\%), sepsis (1.3\%), septic shock (1.2\%), and cardiac disorders (1.1\%).

**DISCUSSION**

The data from the EU-CORE registry illustrate 8 years of clinical experience of real-world usage of daptomycin against a variety of Gram-positive infections including drug-resistant pathogens (MRSA, CoNS, and VRE) in patients with multiple co-morbidities. Overall, daptomycin used either as first- or second-line therapy was associated with high clinical success rates. The data demonstrated a favorable effectiveness and safety profile of
daptomycin in the real-world setting, expanding on the results from randomized clinical trials and analyses of interim data from EU-CORE [20–22]. Patients from many sites across the 18 countries in Europe, Latin America, and Asia were enrolled in EU-CORE, allowing for the inclusion of a wide spectrum of infections and microbiologic data to be studied.

In this registry, although cSSTIs and bacteremia were the most common infections, daptomycin was also used to treat severe and deep-seated infections such as osteomyelitis and foreign body/prosthetic infections. These infections are of increasing clinical importance, where long-term treatment options are limited [23, 24]. Daptomycin retains advantage in this context because of its suggested activity in biofilms [25, 26]. The clinical success rates for different primary infections were high. Daptomycin was also demonstrated to be effective against VRE infections that are generally challenging to treat. In addition, the rapid bactericidal activity of daptomycin is expected to reduce the opportunity for development of potential resistance [18, 21, 27, 28].

Data from previous studies suggest that daptomycin is mostly used as second-line therapy; however, in approximately 10–40% of patients it is used as first-line therapy, based on type of infection [29]. In this study, daptomycin showed favorable effectiveness whether used as first-line (83.0%) or second-line (79.2%) therapy with or without concomitant antibiotics. Daptomycin has an important role as first-line therapy for Gram-positive infections in terms of both effectiveness and cost considerations [21, 30]. Additionally, the present study demonstrated similar effectiveness with daptomycin treatment against both MRSA and methicillin-susceptible S. aureus infections, thus supporting its use as an empirical therapy for S. aureus infections. This observation is in line with published guidelines that recommend daptomycin as the first alternative to vancomycin [31, 32].

The recommended first-line therapies for treating MRSA infections are vancomycin and linezolid; however, these are associated with various safety concerns, particularly in long-term use. Nephrotoxicity and ototoxicity are the known major adverse reactions related to vancomycin use. The monitoring of trough concentrations to prevent nephrotoxicity is recommended (i.e., sustained troughs of 15–20 g/mL), especially in patients with unstable renal function or therapy for longer than 3–5 days [33, 34]. On the other hand, linezolid therapy has been reported to be associated with myelosuppression, peripheral and optic neuropathy, and lactic acidosis especially with prolonged use [35]. Further, linezolid-associated serotonergic and adrenergic drug interactions can lead to severe AEs such as hypertensive episodes [36]. The rates of AEs reported for daptomycin in this retrospective observational study were low, although these may not be compared to AE reporting in a controlled clinical trial [23].

Most patients in this study received doses up to 6 mg/kg/day of daptomycin and 18% received doses >6 mg/kg/day. No new or unexpected safety findings were reported even when patients received doses >6 mg/kg/day (including doses >10 mg/kg/day). On the basis of the linear pharmacokinetic profile and concentration-dependent activity of daptomycin, doses >6 mg/kg/day are increasingly utilized [35, 37, 38]. Higher doses are also recommended for endocarditis and osteomyelitis by the Infectious Diseases Society of America guidelines [31, 39]. Furthermore, toxicity may be a concern while increasing the dose of daptomycin and previous
reports showed that high-dose daptomycin (>6 mg/kg/day) may cause elevations in CPK levels at an incidence rate of 2.5–8.3% [27, 40–47]. However, CPK elevation during daptomycin therapy is not always associated with adverse musculoskeletal effects [40, 48]. In this study, a small proportion of patients experienced serum CPK elevation (1.7%) and severe skeletal muscle toxicity (0.1%).

Although rare cases of eosinophilic pneumonia were reported as AEs related to daptomycin (3 patients), patients recovered upon discontinuation of daptomycin therapy. Altogether, these outcomes reaffirm the safety profile of daptomycin treatment.

The inclusive nature of the registry was a strength; however, there are some inherent limitations such as the non-randomized, non-blinded design, and the patient outcomes that were solely determined by the treating physician. Despite these limitations, this registry reflects real-world clinical settings and permits the inclusion of diverse infections treated with concomitant antibiotics.

**CONCLUSIONS**

These results from 8 years of clinical experience complement the data from randomized clinical studies and show that daptomycin is a valuable treatment option in the management of various Gram-positive infections including those which are difficult to treat. However, further data explorations are required to examine infection- and population-specific outcomes within the EU-CORE registry in detail.

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Compliance with ethics guidelines. The protocol was approved by the health authority and the Institutional Review Board (IRB) or Ethics Committee (EC) in each country and written informed consent was obtained according to the requirements of the IRB or EC and/or the local data privacy regulations.

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