UDC: 616-071(497.7)"2022/2024"
Professional paper

A RETROSPECTIVE ANALYSIS OF CLINICAL TRIAL APPLICATIONS IN NORTH MACEDONIA (2022-2024): PHASES, THERAPEUTIC AREAS, AND SITE DISTRIBUTION

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Abstract

Aim: This study analyses the trends of clinical trial applications in North Macedonia from January 2022 to December 2024.
Method: The data were extracted from two primary local sources: the public registry of clinical trials in North Macedonia and the internal database of the Agency for Medicines and Medical Devices.
Results: A total of 82 clinical trial applications were submitted during this period, 38 applications are for clinical trials and 44 bioequivalence (BE) studies applications. The clinical trials were categorized by study phase, therapeutic area, and trial site location. In all three years the majority of applications were for Phase 3 studies (45%), followed by Phase 1 (26%), than Phase 2 (18%), and Phase 4 (11%). In terms of therapeutic areas, clinical trials in the area of Neurology are the greatest (7), followed by Oncology (6), Dermatology (5) and Pulmonology (5), Gastroenterology (4), Haematology (4), Cardiology (2) and Rheumatology (2), Endocrinology (1), Nephrology (1) and Antibiotics (1). All submitted studies were multi centric, having prior approval in other countries. Regarding trial site distribution, 21 of the clinical trials were approved for a single site in North Macedonia, as well as 44 BE studies, while 17 clinical trials are conducted in multiple sites. Geographically, 27 of the clinical trials and 44 bioequivalence (BE) studies were conducted exclusively in Skopje.
Conclusion: The findings indicate a modest level of clinical trial activity in the country. To enhance clinical research engagement, aligning North Macedonia's clinical trial legislation with European Union standards could improve regulatory efficiency and attract more sponsors.

Key words: clinical trials, study phase, bioequivalence (BE) studies

1. Introduction

Clinical trials play a vital role in advancing medical research and improving patient care. These trials are carefully designed experiments that evaluate the effectiveness and safety of new drugs, treatments, or interventions in humans (Jager, 2023). Clinical trials are essential for determining the appropriate dosage and administration of new drugs and medical devices. They provide valuable data on the long-term safety and efficacy of treatments (Berridge, 2023).
Clinical trials involve a diverse range of participants, including individuals with specific medical conditions or healthy volunteers, depending on the nature of the study (Jager, 2023). Participating in clinical trials provides several benefits for patients, including access to new and innovative treatments that may not be available through other means. Clinical trials also provide patients with access to expert medical care and monitoring throughout the trial period, which can help to improve their overall health and wellbeing. Moreover, participating in clinical trials can give patients a sense of empowerment and control over their health. By participating in these trials, patients can contribute to the advancement of medical research and potentially help to improve the lives of others (Berridge, 2023).
In view of the increased cost of the drug discovery process, developing, and low-income countries depend on the production of generic drugs. The generic drugs are similar in composition to the patented/branded drug.Once the patent period is expired generic drugs can

be manufactured which have a similar quality, strength,and safety as the patented drug. The bioequivalence (BE) studies review the absorption, distribution, metabolism, and excretion (ADME) of the generic drug. These studies compare the concentration of the drug at the desired location in the human body, called the peak concentration of the drug (Cmax). The extent of absorption of the drug is measured using the area under the receiver operating characteristic curve (AUC), wherein the generic drug is supposed to demonstrate similar ADME activities as the branded drug (Kandi and Vadakedath, 2023).

The objective of this article is to conduct a comprehensive analysis of clinical trial application trends and bioequivalence (BE) studies in North Macedonia over the past three years. The aim of the study is to evaluate the annual variation in the number of submitted applications, characterizing the clinical trials according to their study phases, to identify the predominant therapeutic areas and to determine the primary geographic locations where these studies are being conducted. Through this analysis, the article seeks to provide a clearer understanding of the current landscape of clinical research in the country.

2. Methods

This analysis was conducted using data from two primary local sources: the public registry of clinical trials in North Macedonia and the internal database of the Agency for Medicines and Medical Devices, the national authority responsible for the evaluation and approval of clinical trial applications. The data in this article are from January 2022 to December 2024.

The study phase of each trial was classified in accordance with established categorizations in the existing literature as follows: Phase 1 (including studies labeled as 0, 1, 1/2, 1/2a and 1/3), Phase 2 (2, 2a, 2b and 2/3), Phase 3 (3, 3a, 3b and 3/4), Phase 4 (Huh, Hwang and Lee, 2018). Information on the study phase was extracted directly from the local registry without further modification.

Therapeutic areas were determined based on the primary investigational product (IP) under study and the medical specialty of the clinical department in which the study site was located. This classification allowed for the grouping of trials into major therapeutic domains.

In the case of multicenter studies, each individual study site was counted separately when calculating the total number of clinical trial locations by city. This approach enabled a more accurate depiction of the geographic distribution of trial activity across the country.

3. Results

The total number of applications for the period from January 2022 to December 2024 is 82. 38 applications are for clinical trials and 44 bioequivalence (BE) studies applications. The trends in the number of applications for clinical trials (Figure 1) and bioequivalence (BE) studies (Figure 2) over the past three years are illustrated in the graphs below.

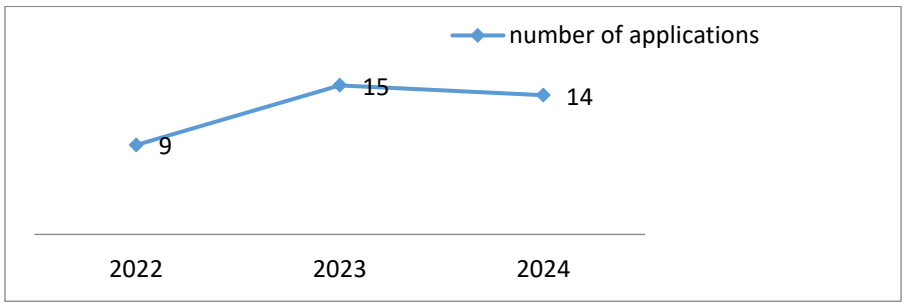

Figure 1. The trends of applications for clinical trials in 2022-2024

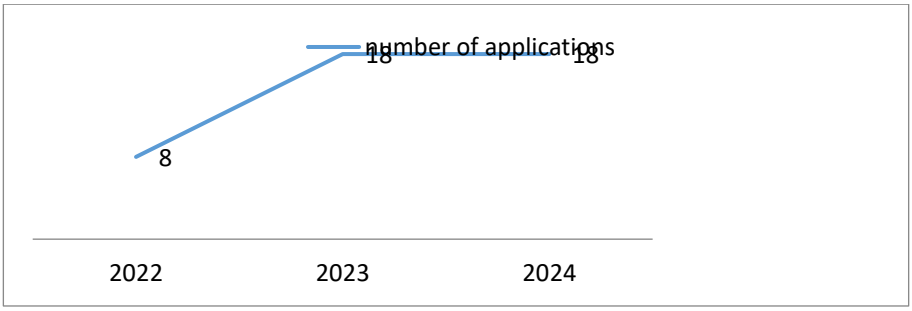

Figure 2. The trends of applications for bioequivalence (BE) studies in 2022-2024

Clinical trial applications according to study phase are shown in Figure 3. In 2022 there was one application in eache phase 1, 2 and 4, and six applications for clinical trials in phase 3. In 2023 the number of applications in phase 1 is rising to five application, the same as phase 3, three applications in phase 2 and two applications in phase 4. In 2024 the highest number of applications are in phase 3, six applications, followed by phase 1 with four, then phase 2 are three applications and phase 4 only one. The presented Table 1 categorizes clinical trial applications based on the phase of the clinical trial with data provided separately for each year. The applications are further divided into studies conducted at a single site within North Macedonia, those conducted at multiple sites within the country, and the total number of studies regardless of site distribution.

Table 1. Summary of clinical trials according to study phase and multicenter status

study phase	multi center in NM			single centre in NM			total			
	2022	2023	2024	2022	2023	2024	2022	2023	2024	2022-2024
1	0 (0%)	2 (13.33%)	2 (14.28%)	1 (11.11%)	3 (20.00%)	2 (14.28%)	1 (11%)	5 (33%)	4(28.6%)	10(26.31%)
2	1 (11.11%)	1 (6.67%)	1 (7.14%)	0 (0%)	2 (13.33%)	2 (14.28%)	1 (11%)	3 (20%)	3 (21.43%)	7(18.42%)
3	3 (33.34%)	5(33.34%)	2 (14.28%)	3(33.33%)	0 (0%)	4 (28.6%)	6 (67%)	5 (33%)	6(42.83%)	17(44.74%)
4	0 (0%)	0 (0%)	0 (0%)	1 (11.11%)	2 (13.33%)	1 (7.14%)	1 (11%)	2 (14%)	1(7.14%)	4(10.53%)

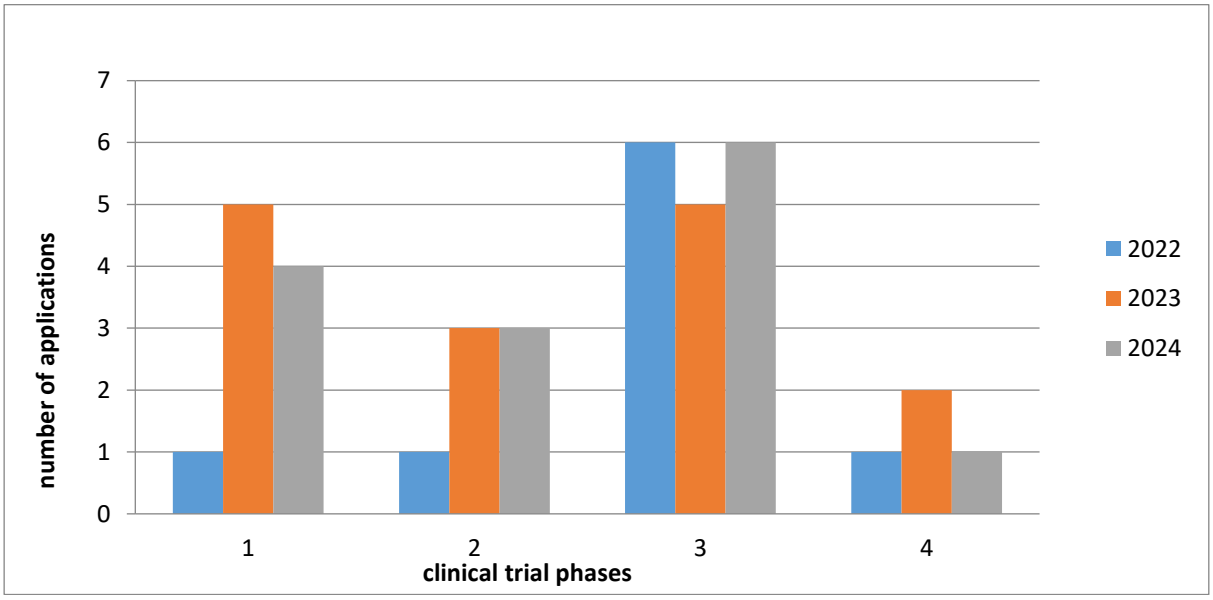

Figure 3. Categorization of clinical trial applications based on the phase of the clinical trial

Based on therapeutic area, the majority of clinical trial applications were in Neurology (18%), followed by Oncology (16%), then Pulmonology (13%) and Dermatology (13%). Applications were also notable in Gastroenterology (11%), Hematology (10%), Cardiology and

Rheumatology (5%), with fewer applications observed in Endocrinology, Nephrology and Antibiotics (3%) (Figure 4).

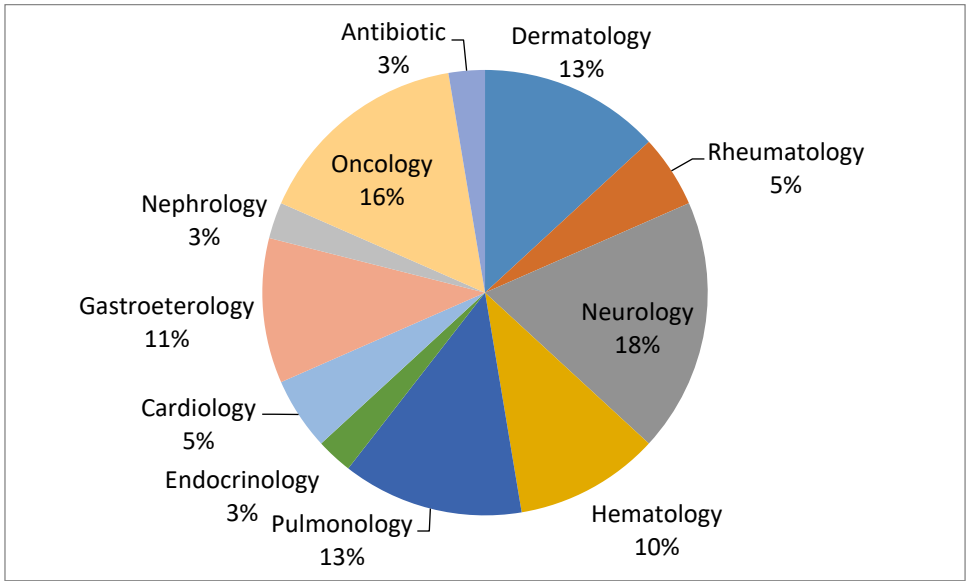

Figure 4. Clinical trial application according to therapeutic area- based classification

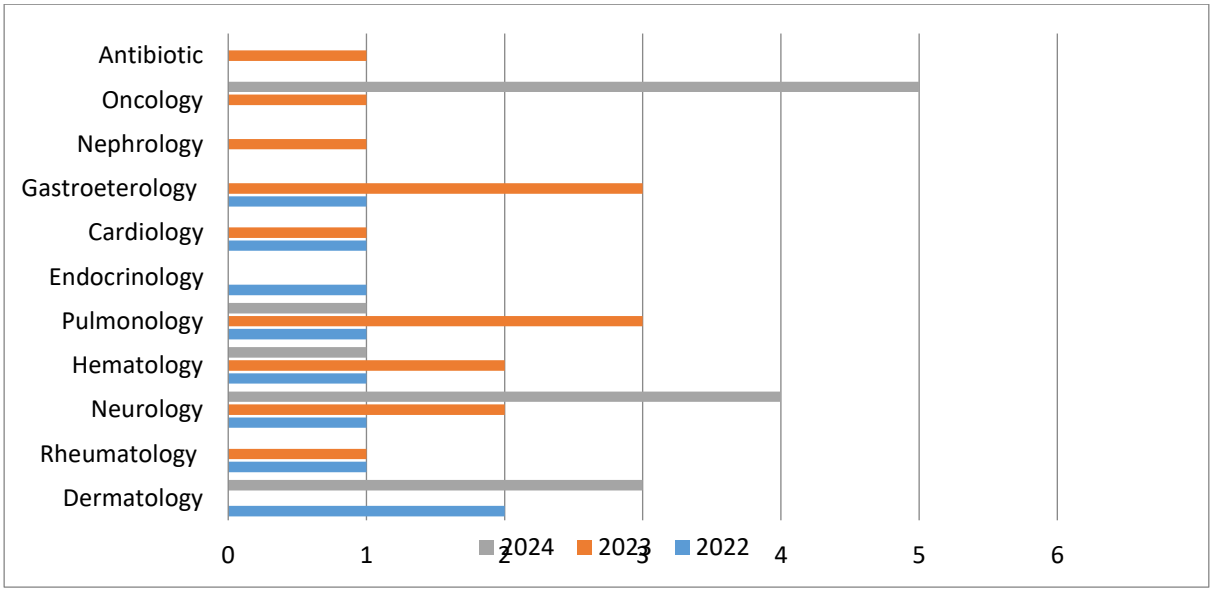

Figure 5. Clinical trial applications by therapeutic area, presented annually (2022–2024)

Regarding trial site distribution, 21 of the clinical trials were approved for a single site in North Macedonia, while 17 were for multiple sites (Figure 7). Bioequivalence (BE) studies are single site studies as well. Geographically, 71% of the trials were conducted exclusively in Skopje (Figure 6). All bioequivalence (BE) studies were conducted in Skopje.

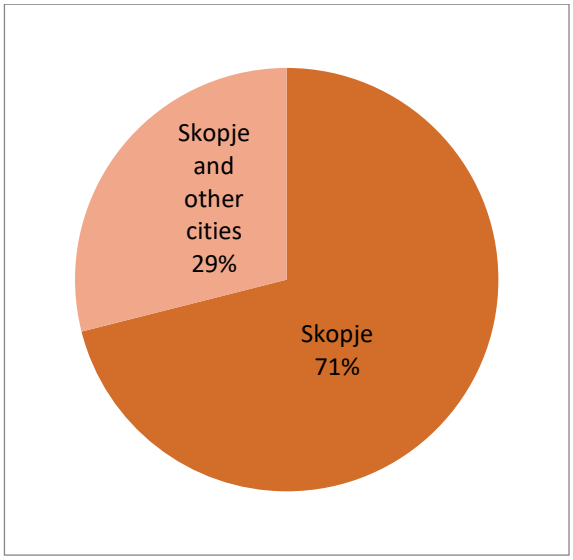

Figure 6. Geographic distribution of clinical investigation site

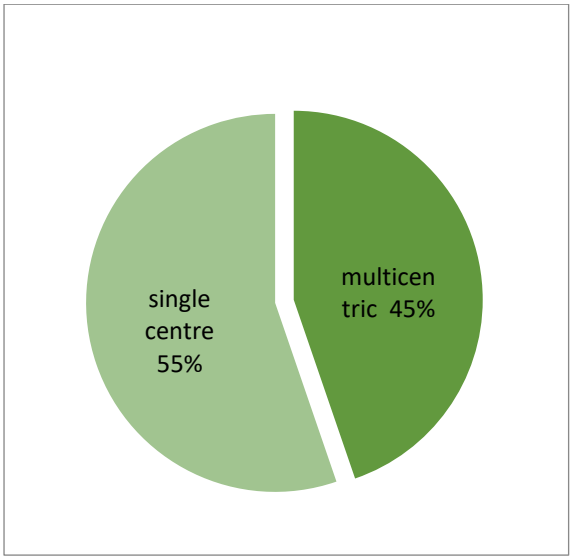

Figure 7. Clinical trial distribution by trials by city

4. Discussion

The analysis of clinical trial applications over the past three years reveals a dynamic trend in research activity. In 2023, the number of clinical trial applications increased significantly compared to the previous year, indicating a strong upward trend in research engagement. However, this growth was not sustained into 2024, where a slight decline in the number of applications was observed. Despite this decrease, the overall level of activity remains higher than in 2022, suggesting a net positive trajectory in the clinical research landscape.

A particularly noteworthy development was observed in bioequivalence studies. Applications for these studies rose sharply in 2023, reflecting a growing interest in generic drug development and regulatory pathways focused on equivalence. Interestingly, the number of bioequivalence study applications remained stable in 2024, maintaining the elevated level reached in 2023.

A significant shift was also observed in the distribution of trial phases. While phase 3 trials continued to represent the majority of applications, there was a marked increase in the number of phase 1 and phase 2 trials. This shift suggests a growing interest in early-stage research, possibly reflecting increased investment in novel compounds and the exploration of new drugs.

Related to therapeutic areas, dermatology is the leading area in 2022. In 2023 there were a higher number of applications in gastroenterology and pulmonology, followed by a wider variety of therapeutic areas represented. By 2024, oncology and neurology have the most applications, showing a growing interest in a more complex and challenging diseases (Figure 5).

The analysis of clinical trial site distribution reveals a noticeable preference for conducting studies at single locations, particularly in the case of bioequivalence (BE) studies, which are typically designed for tightly controlled settings. While multicentric trials are also present.

Most of the clinical trials are conducted in the capital city, which has become the main place for research activity in the country. This is more evident in the case of bioequivalence studies, they are all conducted in Skopje. The capital city has modern facilities, a lot of medical institutions, and plenty of experienced researchers, which makes it the first choice for hosting these trials.

5. Conclusion

This overview of clinical trial activity in North Macedonia shows a period of meaningful growth and evolving research priorities. The significant rise in applications, particularly in 2023, indicates a growing interest in clinical trials, with more focus in both innovative therapies and generics. Although there is a slight decline in applications in 2024, the overall trend suggests a strengthening research landscape.

Shifts in study phases show that there is a growing interest for early phase trials happening, while phase 3 studies remain the bases of clinical activity. The therapeutic focus has also changed over the years from dermatology to more attention toward oncology and neurology. This shows what is needed in health care here and around the world.

Most of the trials are conducted in the capital city, because that is where most of the research facilities are located. This makes it easier to conduct studies consistently, especially for the bioequivalence studies. At the same time, there is a chance to spread trials to other cities in the country, which could help with access, variety, and strength in the clinical trial system.

These trends show that the clinical research in North Macedonia is really growing and evolving. People are getting more involved, and it is exciting to see how this can develop even further. There is a sense that things are changing for the better, and it feels like the country is on the right path to becoming even more active in the research field. With all these shifts taking place, it is a great time for North Macedonia to take advantage of this and make even more progress in clinical research. Continued support, investment in infrastructure, and strategic policy efforts will be essential to keep this growth and enhance the country's position in the regional and global clinical research perspective.

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